Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognize the author's right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form and Deposit Licence.
Improving adherence and asthma outcomes in school aged children with asthma

Amy Hai Yan Chan

A thesis submitted in partial fulfilment of the requirements for the degree of
Doctor of Philosophy in Pharmacy
The University of Auckland, 2016
Abstract

Asthma is one of the most common chronic conditions in children. Effective treatments are available, the most important of which are inhaled corticosteroids, which reduce morbidity and mortality. Despite the availability of effective preventive therapies, asthma control continues to be poor, primarily due to poor adherence. Interventions have been developed to improve adherence; however, changes have been modest, or not sustained. Where there have been significant increases in adherence, these have not translated to improvements in outcomes. A novel approach to adherence support is needed.

Electronic monitoring devices (EMDs) have risen to prominence over the last decade, assuming an important role in adherence measurement and intervention. The ability of EMDs to provide objective, real-time data and user feedback places EMDs at the forefront of contemporary adherence interventions. This thesis discusses adherence in chronic disease, specifically asthma, and the role of EMDs in adherence promotion. Studies using EMDs to improve adherence in asthma have shown improvements in adherence, but the link to outcomes has been inconclusive. This thesis presents the main findings from a randomised controlled trial (RCT) investigating the use of an EMD in children with asthma. The results from this trial provide the first unequivocal evidence of the beneficial effects of EMDs on clinical outcomes. It provides a direction for future adherence research, focusing on the effect of EMDs on clinical outcomes, beyond adherence promotion.

This thesis also presents the first performance and patient acceptability data for EMDs in children. The positive findings highlight the potential for EMDs to be used outside of the research setting, though key issues of quality control, usability and cost-effectiveness need to be addressed before EMDs can be integrated into practice. Other factors influencing adherence are also discussed. This study found associations between higher adherence and female sex, Asian ethnicity, smaller household size and a younger age at diagnosis. These findings can help identify those at risk of non-adherence to help target adherence interventions.

This thesis highlights areas of knowledge growth and areas where questions remain unanswered. It provides a platform for future research, presenting new possibilities for improving medication adherence and clinical outcomes.
Acknowledgements

I would like to thank my primary supervisor Dr Jeff Harrison for his unfaltering support through my PhD journey. His belief in my abilities has helped motivate me through the ups and downs and his steady wisdom and quiet confidence are appreciated. He has been my role model since the start of my university days – and remains very much so, if not more, today. I look forward to many more years of collaboration both as a research colleague and friend. Thank you to my co-supervisor, Professor Edwin Mitchell, for his extensive experience and wise counsel, which have helped shaped my approach to research and provided me with a solid foundation on which to build my research career.

There are people who have passed since I started this journey who deserve a special mention. Professor Peter Black sadly passed away in 2010; without him this doctorate would not have originated in the first place. I dedicate much of the research output and this thesis to him. His passion and dedication to health and research were admirable – and resonate in the lives of those who were lucky enough to have met him. My grandfather, Shiu Man Lee, left us in 2011; he believed research is what would change the world and is the reason I chose to follow this research path. There is not a day that passes without both of these extraordinary people being remembered, and this research and the others that follow, will continue their legacy.

I would like to thank my advisors, Mr Alistair Stewart and Dr Juliet Foster, both of whom have been pivotal to this research. The statistical expertise of Mr Stewart, along with his patience and perseverance, were central to the development of my statistical knowledge and understanding. I am grateful for the guidance and inspiration shown to me by Dr Juliet Foster, who has helped me grow from a doctoral student to a researcher. Special thanks to Professor Carlos Camargo Jr and Dr Mitesh Patel for their expertise and stimulating research discussions, and to Academic Consulting for their assistance with proofing and editing.

This study was made possible with funding from the Health Research Council and Cure Kids. I thank both for supporting this research, which has the potential to help many, both in New Zealand and internationally. Thank you to the study participants and families without whom this study would not have taken place. Thank you also to Auckland and Waitemata District Health Boards for making the study feasible, and to ADHB Pharmacy Department for supporting my research role. Last but not least, thank you to my parents – Dr Sam and Margaret Chan – and my sister – Dr Karen Chan – for their unconditional support and understanding through all these years, without whom I would not be who I am today. Thank you also to my partner David Wilson for his unfailing encouragement and motivation.
“To the discovery of the most important truths the observation of the rare and hidden phenomena, only to be produced by experiments, does not lead; but rather the observation of the openly displayed phenomena, accessible to everybody. Therefore the problem is not so much, to see what nobody has yet seen, but rather to think concerning that which everybody sees, what nobody has yet thought.”

– Arthur Schopenhauer, Parerga und Paralipomena, 1851
Table of Contents

Abstract ........................................................................................................................................ ii
Acknowledgements .................................................................................................................. iii
List of Tables ........................................................................................................................... ix
List of Figures ........................................................................................................................ xi
List of Abbreviations and Glossary ....................................................................................... xii
Co-Authorship Forms ............................................................................................................ xiii
Chapter 1: Introduction ............................................................................................................ 1
  1.1 Background ........................................................................................................................ 1
      1.1.1 Asthma – a chronic inflammatory condition ..................................................... 1
      1.1.2 The New Zealand (NZ) context ........................................................................ 1
  1.2 Aims of the research ....................................................................................................... 3
  1.3 Structure of the thesis ...................................................................................................... 3
Chapter 2: Medication adherence: an overview ................................................................. 6
  2.1 Adherence – definitions in this thesis ......................................................................... 7
  2.2 Types of non-adherence .............................................................................................. 8
  2.3 Methods to measure adherence ................................................................................. 9
      2.3.1 Direct methods ............................................................................................... 9
      2.3.2 Indirect methods .......................................................................................... 11
  2.4 Determinants of medication adherence ..................................................................... 17
      2.4.1 Medication adherence in chronic disease ................................................... 18
      2.4.2 Medication adherence in asthma .................................................................. 36
      2.4.3 Medication adherence in children with asthma ......................................... 46
  2.5 Strategies to improve adherence .............................................................................. 53
      2.5.1 Adherence interventions in chronic disease ............................................. 54
      2.5.2 Adherence interventions in asthma ............................................................ 57
      2.5.3 Adherence interventions in children with asthma ................................... 63
  2.6 Gaps in knowledge in adherence ............................................................................ 64
Chapter 3: Literature review: use of electronic adherence monitoring devices in chronic disease .......................................................... 66
  3.1 The role of electronic adherence monitoring in medication adherence ................... 66
  3.2 Methodology of review .............................................................................................. 67
      3.2.1 Study selection ............................................................................................. 67
      3.2.2 Search strategy ............................................................................................ 68
      3.2.3 Study review and classification procedures ........................................... 69
      3.2.4 Data extraction ............................................................................................ 69
  3.3 Results from the literature review ............................................................................ 70
      3.3.1 Characteristics of included studies ............................................................ 72
Chapter 4: Electronic monitoring devices in research and practice: a review

4.1 Abstract

4.2 Paper I: Adherence monitoring and e-health: how clinicians and researchers can use technology to promote inhaler adherence in asthma

4.2.1 Medication adherence in asthma is suboptimal

4.2.2 Why are electronic monitoring devices for inhalers needed?

4.2.3 Features and reliability of currently available electronic monitoring devices

4.2.4 The role of electronic devices in monitoring adherence with asthma inhalers

4.2.5 The role of electronic monitoring devices in adherence promotion in asthma

4.3 Discussion

4.3.1 What are the evidence gaps?

4.3.2 What are the most promising areas for use of Electronic Monitoring Devices?

4.3.3 Limitations of current EMDs

4.3.4 Moving EMDs from research into clinical practice – what is needed?

Chapter 5: Factors to consider when using electronic monitoring devices in research and practice

5.1 Abstract

5.2 Paper II: Using electronic monitoring devices to measure inhaler adherence: practical guide for clinicians

5.2.1 Introduction

5.2.2 Available EMDs

5.2.3 Regulation and insurance for EMDs

5.2.4 Using EMDs in clinical settings

5.2.5 Implementing EMD checks

5.2.6 Working with newly developed EMDs

5.3 Summary

5.4 Appendix A1: Detailed testing of new EMD devices

5.4.1 Evaluating new EMDs in the clinic office setting

5.4.2 Patient-based checks of the new EMD

5.5 In-vitro validation testing of a simple electronic adherence monitoring device, the Smartinhaler

5.5.1 Abstract

5.5.2 In-vitro validation testing of electronic adherence monitoring devices
Chapter 6: Using electronic monitoring devices to improve adherence and asthma outcomes – a randomised controlled trial ............................................. 148

6.1 Abstract........................................................................................................... 149
6.1.1 Background ................................................................................................ 149
6.1.2 Methods ..................................................................................................... 149
6.1.3 Findings ..................................................................................................... 149
6.1.4 Interpretation ............................................................................................. 150

6.2 Paper IV: The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial ......................................................... 150
6.2.1 Introduction ............................................................................................... 150
6.2.2 Methods ..................................................................................................... 150
6.2.3 Results ....................................................................................................... 155

6.3 Discussion ...................................................................................................... 161
6.4 Appendix ........................................................................................................ 165

Chapter 7: Performance and acceptability of electronic monitoring devices in children .......... 167

7.1 Abstract.......................................................................................................... 168
7.2 Paper V: Electronic adherence monitoring device performance and patient acceptability: a randomized control trial ................................................................. 168
7.2.1 Introduction ................................................................................................ 168
7.2.2 Methods ..................................................................................................... 170
7.2.3 Results ....................................................................................................... 173

7.3 Discussion ...................................................................................................... 179
7.3.1 EMD performance....................................................................................... 180
7.3.2 Limitations – EMD performance ................................................................. 180
7.3.3 EMD acceptability ..................................................................................... 180
7.3.4 Limitations – EMD acceptability ................................................................. 181
7.3.5 Conclusions ................................................................................................ 182

Chapter 8: Factors affecting medication adherence in school aged children to inhaled corticosteroids ................................................................................. 183

8.1 Abstract.......................................................................................................... 184
8.2 Paper VI: Factors associated with medication adherence in school-aged children with asthma .............................................................................................................. 184
8.2.1 Introduction ................................................................................................ 184

8.3 Material and methods ..................................................................................... 185
8.3.1 Study subjects and design ........................................................................ 185
8.3.2 Adherence measurement .......................................................................... 186
8.3.3 Analysis of factors associated with adherence .......................................... 186
8.3.4 Statistical analysis ...................................................................................... 187
List of Tables

Chapter 3
Table 1. Characteristics of included studies ................................................................. 73
Table 2. Effectiveness of interventions and characteristics of studies relating to effectiveness .... 81

Chapter 4
Table 1. The features and reliability of currently available electronic monitoring devices.......... 97

Chapter 5
Table 1. Useful features of currently available electronic monitoring devices for clinical practice .. 111
Table 2. Considerations for use of electronic monitoring devices by clinicians and patients and regulatory considerations ......................................................................................... 114
Table 3. Common EMD malfunctions and their management .............................................. 119
Table E1. Brief EMD performance checklist ................................................................ 132
Table E2. Clinic-based checks – a checklist of parameters to check in a new inhaler EMD .......... 134
Table E3. Recommended actuation recording accuracy and battery life checks ...................... 136
Table E4. Patient-based checks – a checklist of parameters to check in a new inhaler EMD ........ 138
Table 4. Comparison of Doser CT with MDI Log ............................................................ 141
Table 5. Monitor functions tested over the 24-week period ................................................. 145
Table 6. Results of testing process .................................................................................. 146

Chapter 6
Table 1. Baseline characteristics ..................................................................................... 157
Table 2. Change in Childhood-Asthma Control Test scores, lung function and exacerbations .... 159
Appendix Table 1. Baseline characteristics of patients aged 6–15 years presenting to ED with asthma .............................................................................................................................. 165

Chapter 7
Table 1. Baseline participant characteristics by trial randomisation group ......................... 174
Table 2. Pre-issue and return quality control testing results ............................................... 176
Table 3. Electronic monitoring device acceptability scores by trial randomisation group .......... 177
Table 4. Feedback on the electronic monitoring device from participants or their caregivers.... 178

Chapter 8
Table 1. Characteristics of participants in the analytical cohort and unadjusted analyses of 20 factors associated with adherence ......................................................................................... 189
Table 2. Multivariable regression analysis with objective adherence as independent variable (n=87) .......................................................... 192
List of Figures

Chapter 3
Figure 1. Flowchart of study inclusion ................................................................. 71

Chapter 4
Figure 1. Images of some electronic monitoring devices discussed in this paper .................. 100

Chapter 5
Figure 1. Images of currently available electronic monitoring devices and details on where to obtain supply, development status, mechanism of actuation detection and inhaler compatibility .......... 116
Figure 2. Example of a patient actuation diary ..................................................... 127

Chapter 6
Figure 1. SmartTrack inhaler .............................................................................. 152
Figure 2. Trial profile ............................................................................................ 156
Figure 3. Percentage distribution of adherence over the study period ......................... 158
Appendix Figure 1. Morning (AM) versus evening (PM) percentage adherence over time by group ........................................................................................................ 165
Appendix Figure 2. Change in percentage adherence over time.................................. 166
List of Abbreviations and Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD – Chronic Obstructive Pulmonary Disease</td>
<td>A lung disease characterised by chronic obstruction of lung airflow that, unlike asthma, is not fully reversible. The airflow limitation is usually progressive, and the obstruction interferes with normal breathing. Main symptoms include abnormal shortness of breath, chronic cough and sputum production.</td>
</tr>
<tr>
<td>DHB – District Health Board</td>
<td>In New Zealand, District Health Boards are organisations established by the New Zealand Public Health and Disability Act 2000, responsible for providing or funding the provision of health and disability services to populations within a defined geographical area.</td>
</tr>
<tr>
<td>ED – Emergency Department</td>
<td>The department within a hospital that is responsible for the provision of emergency care.</td>
</tr>
<tr>
<td>EAM – Electronic Adherence Monitoring</td>
<td>The monitoring of adherence to a particular treatment via electronic means.</td>
</tr>
<tr>
<td>EMD – Electronic Monitoring Device</td>
<td>An electronic device that has the ability to monitor adherence, either remotely or attached to the medication delivery device. The devices exist for a variety of dose forms, including oral or inhaled medication.</td>
</tr>
<tr>
<td>FEV1 – Forced Expiratory Volume in 1 second</td>
<td>The volume of air a person can exhale during the first second of a forced exhalation.</td>
</tr>
<tr>
<td>FVC – Forced Vital Capacity</td>
<td>The maximum volume of air a person can expel from their lungs after a maximum inhalation.</td>
</tr>
<tr>
<td>GPS – Global Positioning System</td>
<td>A satellite navigation system that provides information on location and time under all weather conditions, anywhere on or near the earth. It relies on an unobstructed line of sight to four or more GPS satellites.</td>
</tr>
<tr>
<td>ICS – Inhaled Corticosteroids</td>
<td>Anti-inflammatory, cortisone-like medication delivered either as a powder or aerosol spray via the inhaled route. It is used as a preventive treatment for long-term asthma control.</td>
</tr>
<tr>
<td>LABA – Long-Acting Beta-Agonist</td>
<td>A beta-adrenoceptor agonist (bronchodilator actions) with a long duration of action (typically 12 hours).</td>
</tr>
<tr>
<td>LED – Light Emitting Diode</td>
<td>A semiconductor diode which glows when a voltage is applied. It can be used in electronic devices to allow text and visual displays.</td>
</tr>
<tr>
<td>OECD – Organisation for Economic Co-operation and Development</td>
<td>An organisation dedicated to economic development, currently consisting of 34 member countries.</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>pMDI – pressurised Metered Dose Inhaler</td>
<td>A pocket-sized device used to deliver medication in the form of a short burst of aerosolized medicine for inhalation. It delivers a specific amount of medication (metered-dose), and is usually self-administered by the patient.</td>
</tr>
<tr>
<td>RCT – Randomised Controlled Trial</td>
<td>A type of research study design where people are randomly allocated to one of several different treatments to compare the effect of the treatment between the groups.</td>
</tr>
<tr>
<td>SABA – Short-Acting Beta-Agonist</td>
<td>A beta-adrenoceptor agonist (bronchodilator actions) with a short duration of action (typically four to six hours). Used for the acute relief of bronchospasm in asthma.</td>
</tr>
<tr>
<td>USB – Universal Serial Bus</td>
<td>An industry standard that defines a particular type of connection used for communication between computers and electronic devices.</td>
</tr>
<tr>
<td>WHO – World Health Organization</td>
<td>A global health organisation set up in 1948 to promote health and control communicable diseases.</td>
</tr>
</tbody>
</table>
Co-Authorship Forms

Co-Authorship Form

This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. Please include one copy of this form for each co-authored work. Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.

<table>
<thead>
<tr>
<th>Nature of contribution by PhD candidate</th>
<th>Literature review, manuscript write-up and review for submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of contribution by PhD candidate (%)</td>
<td>50 %</td>
</tr>
</tbody>
</table>

**CO-AUTHORS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peter Black</td>
<td>Paper conception, literature review, manuscript write-up and review for submission</td>
</tr>
</tbody>
</table>

**Certification by Co-Authors**

The undersigned hereby certify that:
- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>on behalf of Peter Black (deceased)</td>
<td>[Signature]</td>
<td>30/07/2015</td>
</tr>
</tbody>
</table>

Last updated: 23 March 2013
This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. Please include one copy of this form for each co-authored work. Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

<table>
<thead>
<tr>
<th>Nature of contribution by PhD candidate</th>
<th>Extent of contribution by PhD candidate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper conception, literature review, co-ordination of paper write-up, data collection on different devices, manuscript write-up and review for submission</td>
<td>70</td>
</tr>
</tbody>
</table>

**CO-AUTHORS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helen Reddel</td>
<td>Literature review, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Andrea Apter</td>
<td>Literature review, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Michelle Eakin</td>
<td>Literature review, data collection on different devices, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Kristin Riekert</td>
<td>Literature review, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Juliet Foster</td>
<td>Paper conception, literature review, co-ordination of paper write-up, manuscript write-up and review for submission</td>
</tr>
</tbody>
</table>

**Certification by Co-Authors**

The undersigned hereby certify that:
- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helen Reddel</td>
<td>[Signature]</td>
<td>10/07/2015</td>
</tr>
<tr>
<td>Andrea Apter</td>
<td>[Signature]</td>
<td>7/10/2015</td>
</tr>
<tr>
<td>Michelle Eakin</td>
<td>[Signature]</td>
<td>10/07/2015</td>
</tr>
<tr>
<td>Kristin Riekert</td>
<td>[Signature]</td>
<td>10/07/2015</td>
</tr>
<tr>
<td>Juliet Foster</td>
<td>[Signature]</td>
<td>10/07/2015</td>
</tr>
</tbody>
</table>

*Last updated: 25 March 2013*
This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

<table>
<thead>
<tr>
<th>Nature of contribution by PhD candidate</th>
<th>Extent of contribution by PhD candidate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper conception, literature review, collection of data on different devices, development of testing frameworks / checklists and how to troubleshoot problems found, co-ordination of paper write-up, manuscript write up and review for submission</td>
<td>80</td>
</tr>
</tbody>
</table>

### CO-AUTHORS

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeff Harrison</td>
<td>Development of testing frameworks, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Peter Black</td>
<td>Contribution to original study conception regarding need for testing of electronic monitoring devices and development of original test frameworks</td>
</tr>
<tr>
<td>Ed Mitchell</td>
<td>Development of testing frameworks, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Juliet Foster</td>
<td>Paper conception, literature review, development of testing frameworks / checklists and how to troubleshoot problems found, manuscript write up and review for submission</td>
</tr>
</tbody>
</table>

### Certification by Co-Authors

The undersigned hereby certify that:
- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeff Harrison</td>
<td></td>
<td>30/07/2015</td>
</tr>
<tr>
<td>on behalf of Peter Black</td>
<td></td>
<td>30/07/2015</td>
</tr>
<tr>
<td>Ed Mitchell</td>
<td></td>
<td>3/02/2016</td>
</tr>
<tr>
<td>Juliet Foster</td>
<td></td>
<td>10/07/2015</td>
</tr>
</tbody>
</table>
This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. Please include one copy of this form for each co-authored work. Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.


| Nature of contribution by PhD candidate | Literature review, study conception and development of testing framework for device, data collection, results analysis, creation of poster, presentation of poster at conference |

| Extent of contribution by PhD candidate (%) | 85 |

**CO-AUTHORS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maye Hamed</td>
<td>Data collection and review of testing frameworks</td>
</tr>
<tr>
<td>Juliet Foster</td>
<td>Development of testing frameworks, results analysis, review of poster for submission and presentation</td>
</tr>
<tr>
<td>Jeff Harrison</td>
<td>Original study conception regarding need for testing of electronic monitoring devices and development of test frameworks, results analysis, review of poster for submission and presentation</td>
</tr>
<tr>
<td>Peter Black</td>
<td>Original study conception regarding need for testing of electronic monitoring devices and development of test frameworks, data collection, results analysis, review of poster for submission and presentation</td>
</tr>
</tbody>
</table>

**Certification by Co-Authors**

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maye Hamed</td>
<td></td>
<td>9/02/2016</td>
</tr>
<tr>
<td>Juliet Foster</td>
<td></td>
<td>10/07/2015</td>
</tr>
<tr>
<td>Jeff Harrison</td>
<td></td>
<td>30/07/2015</td>
</tr>
<tr>
<td>on behalf of Peter Black (deceased)</td>
<td></td>
<td>30/07/2015</td>
</tr>
</tbody>
</table>

Click here
Co-Authorship Form

This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. Please include one copy of this form for each co-authored work. Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.

<table>
<thead>
<tr>
<th>Nature of contribution by PhD candidate</th>
<th>Extent of contribution by PhD candidate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of testing framework, manuscript write-up and review for submission</td>
<td>10</td>
</tr>
</tbody>
</table>

**CO-AUTHORS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitesh Patel</td>
<td>Literature review, study conception and design, development of testing frameworks, data collection, results analysis and interpretation, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Janine Pilcher</td>
<td>Literature review, study design, results analysis and interpretation, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Kyle Perrin</td>
<td>Literature review, study conception and design, results analysis and interpretation, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Peter Black</td>
<td>Original study conception regarding need for testing of electronic monitoring devices and development of test frameworks</td>
</tr>
<tr>
<td>Richard Beasley</td>
<td>Literature review, study conception and design, development of testing frameworks, data collection, results analysis and interpretation, manuscript write-up and review for submission</td>
</tr>
</tbody>
</table>

**Certification by Co-Authors**

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and

- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitesh Patel</td>
<td></td>
<td>13/07/2015</td>
</tr>
<tr>
<td>Janine Pilcher</td>
<td></td>
<td>10/07/2015</td>
</tr>
<tr>
<td>Kyle Perrin</td>
<td></td>
<td>13/07/2015</td>
</tr>
</tbody>
</table>

Last updated: 25 March 2013
<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peter Black (signed by Janine Picher as deputy director of MRINZ - Peter Black worked with MRINZ to initiate this study before he passed away)</td>
<td></td>
<td>7/08/2015</td>
</tr>
<tr>
<td>Richard Beasley</td>
<td></td>
<td>10/07/2015</td>
</tr>
</tbody>
</table>
This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. Please include one copy of this form for each co-authored work. Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.


| Nature of contribution by PhD candidate | Literature review, study design, data collection, results analysis and interpretation, manuscript write-up and review for submission |
| Extent of contribution by PhD candidate (%) | 85 |

## CO-AUTHORS

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alistair Stewart</td>
<td>Study design, results analysis and interpretation, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Jeff Harrison</td>
<td>Results analysis and interpretation, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Carlos Camargo Jr</td>
<td>Results analysis and interpretation, manuscript write-up and review for submission</td>
</tr>
<tr>
<td>Peter Black</td>
<td>Literature review, study conception and design</td>
</tr>
<tr>
<td>Ed Mitchell</td>
<td>Literature review, study conception and design, results analysis and interpretation, manuscript write-up and review for submission</td>
</tr>
</tbody>
</table>

## Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alistair Stewart</td>
<td></td>
<td>16/02/2016</td>
</tr>
<tr>
<td>Jeff Harrison</td>
<td></td>
<td>30/07/2015</td>
</tr>
<tr>
<td>Carlos Camargo Jr</td>
<td></td>
<td>19/02/2016</td>
</tr>
<tr>
<td>on behalf of Peter Black (deceased)</td>
<td></td>
<td>30/07/2015</td>
</tr>
<tr>
<td>Ed Mitchell</td>
<td></td>
<td>3/02/2016</td>
</tr>
</tbody>
</table>
This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

<table>
<thead>
<tr>
<th>Nature of contribution by PhD candidate</th>
<th>Conceptualized and designed the study and data collection instruments, coordinated and supervised data collection, drafted the initial manuscript, analysed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of contribution by PhD candidate (%)</td>
<td>85</td>
</tr>
</tbody>
</table>

### CO-AUTHORS

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alistair Stewart</td>
<td>Designed the study and the data collection instruments, analysed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.</td>
</tr>
<tr>
<td>Jeff Harrison</td>
<td>Designed the study and data collection instruments, supervised data collection, analysed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.</td>
</tr>
<tr>
<td>Peter Black</td>
<td>Conceptualized and designed the study and the data collection instruments, and supervised data collection.</td>
</tr>
<tr>
<td>Edwin Mitchell</td>
<td>Conceptualized and designed the study and the data collection instruments, supervised data collection, analysed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.</td>
</tr>
<tr>
<td>Juliet Foster</td>
<td>Designed the study, analysed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.</td>
</tr>
</tbody>
</table>

### Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alistair Stewart</td>
<td></td>
<td>16/02/2016</td>
</tr>
<tr>
<td>Jeff Harrison</td>
<td></td>
<td>19/02/2016</td>
</tr>
<tr>
<td>Peter Black (on behalf of)</td>
<td></td>
<td>19/02/2016</td>
</tr>
<tr>
<td>Edwin Mitchell</td>
<td></td>
<td>10/02/2016</td>
</tr>
</tbody>
</table>

Last updated: 25 March 2013
This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. Please include one copy of this form for each co-authored work. Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

<table>
<thead>
<tr>
<th>Nature of contribution by PhD candidate</th>
<th>Study conception and design, original literature search, overall study data collection, data analysis, interpretation, writing and review of the report and the decision to submit for publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of contribution by PhD candidate (%)</td>
<td>85</td>
</tr>
</tbody>
</table>

**CO-AUTHORS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alistair Stewart</td>
<td>Study conception and design, original literature search, data analysis, interpretation, writing and review of the report and the decision to submit for publication</td>
</tr>
<tr>
<td>Juliet Foster</td>
<td>Data analysis, interpretation, writing and review of the report and the decision to submit for publication</td>
</tr>
<tr>
<td>Edwin Mitchell</td>
<td>Study conception and design, original literature search, data analysis, interpretation, writing and review of the report and the decision to submit for publication</td>
</tr>
<tr>
<td>Carlos Camargo Jr</td>
<td>Data analysis, interpretation, writing and review of the report and the decision to submit for publication</td>
</tr>
<tr>
<td>Jeff Harrison</td>
<td>Original literature search, data analysis, interpretation, writing and review of the report and the decision to submit for publication</td>
</tr>
</tbody>
</table>

**Certification by Co-Authors**

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alistair Stewart</td>
<td>[Signature]</td>
<td>16/02/2016</td>
</tr>
<tr>
<td>Juliet Foster</td>
<td>[Signature]</td>
<td>10/02/2016</td>
</tr>
<tr>
<td>Edwin Mitchell</td>
<td>[Signature]</td>
<td>10/02/2016</td>
</tr>
<tr>
<td>Carlos Camargo Jr</td>
<td>[Signature]</td>
<td>19/02/2016</td>
</tr>
<tr>
<td>Jeff Harrison</td>
<td>[Signature]</td>
<td>19/02/2016</td>
</tr>
</tbody>
</table>

Last updated: 25 March 2013
Chapter 1: Introduction

1.1 Background

1.1.1 Asthma – a chronic inflammatory condition

Asthma is defined as a “chronic inflammatory disorder of the airways” causing symptoms associated with “widespread, but variable, airflow obstruction that is often reversible either spontaneously or with treatment”\(^1\). The chronic inflammatory nature of the condition was only recognised just over 20 years ago, as researchers elucidated the inflammatory mechanisms underlying the bronchial hyper-responsiveness commonly seen in asthma\(^2\). This led to a shift in asthma treatments, with a change in focus from symptom relief with bronchodilators to prevention with inhaled corticosteroids (ICS)\(^3\). The use of ICS were shown to improve asthma control and reduce exacerbations\(^4,5\). Since then, ICS have been recognised as the most effective treatment available for asthma and form the basis of treatment recommendations from the Global Initiative for Asthma\(^6\).

However, despite the identification of effective treatment, asthma remains a serious public health problem across both high- and low-income countries, particularly in children\(^7\). Significant morbidity and mortality from asthma continue to exist, with some 235 million people suffering from asthma worldwide\(^8\). The morbidity rates do not reflect the advances in knowledge around asthma management. The percentage of children with asthma has not reduced over the past decades, and in many countries, the prevalence is on the rise. This is particularly true for low- and middle-income countries, leading to an overall increase in disease burden worldwide due to the large population sizes of these countries\(^8,9\). Much of this is due to an underutilisation of ICS. As with other chronic conditions where long-term medication is required for disease control, asthma preventive treatment needs to be taken regularly to achieve optimal asthma control\(^6,8,10\). Studies have demonstrated a link between poor ICS adherence and increased asthma morbidity and mortality\(^10-12\). Non-adherence to ICS remains a major barrier to achieving therapeutic outcomes across all countries regardless of income. The reasons underlying this vary from country to country, with financial resourcing and access to medication being primary adherence barriers in low- or middle-income countries. Other factors such as difficulties with diagnosis, poor understanding of asthma, poor health literacy and under-prescribing by health providers also contribute\(^6,10,13\).

1.1.2 The New Zealand (NZ) context

In New Zealand, asthma is one of the most prevalent chronic conditions in children\(^9,14\). The percentage of children with asthma is particularly high in New Zealand compared to the rest of the world, with over 25% of children reporting ever having asthma compared to a global average of
around 10%\textsuperscript{9}. New Zealand has one of the highest rates of hospitalisation among the Organisation for Economic Co-operation and Development (OECD) countries\textsuperscript{9,14-16}. Age-sex standardised admission rates in the OECD Health Statistics 2015 report were 72.2 per 100,000 population in New Zealand compared to the OECD average of 43.8 per 100,000\textsuperscript{16}. There is a high prevalence of asthma symptoms, with reports of current wheezing in as high as 23.7% of all six to seven year olds and 32.6% of all 13 to 14 year olds in some areas of New Zealand\textsuperscript{9}. Māori, Pacific and minority ethnic groups are disproportionately affected by more severe symptoms, hospital admissions and higher mortality rates\textsuperscript{17-20}. Māori children are 1.5 times more likely to have asthma than their non-Māori counterparts\textsuperscript{21} and mortality rates are 4.8 times higher in Māori\textsuperscript{17}. A New Zealand study in 2003 found that of the 327 adults in the study, 93% had asthma that was sub-optimally controlled, of which 19% had asthma that was markedly out of control\textsuperscript{22}. The data for children were similar, with 90% of 118 children having sub-optimal asthma control, of which 4% were markedly out of control\textsuperscript{22}. Poorly controlled asthma poses a significant burden of disease through increased morbidity\textsuperscript{23} and mortality\textsuperscript{12}, and cost to society. In 2014, the economic burden of asthma across all ages in New Zealand was estimated to be $799.6 million each year with direct medical costs of $155 million, and indirect costs, such as days off school or work, disability and mortality, estimated at $644.7 million\textsuperscript{17}. There is a clear socioeconomic gradient – those living in the most socioeconomically deprived areas have triple the hospitalisation rates of those residing in the least deprived areas\textsuperscript{17}. In children, asthma is one of the leading causes of school absences and as asthma morbidity increases, so does the rate of absences\textsuperscript{24,25}. Together, these cumulative effects of poorly controlled asthma represent a significant public health concern. This raises a call for action to prevent the ongoing morbidity and costs currently seen with asthma in New Zealand\textsuperscript{5,14} and its contribution to the health disparities between Māori and non-Māori populations\textsuperscript{20}. Furthermore, there is an obligation under the Treaty of Waitangi to address these disparities.

One of the key target areas that need to be addressed is non-adherence. New Zealand, like many other developed countries with indigenous populations, suffers from a disproportionate sharing of disease burden between different ethnic groups. Indigenous populations commonly report poorer outcomes, with higher morbidity and mortality, from asthma\textsuperscript{18,19,26-28}. Although it is not clear why such differences exist, a recent New Zealand study highlighted significant differences in medication use between Māori and non-Māori. Māori were more likely to overuse reliever medication and under-use preventive therapy\textsuperscript{29}. This suggests that non-adherence with prescribed medication could underpin some of the disparities in asthma outcomes in New Zealand. This may be applicable to other developed countries; factors governing asthma outcomes in low- or middle-income countries may be different.
Medication adherence remains a major challenge that faces patients, healthcare providers and policy makers. Indeed, the key question remains how best to improve adherence in a sustainable and cost-effective manner. Interventions demonstrating meaningful improvements in adherence have been complex and resource-intensive to implement, with limited effectiveness. In an economic climate where resources are limited, there is a need to consider adherence promotion approaches that can maximise outcomes with minimal resource investment. Recent reviews have called for innovative approaches to promote adherence, as traditional interventions have shown only modest improvements in adherence with variable effects on health outcomes. In this era of technological advancement, there are opportunities to use healthcare information technologies in adherence interventions, and consider a new approach to the age-old problem of non-adherence. Electronic monitoring devices (EMDs) have increasingly been used as part of adherence research and interventions over the last two decades. Data from current literature support the use of EMDs in adherence promotion, with adherence interventions involving EMDs in asthma demonstrating clear benefits on adherence. The effect of EMDs on asthma outcomes is however less clear. Further research in larger populations is needed.

1.2 Aims of the research

The aim of this research was to determine the effect of an EMD on medication adherence and asthma outcomes in school-aged children with asthma.

Broadly, the objectives were:

- To determine the effect of an EMD with an audiovisual reminder function on ICS adherence and asthma outcomes in children presenting to the regional emergency department (ED) with asthma;
- To investigate the performance and patient acceptability of the EMD when used in a real-world clinical trial setting;
- To identify the factors associated with medication adherence in this high risk population.

1.3 Structure of the thesis

This is a thesis with publications, where the thesis includes chapters which are published in peer-reviewed journals, as well as conventional chapters. The thesis begins with Chapter 2, which presents an in-depth overview of the literature on medication adherence and the evolution of this concept over time. It opens with a discussion on the definition of adherence and methods to measure adherence. This is followed by a comprehensive review of the literature around factors...
associated with adherence, beginning with a review of determinants in chronic disease in general, beyond asthma and children. Factors pertaining to asthma and asthma in children specifically are subsequently reviewed, focusing on how the adherence literature differs from chronic disease and asthma in adults respectively. The chapter then concludes by examining different strategies to improve adherence. As there is comparatively less adherence research in children, it was felt that presenting this literature in the broader context of research on adherence, including in adults, was important. This helped to ensure that all aspects of adherence determinants were captured and an overarching background to the adherence research was provided. Evidence supporting the potential of EMDs to improve medication adherence in chronic disease is presented in a systematic review in Chapter 3. Knowledge gaps around the association of adherence and outcomes are highlighted. These beginning chapters set the scene upon which the other chapters are built and provide the context for the research that follows.

Chapters 4 to 8 comprise the main body of the thesis, presenting six papers (five published, one under review at time of submission) across these chapters. These examine the use of EMDs in research and practice, report on the results of a randomised controlled trial (RCT) investigating the effect of an EMD in children presenting to ED with asthma, explore the performance and acceptability of the EMD, and discuss the factors associated with medication adherence in this population.

Chapter 4 presents the first of the six papers – Adherence monitoring and e-health: how clinicians and researchers can use technology to promote inhaler adherence in asthma – which introduces the role of EMDs in a research setting and briefly discusses the potential for use in clinical practice. It reviews the current literature around EMDs and highlights the opportunities for using EMDs to improve adherence.

Chapter 5 discusses the practicalities that need to be considered when using EMDs in research and practice and details the EMD testing methods used in this research. The chapter includes two publications – the first of these – Using electronic monitoring devices to measure inhaler adherence: a practical guide for clinicians – expands on the ideas introduced in Chapter 4, exploring the problems that may be encountered during EMD use and providing suggestions on how to overcome these. The second publication – Six-month in vitro validation of a metered-dose inhaler electronic monitoring device: Implications for asthma clinical trial use – along with data which were presented at the Australasian Pharmaceutical Science Association Conference 2009, describe the results of in-vitro quality control (QC) tests of two different EMDs.

Chapter 6 presents the fourth of the six papers – The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in
children with asthma: a randomised controlled trial. This presents the findings from the RCT conducted over 21 months, which evaluated the effect of an EMD with audiovisual reminder function on ICS adherence and asthma outcomes. This concludes with a discussion of the limitations and questions arising from the research, and potential for application in a clinical setting.

Chapter 7 presents the manuscript – Electronic adherence monitoring device performance and patient acceptability: a randomized control trial – which reports on the performance data of the EMD used in the RCT and compares these to data from other available EMDs. Quantitative and qualitative patient acceptability data are presented and discussed.

Chapter 8 consists of the final paper – Factors associated with medication adherence in school-aged children with asthma – which describes some of the factors that affect adherence in this high-risk population of children presenting to ED with asthma. Risk factors are identified and the relationship between these factors and adherence are examined and quantified.

Chapter 9 draws together the findings of this research, culminating in a discussion and overview of the findings, its contribution to the current literature and its strengths and limitations. The implications of these results on the direction of future research are considered and discussed.
Chapter 2: Medication adherence: an overview

The concept of adherence has evolved over time, from “compliance” with orders from a healthcare provider, to “adherence” with an agreed plan\(^{38,39}\). The World Health Organization (WHO) defines adherence as “the extent to which a person’s behaviour (such as taking medication) corresponds with the agreed recommendations from a healthcare provider”\(^{40}\). There are several terms that have been used in the literature to describe this behaviour – compliance, concordance, adherence and persistence\(^{38,39}\). These have been used interchangeably, however important differences between these terms exist\(^{41}\). Compliance is the term used in earlier literature, but has since been replaced with the more autonomous and self-determining notion of adherence\(^{42}\). Compliance views the patient as a passive entity who responds to orders from health providers without any active involvement of the patient in the process\(^{38,39}\). It is a paternalistic term; inherently implying a position of power over the patient where compliant patients ‘followed’ prescribed advice; non-compliant patients did not\(^{42}\). Patients’ freedom of choice or autonomy for decision-making was seemingly overridden. The fact that patients could choose not to ‘follow’ out of autonomy and self-determination was seldom considered, and older interventions to improve compliance reflected this model.

Adherence became increasingly popular in the 20th century\(^{41}\), as the positive concepts of co-operation, alliance, mutual decision-making and self-determination were encapsulated in the terminology\(^{42}\). This is highlighted in the WHO definition, with keywords such as “corresponds” and “agreed” found in the definition\(^{40}\). It emphasises that adherence should involve active patient participation, recognising that the patient can decide whether or not to ‘follow’ advice given\(^{39}\). Unlike compliance, the patient is no longer a passive entity for which treatment decisions are made and applied; the patient is an active participant in the health provider-patient relationship and has a voice and responsibility in their own treatment and outcomes. Adherence is now the preferred term as it implies a therapeutic alliance between the provider and patient\(^{38,39}\).

With the changes in the way that the provider-patient relationship was viewed and the corresponding move from compliance to adherence, a new term ‘concordance’ arose. Concordance describes the process of shared decision-making, with co-operation between the patient and prescriber to form an agreed plan of action\(^{39,41}\). Originally used to refer specifically to the act of agreeing the plan or medication regimen that the patient will take\(^{43}\) with respect to the beliefs and wishes of the patient, the term has widened to encompass prescriber communication as well as patient medication-taking support\(^{44}\). It has also been used loosely to refer to adherence, but the two differ in that concordance refers to the provider-patient relationship and the shared decision-making process, against which adherence – “the extent to which the resulting patient behaviour
corresponds with agreed recommendations from the healthcare provider” – is measured\textsuperscript{39, 40}. Both compliance and adherence are quantifiable; concordance is the construct describing the need for cooperation and agreement between the patient and healthcare provider in order to achieve adherence\textsuperscript{41}.

A relatively newer concept – ‘persistence’ – has been introduced in recent times\textsuperscript{41, 45}. With the increase in chronic conditions, the duration of adherence becomes an important factor to consider as medicines need to be taken long-term. This is where the terms ‘persistence’ or ‘discontinuation’ play a role. Persistence has been defined as “the length of time a patient remains on therapy” and is significant in the management of long-term maintenance medication\textsuperscript{45}. Antoniu describes persistence as a component of adherence, with adherence meaning being both persistent and compliant. The compliance aspect refers to the taking of medication as prescribed (regardless of the length of time that the patient takes them), while persistence refers to the act of taking the medication (regardless of how it is taken and whether or not it is taken as prescribed)\textsuperscript{45}.

As adherence research evolved over time, so did the terminology that was used to describe the concepts\textsuperscript{41, 44}. As a result, there was a lack of a clear definition for each term, with ‘compliance’, ‘concordance’, ‘adherence’ and now ‘persistence’ used interchangeably\textsuperscript{42, 44}. Vrijens et al. recognised this confusing taxonomic structure and proposed a new adherence taxonomy to describe medication-taking behaviour\textsuperscript{41}. Using a descriptive synthesis of the data extracted from a systematic review, the authors analysed the evolution of adherence terminology from 1975 to 2009 and proposed that adherence should be considered as a sum of three distinct components – initiation, implementation and discontinuation. Initiation describes the starting of therapy and is marked by the time when the patient takes the first dose of a medication. Implementation corresponds more closely with traditional adherence definitions, referring to the extent to which a patient’s dosing regimen matches what was prescribed. Lastly, discontinuation indicates the stopping of treatment – the time when the next dose is omitted and no further doses are taken. Persistence therefore refers to the time between initiation and the last dose. As such, a patient may be non-adherent if they do not begin the prescribed therapy (also described as primary non-adherence\textsuperscript{44, 46}); do not take their medication as prescribed; or stop the medication without agreement from the healthcare provider. Medication that is taken regularly as prescribed but only for two weeks will be deemed as being implemented correctly but discontinued early.

### 2.1 Adherence – definitions in this thesis

In view of the range of terminology that has been used to describe medication-taking, adherence, for the purposes of this thesis, will be defined as “the extent to which a patient takes their medication as prescribed throughout the study period” and will refer primarily to the
implementation aspect of adherence. In a previous study using EMDs, adherence was evaluated as a “percentage of prescribed doses recorded by the Smartinhaler [EMD] between midnight and midday or between midday and midnight for morning and evening doses respectively”47. This study will similarly examine adherence in terms of frequency of dosing (whether the patient takes their medication on time) and accuracy of dosing (whether the patient takes the correct number of doses on each occasion). The concept of timing adherence will be accounted for when considering morning versus evening adherence, as past studies have shown differences between time of day and adherence48-50. Where the patient does not ‘persist’ with therapy, this will be regarded as being ‘non-adherent’ for those periods where they are not taking their medication.

2.2 Types of non-adherence

Adherence, or non-adherence, exists as different types. The literature differentiates between “intentional” and “unintentional” non-adherence51, 52. Intentional non-adherence exists when a patient chooses not to take a medication or to take it differently to what is prescribed due to certain beliefs. It has been described as “intelligent” non-adherence, as it is a conscious decision to not follow the prescribed regimen45. Situations where this behaviour might occur include when the patient does not believe the medication is effective; is concerned about adverse effects or interactions; feels there is no need for the medication45, 51-53; or simply does not like taking the medication (taste, colour, formulation)54, 55. “Unintentional” non-adherence occurs when the patient does not adhere to the prescribed regimen due to factors not directly within their control44, 52. Patients may have the intention of following the regimen, but do not due to a complex interplay of both internal and external factors52, 56, 57. Such examples include when the patient does not have the resources (financial or time) to take the medication44, 51, 52 or does not understand the regimen58. This type of non-adherence has been subdivided into “erratic” and “unwitting” non-adherence45. In “erratic” non-adherence, patients do not follow the regimen due to forgetfulness, busy schedules or difficulty in accessing medication. This leads to an “erratic” pattern of non-adherence, which becomes more common when the regimen is complex, such as with multiple daily dosing60. Patients do however know what the correct medication regimen is meant to be. This is different from “unwitting” non-adherence, where the patient does not know the correct way to take the medication and therefore does not adhere correctly. As a result, both the patient and health professional may not be aware of the non-adherence as both believe the patient is taking the medication as prescribed. This could occur in situations where cultural or language barriers exist59; there is unclear communication between parties such as with translation or third-party communication of information60, 61; when the prescriber does not give enough information to enable the patient to understand what they need to do45, 62, 63; or there is cognitive impairment64.
2.3 Methods to measure adherence

One of the key aspects of adherence is the need to measure medication adherence accurately, precisely and in a standardised way, to allow comparisons between different interventions and to understand the factors associated with adherence. Methods to measure adherence however vary between studies, making generalisability difficult\textsuperscript{65}. This lack of a gold standard for measuring adherence is one of the key factors that have limited adherence studies, though there is increasing recognition of the importance of using objective and consistent adherence measures\textsuperscript{30}. Each method measures slightly different aspects of the medication-taking process – from the point of prescribing to the ingestion and absorption of the medication – but there is some overlap. The accuracy of these methods varies in terms of their sensitivity and specificity when compared to a standard reference source\textsuperscript{66}. Sensitivity refers to the proportion of adherent patients that are correctly identified as being adherent; specificity describes the proportion of non-adherent patients who are correctly identified as non-adherent\textsuperscript{65}. Unfortunately data on these parameters do not routinely exist in the literature, as there is a lack of a consistent measurement method as the reference source; studies do not routinely compare different adherence measures directly; and the percentage threshold below which a patient is deemed ‘non-adherent’ varies from one study to the next\textsuperscript{65}. The choice of method therefore depends on the condition and medication regimen, purpose, duration and ease of measurement, patient acceptance and available resources including cost\textsuperscript{67, 68}. Measures appropriate for one particular purpose or medication regimen may not be appropriate for others. Most recent studies use composite measures of adherence, where more than one measure is used to increase accuracy of data capture\textsuperscript{67-69}.

This section will provide an overview of the methods that have been used in the literature, what aspect of medication-taking each measures, and their strengths and limitations. The methods used to measure adherence can be divided into two different categories which are discussed below: direct and indirect methods.

2.3.1 Direct methods

Direct methods provide evidence that the patient has actually taken the medication and are therefore the most accurate\textsuperscript{65, 67, 70}. However, these tend to be invasive and resource-intensive, and therefore have low patient acceptability. These include detection of drug or metabolite in biological fluids; use of adjunct biological markers (biomarkers); or direct observation of patient ingestion of treatment.
2.3.1.1 Detection of drug or metabolite in biological fluids

This involves laboratory testing of drug levels in bodily fluids, commonly in blood, urine or saliva samples. It has the advantages of being a direct, objective and reliable measure that provides confirmation of recent medication ingestion\(^65,68\). Levels are easily quantifiable and can provide data on dose-response\(^71\). However, this method is less commonly used due to its invasiveness and potential impact on adherence behaviour. Tests can be costly and time-consuming, making this method impractical for routine monitoring\(^70\), but potentially suitable for short-term monitoring\(^68\). Blood levels are only routinely available for some medicines, such as digoxin, lithium and some antiepileptic and antipsychotic medication. Urine testing can be used for some infectious diseases such as tuberculosis\(^72\) or in substance abuse populations to track drug usage. For many other medicines, their levels cannot be monitored using a drug assay, thus limiting the range of medication for which this method can be applied\(^68\).

This method is only accurate if the half-life of the medication is long enough that patients need to take the medication routinely over a period of time to obtain a therapeutic level. For patients who take the prescribed doses only in the time leading up to the drug level test, such as in ‘white-coat compliance’, this can lead to a falsely elevated level with medicines that have short half-lives\(^67,68\). At best, most assays only reflect medication use over the last five half-lives\(^73\), making this method accurate for assessing adherence only over short periods\(^68\). The effects of interacting drugs and sampling time also need to be considered\(^74\). Drug levels can exhibit large inter-patient variability due to differences in drug handling, leading to a lack of consistent relationship between drug dosing and levels\(^65,68,75\) and difficulties drawing comparisons between patients. Non-detection of a drug in bodily fluids does not always equate to non-adherence, and vice versa\(^65\). Assays need to be interpreted correctly to understand what the levels mean for the individual patient, which may require some knowledge of pharmacokinetics. Most levels require sampling just prior to the next dose, so knowledge of when the last dose was taken is required for accurate interpretation, but this could be subject to patient recall bias\(^76\). Levels do not provide information on fluctuations in adherence or patterns of medication-taking\(^70\), unless repeated samples are drawn, though this still does not provide a comprehensive picture\(^65\).

2.3.1.2 Detection of adjunct biological markers

Use of drug tracers, also known as biologic markers, have been reported in older studies to track medication adherence\(^77,78\). This is where an additional readily detectable but inert, stable and non-toxic substance such as riboflavin is added to the ingested medication, either directly into the drug formulation or taken as an adjunct to therapy\(^65,79\). It allows easily quantifiable confirmation of medication-taking and can demonstrate a dose-response relationship. It has the added advantage of being able to be used for medicines that have no standard drug assays\(^76\). However, there are
disadvantages of inconvenience, cost and invasiveness, as well as an inability to provide information on day-to-day medication use\textsuperscript{65}. Like drug assays, measured levels can vary due to pharmacokinetic variations. Patients may refuse to take the additional biomarker, if the tracer is a separate formulation, or they may not consent to addition of the tracer into their medication\textsuperscript{67}. Addition of the marker could compromise medication stability and effectiveness. If the tracer is one that is ubiquitous, the results may be contaminated by patient ingestion of dietary or other sources of the tracer, such as from riboflavin-containing foods\textsuperscript{73,78}. For certain medicines, endogenous biomarkers can be used such as for ACE inhibitors, where urinary N-acetyl-Ser-Asp-Lys-Pro has been used as a biomarker of ACE inhibition – the higher the biomarker relative to urinary creatinine, the greater the level of ACE inhibition and therefore adherence\textsuperscript{80}. Unlike radioactive assays, this method relies on a naturally occurring by-product of a medication’s effects and is therefore relatively inexpensive and easy to measure, using only a spot of urine for sampling. However, this method is specific to ACE inhibitors; endogenous biomarkers are not readily available for other medication classes\textsuperscript{70}.

2.3.1.3 Direct observation of patient ingestion of treatment

This method of measurement provides direct proof of medication ingestion as the patient is observed whilst they take the dose in front of another person. Studies have used both independent observers, as well as family\textsuperscript{81}, as observers of treatment. This method benefits from being direct and allows interaction with the patient, which could reveal other aspects of their lifestyle and environment that are affecting their adherence\textsuperscript{76}. It enables assessment of other important aspects of adherence, such as administration technique\textsuperscript{71,76}. Directly observed therapy has been used with tuberculosis\textsuperscript{82}, hepatitis\textsuperscript{83}, human immunodeficiency virus (HIV)\textsuperscript{84,85} and methadone\textsuperscript{86} treatments and in cases where the consequences of non-adherence are great\textsuperscript{82}. Questions of its effectiveness in reinforcing adherence and issues of patient respect have however arisen\textsuperscript{81,87,88}, particularly as the method is intrusive to the patient and resource-intensive, requiring repeated healthcare provider visits\textsuperscript{65,85}. Despite direct observation, this method also remains susceptible to patient manipulation such as when patients hide medication in the mouth and feign ingestion\textsuperscript{65,67,89}. As such, this method is generally impractical to use for long-term adherence monitoring, though it may have a place in monitoring short-term therapies\textsuperscript{67}.

2.3.2 Indirect methods

The majority of adherence measures use indirect methods, which measure adherence using patient-generated or third-party information. These include patient self-report via interviews, diaries, surveys or adherence questionnaires; medication counts (pill counts or canister weights); prescription refill (pharmacy dispensing) records; and electronic adherence monitoring (EAM)\textsuperscript{65,67}. Most older studies have traditionally used patient self-report\textsuperscript{45}, though in recent years, there has
been a move to the use of measures that are less prone to bias\textsuperscript{30} such as medication counts, prescription refill records and, in the last two decades, EMDs. As with all indirect measures of adherence however, these methods are unable to determine whether or not actual medication-taking occurred, nor identify ‘true adherence’. True adherence takes into account both correct medication-taking in terms of dose and frequency, but also how the medication is taken – a measure of medication competency or the ability to use the medication in the correct way to ensure effectiveness\textsuperscript{90}. An example of this is the assessment of inhaler technique for inhaled medication\textsuperscript{50, 91}, though technologies that can assess medication competency are in development\textsuperscript{50, 92}.

2.3.2.1 Patient self-report

Self-report can take many forms including patient interviews, diary cards, journals, calendars, surveys or validated adherence questionnaires and rating scales\textsuperscript{45, 65, 72}. It is a simple, cost-effective and convenient method of measuring adherence and its use is well-documented in the literature\textsuperscript{45, 67, 68, 76, 89, 93}. This measure is the most commonly used method in clinical practice, through direct questioning of the patient, as it does not require any extra planning or resources to implement, thus increasing feasibility and data accessibility\textsuperscript{76, 91}. Where data are obtained from patient diaries, journals or interviews, the reports are able to provide detailed information on adherence patterns and an insight into factors that enable or prevent medication-taking, including whether or not the patient themselves have insight into their own adherence behaviour\textsuperscript{67, 70}. This could help identify patients who may be more responsive to interventions, as those who admit to non-adherence are generally correct\textsuperscript{65}, and may be more amenable to advice than those who deny non-adherence\textsuperscript{69}.

The reports have the advantage of being individualised to the patient, thus encouraging patient involvement in their own healthcare, and can be more easily integrated into disease-management programmes than other adherence measures by facilitating provider-patient discussions\textsuperscript{71}. Patient interviews however may suffer from recall bias, especially if recall over long periods is required\textsuperscript{67, 68}. The maximum limit for accurate recall has been reported to be less than two weeks\textsuperscript{73}. Collecting data at multiple time points can help increase accuracy by allowing average adherence over time to be assessed. Daily diaries, journals or calendar entries attempt to minimise this bias by requiring daily recording of medication use, though in reality this may not occur, and entries may be entered retrospectively based on recall\textsuperscript{94}. Furthermore, those who adhere to regular diary entries also tend to be the patients who adhere to treatment\textsuperscript{95}, thus data collected may not be representative of the whole sample population.

The other primary drawback of self-report is the lack of objectivity. The accuracy of the self-report relies on the patient’s ability and willingness to disclose information about their medication use. This might be affected by the method in which information is elicited – for example, questionnaires and diaries have been shown to provide more accurate adherence data compared to patient
interviews. This may be due to the perception of anonymity of responses by patients when information is provided in a written format, compared to a direct questioning of the patient. The manner in which questions are asked can also influence the types of responses elicited, with the risks of misreporting being greater when patient demands are greater. Use of detailed objective questions increase the accuracy of self-report, as do questions which are non-judgemental, direct, specific and time-limited, as the patient is less likely to react defensively, misunderstand the questions, or give evasive responses. Responses are also influenced by the relationship between the interviewer and interviewee, motivating factors for the interviewee and the skill and experience of the interviewer. Accuracy may also be affected if the parameter being assessed is subjective itself – such as their understanding of what adherence means – leading to inter-participant variability.

Validated adherence questionnaires and rating scales can overcome some of these issues, by providing a standardised structure to the interviewing process. Examples of these include the Morisky scales, the Brief Medication Questionnaire and the Medication Adherence Rating Scale. These reduce the risk of social desirability bias that is inherent to self-report – a bias that results from a patient’s desire to be viewed positively by others, thus leading to over-reporting as the patient wishes to be seen as adherent. Questionnaires and rating scales make the process less personal as the questions are indirect, often impersonalised using numerical ratings and therefore less easily identifiable. Nevertheless, these measures remain subjective and still carry the risk of overestimation of adherence when compared with objective measures as well as running the risk of recall bias. Adherence questionnaires vary in terms of the length, question format, types of questions, purpose of the questionnaire and reference time frames (such as whether the questions refer to medication-taking in the past four weeks or six months), thus making comparisons difficult. They are unable to give the same level of detail about patient behaviour and potential facilitators or barriers to adherence as patient interviews and diaries, due to their less comprehensive nature. They are however less labour intensive to complete than interviews for the patient and provider, and can allow comparisons between individuals and populations to be drawn if the same adherence questionnaire has been used.

There is a risk inherent in the use of subjective data – a risk of incorrect reports of adherence, which may be intentional (misrepresentation) or unintentional (misinterpretation). This problem can occur even when reports are not directly of one’s own behaviour, for example when parents, caregivers, school nurses or teachers are involved in assessing a child’s adherence behaviour. These ‘proxy informants’ may not be aware of the patient’s behaviour as it is not practical to observe the patient all the time. This can be particularly difficult during adolescence when patients seek their own autonomy and independence from parental supervision.
parental report, when used to report on childhood adherence to asthma inhalers, overestimated adherence when compared to objective data collected via EMDs. Child self-report of their own usage was also significantly higher than objectively monitored usage. Other studies confirm that both parental and child self-report grossly overestimate adherence and do not accurately reflect actual medication use.

Healthcare provider estimations of adherence are an extension of self-report, as these estimates or ratings are drawn from information reported by the patient or their families. Like self-report, provider estimates have the advantages of being simple, convenient and inexpensive, particularly in a clinical setting. They however suffer from the same issues as patient self-report, with a high risk of overestimation of adherence. Studies report that estimates may not be any more accurate than what might be achieved by chance alone. During a study investigating the accuracy of subjective adherence measures in children, parents and physicians were asked to estimate the child’s medication usage. Parental measures overestimated usage and the physician was unable to tell which parents reported correct estimations of adherence.

Despite the lack of objectivity and other shortcomings of self-report, this method of monitoring adherence, along with medication counts, are the approaches that are most often used, and in many studies, this is the sole method used to monitor adherence. Self-report may have a role when used in combination with more objective adherence measures, such as prescription refill data or EAM, to provide a more accurate and comprehensive measure of adherence. There is also the possibility of using technology to increase the accuracy of self-report, such as electronic diaries that monitor when diaries are opened, thus providing some insight into the accuracy of the diary records.

### 2.3.2.2 Medication counts

Medication counting, also known as dose counting, either in the form of pill counting or weighing of canisters for inhaled medication, is a commonly used alternative to self-report and has been used in over half of the RCTs assessing adherence. It involves a physical count of the number of doses that remain in a patient’s medical bottle, delivery device, or other medication management system, after a pre-determined period of monitoring and compares this with the expected number of doses that would remain if the patient had taken the medicine exactly as prescribed. It is a simple, economical way of quantifying medication use without relying on patient self-report. It enables medication use to be monitored without the patient being aware of the parameter being measured. As medication counts have been used in a large number of studies, this measure allows ease of comparison and calculation of summary measures across studies. This has also been used to validate other adherence measurement methods, and has been shown to be more accurate than
self-report and prescription refill data. It allows some detection of changes in adherence, albeit the level of detail depends on the frequency of repeated dose counts over time\textsuperscript{68, 112}.

Disadvantages include a lack of detailed information on the patterns of usage over time, including drug holidays – a term used to describe when medicines are omitted on three or more consecutive days\textsuperscript{68, 89} – and wide variation in the accuracy of medication counts. It can be difficult to determine the dates of treatment as patients may take the medication before or after the agreed start date. The dispensing date on the medication label may not be the date the patient starts the medicine\textsuperscript{67}.

Some patients may combine multiple prescription refills in the same container, or use multiple containers\textsuperscript{69, 73}, or the medication may be shared with other people\textsuperscript{67, 76}. Patients may find the need to return their medication bottles or canisters inconvenient\textsuperscript{70}, with some patients suspecting that their adherence is being monitored when they are asked to return these. This could lead to intentional discarding of medication prior to visits (termed “dose dumping”)\textsuperscript{69, 71, 89}, alterations in behaviour and overestimation of adherence\textsuperscript{76, 113}. Unannounced medication counts conducted in the patient’s home may counteract these issues, though this may not be acceptable to the patient\textsuperscript{65}.

2.3.2.3 Prescription refill records

Prescription refill records, or pharmacy claims data, have been used in research and practice to measure adherence\textsuperscript{91, 114}. These are usually electronic records of prescription claims made by a pharmacy, though in the past this involved a manual process of prescription review\textsuperscript{65}. It provides objective data, is easily accessible and readily available in most cases\textsuperscript{89}. This reduces the risk of the Hawthorne effect as patients are not aware of the adherence monitoring, and large-scale population analyses can be carried out\textsuperscript{67, 69}. Refill records enable ease of patient follow-up, from the first to the last prescription record, to determine trends over prolonged periods of time. This allows assessment of the different stages of medication-taking – from initiation (whether or not the medication was dispensed) to discontinuation (cessation of prescription refill after initial dispensing)\textsuperscript{65}. Access to this level of detail however has its drawbacks as it allows multiple methods of data interpretation and analysis. In a systematic review by Hess et al., 11 adherence measures using prescription refill data were identified\textsuperscript{115}. This large number of measures can make comparisons between studies difficult, and the authors recommended that a single measure should be used to allow standardisation\textsuperscript{115}.

Other limitations of using refill data is the delay for data to become available – data can take up to three months or more before it shows up in the pharmacy claims system\textsuperscript{67}. Refill data only serves as a proxy measure as dispensed medicines are not always picked up or taken as prescribed, and some patients may use more than one pharmacy\textsuperscript{65, 67}. This method is more accurate when the pharmacy system is a closed one, where the number of pharmacies involved in medication supply is restricted.
Examples of such a system include health maintenance organisations, prescription benefit managers\textsuperscript{65}, pharmacies supplying to residential care facilities, non-government organisations and healthcare systems\textsuperscript{89}. For this measure to be accurate, complete pharmacy refill records need to be accessed at several time points to provide a representative picture of medication-taking over time\textsuperscript{69,89}. The refill data must also be correct in the system for this measure to be accurate\textsuperscript{65}.

2.3.2.4 Electronic adherence monitoring (EAM)

Dose counting via EMDs is a relatively new concept that arose in the 1980s. EMDs record medication use through monitoring the opening of medication bottles for oral medicines, the dispensing of drops from eyedrop bottles, and the depression of canisters for inhaled medication\textsuperscript{65,89}. Most EMDs record both the date and time of medication use, providing detailed information on medication-taking\textsuperscript{89}, which can help advance our understanding of adherence behaviour\textsuperscript{91,116}. The first trial using an EMD was by Spector et al. in 1986. The authors investigated use of the Nebulizer Chronolog in patients with asthma and found that patients over-reported adherence more than 50% of the time\textsuperscript{117}. In 1987, Eisen et al. described a new method of electronically monitoring oral medication intake\textsuperscript{118}, a device that was later developed into the Medication Event Monitoring System (MEMS)\textsuperscript{67} – currently one of the most commonly used oral adherence monitors. Two years later, Cramer et al. conducted the first study using MEMS for oral medication monitoring in patients with epilepsy, reporting that pill counts and serum drug levels overestimated adherence, when compared with electronically monitored data\textsuperscript{75}. Since then, use of EMDs for adherence monitoring has increased. Studies have compared different EMDs\textsuperscript{119-121}, or different adherence measurement methods, using EMDs as a reference standard\textsuperscript{107,122}. Many now quote EMDs as the gold standard of adherence measurement\textsuperscript{65,121}. EAM is considered to be the most accurate indirect measure of adherence, providing objective, non-biased data that are not reliant on patient self-interpretation of their own behaviour, thus making EAM less prone to patient deception\textsuperscript{107}. Where deception does occur, such as with ‘dose dumping’, EMDs are able to detect these aberrant events\textsuperscript{67}.

EMDs are however not infallible, with several studies reporting inaccurate data recordings or data loss due to device malfunction, loss, damage or incorrect patient use\textsuperscript{69,119,124-129}. Data capture relies on the device being returned for data retrieval or upload\textsuperscript{128}. Patients can place other medicines into the monitored container, or use medication from an unmonitored container. Even if the EMD monitors medication administration correctly, there is still no confirmation of medication ingestion\textsuperscript{65,67,89}, though EMDs that attempt to capture medication use are being developed. One device for use with inhalers has a microphone incorporated to detect actuation and inhalation sounds\textsuperscript{130}, whilst another is an ingestible sensor that conveys medication ingestion and adherence information via a digital signal\textsuperscript{128,131}. Cost remains a barrier to EMD use as the devices are expensive and not currently covered by insurance\textsuperscript{69,91,132}, though cost reduction is likely to occur as these
devices become more commonly used\textsuperscript{68}. They can be impractical\textsuperscript{65, 133} and complex to use, requiring patient training\textsuperscript{134, 135}, thus limiting patient acceptability. There are also ethical considerations to using EMDs for monitoring behaviour\textsuperscript{136}, and some patients may object to their use\textsuperscript{76}. One study reported increased levels of anxiety, depression and somatic complaints from EAM\textsuperscript{137}. This may limit use of EAM to only short-term monitoring, or specific groups of patients\textsuperscript{65}. Data on patient acceptability of EAM is however scarce; additional research is needed in this area.

The presence of the device itself may also change patients’ behaviour\textsuperscript{69}, leading to a reactivity bias. EMDs are generally specific for only one medication per device, so patients may need to use multiple EMDs if monitoring of several different medicines is required\textsuperscript{67}. Most EMDs are not compatible with medication management systems, such as pill boxes or unit dose packs\textsuperscript{69, 138}, which may reduce adherence by disrupting routines and preventing the patient from using their usual medication management systems. New EMDs are being developed which can be used with medication organisers, such as the Polymedication Electronic Monitoring System (POEMS) which utilises an electronic film that attaches to a unit dose pack to detect pack openings\textsuperscript{139}, or the Med-eMonitor, which has multiple medication compartments\textsuperscript{140}.

Conversely, adherence may be increased by the EMD due to patient awareness of the monitoring\textsuperscript{141}. This can make it difficult to determine whether an observed effect is due to the adherence intervention or the monitoring itself\textsuperscript{141, 142}. Several studies have investigated the effect of EAM on adherence\textsuperscript{137, 142-147}. Patients were informed of the monitoring function of the EMD in some studies\textsuperscript{137, 143-146} but not others\textsuperscript{142, 147}. Results have been mixed, with some studies showing no effect from EAM\textsuperscript{137, 144, 147}, whilst others have shown increased adherence\textsuperscript{142, 145, 146}; this appeared to be independent of whether or not the patient was aware of the monitoring. Sutton et al. concluded that whilst there may be potential for devices themselves to increase adherence, the effect is slight, and the benefits of monitoring using EMDs outweigh this limitation\textsuperscript{142}. From these studies, it generally seems that if EMDs are to have an effect on adherence, it would be one of increasing adherence, but the effect size is small and statistically non-significant. This reactivity bias is also thought to be short-lived as most patients generally return to their usual medication-taking behaviours after a short period\textsuperscript{67, 129}.

### 2.4 Determinants of medication adherence

Medication adherence is complex and multifaceted\textsuperscript{32, 40}. There are multiple adherence determinants, which vary widely between patients and populations\textsuperscript{40, 148, 149}. These determinants can be classified into five different dimensions, based on the WHO report on adherence: patient-related, therapy-related, condition-related, healthcare team and health system related, and social and economic, factors\textsuperscript{40}. Patient-related factors refer to the capabilities that a patient has to use
medication, such as their knowledge, attitudes, beliefs, perceptions and expectations. It includes factors such as their self-efficacy and motivation to manage their condition. Therapy-related factors describe the characteristics of the treatment regimen that affect adherence. It includes treatment duration, regimen complexity, and positive and negative effects of the medication. Condition-related factors encompass the aspects of the condition that influence the level of disability experienced by the patient, symptom severity, and the impact of the disease on their quality of life. Healthcare team and system related factors describe the effects of the health system infrastructure and the way in which health providers interact with patients. Lastly, social and economic factors consider the wider social and economic environment in which the patient resides, and includes the patient’s socioeconomic status, level of social support, costs of treatment and sociodemographic variables such as age, marital status, gender, education and income level.

These factors all interweave to determine adherence behaviour. Current adherence literature has examined these determinants and identified various strategies to improve adherence. This section will explore the factors associated with adherence in chronic disease which have been reported in the literature. The particular determinants linked with adherence in asthma will then be highlighted, followed by a discussion of factors that warrant special consideration in children with asthma. The discussions will be grouped into subsections based on the five WHO dimensions. This provides a background for consideration of areas to target when designing strategies to improve adherence. These strategies and their supporting evidence will be described in Section 2.5.

2.4.1 Medication adherence in chronic disease

Medication adherence is pivotal to both acute and chronic disease management. Adherence to short-term medication in acute illness, such as adherence to antibiotics for infection, is important to prevent disease deterioration and complications. Adherence to chronic therapy is even more essential for clinical outcomes and disease control. However, adherence in long-term conditions is often more difficult to achieve than in acute illness due to the longer treatment duration and the lack of acuity of the condition, as the condition may be asymptomatic or treatment purely preventative. Treatments are often discontinued early or in some cases, never initiated.

The literature on medication adherence focuses primarily on adherence barriers in chronic disease and is extensive, dating back to the 1970s. Reported adherence in chronic disease averages around 30% to 50%, with even lower rates in minority populations and developing countries. Adherence is crucial to the management of chronic disease, and is the bridge between treatment efficacy and clinical outcome. Studies that investigate treatment efficacy are conducted in a controlled environment, often with monitoring of adherence, and do not reflect the
suboptimal adherence seen in real life. Clinical outcomes that are achieved through clinical trials of medicines are therefore often in the context of high levels of medication adherence; there is little information on whether the same outcomes can be achieved with the lower adherence levels seen in real life. Some medicines may not need to be taken daily and there may be a threshold below which non-adherence becomes clinically significant. This phenomenon has been termed “medication forgiveness” – defined as the “ability of a medication to maintain its action” despite lapses in medication adherence and depends on the pharmacokinetics of the medication. For example, in hypertension, 80% adherence is needed to achieve blood pressure reduction from medication, whilst in children prescribed penicillin for rheumatic fever prophylaxis, only 33% adherence is needed for protection against recurrent rheumatic fever. In asthma, at least 75% adherence is needed to prevent asthma exacerbations. Whatever the adherence threshold is, one thing is certain – there remains a gap between medical advances and clinical outcomes – a gap that is hypothesised to be due to suboptimal medication adherence. This suboptimal adherence leads to treatment failure, disease exacerbation, hospital admissions and an increased use of healthcare resources, across a variety of disease states. This represents a significant burden on society, particularly as it is a potentially preventable cause of resource utilisation. The factors influencing adherence are discussed below, based on the five WHO dimensions.

2.4.1.1 Patient-related factors
There have been multiple patient-related factors which have been reported to be associated with adherence but whether these influence adherence positively has not been consistently shown. Indeed, not all patients who exhibit the characteristics associated with positive adherence are good adherers to treatment, nor are patients who exhibit only some or few of the reported traits, definitely poor adherers. As with all studies investigating associations between factors, one can only report on the likelihood that a particular factor is related to adherence; each patient still needs to be considered on a case-by-case basis. Patient-related factors that have been studied include health psychological factors, health literacy, knowledge, and mental health factors.

Health psychological factors
One of the strongest factors that has been linked with adherence are health psychology factors – in particular, illness perceptions and health beliefs. Patients often have pre-existing ideas about their condition and associated treatment even before a medication is started, which can positively or negatively influence their adherence. Work around the role of health psychological principles and social cognition models in adherence began in the late 1970s. Becker et al. first proposed in 1975 a need for adherence research to move away from “easily identified and quantifiable dimensions”, such as patient, regimen or illness characteristics, and to focus instead on developing a “sociobehavioural compliance” model. However, it was not until the late 1990s that a
psychometric questionnaire was developed that was able to score and quantify these health beliefs based on such a model. The Beliefs about Medicines Questionnaire (BMQ) quantifies beliefs about the necessity of treatments and concerns about potential adverse effects\textsuperscript{176}, and is based on the “Necessity-Concerns Framework” – a model that describes how patient beliefs underpin attitudes towards treatment and adherence\textsuperscript{174}. The development of this simple quantitative measure has helped facilitate research into health beliefs, and has since been used in many adherence studies as the standard measure of medication beliefs\textsuperscript{177}. The availability of this standard measure has helped strengthen this particular area of adherence research by allowing systematic comparison of findings across disease states\textsuperscript{177}, thus raising the profile of health psychological factors as a strong determinant of adherence above other determinants.

Horne and Weinman have done extensive research in this area, identifying that patients whose perceived necessity of the prescribed treatment outweighed their concerns had significantly higher adherence\textsuperscript{174}. These medication beliefs demonstrated more powerful relationships with adherence than any other clinical or sociodemographic factors. A recent meta-analysis investigating the effect of health beliefs on adherence in chronic disease\textsuperscript{177} reported that the odds of adhering were 1.7 times higher for each standard deviation increase in perceived necessity, and the odds of adhering halved for each standard deviation increase in concerns about treatment\textsuperscript{177}. Kripalani et al. noted that patients who had poor motivation – such as those who relied on reminders from others to take medication, or waited to refill a medicine only when it was nearly finished – had 3-fold greater odds of non-adherence\textsuperscript{178}. Many other studies have supported this\textsuperscript{52, 56, 57, 171, 179}. A similar relationship has been reported with perceived disease severity, where patients who perceived their condition as serious were more likely to adhere\textsuperscript{172}. These factors are also true in adolescents with chronic disease – those who are motivated and have a positive attitude towards the condition or treatment, and show the energy and willpower to take care of themselves, have better adherence\textsuperscript{42}.

Although many studies have demonstrated a clear link between these health psychological factors and adherence, it is worth noting that the majority have used self-report as their primary measure of adherence, which as discussed earlier, may introduce potential biases. Few studies use objective measures, with even fewer using EAM; the results of those that use objective measures vary widely in effect size and statistical significance due to the low number of studies\textsuperscript{177}. One meta-analysis reported an attenuation of the relationship between treatment concerns and adherence when only studies using objective adherence measures were included, though the overall relationship between health beliefs and adherence was not affected\textsuperscript{177}. Further research into the impact of self-report bias on the reporting of medication beliefs would help inform this relationship. There are also few studies in children or adolescents; one study that did include children only assessed the beliefs of the parents\textsuperscript{180}. Some conditions remain under-represented in this area of research, such as epilepsy,
pain syndromes, and mental health disorders. The impact of different formulations of medicines on medication beliefs is also unknown. Together, these factors represent an area for further research.

Health literacy

Health literacy is defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate decisions”\(^\text{181}\). It is pivotal to a patient’s understanding of their medicines and plays an important role in medication adherence. Health literacy tends to be poorer in older patients\(^\text{182}\), indigenous populations\(^\text{183}\), and those with low literacy\(^\text{184}\). Health literacy however goes beyond simple literacy – the ability to read or write – and refers to the patient’s ability to assimilate information given and apply it to health decisions and practices. Despite this difference, much of the research conducted assesses the relationship between literacy in general and adherence, rather than health literacy per se\(^\text{58}\). DeWalt et al. conducted a systematic review of literacy and its relationship with adherence and health outcomes, acknowledging the absence of studies that have measured health literacy as a broader construct, and therefore choosing to focus on studies that have examined literacy. This review identified only two studies that examined the relationship between literacy and medication adherence, both in HIV patients, and the results were conflicting. One study examined medication adherence, assessed by electronic monitoring, pill counts and self-report, in 117 adults with HIV and found no relationship between adherence and literacy\(^\text{185}\); another study, utilising self-reported 48-hour adherence in 184 patients, found that lower literacy was associated with a 3.9 times higher odds of poor adherence, after adjusting for other socioeconomic factors\(^\text{186}\). This difference in findings may be related to the adherence measure used; those with poor literacy may be more likely to self-report poorer adherence. Indeed, poor health literacy can negatively impact on patients’ satisfaction with health provider communication, affect responses to questions about their medication-taking\(^\text{187}\), and their ability to understand information\(^\text{188}\). These effects may explain the variation in results seen with studies that use self-reported versus objective adherence measures.

Other studies on health literacy have focused on health outcomes. A systematic review in 2011 examined the effect of health literacy on outcomes, including medication-taking, and identified six studies that reported poorer medication-taking ability with poorer health literacy. These studies, however, used questions or mock scenarios to assess “intended adherence”, or examined other measures of medication-taking ability, rather than measuring actual adherence\(^\text{188}\). Other recent studies have been unable to shed any further light on the association between adherence and health literacy despite using objective adherence measures. Kripalani et al. found that the odds of non-adherence, as determined by prescription refill data, were two times higher in those with marginal or inadequate health literacy\(^\text{178}\); Mosher et al. found no such association despite also using refill data, though patients with poorer health literacy did have poorer medication knowledge\(^\text{189}\).
The heterogeneity of the measures used to assess literacy and adherence in these studies make it difficult to draw definitive conclusions about the relationship between these two factors. It is possible that health literacy influences adherence by impacting on domains that indirectly interact with adherence – for example, patients with lower literacy have been reported to be more likely depressed than those with higher literacy skills\textsuperscript{190}; this could in turn impact on adherence, as depression has been linked with poor adherence\textsuperscript{191}. Health literacy could influence the health of a patient by affecting their access to healthcare, interaction with health providers and ability to self-care\textsuperscript{192}, which could all have downstream influences on adherence and ultimately health outcomes. Future studies should use standardised measures of health literacy and objective measures of adherence, such as electronically monitored adherence data, to help elucidate the influence of health literacy on adherence.

\textit{Knowledge}

Few studies have examined the relationship between knowledge and medication adherence as the primary focus of the study\textsuperscript{193-197}; most have included knowledge only as one of a large number of determinants investigated\textsuperscript{198-202}. Those that have evaluated this relationship report an association between poor knowledge and poor adherence\textsuperscript{194-199, 203, 204}. This is likely mediated through a lack of patient understanding, leading to unintentional non-adherence; however, increasing knowledge through education alone does not significantly impact adherence\textsuperscript{30, 31, 205}. The relationship between knowledge and adherence is likely a complex one, dependent on the content of the knowledge. In a cross-sectional study of 227 patients with hypertension, several knowledge-based variables relating to the medicine were measured to determine the effect on medication adherence\textsuperscript{194}. Knowledge about duration and reason for medication use, cause of hypertension and target blood pressure were positively associated with adherence; knowledge of side effects had a negative effect. Knowledge of medicine name and effects of hypertension had no effect. Other studies in hypertension have examined the effect of knowledge on outcomes, reporting that knowledge of blood pressure goal was associated with better blood pressure control\textsuperscript{196, 206}, however, adherence was not assessed. In diabetes, knowledge has been linked with improved adherence\textsuperscript{195} and glycaemic control\textsuperscript{197}.

Other studies investigating knowledge and medication-taking have focused on measuring effects on comprehension\textsuperscript{204}, or treatment efficacy\textsuperscript{203, 206, 207}, rather than medication adherence. Of the studies that exist on knowledge and adherence, there is significant heterogeneity in the type of knowledge measured, such as whether the knowledge related to the medication, condition or both; how knowledge was assessed; and the type of adherence measure used. As for health literacy, future studies should use standardised measures to allow comparisons to be drawn across studies.
remains a lack of literature in this area; further research into the relative importance of different aspects of knowledge and their contribution to adherence behaviour is needed.

*Mental health factors*

Poor adherence has been reported in patients with impaired cognitive functioning and psychological distress, including mood disorders such as depression and anxiety. Several meta-analyses have found a significant association between adherence and depression. The most recent meta-analysis was in patients with long-term conditions, which reported that the odds of a depressed patient being non-adherent were 1.76 times the odds of someone who was not depressed, independent of disease type. This could be related to the hopelessness and lack of motivation experienced, as well as difficulties with provider-patient communication. Most studies investigating adherence and depression have used self-report to measure adherence, though eight studies did use EAM. Depression was predominantly measured using self-report scales, which consisted of a range of depression instruments. A large proportion of studies were in cardiovascular conditions, such as hypertension and coronary heart disease, and in diabetes. Future research would benefit from the use of objective measures of adherence and depression, across a range of chronic conditions and ages, as there remains little literature concerning the impact of depression on adherence in other conditions beyond cardiovascular and diabetes, and in children.

Co-morbid substance abuse, such as smoking and alcohol use, has been linked with poor adherence with treatments for COPD, mental health, and HIV. This could be due to the cognitive and behavioural disturbances that can arise from substance misuse, which often co-exists with depression and psychological distress. In a study of 140 adults with HIV on antiretroviral therapy, those who actively used drugs of abuse took only 59% of doses compared to 72% for non-users, and those who drank alcohol took 66% of doses versus 74% for non-drinkers, as evaluated by EAM, pill count and self-report. Similar findings have been demonstrated in other populations with HIV, as well as in other chronic conditions, though evidence remains limited in this area.

The majority of the literature on the impact of mental health factors on adherence focuses on depression, with fewer studies investigating other related factors, such as substance abuse. Whilst there is evidence supporting the relationship between these mental health factors and adherence, it remains unknown whether treating these factors would lead to improvements in adherence, or if the factors are non-modifiable.

**Summary**

Several patient-related factors have been associated with medication adherence, of which the most important appear to health psychological factors. Extensive research into these factors has been
conducted. The availability of a validated quantitative questionnaire has allowed systematic comparisons to be drawn between studies, which together demonstrate a strong relationship between health beliefs and adherence, a link that is stronger than with other adherence determinants. These factors are particularly important as unlike non-modifiable determinants, such as sociodemographic variables, these have the potential to be altered as part of adherence interventions. The relative contribution of other patient-related factors, such as knowledge, to adherence requires further exploration. The lack of standardised objective measures in these research areas makes data assimilation across studies difficult. Research in certain conditions such as mental health, and in certain populations such as children, continue to be scarce, thus representing areas of priority for future research.

2.4.1.2 Therapy-related factors

Medication treatment comprises several components which all impact on medication-taking – dose frequency and overall ‘medication burden’ (the number of medicines a patient needs to take, also referred to as ‘polypharmacy’ when there are multiple medicines). Polypharmacy is a factor that is shared across chronic conditions that require ongoing treatment, often with two or more medicines. Complex regimens, such as those involving a high dose frequency, combined with polypharmacy, increase the risk of non-adherence. The effects of the medication, both positive and negative, can also impact on the patient’s willingness to take the therapy. These factors are discussed below.

Dose frequency

Several systematic reviews have reported on the effect of dose frequency on adherence, with regimens that consist of once-daily dosing being associated with higher adherence than those with more frequent dosing. Many studies, however, did not use EAM to provide objective adherence data, possibly as adherence was not the primary outcome being researched in most of these dosing studies. There is also a lack of information in some chronic diseases, particularly in mental health and chronic pain, whilst extensive research exists for HIV and, to a lesser extent, diabetes and cardiovascular disease. There may be a threshold below which reducing dosing frequency has a negative impact on adherence; regimens that are dosed less frequently than daily, such as on alternate days, may be associated with poorer adherence, though adverse effects may be decreased. However, studies examining weekly versus daily dosing of bisphosphonates for osteoporosis found weekly dosing to be superior to daily dosing. A review of the effect of intermittent dosing regimens on adherence was published by Kruk and Schwalbe. Although the review only included 11 trials which met the inclusion criteria, the authors found that overall adherence was greater with weekly
compared to daily dosing, and in a single study of a monthly agent, adherence was similar to that achieved with daily dosing. Patients also indicated a preference for intermittent dosing\textsuperscript{229}. There remains potential for further research on the effect of intermittent dosing on adherence.

**Medication burden (number of medicines)**

The relationship between medication burden and adherence is mixed. In a large observational study of 1,000 patients with hypertension, adherence was significantly higher in those on just one tablet per day compared to those on more than one tablet\textsuperscript{230}. In contrast, a study of 350 patients with heart failure found the opposite effect – an increased number of medicines was associated with better adherence\textsuperscript{231}. This study used prescription refill data whilst the hypertension study used self-report. This may explain the difference in findings – patients on more medication may express greater dissatisfaction with treatment and therefore lower self-reported adherence. The difference in condition may also explain the findings, as congestive heart failure is a condition requiring strict monitoring, routines and restrictions on activity and diet. Correspondingly, patients on a greater number of medicines may have a more severe stage of heart failure requiring highly structured routines, which may translate into more routine medication-taking\textsuperscript{231}. This phenomenon has occurred in other studies involving cardiovascular medicines\textsuperscript{224,232}, as well as other long-term medicines\textsuperscript{233}, where an increase in medication burden is linked with improved adherence. Patients may be more likely to forget a single medicine, compared to multiple medicines, as the need for multiple doses or medicines may act as a reinforcement for medication-taking behaviour.

This relationship between the medication burden and adherence is a difficult one to elucidate, as the number of medicines is closely related to the number of co-morbidities, and severity of the condition, which are condition-related factors. One study found that patients with a high number of chronic conditions demonstrated better adherence\textsuperscript{233}; this may be a mediating factor in why an increase in medication burden leads to better adherence. Furthermore, medication may be co-prescribed to help minimise the adverse effects or to enhance the efficacy of another treatment. In such cases, the potential disadvantages of increasing the medication burden are likely offset by the benefits gained from improvements in the effects of therapy. For example, a meta-analysis comparing the effects of treatment with an antidepressant co-prescribed with benzodiazepines versus treatment with an antidepressant alone, found that those receiving the combination were 37\% less likely to discontinue therapy than those receiving the antidepressant alone\textsuperscript{234}.

Although an association between medication burden and adherence is suggested, the direction of these associations are unclear. The absolute number of medicines is likely only a small contribution to a patient’s overall adherence, and other related factors, such as the severity of the patient’s condition and the ‘fit’ of the regimen to the patient’s lifestyle, may play a greater role in influencing
adherence. The complexity of the treatment regimen may affect adherence to a greater extent than simply the number of medicines; medication that is easier to take in terms of food or storage restrictions are likely to facilitate adherence.

Effects of therapy
In line with the necessity-concerns framework described previously, the perception of adverse effects reduces adherence, whilst medicines that improve symptoms promote adherence. Adverse effects lead to non-adherence typically by affecting persistence with therapy – patients tend to discontinue therapy early or request changes to their medication if adverse effects occur. In a study of 336 patients started on antiretroviral therapy, the reporting of adverse effects at one-month post-initiation of therapy was the single most important predictor of non-adherence at four months, more so than medication burden or dosing frequency, with an odds ratio of 1.13 per side effect experienced by the patient. Similarly, in a survey of 876 people on antipsychotic medication, 86% reported experiencing one side effect, which corresponded with a significantly reduced likelihood of adherence. The odds of non-adherence differed depending on the type of side effect experienced – extrapyramidal effects and agitation were associated with a 43% reduction in the odds of being adherent, whereas sedation was associated with a 30% reduction. In contrast, the experience of positive medication effects early on in treatment, such as a reduction in menstrual cramping or bleeding with oral contraceptive use, predicts ongoing adherence. The influence of these treatment effects depends on the contextual issues surrounding the individual and the stage of disease – patients with symptomatic disease, for example in HIV, may derive great benefits from antiretroviral treatment, whereas in asymptomatic patients, the presence of adverse effects can negatively affect quality of life, and therefore adherence. In general, the literature exploring this relationship between therapy effects and adherence relate to the necessity-concerns research described earlier in this section; little literature is available that specifically focuses on medication effects and adherence, with the exception of studies in HIV, where the impact of short- and long-term treatment effects on adherence are well-studied.

Summary
This section presents factors influencing adherence that relate to the therapy, including dose frequency and number of medicines. Collectively, these factors describe a patient’s medication regimen and the complexities arising from it. Regimen complexity however extends beyond dosing frequency and medication burden; it encompasses medication administration and storage requirements, diet restrictions and any medication preparation required prior to administration. Complexity is important to consider, as many chronic diseases require treatment with a range of medicines that may all have different administration requirements. There remains a lack of an available measure to assess treatment complexity per se, and as such there is limited research on
this and adherence. Other studies have examined therapy effects in the context of a necessity-concerns framework. Research using this framework is likely to expand as the health psychological aspects of adherence increase in prominence. Available literature generally focuses on HIV; there is a paucity of literature in other chronic conditions. There is also minimal research on the effect of therapy duration on adherence. Future studies of therapy-related factors should aim to incorporate measures of regimen complexity and therapy duration across a range of conditions.

2.4.1.3 Condition-related factors

Most of the literature around condition-related factors relate to disease severity, or a factor related to severity, such as symptom prominence, level of disability, and health status. As such, this section will focus on disease severity. The presence of certain co-morbidities, in particular depression, anxiety and substance abuse, are also important condition-related factors but as these have been discussed under the patient-related factors section, they will not be revisited here.

Previous studies have suggested a link between disease severity and adherence; however, the direction of effect on adherence has been inconsistent. Participants in the Lung Health Study who had more severe disease reported higher adherence, and fewer symptoms and hospitalisations. This suggests that patients with more severe disease may be more motivated to adhere to treatment, leading to better disease control. However, this cause-and-effect relationship has not been consistent across studies. In the Bosley et al. study, which also examined adherence in COPD patients, but to home nebulized medication including bronchodilators, anticholinergics and corticosteroids, patients who had a more impaired health status reported poorer adherence.

This contradicts the Lung Health and Intermittent Positive Pressure Breathing (IPPB) studies. One of the potential reasons for these conflicting results is the lack of a consistent definition of disease severity and whether it relates to perceived or actual severity. As previously described, perceived severity relates to health beliefs and illness perceptions, where patients who perceive their condition as severe are more likely to adhere, compared to those who do not. This phenomenon has been described as ‘disease threat’ and relates both to the perceived “likelihood of its occurrence (perceived susceptibility) and its potential for causing physical harm and interfering with social functioning (perceived severity)” Actual severity refers to actual disease and relates to the patient’s health status, including symptom burden, disease progression and stage of disease. These differences in disease severity definitions and measurement – through physician-rated, self-rated, parent-rated or objectively measured methods – add to the difficulties in examining this relationship between disease severity and adherence.

DiMatteo et al. conducted a comprehensive meta-analysis that investigated all these factors and found several interesting relationships which confirm previous findings – the relationship between
perceived disease severity threat and adherence was strongly positive and significant; and similarly, patients with poorer health, as rated by their physicians, were found to be more adherent. However, when conditions were separated into less or more serious disease, patients with more serious conditions, and who were in poorer health, were found to be significantly less adherent, regardless of whether this was self-rated, parent-rated or objectively rated, for example using laboratory measures. Conversely, those with less serious disease but poorer health were more likely to adhere than those with better health. It may be that those who are severely ill with serious conditions are limited in their capacity, both physically and psychologically, to adhere to treatment; routine medication-taking requires significant effort and motivation, which can become increasingly challenging as health status declines\textsuperscript{245}.

This meta-analysis raises important questions around disease severity, its measurement, and the effect of condition seriousness on the relationship with adherence. It signals that those patients with serious diseases who are severely ill are at the highest risk of non-adherence, and as such should be targeted for adherence interventions. Future research into disease severity should focus on elucidating some of the reasons for this effect of condition seriousness on adherence. Information relating to children need further examination. A total of 11 studies in children were included in this meta-analysis, which found a 14% higher risk of non-adherence with objectively poorer health; a relationship that was not observed in adult samples. The meta-analysis also highlighted the influence of parental perceptions of disease severity. These factors, which relate uniquely to children, require further research to understand the practical and clinical implications.

There remains limited research in mental health conditions. Sirey et al. reported increased adherence to antidepressants with higher self-rated illness severity\textsuperscript{246}. Similarly, Adams and Scott noted a positive association between perceived illness severity and adherence in patients with severe mental illness\textsuperscript{247}. However, the use of self-perceived disease severity is likely to reflect self-awareness or insight into the disease rather than actual disease or symptom severity. This was demonstrated in a review of factors influencing adherence in schizophrenia, which reported conflicting findings to Sirey et al., and Adams and Scott. The review found an inverse relationship between symptom severity and adherence – potentially as patients with poorly controlled disease may have increased difficulties with medication-taking. The prospective nature of two of the studies in the review support this direction of effect\textsuperscript{248, 249}. The relationship between adherence and insight into the illness was however positive\textsuperscript{250}, suggesting that self-rated disease severity may be reflecting illness insight rather than true severity. Future studies would benefit from distinguishing whether disease severity is self-perceived or objectively assessed, as described by DiMatteo et al.\textsuperscript{172}. 

28
**Summary**

A strong association between disease severity and adherence exists, supported by a large number of studies in this area. The direction of effect seems to be an influence of disease severity on adherence, rather than adherence affecting disease severity, though further research using a prospective design will help confirm this. Differences in effect between perceived and actual disease severity appear to exist, and it would be pertinent for future studies to distinguish between these two different, but related, assessments of disease severity. There is evidence to support a differential effect of disease severity on adherence depending on the seriousness of the condition. Further research into this area is needed to understand the mechanisms that drive this effect.

**2.4.1.4 Healthcare team and system factors**

Research on the effects of the healthcare team and system on adherence is relatively scant compared to the other four dimensions of adherence\(^40\), as most of the ideas relating to these determinants are relatively new. The focus on patient self-determination and autonomy in recent times has highlighted the importance of considering healthcare team and system factors in adherence, which are discussed below.

**Healthcare team**

The quality of the relationship with the healthcare provider is an important determinant of adherence\(^251,252\) and health outcomes\(^253\) across a wide range of chronic conditions. A collaborative relationship between the health provider and patient, where explicit treatment goals are agreed on and both parties co-operate to achieve these, has been termed a “therapeutic alliance”. This alliance is formed through an emotional bond, where the provider and patient both trust each other\(^254,255\). The key components within the relationship that affect patient behaviour appear to relate to the way health providers communicate and interact with patients\(^174\). A meta-analysis in 2009 reviewed 127 studies on the relationship between health provider communication and adherence, and the effect of health provider training interventions, targeted at improving communication skills, on adherence. The meta-analysis included studies where communication was assessed by the patient or researcher, and adherence measured by self-report or objective measures. The authors found a significant positive correlation between health provider communication and adherence, with a 19% higher risk of non-adherence in patients with a health provider who communicated poorly with them compared to those with a provider who communicated well. The correlation was significantly higher in studies with a smaller sample size; when objective adherence measures were used; and when communication was not patient-assessed\(^61\). This highlights the need for future studies to consider the effect of different methods of assessment, of both adherence and communication, and other methodological influences, on adherence outcomes.
The way in which the provider interacts with the patient is also a key factor, with studies showing that clinicians who express empathic understanding and multicultural competence result in greater adherence and patient satisfaction\(^{256, 257}\). Patient participation in a shared decision-making process has been linked with greater adherence, via direct positive effects on the therapeutic relationship, and indirectly by improving patient understanding of the medication and patient satisfaction\(^{253, 258-260, 222}\). There is a greater chance adherence will improve where health providers are able to share similar beliefs as their patients, such as how patients should be involved in their care, and effect cohesive partnerships\(^{260, 261}\). This ultimately helps foster trust in the therapeutic relationship, which was the single most important variable found to be associated with patient satisfaction. Adherence rates were reported to be 2.6 times higher in one study where there were high levels of trust in the relationship and the health provider had comprehensive knowledge about the patient\(^{262}\).

Indeed, the provider-patient relationship is an important factor in achieving adherence. The impact of different modalities of communication, such as through mobile phones and computer systems, on this relationship and consequently adherence, will need to be explored further. As communication expands globally, more research will be needed to understand the influence of different cultures and demographics on preferred communication styles and the provider-patient relationship\(^{260}\).

**Health system**

Beyond the medication, health provider and patient, lies the health environment in which all of these factors interplay. The health system is a crucial factor that has the power to affect the health behaviours of not just one, but many. The infrastructure governs and controls how people access healthcare, the funding mechanism surrounding it and the quality of care delivered. The system can dictate who that healthcare might be delivered to and whether or not there are any access restrictions to treatments. Ultimately, these health system factors can affect medication adherence directly and indirectly by determining resource allocation and whether health providers are supported to develop quality therapeutic relationships\(^{263}\), so patients can be engaged in a meaningful manner to encourage adherence\(^{170}\), providing a system that either supports or opposes the prioritisation of adherence interventions\(^{264}\), and influencing continuity of care\(^{265, 266}\). Stability and continuity are factors that can impact on adherence with studies demonstrating higher adherence and better outcomes in patients who have a consistent healthcare provider and stable medication regimen\(^{230}\).

The model in which healthcare is delivered can affect access to medication and outcomes. For example, in the United States, health insurance is provided to help cover healthcare costs with remaining charges covered by additional insurance or other out-of-pocket financial resources. People can choose to receive their care either through a traditional fee-for-service model or via a
prepaid health maintenance organisation system; the latter refers to an organisation that arranges managed care for the patient as part of an integrated system with a primary physician responsible for coordinating the care for each patient\(^{267}\). In a cross-sectional observational survey of Medicare insurance beneficiaries across 13 states, Safran et al. found that performance across most health indicators in primary care, including continuity of care, favoured a fee-for-service system, though financial access favoured health maintenance organisations, which presented fewer cost-related barriers to care. The authors concluded that a cost-quality dilemma exists – with higher quality associated with higher out-of-pocket costs under a fee-for-service system\(^{268}\). Whether these costs translate into higher or lower medication adherence was not discussed in the study; however, it is known that financial constraints can limit adherence, particularly in low-income families\(^{269}\). On a wider scale, these financial barriers can contribute to or minimise health disparities and influence health outcomes. Other studies have confirmed that minimising out-of-pocket costs and other financial barriers to the patient, such as co-payments, improves adherence\(^{270, 271}\). A recent meta-analysis investigated the effect of co-payments on adherence in publicly insured populations, and demonstrated an 11% increased odds of non-adherence in populations where co-payments were required\(^{270}\). This is in line with a previous review which reported a reduction in adherence by 0.4% for every dollar increase in patient co-payments\(^{272}\). Most of the studies included were in cardiovascular disease and diabetes. The relevance of these findings in other conditions, such as chronic pain, cancer and neurological conditions, is unclear. Some studies also excluded the poorest members of society, which are the group most likely impacted by financial barriers to medication access. Indeed, coverage has been noted to be inadequate for those with low incomes, resulting in non-adherence due to cost\(^{273}\). There was no information on how these findings affect younger age groups, such as children and adolescents, who may be impacted differently by financial barriers. There is a pressing need for future studies to focus on these vulnerable groups, in particular those with low socioeconomic status and in children.

The effect of co-payments on medication adherence may also differ depending on the patient’s co-morbidity burden. Patient responses to the need for cost-sharing is likely heterogeneous in a population due to differences in perceived benefits and risks of medication adherence by different patient groups\(^{274}\). Wang et al. conducted a retrospective observational study where patients required to pay co-payments were compared to those who were exempt, and examined how this effect differed between those with high versus low co-morbidity\(^{275}\). Adherence was assessed using prescription refill data and co-morbidity burden measured using the Diagnostic Cost Group Hierarchical Condition Category (DCG/HCC) model, which predicts healthcare costs of populations based on diagnosis\(^{276}\). The study found that co-payment increases had a more negative impact on adherence in those with lower co-morbidity burden compared to those with higher co-morbidity.
The authors suggest that those with higher co-morbidity have a greater need for treatment due to the larger disease burden, and as such, their medication adherence is less sensitive to changes in co-payments, as treatment need outweighs the disadvantages of increased costs. Although disease severity was not assessed, the measure of co-morbidity used (DCG/HCC) captures an element of the seriousness of the patient’s disease and their health status. The findings are therefore in line with trends seen in other studies, where greater disease severity and poorer health (both of which are more likely in patients with higher co-morbidity) predict better adherence.

Despite a clear relationship between worsened adherence and increasing medication costs, non-adherence can still be problematic even when medicines are free. A perspective article by Cutler and Everett stresses that more should be done beyond simply reducing financial barriers; the authors suggest that patients, as well as health providers, should be given financial incentives to reward adherence and its promotion. Indeed, financial incentives appear to be effective in promoting adherence; however, the sustainability and practicalities of these interventions outside of the research setting require further investigation. The article also discusses the potential for health information technology to collect and share adherence data amongst different care providers to facilitate adherence initiatives. The ethical implications of this data sharing, and the suggestion of using financial incentives to motivate behaviour, will need to be considered.

Summary
The literature examining the impact of healthcare team and system factors on adherence is expanding, though it remains a relatively new area of research. Available evidence highlights the importance of considering the provider-patient relationship when delivering adherence initiatives, though further research into how this is affected by different communication modalities and cultures is needed. Current literature also reports on the effect of the health system on access and financial barriers to adherence. There remains little research on health system factors in vulnerable populations, such as children, which should form the subject of future adherence research.

2.4.1.5 Social and economic factors
Social and economic factors are considerable areas that encompass both the traditional demographic factors relating to the individual as well as their wider social and economic environment. These two aspects are examined below.

Sociodemographic variables
Sociodemographic factors such as age, ethnicity, gender, income, education level and employment status have been studied. As adherence is a behaviour, adherence is likely to change over different life stages, and not surprisingly, age is a well-studied adherence determinant. Older age is generally linked with higher adherence, though in certain conditions, cognitive
decline may complicate this relationship. In a study of 148 adults with HIV infection, older patients were three times more likely to have adherence of at least 95% or more; however, presence of neurocognitive impairment increased the risk of poor adherence by 2.5 times. This positive effect of increasing age on adherence has been reported with a wide range of medicines, with the exception of oral anticancer agents, which was shown in a systematic review to have an opposite effect, with both younger and older age being linked with non-adherence. It is possible that in older patients, the adverse effects of oral anticancer agents are greater compared to other medicines used in chronic disease, which may explain the unexpected poorer adherence seen with older age. The difference may also be due to the definitions used, as younger age referred to those aged 45 years or less and older age as 85 years or older, whilst other studies have used different age categories. Future studies would benefit from a linear examination of age, as it is a continuous variable, rather than using categories; or if categories are required, several different categories should be tested as a sensitivity analysis to identify the best cut-off points to use.

The association between ethnicity and adherence has also been studied extensively, with ethnic minorities being at risk of non-adherence and those of ‘white’ ethnicity have higher adherence. In the Lung Health study, one of the largest studies examining adherence with inhaled medication in COPD patients, participants of “white” ethnicity had higher adherence than other groups. This has been supported by the IPPB study and studies in other chronic conditions. Conversely, evidence has shown that ‘non-white’ or minority ethnic groups have poorer adherence. Singh et al. investigated adherence to antiretroviral treatment in a longitudinal observational study. Adherence was significantly lower in those of “black” ethnicity. Similarly, Golin et al. identified several predictors of poor adherence to antiretroviral medication which included being of African-American ethnicity, as well as having lower income and education. In a study of 14,464 people, the risks of failing to fill a prescription were notably higher in ‘non-white’ patients. These ethnic differences may result from difficulties with health literacy, access to treatment or differences in health beliefs and treatment acceptability. These differences contribute to existing, and often widening, health disparities, and therefore demand urgent research attention to understand the reasons driving disparity.

Other sociodemographic variables that have been associated with adherence include gender, income, education level, and employment status. These factors have shown inconsistent relationships with adherence. Several studies have highlighted gender as a potential adherence determinant, but the direction of effect has been heterogeneous, both within and between systematic reviews. Likewise, income and education have been linked with adherence, but the direction of effect is also unclear. Systematic reviews of studies in Parkinson’s disease, heart failure, cancer and other conditions have shown no effect or an unclear effect of income.
and education on adherence. In a study of prescription drug coverage in older people, a significant percentage of low-income seniors reported cost-related non-adherence – in those without drug coverage, 41% had not filled prescriptions in the past year due to costs and 36% had skipped doses to make medication last longer. Similarly, in patients with chronic conditions, those with annual incomes of US$30,000 or less were more likely to report not filling prescriptions. Both lower income and less education were found to predict worse adherence in patients with HIV on antiretrovirals; in contrast, in a study of African-Americans with hypertension, neither income nor education were associated with adherence. Similar conflicting results have been noted in other studies. The evidence is equally mixed for education – in a study of COPD patients, higher education was linked with better adherence; the opposite was true in patients with schizophrenia on antipsychotic treatment and in patients on warfarin. Other studies indicate no effect.

Both income and education can impact on employment, which may be a separate adherence determinant. Employment was positively associated with adherence in patients with schizophrenia, possibly as employment status may serve as a proxy in this group for level of functioning and therefore associated higher adherence. A similar effect has been observed for other conditions but not consistently – in one study of adults on warfarin, those who were unemployed or retired had higher adherence, whilst no relationship with employment was reported in a study of adults with HIV.

These findings concerning sociodemographic factors present a mixed picture, largely due to the inconsistency of the study aims and populations. Sociodemographic factors are generally studied as part of a large number of adherence determinants and are seldom the primary study focus. Interestingly, some studies report that socioeconomic factors are more strongly associated with adherence than disease factors such as symptom severity, whilst others suggest that system factors have a greater influence on adherence than sociodemographic variables. The size of the contribution of these factors to adherence remains largely undefined, primarily due to the heterogeneous nature of available studies.

Social support

The concept of social support and health has received increasing attention in adherence research. Many definitions of social support exist, which is a complex concept consisting of qualitative and quantitative elements. Generally, social support refers to the value and perceived meanings that people derive from social relationships, which can come in a variety of forms including friendships, family, group memberships and marriage. Social support is an important factor in many aspects of health, including health maintenance and disease recovery, and more recently in disease self-management and medication adherence. Gallant conducted a literature review on social
support and self-management in chronic disease, and noted a positive, but modest, relationship. DiMatteo expanded on these findings and conducted a more extensive review and meta-analysis of 122 studies reporting on the role of social support in adherence specifically. He described two aspects of social support: structural, which refers to family structure such as marital status and living arrangements, and functional, which refers to practical (e.g. instrumental support, assistance, reminders) or emotional (e.g. nurturance) support or family functioning (e.g. family cohesiveness, conflict).

Many studies have focused on the structural aspect of social support on adherence, with marital status or living arrangements being used as a proxy for social support – being married or in a domestic partnership appears to be significantly correlated with improved adherence, whilst those in unstable living conditions, such as in a shelter, report poorer adherence. This effect was small but significant – the odds of adhering were 1.27 times higher in those that were married compared to those that were unmarried. The effect on adherence in children was greater – the risk of non-adherence in children with unmarried parents was 1.35 times higher than in children with married parents. A similar effect was observed in adults for living arrangement – adults who lived with another person had a 1.38 times higher odds of adherence than those living alone; the effect was stronger for acute compared to chronic illnesses. In children however, a trend towards an opposite effect was found, where the greater the number of people living in the household, the poorer the adherence, though this was not significant.

In terms of functional support, practical support had the greatest correlation with adherence over emotional support or family functioning, with a number of studies supporting this association. The odds of adherence were 3.60 times higher among those who received practical support compared to those who did not. Comparatively for emotional support, the odds of adherence was 1.83 times higher for those with emotional support than for those without. Family cohesiveness was another mediating factor, with a 3.03 times higher odds of adhering in patients who had close and cohesive families; conversely, greater family conflict was associated with poorer adherence – the odds of non-adherence was 2.35 times greater in high versus low conflict families. When comparing the two types of social support – structural and functional– functional support had stronger effects on adherence than structural support, which may indicate that the qualitative elements of support (i.e. quality of the relationships) may be more important than the quantitative elements (i.e. presence of relationships).

The meta-analysis bears some limitations that should be considered when interpreting these findings. All studies involving medical treatments were included and, as such, the review was not focused solely on adherence to medication. Both objective and subjective (self-report) adherence measures were used in the studies, which could influence the validity of the results – indeed, the
meta-analysis noted that correlations tended to be higher if self-report measures were used. Future studies should use objective adherence measures where possible to increase the validity of the findings. Nonetheless, the review gives a good overview of the direction of interaction between various parameters of social support and adherence.

There remain some gaps in the literature on social support and adherence – particularly in children, where the number of studies were low relative to adults. Evidence suggests social support can influence adherence in a similar manner to adults; adolescents with chronic disease, for example, were found to have better adherence if they had strong support networks. The effect of social support on adherence in mental health conditions is also unknown. These questions should form the subject of future research initiatives into social support and adherence.

Summary
There is a vast body of literature on social and economic factors relating to adherence, with many of these factors being studied as part of a wider range of adherence determinants rather than as the sole focus of the research. There is sufficient evidence to allow relatively robust meta-analyses to be completed, which have helped provide important information on the relative contributions of each of these social and economic variables, as well as signalling the direction for future research. Age and ethnicity appear to be important factors which have demonstrated consistent relationships with adherence. Future research should focus on unravelling the reasons driving these differences seen with age and ethnicity, in order to develop effective adherence interventions. The strength of evidence behind the relationship with social support reinforces the need to consider these factors when designing and delivering adherence interventions, though further studies are needed in children.

2.4.2 Medication adherence in asthma
A large number of studies recognise the importance of adherence in the management of asthma. However, adherence with preventive asthma medication remains suboptimal, with mean adherence rates reported in the range of 30% to 70%, comparable to the rates reported with other chronic diseases. Poor adherence with preventive treatment is linked to increased exacerbations, symptoms, hospital admissions, increased healthcare costs and mortality.

Similar to other chronic diseases, the adherence determinants in asthma can be categorised into patient-related, therapy-related, condition-related, healthcare team and system, and social and economic factors. As there is overlap with the adherence determinants for chronic disease that were discussed previously, this section will focus specifically on how these determinants manifest in
asthma and the unique factors to consider in this condition. The discussion will refer to all age groups with asthma; any factors that affect children specifically will be examined in Section 2.4.3.

2.4.2.1 Patient-related factors in asthma

Similar to those described in chronic disease, several patient-related factors impact on adherence in asthma, which include factors related to health psychology, health literacy, knowledge and mental health.

Health psychological factors

Patient beliefs about asthma treatment are a significant factor in determining adherence, and have been shown in several studies to be more strongly associated with medication adherence than any other factor\(^{39,59,171}\). In a study by Horne et al.\(^{171}\), 100 community-based patients were surveyed on their perceptions of their asthma, beliefs about preventer inhalers and adherence. The study highlighted that those who were non-adherent tended to have doubts about the necessity of treatment and had more concerns about adverse effects. These patient perceptions and beliefs were stronger predictors of adherence than sociodemographic or condition-related factors.

Similarly, Bender et al. presented results from 32 patient-interview studies which revealed concerns about safety and dependence of the asthma medication, as well as issues of trust, access and cost in low-income and minority patients\(^{305}\). Patients also perceived numerous adverse effects from the medication\(^{306}\) and a belief that ICS were not necessary when asymptomatic\(^{307}\). These negative perceptions about ‘steroid’ treatments can profoundly affect adherence decisions, and modification of these beliefs can potentially have great benefits.

Apter et al. conducted a study with 85 adults, including African-Americans as a minority population, to determine modifiable sociobehavioural factors associated with adherence. The authors found that ‘attitude’ – as determined by perception of adverse effects and belief in medication benefits – was strongly associated with adherence across all ethnicities, but this effect was not attenuated when taking ethnicity into account, indicating that the effect of attitude was separate from that of ethnicity\(^{59}\). In a recent meta-analysis of studies evaluating the relationship between beliefs about necessity/concerns and adherence, using the necessity-concerns framework\(^{177}\), nine studies were identified in adults with asthma\(^{171,174,308-314}\). The strength of the correlation with adherence was significant, with asthma being only one of two conditions (the other being inflammatory bowel disease) that demonstrated a significant association between adherence with both necessity and concern beliefs. The effect size was also one of the largest – in asthma patients with high necessity beliefs, the odds of adhering were 2.6 times higher than the odds of adherence in patients with low necessity beliefs, whilst the odds of those with high concerns scores adhering were 0.4 times the odds of adhering in those with lower concerns\(^{177}\). Although the meta-analysis focused only on
studies that measured health beliefs using the BMQ, other studies that have investigated health beliefs using other measures have found similar correlations\(^{39, 59, 307, 311, 315-322}\). Patient expectations about treatment efficacy can also affect adherence\(^{323}\). Together these studies highlight the importance of considering patients’ health beliefs in adherence interventions. The majority of the studies in asthma have, however, used self-report to measure adherence, which could influence the validity of the findings relating to the adherence-beliefs association. No studies have used electronic monitoring – future studies investigating health beliefs and adherence in asthma would benefit from using electronically monitored data to confirm these results.

**Health literacy**

Similar to that in other chronic diseases, the research on health literacy primarily focuses on general literacy and asthma knowledge, which are related but not identical concepts, with only a small number of studies focusing on health literacy specifically. Studies have assessed the effect of several aspects of literacy on asthma, including reading ability\(^{324, 325}\), aural literacy\(^{326}\) and numeracy\(^{327, 328}\). The majority of these studies did not assess medication adherence and study outcomes focused on markers of health behaviour and asthma control, such as asthma knowledge, inhaler technique\(^{324}\), symptoms\(^{326}\), hospitalisations or ED visits\(^{327}\) and quality of life\(^{328}\). These studies all demonstrated poorer outcomes with poorer literacy. One study conducted in asthma clinics in Tehran found a positive relationship between literacy and self-reported adherence\(^{325}\) and a recent study, examining health literacy specifically, found a similar relationship with electronically monitored adherence\(^{329}\). Asthma control and quality of life were also greater in those with higher health literacy. A recent systematic review examining the evidence between health literacy and asthma however report an unclear association between health literacy and medication use\(^{330}\), mainly due to the low number of studies that have examined health literacy and adherence as most have focused on other outcomes. More studies investigating the relationship between health literacy and adherence specifically are needed to corroborate existing findings and understand the implications for adherence promotion.

**Knowledge**

Asthma knowledge has been linked with adherence, but most studies have been conducted with children, with few studies in other age groups. As such, the bulk of the discussion of knowledge and adherence will be in section 2.4.3, as it focuses specifically on children with asthma. Available studies in adults report conflicting results. One study with 160 adults reported a significant correlation between asthma knowledge and self-reported adherence\(^{325}\) but the assessment of knowledge was based only on two questions about whether or not the patient had received information and education about asthma, and whether they preferred to take medication orally, as an inhaler or both. These questions were not based on validated knowledge measures, and also
lacked face validity, which sheds doubt on the reported findings\textsuperscript{325}. Other studies using more comprehensive knowledge measures did not find an association between knowledge and self-reported adherence\textsuperscript{331, 332}. The inconsistent findings may reflect a difference in effect of knowledge depending on ethnicity – one study found knowledge did not influence adherence in African-American patients, but was an important adherence determinant in white patients\textsuperscript{333}. A correlation between knowledge and ability to manage asthma exacerbations may exist\textsuperscript{332} but this has not been consistently demonstrated\textsuperscript{334}. Whether knowledge effects on outcomes are mediated through adherence is unknown; studies using interventions to improve knowledge have not shown an effect on adherence\textsuperscript{335-337}. Further studies investigating the effect of knowledge on adherence and outcomes in adults with asthma, and potential differences between different populations, are needed.

\textit{Mental health factors}

Several studies have reported a significant association between depression and adherence in asthma\textsuperscript{109, 209, 210}. Bosley et al. investigated mental health factors associated with electronically monitored adherence in patients with asthma. The study found that although anxiety scores were no different between adherent and non-adherent groups\textsuperscript{109}, patients with a higher mean score of depression had higher rates of non-adherence\textsuperscript{109}. Two other studies confirm these findings\textsuperscript{209, 210}. A prospective cohort study of 59 adults reported an 11.4-fold increase in the odds of poor adherence in those with high levels of depressive symptoms, even after adjustment for confounders\textsuperscript{209}. In contrast, two studies did not find an association with adherence despite having similar participant numbers and using identical measures of depression\textsuperscript{59, 338}. The studies used a mix of either electronic monitoring or self-report adherence measures, which did not appear to influence the results found. The difference in findings may arise from differences in the study population, which ranged from patients admitted to hospital with asthma to outpatients, and differences in ethnicities, which may affect how depression interacts with adherence. The relationship of depression with adherence remains inconclusive and represents an area requiring further research.

\textit{Summary}

Similar to the findings in chronic disease, the most well-studied patient-related adherence factors in asthma were health psychological factors. These have consistently demonstrated a significant association with adherence. Research into the contribution of other patient-related factors to overall medication adherence in asthma have shown contradictory findings, which remains an area for future research.
2.4.2.2 Therapy-related factors in asthma

Medicine formulation is a therapy-related factor that is unique to asthma, though dose frequency, medication burden and therapy effects also play a role as in other chronic diseases.

Formulation

The majority of asthma medication is delivered via the inhaled route to reduce systemic effects of the treatment. Even though there is only one primary route of administration, inhaled medicines have been formulated in different ways to cater for different preferences. Indeed, satisfaction with the inhaler delivery device, rather than the medication itself, is an important factor as it can impact on adherence and asthma outcomes\(^{339}\). One study found that patients who were satisfied with their inhaler device were significantly more likely to adhere to therapy, and have a better quality of life, fewer exacerbations and sleep disturbances, and lower healthcare utilisation\(^{339}\). Factors that relate to higher inhaler satisfaction include having a device that will last, is easy to hold and carry, simple to use, delivers the same amount of medication each time, and does not require extra handling prior to use. These factors should be considered when designing new inhaler devices to promote adherence.

Whilst the literature reports no difference in clinical effectiveness between different inhaler formulations\(^ {340}\), evidence suggests adherence is affected by inhaler type. Improved adherence has been demonstrated with dry-powder inhalers over traditional metered-dose aerosol inhalers\(^ {341, 342}\), Diskus over Diskhaler dry-powder inhalers\(^ {343}\), and extra-fine over large-particle inhaled formulations\(^ {344}\). Although spacers are routinely recommended to optimise medication delivery, one study found better adherence in patients who did not use a spacer, a finding which suggests the benefits of improved drug delivery may be offset by reduced adherence. This effect on adherence will need to be considered when encouraging inhaler use with spacers\(^ {325}\). Other studies have compared the effect on adherence of oral medication, such as theophylline or montelukast, versus inhaled therapies\(^ {179, 345-347}\). Kelloway and colleagues compared adherence rates of oral theophylline versus twice-daily ICS and found improved adherence with the oral formulation\(^ {179}\). These findings have been confirmed by other studies that report higher adherence with oral versus inhaled formulations, possibly as oral therapies are easier to self-administer than inhaled medication, which require more skill and co-ordination\(^ {345-348, 349}\). These results reinforce the need to consider patient preference in achieving adherence, as formulations that are easier to take appear more positively associated with adherence. Oral asthma therapies have however been shown to be less effective than ICS\(^ {350}\). Whether this reduced effectiveness is offset by the higher adherence seen with oral treatments requires further investigation.
**Dose frequency**

Similar to the trends seen with medication regimens in other chronic conditions, asthma therapies that are complex and require frequent dosing tend to be associated with poorer adherence\(^\text{219, 220, 351, 352}\). Generally, most inhaled asthma medicines are licensed for twice-daily dosing. There have been several studies which have investigated the effect of reducing dosing frequency from twice- to once-daily dosing. Wells et al. evaluated the effects of once-daily versus more frequent dosing of ICS on adherence in 1,302 patients and found that those who had once-daily dosing had a 20% higher adherence compared to twice-daily or more frequent dosing\(^\text{352}\). This effect was seen even amongst patients who crossed over from twice- to once-daily and vice versa; the likelihood of adherence increased in those who switched to less frequent dosing, and decreased in those with more frequent dosing. Other studies have confirmed these findings\(^\text{351-355}\), with patients also reporting improved health-related quality of life\(^\text{355}\) and increased satisfaction with reduced dosing frequency\(^\text{353}\).

Healthcare resources and management costs related to asthma care are potentially lower with once-daily dosing\(^\text{356}\).

There are however studies which show no effect. One study found no difference in adherence for patients on twice-daily theophylline or ICS compared to those on thrice-daily dosing\(^\text{179}\). Purucker et al. reported on six studies which highlighted reduced efficacy with once-daily dosing of fluticasone and no adherence advantage compared to twice-daily dosing\(^\text{357}\). This outcome of reduced efficacy requires further investigation, as other studies have not reported differences in efficacy with reduced dosing, though they have not been powered to detect differences in outcomes\(^\text{352}\). Although studies have generally supported improved adherence with reduced dosing frequency, conflicting evidence exists which require further exploration to identify the populations most likely to benefit from reducing dosing frequency. Further research into the impact on medication efficacy and asthma outcomes is also needed.

**Medication burden**

Although several studies have demonstrated that the number of inhalers that a patient requires is not associated with adherence\(^\text{339, 352, 358, 359}\), improved adherence with combination inhalers compared with individual inhalers has been reported\(^\text{349, 360}\), which will be discussed further in section 2.5.2.1, as a strategy to improve adherence in asthma. Briefly, studies have generally demonstrated improved adherence with use of combination inhalers\(^\text{349, 360}\), however, one study reported no adherence benefits\(^\text{361}\). The difference in findings may be due to the difference in adherence measurement methods. Questions remain as to whether medication burden itself is an independent adherence determinant, or whether the benefits seen with combination inhalers on adherence is actually mediated by another influencing factor rather than medication burden *per se*. Further exploration into the effect of medication burden on adherence is needed.
Effects of therapy

The therapeutic delays experienced with ICS treatment represents a unique therapy-related adherence barrier in asthma. Often the benefits of preventive treatment are not evident to the patient or are delayed; in contrast, the benefits from reliever therapy are instantaneous\(^{362}\). Patients may not feel their preventer is effective as it does not provide immediate symptomatic relief, unlike their reliever\(^{362}\) and, as a result, reliever use is typically higher than for preventive medication\(^ {322, 363}\). This lack of immediacy of medication effect further reinforces the perceived lack of necessity for preventive medication\(^ {177}\), as the separation of therapeutic effect from the taking of the medication does not emphasise that ICS are important for asthma control. These therapy-related factors, coupled with their impact on health beliefs, can reduce overall adherence\(^ {179}\). This may explain why improved adherence is seen with oral anti-leukotriene or bronchodilator therapies, as these have a faster onset of effect than ICS\(^ {179, 364}\), though the difference in formulation and dose frequency, as discussed above, confounds this effect making it difficult to report conclusive results.

Summary

A wide range of therapy-related factors have been studied. The relative importance of each of these factors in adherence is unknown as no studies have compared all these factors. Much of the research has focused on formulation and dose frequency, with therapy effects generally investigated in the context of health beliefs. Available literature suggests a trend towards improved adherence for oral over inhaled medication, and for once-daily over more frequent dosing. These reflect a preference for more convenient regimens to achieve adherence.

2.4.2.3 Condition-related factors in asthma

A number of studies have investigated condition-related factors in asthma but have shown varying results\(^ {358}\). Asthma symptoms have been frequently linked with adherence. It is well known that poor adherence is associated with poor asthma control\(^ {10, 11, 102, 365}\), so it is not surprising that asthma symptoms and adherence are correlated. However, the direction of this relationship is less clear. Whilst poor adherence can lead to poor asthma control, poor asthma control could reinforce poor adherence as patients do not have the incentive of having better asthma control to motivate medication-taking\(^ {366}\). Asthma severity may also play a role, with a link between poor adherence and mild severity, as the frequency and severity of symptoms are too low to ‘drive’ adherence behaviour. Bender et al. noted that patients on higher ICS doses, who had previous prescriptions for relievers or had co-morbid conditions, had higher adherence, reflecting symptom- or severity-driven medication adherence\(^ {367}\). Asthma symptoms alone, however, do not seem to be sufficient to cue medication-taking. Mann et al. monitored the use of albuterol (a short-acting reliever) in ten patients with moderate-to-severe asthma over nine weeks and its correlation with asthma symptoms and peak expiratory flow rates\(^ {368}\). Despite asthma exacerbations being present in six of
10 patients, no relationship between asthma symptoms and inhaler use was found, suggesting that use of ICS may not be solely driven by symptoms, though the sample size was too small to draw any conclusions. A recent systematic review examined the relationship between severe asthma exacerbations and adherence, including only studies using objective adherence measures. An association between poor adherence and increased risk of exacerbations was reported, but the direction of effect could not be determined as the studies were observational. Quality of life has also been linked with adherence, though an equal number of studies report no effect. Due to the nature of these condition-related adherence determinants, it is difficult to employ study designs that are not observational in nature, thus preventing firm conclusions from being drawn.

Summary
These findings illustrate the complexity of medication-taking as a behaviour and situational differences in how patients may respond to changes in their condition and symptoms. Difficulties with measuring asthma severity and symptoms, as well as the large variation in populations studied, add to these challenges. These can be minimised in future studies by choosing standardised measures of asthma control to allow comparisons of findings between studies. Prospective studies that use objective measures are needed to elucidate the direction of association between adherence and condition-related factors in asthma.

2.4.2.4 Healthcare team and system factors in asthma
The effect of the healthcare team and health system on adherence in asthma is comparable to that observed in other chronic conditions, and as such, will only be briefly discussed.

Healthcare team
Several studies have shown that the quality of the provider-patient relationship impacts on medication adherence in asthma. Adams et al. conducted a population-based survey of 393 adults with asthma in Australia, and found that those who viewed their relationship with their health provider positively were more satisfied with their treatment and correspondingly more likely to adhere, regardless of asthma severity. This is similar to other reported findings where patients demonstrate higher ICS use with physicians who involve them in the treatment decision-making.

In contrast, Schneider et al. reported a negative relationship between medication adherence and patient preference for involvement in treatment decisions. Those who preferred being involved tended to have lower adherence, as assessed by self-report. This seems to contradict the studies supporting improved adherence with health providers who are more participatory; however, it may be that those patients who wish to be involved are the ones who are more at risk of non-adherence if faced with a provider whose style is non-participatory, but end up being more responsive to
providers who do involve them, leading to better adherence. Indeed, the authors recommended that their findings should be used to encourage health providers to utilise their patient’s participation preference to enhance adherence. Schmier et al. surmised that the provider-patient relationship with adherence may be curvilinear – that adherence is poor when the provider-patient relationship is poor, levels off if the relationship is average, then increases again when there are high levels of rapport between the provider and patient – and that certain patient groups may be influenced more than others by this relationship\textsuperscript{374}. Additional exploration to identify the patient groups who are more likely to be affected by the provider-patient relationship is needed. Evidence shows that patients who are middle aged (between 45 and 64 years), with higher education levels and household incomes, are more likely to rate their health providers as being participatory\textsuperscript{370, 372, 375, 376}, but whether this translates into improved adherence is unknown.

The method of adherence measurement may also explain the variation in findings. Self-reported adherence data can be susceptible to acceptability bias – where the patient is more likely to perceive their medication use positively if they find the treatment acceptable, which may be influenced by the provider-patient relationship – thus leading to overestimations of self-perceived medication-taking\textsuperscript{107}. This phenomenon may have occurred in the Adams et al. study, as the proportion of participants self-reporting regular preventer use (42.5%) was higher than the usual 13% to 37% reported in studies using objective adherence measures\textsuperscript{347, 377-379}. Future studies using objective measures are needed to determine the effect of the provider-patient relationship on adherence.

*Health system*

Studies investigating the role of the health system in adherence to asthma treatment have focused mainly on prescription coverage and effect of co-payments. As with other chronic diseases, financial barriers such as treatment costs and co-payments prevent adherence\textsuperscript{333, 367}. Studies have evaluated whether the type of medication insurance plan (commercial, private, public, uninsured) affects adherence in asthma; one study found that having commercial versus other types of insurance to cover prescription charges was linked with better adherence\textsuperscript{59}, other studies did not find any effect\textsuperscript{13, 380, 381}.

*Summary*

Available evidence seems to support the role of the provider-patient relationship in determining adherence in asthma, though cause and effect cannot be established from observational studies, which form most of the evidence base. As there have been no prospective studies to date, a clear link between a positive provider-patient relationship and improvements in adherence still needs to
be demonstrated. Minimal research on the effect of the health system in asthma exists beyond investigation of financial barriers, and represents an opportunity for further research.

2.4.2.5 Social and economic factors in asthma

The influence of social and economic factors on adherence in asthma follows similar patterns to that reported in other chronic diseases. This is true across almost all sociodemographic factors such as age, gender, ethnicity, income, education and employment status. As with other chronic diseases, a consistent link between any one particular social and economic factor and adherence has not been shown, and results are mixed. As the relationships are comparable to that described in other chronic diseases, discussion will be brief where there are similarities, with a more detailed description given where differences occur.

Sociodemographic variables

As with other chronic diseases, the evidence surrounding sociodemographic variables and adherence is mixed\(^{358}\). Most studies have demonstrated increased adherence with older age, whereas findings relating to gender are inconsistent\(^{358}\). Poorer adherence has generally been demonstrated in patients who are of a minority or non-white ethnicity\(^{13, 28, 59, 365, 382}\), have low income\(^{13, 59, 333, 338}\) or education\(^{13, 59, 381}\) and are unemployed\(^{381}\). These factors all relate to socioeconomic status, and together suggest a possible relationship between poor socioeconomic status and poor adherence, though the presence of negative studies prevent firm conclusions being drawn\(^{358}\). The relationship between socioeconomic status and adherence may also be mediated by other adherence determinants. For example, patient-related factors (e.g. poor asthma knowledge\(^{300}\) or anxiety and depression\(^{383}\)) and health system-related factors (e.g. difficulties with access to treatments\(^{384}\)) can interact with the patient’s social and economic environment (e.g. family dysfunction\(^{300}\) and poor education\(^{13}\)), thus adding to the complexities of the relationship. Studies also differ in methodological quality and the measurement tools used for adherence and outcomes. Given the heterogeneity of these, ongoing research should consider using established study designs and validated measures to reduce variation in the literature.

Social support

Compared to literature available on the role of social support in chronic disease adherence, the evidence in adults with asthma is sparse – most of the available literature relates to children, which will be discussed in Section 2.4.3.5. In adults, only three studies have investigated social support, all of which have found no relationship with adherence\(^{59, 109, 385}\). The methods of measurement of social support have however been inconsistent – for example, Bosley et al. used only a single item to measure support\(^{109}\) whereas Apter et al. used a validated social support survey that yielded a numerical measure of support\(^{59}\). These differences in methodological quality as well as the low
number of studies make it difficult for valid conclusions to be drawn. Although none of the studies found a relationship between adherence and social support, Bolman et al. noted a relationship with social norms, which form part of the social influence construct and are closely related to social support\textsuperscript{385}. Social norms describe the opinions of people who are in the social environment that the patient is exposed to. The study found that the presence of a supportive norm was positively associated with adherence for patients who had weak habits, but the opposite was true if patients had strong pre-existing habits. The practical implications of these findings remain unknown. There is clearly a role for further studies to be undertaken to investigate the role of social support and how this may interact with adherence through other social factors.

Summary
Despite a large number of studies examining the relationship between various social and economic determinants and adherence, few have been consistently linked with adherence. A trend towards poorer adherence in those who have poorer markers of socioeconomic status has been signalled in several studies, however, studies vary widely in methodological quality, and types of measures used to assess outcomes. It is likely that these inconsistent findings reflect the difficulties in using patient-specific variables to formulate predictions about the risk of non-adherence; as adherence is a behaviour, it is expected that findings will show wide variability. The lack of studies in the area of social support and asthma adherence signals a need for further research, particularly in light of the significance of this variable in other chronic diseases.

2.4.3 Medication adherence in children with asthma
Asthma is one of the most common conditions in children\textsuperscript{9,386}. Beyond primarily being a condition of childhood, there are several other reasons why there should be a focus on adherence determinants in children. The impact of asthma is more widely felt due to the indirect costs resulting from days lost from school, as well as days lost from work by the child’s parent or caregiver\textsuperscript{387}, and school absenteeism can potentially lead to long-term negative effects on the child’s education\textsuperscript{388} and academic performance\textsuperscript{389}. Children with asthma, as well as their caregivers, report poorer health-related quality of life\textsuperscript{390} with higher levels of anxiety and depression than their peers who do not have asthma\textsuperscript{391}. Adherence in this age group also presents unique challenges that need to be addressed separately from general adherence. In particular, the behaviour of children, especially in younger children, is in part governed by their caregivers, which presents an extra variable to consider when determining adherence in children.
Although there are unique barriers in children, there is also significant overlap with the factors discussed in the previous section which relate to asthma in general, regardless of age. Factors where the effects are generally similar across all ages, such as condition-related factors (e.g. asthma severity)\textsuperscript{10} and healthcare team and system factors (e.g. the provider-patient relationship), or where there is no additional literature to suggest a difference in children, will not be discussed again. Note the term “caregiver” will be used in this section to describe the child’s primary carer, and include parents, family, relatives and other adult caregivers.

2.4.3.1 Patient- or caregiver-related factors in children with asthma

Patient-related factors in this age group extend to include factors related to the caregiver. Children often have their medicines managed by their caregiver, and as such, the health beliefs, health literacy, knowledge and mental health of the caregiver need to be accounted for\textsuperscript{321}, as well as how medication management responsibilities are shared between the caregiver and child. The impact of these on the child’s adherence, as well as any differences in how these factors manifest in children, will be discussed below.

Health psychological factors

The medication beliefs of the caregiver can affect their willingness and motivation to administer medication to the child\textsuperscript{321}, which may lead to poor adherence in children. Overall understanding by caregivers of asthma and preventive treatment is poor\textsuperscript{392-395}. Many studies have found that caregivers have negative perceptions about ICS and a fear of adverse effects\textsuperscript{321, 395-399}. Despite education, many prefer their child to be on lower doses of steroids or to stop the preventive medication all together when the child has no symptoms due to these perceptions about the child’s treatment\textsuperscript{171, 179}. A relationship between the beliefs of the caregiver and the child’s medication adherence is supported by several studies which demonstrate poorer adherence in the child if strong parental concerns exist\textsuperscript{180, 321, 396}. Gibson et al. found that adherence is no better when medication is given under supervision, such as by the parent or in day care, than if self-administered\textsuperscript{104}. The authors suggest that this may result from the disconnection between those responsible for medication administration (the caregiver) and the person experiencing the symptoms first-hand (the child), as well as an influence of the caregiver’s beliefs.

As a child gains increasing autonomy over their own medication management, the health beliefs of the child themselves become much more relevant\textsuperscript{400}, and in older children, social pressures begin to play a role in shaping these beliefs\textsuperscript{401}. Rhee described four adherence barriers in adolescents which relate to health beliefs, but also other patient-related, social and economic factors which will be discussed in the relevant sections below\textsuperscript{402}. These barriers included negative perceptions towards the treatment and health providers\textsuperscript{401, 402}, denial of the condition or distrust\textsuperscript{403} as well as difficulties
in following advice due to forgetfulness or cognitive difficulties\textsuperscript{400}. These barriers have a complex interplay with other factors – for example, negative perceptions towards treatment and health providers have been found to be worsened by a lack of social or family support\textsuperscript{402}, and cognitive difficulties may arise from substance use or a mental health condition\textsuperscript{404}. These factors can negatively influence adherence though only two studies have examined adolescent health beliefs and adherence\textsuperscript{403, 405}. No studies exist for younger children. This represents an area needing further research as current literature primarily focuses on the beliefs of the caregiver; additional exploration of how these beliefs differ in children is needed.

\textit{Health literacy}

As in adults with asthma, studies investigating health literacy tend to focus on general literacy. Two studies have examined the role of parental health literacy specifically and found an association between poor health literacy and increased perceived disease burden\textsuperscript{406}, and lower self-efficacy\textsuperscript{407}, but neither noted any effect on medication use\textsuperscript{406, 407}. In contrast, one study which focused on general parental literacy found an association between poor literacy and poor ICS adherence, with more frequent reliever use, poorer asthma knowledge and worse asthma outcomes for the child, including a higher number of days off school\textsuperscript{408}. Given the low number of studies on health literacy and asthma in children, further research to help understand the nature of this relationship in children is needed before conclusions can be drawn.

\textit{Knowledge}

Results relating to the effect of asthma knowledge on adherence in children are conflicting. Studies have generally focused on parental rather than child knowledge, and the measures that have been used to assess knowledge vary between studies, as does the age range, which may explain the heterogeneity of the results. Bender et al. used a 25-item Asthma Knowledge Questionnaire to evaluate parental knowledge of asthma and its management, and found that lower levels of knowledge were correlated with non-adherence\textsuperscript{300}, but another study by the same research group using the same knowledge questionnaire did not confirm this association, finding no relationship with adherence nor outcomes\textsuperscript{193}. The lack of association seen in the latter study could potentially be due to its longer study duration (12 months versus three months) and higher number of participants (155 versus 24 children) – factors which increase the validity of the study results. Similarly, this lack of effect of knowledge on adherence has been supported by other studies\textsuperscript{365, 395}, including one that used electronically measured adherence data\textsuperscript{365}. This study also hypothesised that changes in knowledge with age may affect adherence, yet whilst the study found increased knowledge with increased age, adherence decreased with age – an effect that was not mediated by changes in knowledge\textsuperscript{365}. Other studies have not focused on medication adherence per se but have evaluated adherence as part of asthma self-management behaviour\textsuperscript{409, 410}. These studies report a positive
relationship between asthma knowledge and self-management in children\textsuperscript{409} and adolescents\textsuperscript{410} with asthma. The inconsistency of reported findings, however, prevent definitive conclusions being drawn.

\textit{Responsibility for asthma management}

A unique factor relating to children is the dependency on the caregiver for asthma management, in particular medication management, which changes with increasing age. As children become older, there is a slow shift in management responsibility from the caregiver to the child. This has been investigated as a potential factor affecting medication adherence but findings have not supported this. In a study by McQuaid et al., the effects of asthma responsibility between the child and parent were investigated. No association with adherence was found though the authors noted increasing child responsibility for asthma management with increasing age\textsuperscript{365}. Asthma responsibility in this study assessed general asthma management rather than focusing on medication-taking which may explain the lack of association with adherence. Burgess investigated medication-taking specifically and found a trend towards lower adherence if the child was involved in sharing the responsibility for remembering to take medication (61\% versus 78\% adherence) but this was not significant\textsuperscript{106}. Further research into specific factors relating to the child and caregiver are needed – at present, asthma management responsibility does not appear to be an important mediator of adherence.

\textit{Mental health factors}

Whilst there are minimal studies investigating the influence of depression in children and adherence, there has been research into the effect of maternal depressive symptoms on the child’s adherence. In one study of inner-city children with asthma, mothers with higher levels of depressive symptoms were 30\% more likely to have ED visits for their child’s asthma, after controlling for asthma symptoms and maternal age, than those without\textsuperscript{411}. This may be mediated through increased difficulties with supporting the child’s medication therapy and coping with asthma symptoms. In mothers with depressive symptoms, the odds of having problems with using their child’s inhalers were five times higher, the odds of forgetting doses were 4.2 times higher, and the odds of reporting less understanding about their child’s medication were 7.7 times higher, than in mothers without depressive symptoms\textsuperscript{412}.

Focusing on children specifically, Bender et al. noted similar trends to maternal depression, where children displaying negative affect experienced greater school absences due to asthma, but a relationship between negative affect and adherence was not found\textsuperscript{413}. In another paper, Bender described a triad of unhealthy behaviours that commonly occur during adolescence, including depression, substance abuse, smoking or other risk-taking behaviours, which lead to intentional non-adherence\textsuperscript{404}, though presence of smoking in the family home does not seem to be consistently
associated with non-adherence\textsuperscript{414}. Further studies focusing on the effect of mental health factors in children themselves will help increase our understanding of the interplay with adherence.

\textit{Summary}

Most of the traditional patient-related factors investigated in children are centred on caregiver-related measures. Seldom do studies evaluate the impact of these same factors in children themselves. Although current evidence in caregivers have been helpful in providing insight into how factors relating to the caregiver can influence the child’s behaviour, there is a need for future research to assess the child themselves, as over time, children will ultimately become their own caregiver. Questions relating to how early influences of adherence determinants on the child affect medication-taking in later life are of interest, particularly as the role of health beliefs in adherence increase in prominence, since these psychological factors are likely to be the most impressionable factors during a child’s development.

\textit{2.4.3.2 Therapy-related factors in children with asthma}

Similar to the relationship seen in adults, adherence in children is affected by therapy-related factors such as dosing frequency, medication burden and therapy effects. For example, children report lower adherence if the medication regimen is too complex, such as with increased dose frequency, with one study showing a 50% reduction in adherence when the dosing frequency was doubled\textsuperscript{103}. These therapy-related factors do not differ significantly in children, and as such, will not be further addressed. In contrast, medication formulation and administration considerations are of particular importance in children, and will be discussed in detail below.

\textit{Formulation and administration}

As would be expected from a paediatric population, formulation and route of administration play a significant role in adherence\textsuperscript{54, 55}, as do palatability, texture, colour and smell\textsuperscript{54, 415}. Medicines that are not acceptable to children can lead to non-adherence, and the success of the treatment also relies on correct medication delivery. Caregivers or children may however fail to use the medication correctly\textsuperscript{416}, due to practical difficulties with the medication delivery device\textsuperscript{417} or face mask\textsuperscript{418}. Amirav et al. reported that up to 50% of young children cry when face masks are used, indicating fear and distress from the mask, which could potentially also affect medication delivery to the lungs due to the negative effects of crying on breathing patterns\textsuperscript{416}. Young children may have difficulty coordinating the actuation and inhalation from a pressurised metered dose inhaler (pMDI), and where supportive devices such as spacers and masks are used, these may not be fitted correctly thus affecting medication delivery\textsuperscript{416, 419}. In a study of 256 children with asthma, only 46% demonstrated efficient inhalation technique\textsuperscript{420}. Dry powder inhalers may not be a feasible alternative as
physiologically, children below six years of age may not generate sufficient inspiratory flow rates to effectively use dry powder inhalers\textsuperscript{421}.

There have been several studies that have found a relationship between adherence in children and medicine formulation\textsuperscript{54, 415, 422}. One study compared adherence with oral theophylline versus ICS or cromolyn in two age groups: 12–17 years, and 18–65 years, and found that adherence was significantly better with oral rather than inhaled therapy in both groups\textsuperscript{179}. The difference in adherence between the two formulations was larger in the 12–17 year old group (difference of 43%) than in the 18–65 year old group (difference of 23%), suggesting that preference for oral therapy may be more pronounced in younger patients. This could be related to the ease of administration and portability of oral medication at school compared with inhalers. However, as with other studies comparing different medication, this study was complicated by differences in the relative onset of medication effect – patients taking theophylline can experience symptom relief relatively quickly, however such relief does not occur with ICS\textsuperscript{179}. Another study in 132 adolescents aged 12 to 17 years compared zafirlukast tablets with inhaled beclomethasone and found that the majority preferred the oral tablets by a ratio of 2.6:1 over the inhaler, rating the tablet ‘very easy’ to take\textsuperscript{364}. The study also noted that many adolescents (71%) had poor inhaler technique, further strengthening the support for oral therapies in older children. A later systematic review by Cohn supported these findings, concluding that there is a preference for oral over inhaled therapies not only in children and adolescents, but also in caregivers of children with asthma\textsuperscript{422}.

\textit{Summary}

The literature identifies unique factors in children that relate to medication formulation and administration. This knowledge has important implications when considering design of medicines and drug delivery in children and the impact on adherence.

\textbf{2.4.3.3 Condition-related factors in children with asthma}

Similar to adults with asthma, evidence on condition-related factors and adherence is mixed\textsuperscript{10, 365, 414}. There is some indication that children who are more adherent have a 21 to 68% lower risk of exacerbation, an association identical to that reported in adults, but whether asthma exacerbations leads to poorer adherence, or vice versa, is unknown as the studies are observational in nature\textsuperscript{369}. Likewise, adherence is related to asthma control and quality of life, but the direction of effect is not consistent across studies\textsuperscript{414}. As there are no special considerations in children, as opposed to adults, with asthma, the evidence will not be further elaborated on.

\textbf{2.4.3.4 Healthcare team and system factors in children with asthma}

The effects of healthcare team and system factors are similar to those observed in adults, with some studies demonstrating an association between a positive provider-patient relationship and improved
adherence, whilst other studies report no effect\textsuperscript{414}. The primary point of difference lies in the way the health provider interacts with the child \textit{and} the caregiver, which presents unique challenges as the caregiver’s needs have to be considered\textsuperscript{423}. For example, Clark et al. found that the way parents perceived their child’s physician affected healthcare utilisation and that these perceptions were mediated through communication; those whose physicians communicated effectively with the caregiver had reduced healthcare use and more positive perceptions of their physician\textsuperscript{424}. Communication is therefore particularly important in children due to the complexities of family dynamics and the need to communicate with both the child and caregiver\textsuperscript{61}. Information may need to be adapted for the child to encourage adherence and understanding of therapy\textsuperscript{423}. In adolescents, the role of the physician can greatly influence adherence with one study reporting increased adherence among those who perceived support from their physicians, including “showing an interest” in the adolescent and “not ordering” how they should act\textsuperscript{42}. Despite the significance of these factors in children, minimal research attention has been paid to the effect on adherence of the health provider-child relationship\textsuperscript{423}. Further exploration is needed.

2.4.3.5 \textit{Social and economic factors in children with asthma}

Social and economic factors are relatively well-studied in children with asthma, particularly when considering the influences of the social environment on the child’s adherence behaviour. There are unique factors to consider in this section that pertain only to children. These include the role of the family, including family support, conflict and dysfunction, and the vulnerability of the older child to social stresses around medication-taking and acceptance or denial of disease. The adolescent period is commonly connected with behaviour change and associated decreases in adherence\textsuperscript{55, 425, 426}. Sociodemographic factors, on the other hand, do not exhibit significant differences in children, beyond the fact that these factors generally relate to the caregiver or family rather than the child themselves, such as with income. The associations seen with these sociodemographic variables and adherence reflect the trends seen across all ages. For example, age has been associated with adherence, with many studies reporting better adherence with younger age of the child\textsuperscript{48, 107, 365}, though reports of no effect also exist\textsuperscript{414}, as they do for asthma in general\textsuperscript{47, 106}. Mediators of socioeconomic status have similarly mixed effects, with parental income associated with adherence in one study\textsuperscript{395} and not others\textsuperscript{414}. As the findings have significant overlap with those discussed previously, these sociodemographic factors will not be discussed below.

\textit{Social support}

Family influences such as family functioning\textsuperscript{427, 428} and structure\textsuperscript{414} can affect adherence and outcomes. Children in families with high levels of distress, such as from conflict and aggression, experience greater asthma morbidity\textsuperscript{427}, and single-parent families appear to be at higher risk of non-adherence\textsuperscript{414}. In contrast, cohesive family environments tend to foster better adherence\textsuperscript{429}, as
do family routines for medication-taking\textsuperscript{430}. Routines may be particularly important as the primary reason often cited for non-adherence in this children is forgetfulness\textsuperscript{400, 431, 432}.Sibling relationships also play a role in supporting or impeding adherence\textsuperscript{423}. Family support in adolescents continues to be a positive mediator of asthma outcomes, as it can help ameliorate some adherence barriers in adolescents\textsuperscript{402}, for example by reducing fears about treatment\textsuperscript{433}. One study found that higher social support facilitates better self-management behaviours, including medication-taking, in adolescents\textsuperscript{410}. A possible mechanism is that social support may provide a system that promotes maturity in adolescents and encourages responsibility for effective management of their own asthma\textsuperscript{410}.

As described in Section 2.4.3.1, social barriers resulting from relationships with their peers are a significant factor influencing adherence in adolescents\textsuperscript{400-402}, which may take the form of either supportive or discouraging behaviour. Perhaps counterintuitively, supportive opinions may not lead to improved adherence. Van Es et al. found that adolescents were less adherent if they perceived from their general practitioner that the norm was adherence\textsuperscript{405}, though a supportive physician can benefit adherence\textsuperscript{42}. Indeed, the way in which the effect of social support on adherence manifests in children deserves further research attention, as preliminary studies suggest possible nuances in the relationship that are unique to children.

**Summary**

Although the bulk of the social and economic factors relate to adherence in children in a similar manner to other age groups, early evidence suggests the influence of social support may be different. The part that family and peers play in shaping adherence cannot be underestimated. Available literature signals an effect of age on the way social support influences adherence. Indeed, adolescents present a unique group for further research as adherence determinants may behave differently in this group compared to children and adults.

### 2.5 Strategies to improve adherence

As the range of medicines increases, there is an increasing need to improve adherence, in order to fully realise the potential of these medical advances\textsuperscript{40}. The benefits derived from improving adherence might have a far greater impact on the health status of the population than any advances in treatment\textsuperscript{434}. Although the problem is well-recognised globally, there continues to be no solution\textsuperscript{30-32}. The change in adherence taxonomy over time is important to consider when developing strategies to improve adherence and when contemplating why previous strategies have failed. Current strategies need to build on the concepts of autonomy and self-determination as patients become more involved in their own healthcare. Correspondingly, a change in the type of adherence interventions studied has been observed over the last two decades. What has emerged
is a shift in discourse from being treatment- and condition-focused to being patient-focused, and a recognition that intentional non-adherence form a significant part of medication non-adherence. There has been a greater emphasis on factors affecting patients’ perceptions of treatment such as the quality of the provider-patient relationship, and identifying patient-perceived barriers to adherence, to allow personalised interventions to be targeted at these barriers.

There are many studies investigating strategies to improve adherence, which reflects the chronicity and ongoing nature of the problem. This section will describe the strategies that have been used to promote adherence in chronic disease, asthma, and in children with asthma specifically. These interventions can be categorised by each of the five WHO dimensions, as presented in the previous section. However, most adherence interventions target aspects that relate across several dimensions. For example, patient education delivered by health providers targets a patient-related factor as it can improve the patient’s knowledge; a therapy-related factor as the education can help the patient understand the treatment effects; a condition-related factor as education can improve understanding of the disease and how it relates to treatment; a healthcare team-related factor as the education is delivered by the team and indirectly optimises the provider-patient interaction; and social and economic factors as the education could be tailored to the patient’s age and educational level. Therefore, these interventions will be grouped instead into the following categories: simplification of therapy; patient education including strategies that increase patient participation; and reminder systems.

2.5.1 Adherence interventions in chronic disease

2.5.1.1 Simplification of therapy

Simplification of regimens, by reducing the number of medicines the patient needs to take and reducing dosing frequency, has been associated with improved adherence.\textsuperscript{31, 435} Fixed-dose combinations were introduced as a solution to poor adherence arising from difficulties with managing a large medication load. This was shown to improve medication adherence in many chronic diseases. A meta-analysis in 2007 pooled results from studies in hypertension, HIV and diabetes that compared the effectiveness of fixed-dose combinations versus single component preparations.\textsuperscript{158} Use of fixed-dose combinations reduced the risk of non-adherence by 24% to 26% compared to single component regimes, with reduced prescription costs and medication burden.\textsuperscript{158} Existing studies however vary in the way adherence is defined and measured; future studies would benefit from using a standardised approach to adherence and its measurement to corroborate these findings.

Other studies have investigated reducing dosing frequency as an alternative method of regimen simplification, which can be achieved using extended-release formulations or medicines which allow
once- or twice-daily dosing. Richter and colleagues described drug, disease state and patient characteristics to consider which would enable reduced dosing frequency\textsuperscript{220}. Medicines with a long duration of action, but a low risk of adverse effects resulting from an extended dosing interval, may be good candidates for reduced dosing frequency. Reduced dosing frequency may also be warranted in conditions where symptom control is the primary outcome and medicines are the mainstay of symptom control; or non-adherence may lead to disease progression or treatment resistance; or multiple tablets are needed for each dose or multiple doses required each day. Similarly, once-daily dosing may benefit patients who have multiple conditions requiring treatment, or have diminished mental or physical capacity.

Most studies have demonstrated improvements in adherence by reducing dosing frequency from twice- to once-daily\textsuperscript{253, 436-438}. A meta-analysis by Srivastava et al. reviewed 13 studies that reported on the impact of reducing dosing frequency of oral therapies on adherence and found that once-daily dosing was associated with a three times higher odds of adhering than with multiple-dosing, and lower cost of healthcare resources utilisation\textsuperscript{438}. The results of this are in line with previous literature reviews\textsuperscript{219, 222, 439}, including one that only included studies using electronically monitored adherence data\textsuperscript{189}. A recent review of reviews concluded that simplifying dose regimens by reducing dosing frequency appears to consistently improve adherence\textsuperscript{435}. Whilst the evidence supporting reducing dosing frequency as an adherence intervention seems relatively robust, the majority of studies have focused on diabetes, HIV, cardiovascular and respiratory disease. Whether these findings are applicable in other chronic diseases requires further investigation.

2.5.1.2 Patient education

Increasing patient autonomy and participation in their own health management have increasingly been recognised as an essential part of modern day health management. Indeed, many recent adherence interventions have focused not only on increasing patient knowledge through education, but also on improving concordance by targeting health beliefs and the provider-patient relationship. Peterson et al. conducted a meta-analysis of interventions to improve adherence and reported on educational and behavioural interventions, where behavioural interventions described the use of a tool or action to change a patient’s medication-taking behaviour\textsuperscript{205}. Reported effect sizes were small, with overall effect sizes of 0.11 and 0.07 for educational and behavioural interventions respectively, though the authors acknowledge the non-homogeneous nature of the educational interventions made comparisons difficult. Many education methods exist, such as verbal versus written education, but few studies have compared the effectiveness of different education methods on adherence. Katz et al. reviewed the use of pictorial aids and reported an increase in adherence, patient understanding of medication and satisfaction; however, not all picture-based interventions were successful as some icons were too complex to understand\textsuperscript{440}. Pictorial-based interventions
may be best delivered with verbal explanations or complementary text to ensure clarity of information. Further research into the effect of different types of education on adherence is needed.

Whilst there may be a role for educational interventions involving information provision, this intervention type is likely limited to improving unintentional non-adherence. In cases where non-adherence is intentional, education that addresses patient health beliefs may be more effective; however, interventions targeted at changing health beliefs remain sparse as this is an emerging area of adherence intervention. Existing studies that report on psychological-based education interventions have demonstrated positive results, highlighting this as an area warranting further investigation.

Successful education involves effective provider-patient communication, and several studies have reported on the effectiveness of interventions that target this communication specifically. The positive effects of training health providers in communication skills were highlighted in a meta-analysis, where patients had 1.62 times higher odds of adherence when receiving care from a provider who had been trained compared to one who had not. The effect of training was greater if the health provider was a paediatrician; and less if the patient’s condition was serious. In contrast, a recent systematic review of interventions that promote patient-centred care, including interventions that improve communication, found that although the interventions have positive effects on the overall consultation process, the effect on outcomes including adherence was limited and mixed. The studies also tended to target primary care physicians and nurses, with few studies on other health providers.

Given these mixed results, more effective solutions beyond traditional education are needed to improve adherence. Furthermore, the interventions described in the literature often involve many hours of professional time and are not practical to apply in day-to-day practice as the costs exceed any benefits gained. There is a signal that education that targets health beliefs may be effective, but further research is needed.

2.5.1.3 Reminder systems

Patient reminder systems have been shown to be effective for improving adherence, with one review reporting an overall higher adherence of 67% in the reminder group compared to 55% in the non-reminder group. These reminder systems include short message service (SMS), pager and telephone reminders, and on-board reminders on EMDs. These have the advantage of being easily delivered and less labour-intensive to implement compared to educational interventions. Whilst results have been generally positive, a number of studies have reported no effect. This may be due to the variability in adherence measurement methods, method of reminding and study...
duration, with longer studies generally reporting less improvements in adherence\textsuperscript{443-445}. There is some suggestion that SMS or telephone reminders may be more effective due to the ability to tailor the reminder to the patient\textsuperscript{444, 445}, however, there have been no studies comparing different types or components of reminder systems to allow identification of the aspects of the reminder intervention which are most effective. It is also not known whether reminders are effective for all age groups, and whether regular versus intermittent reminders are more effective, though one review did not find any difference in intervention effectiveness by age or reminder frequency\textsuperscript{443}. The number of included studies was however small. Reminders may be more effective in certain conditions, with larger effect sizes for asthma compared to diabetes, and smaller effect sizes for cardiovascular diseases and HIV\textsuperscript{443}. Some studies include an educational component in the reminder intervention, which have demonstrated significant improvements in adherence\textsuperscript{449}. This highlights a potential role for future reminder systems to incorporate other intervention types. Further research is needed to understand which components of a reminder intervention are most important for maximising adherence, and whether these effects are sustainable in the longer term and in different patient groups.

\textbf{2.5.1.4 Conclusions}

There are numerous studies that have investigated strategies to promote adherence in chronic disease. There appears to be robust evidence supporting the effectiveness of simplification of therapy as a strategy to improve adherence. Educational interventions alone seem to have limited benefit on adherence, though further research comparing the effectiveness of different types of education and the use of education in combination with other intervention types is needed before firm conclusions can be drawn. Reminder systems appear effective for short-term intervention; questions remain regarding the long-term effectiveness of reminders and what reminder characteristics are most effective for maximising adherence.

\textbf{2.5.2 Adherence interventions in asthma}

A summary of the strategies to improve adherence in asthma was published as a paper in the \textit{International Journal of Respiratory Care}. An edited version of this paper is included below, not as a publication that forms the thesis with publications, but as an associated work.

\textbf{Title:}

Promoting adherence to asthma medicines

\textbf{Journal:}

Authors:

Peter Nigel BLACK, Amy Hai Yan CHAN

Contributions:

Peter BLACK was involved in paper conception, literature review, manuscript write-up and review for submission for publication.

Amy CHAN conducted the literature review, manuscript write-up and review for submission for publication.

2.5.2.1 Simplification of therapy

A systematic review of interventions to enhance medication adherence in chronic disease found that one of the most effective interventions was reducing dosing frequency. These studies involved treatment of hypertension or hypercholesterolemia but there is evidence that this is also relevant to asthma. Coutts et al. used EAM and found that the days on which all the doses of ICS were taken with two, three and four times daily dosing were 71%, 34% and 18% respectively. Although ICS are usually prescribed twice daily, there are studies demonstrating that mild to moderate asthma can be treated with once daily ICS. The best evidence comes from studies with inhaled budesonide, which suggest that for mild to moderate asthma, the same total dose is as effective when given once a day (or is at worst only slightly less effective) as it does when given as two divided doses. Chisholm et al. found that in mild asthma 200 micrograms once daily had a similar effect (increase in morning peak expiratory flow (PEF) of 1.7 L/min) compared with 100 micrograms twice daily (increase in morning PEF of 4.3 L/min). Once daily ICS may also be associated with improved adherence, but this has not been formally studied using objective measures of adherence such as EAM.

Increasing patients with asthma are being treated with the combination of ICS and LABAs. This has led to the development of combination therapy where the two medicines are provided in a single inhaler. This is more convenient because the patient only has to use one inhaler as opposed to two. It has been suggested that this may also improve adherence because the patient gets symptomatic benefit from the LABA, thus increasing the chances of receiving the ICS which may otherwise not have been used because of the lack of immediate symptomatic relief. There is evidence from studies in other diseases, such as hypertension, tuberculosis and HIV infection, that fixed dose combination therapy increases adherence. This is less well studied with combination therapy in asthma. Most studies have compared ICS and LABAs delivered from a single inhaler as opposed to the same medicines in two separate inhalers; these studies have employed a double dummy design where all participants have to use two inhalers (even if one is a placebo inhaler). As such, these studies cannot confirm whether the use of a single inhaler improves adherence. There are no
studies that have used EAM to assess adherence with a combination inhaler containing an ICS and a LABA as opposed to two separate inhalers. This represents a research gap needing further study. Indirect evidence that the use of combination therapy may improve adherence comes from studies examining prescription refill data. Marceau et al. used a medical insurance database from Quebec to compare refill rates for combination therapy compared with the patients prescribed an ICS and LABA in two separate inhalers. The study found that those prescribed combination therapy were 17% less likely to stop therapy and filled on average 3.5 prescriptions in the following year compared with 2.7 prescriptions in the group treated concurrently with two inhalers. Combination therapy was also associated with a lower likelihood of a moderate or severe exacerbation. Other studies have reported similar findings.

A recent study enrolled patients who were well controlled on fluticasone 100 micrograms twice daily and continued them on this therapy or switched them to a once daily combination of fluticasone 100 micrograms and salmeterol 50 micrograms. There were no differences in asthma control between the two groups, however, using once daily therapy with a combination inhaler provides the opportunity to combine two strategies with the potential to improve adherence.

Formoterol is a LABA with a quick onset of action, allowing it to be used as a reliever as well as a twice daily preventer. This has led to the use of Symbicort™, which is the combination of budesonide and formoterol in a single inhaler, as both a twice daily maintenance therapy and as a reliever for symptoms that occur at other times during the day. This means that the budesonide / formoterol combination is the only inhaler that the patient needs to use. This approach has been named Symbicort Maintenance and Reliever Therapy or SMART. A series of clinical trials has shown a consistent reduction in severe exacerbations (those requiring oral steroids and/or admission to hospital) with SMART along with less consistent improvements in symptoms and lung function. It less clear what the reason is for the benefit seen with SMART. It has been suggested that increased use of the budesonide / formoterol combination at the beginning of an exacerbation may reduce the severity of the exacerbation. However, this idea runs contrary to studies that show no benefit from doubling the dose of ICS during exacerbations. The alternative explanation is that SMART improves adherence. If a patient forgets to take one of their regular doses of budesonide / formoterol they may compensate for this when they use the combination medicine as a reliever and as a result receive the extra dose of ICS that they might otherwise have missed. In the studies of SMART, adherence (as recorded on the diary cards) was reported as 90% or more. This should not be taken as evidence that SMART does not work by improving adherence; self-report is unreliable and patients consistently overstate their adherence. The benefit seen with SMART may well be due to an increase in adherence. There is a need for a study comparing standard therapy with SMART that uses EAM to determine the effect of SMART on adherence.
2.5.2.2 Patient education

Patient education appears to be important in promoting adherence; patients will be more likely to use a medicine as prescribed if they understand how it works and the rationale for using it. Many patients also have concerns about medication safety that need to be addressed. Many studies have investigated the effects of education in patients with asthma; those that have evaluated effects on adherence have generally used patient self-report which is unreliable. Nonetheless the effects of education are likely mediated in a large part through effects on adherence, so these studies are informative even if they do not use any objective measure of adherence. Gibson and colleagues conducted a systematic review of educational interventions that provided information about asthma but did not incorporate regular review, self-management or other approaches that might promote behaviour change. Twelve studies were included. There was no significant effect on doctor visits, lung function or medication use. Two studies did, however, report that perceived symptoms improved. The same authors then conducted a systematic review of education coupled with self-management and regular medical review. All of the studies involved education about self-management and most incorporated self-monitoring of PEF and/or symptoms along with regular medical review. Many also provided written action plans for the intervention group. The review reported a reduction in hospitalisations, ED visits, unscheduled doctor visits and days off work or school, however, the role of adherence was not assessed. It is not entirely clear which components of these interventions are important and whether these effects are mediated through adherence. For example, encouraging patients to monitor their peak flow may promote adherence by giving them a sense of control and by reminding them to take their medicine. Regular medical review may provide the opportunity to reinforce medication-taking and allow medication to be modified as appropriate.

2.5.2.3 Reminder systems

Another strategy to promote adherence is to provide reminders to take the medication. This is most likely to be helpful where there is unintentional forgetting. An interesting new development is the incorporation of an electronic reminder alarm in the inhaler. This can be set to sound twice a day when the patient is due to take their ICS or combination therapy. This approach was studied by Charles et al. in a RCT of 110 adults. Electronically monitored ICS adherence improved from 74% to 93%. This did not translate into an improvement in asthma control, probably because this was an unrepresentative population with relatively mild asthma and high baseline levels of adherence. A smaller study in children also demonstrated an improvement in adherence. In the last two weeks of this study the median adherence with ICS was 85% with the reminder compared with 51.5% in controls (p<0.001) but the study was not adequately powered to demonstrate an improvement in
asthma control, although there was a trend in this direction. There is a need for larger studies in appropriate populations to see if this approach does improve both adherence and asthma control.

2.5.2.4 Conclusions

Poor adherence to prescribed medication is common in asthma and is an important contributor to poor asthma control. Simplifying treatment using less complicated dosing regimens and combination therapy is likely to be helpful. Education alone appears to be of limited benefit and should be coupled to other approaches including regular review. Reminders may be helpful but there is a need for more studies of electronic reminders incorporated into inhalers. With other conditions there is evidence that approaches that incorporate a number of different interventions are more likely to be successful\(^{31}\) and this is also likely true with asthma.

2.5.2.5 Addendum

Since this review was published in 2009, there has been additional research on adherence interventions in asthma, particularly around strategies that involve increasing patient participation in their own treatment and the use of electronic adherence technologies to support this. These studies have shown that monitoring and providing feedback to patients with asthma can reinforce their medication adherence\(^{31}\) as does increasing patient participation in their own asthma management\(^{370}\). Indeed, use of interactive asthma telemonitoring systems, where patients are provided with continuous daily feedback on their asthma management, has been reported to be associated with higher adherence with asthma management\(^{454, 455}\). Several trials have demonstrated that providing feedback of a patient’s medication usage, either through adherence reports or visual displays on an EMD, improves ICS adherence\(^{36, 37, 299, 456-458}\). Other recent studies have incorporated reminders and technology into interventions targeted at other adherence determinants, such as health beliefs\(^{449}\), or to deliver education\(^{459}\). Petrie et al. investigated the effect of a text message programme that targeted illness and medication beliefs on adherence, and found improved self-reported adherence by 10% in the text message group over nine months\(^{449}\). Participants also reported increased perceived treatment necessity treatment and perceived control over their asthma, compared to the control group. No outcomes were assessed. Electronic reminders have also been increasingly used to encourage patient interactions with treatment. Tran et al. published a review in 2014 on patient reminder systems, including mobile phone and EMD reminders, and adherence in asthma and reported on six RCTs. Higher medication adherence was found across all six studies; however, none demonstrated any changes in asthma-related quality of life or clinical outcomes\(^{466}\). Trials with a longer intervention time beyond the reported median of 16 weeks may be needed before effects can be shown, and other factors affecting clinical outcome, beyond adherence, may need to be considered.
Written asthma action plans were briefly mentioned in the original paper as part of patient education, but not further discussed in terms of their effectiveness. The evidence for action plans as an effective intervention alone is dubious, with an increasing number of studies showing no association with preventer use when action plans are used alone as an adherence intervention\textsuperscript{370, 460, 461}. The individualised asthma action plan may have a place as an adherence intervention when used with other components, such as education\textsuperscript{453, 462}. The effectiveness of action plans when combined with other measures echoes the recommendations from the Cochrane Airways group, which recently withdrew the 2011 Cochrane review of the use of asthma management plans in children and adults\textsuperscript{463}. Besides being out-of-date, the Cochrane group cited other reasons for withdrawal that referred to the action plans as a recognised component of asthma self-management but not a standalone intervention. It acknowledged that asthma guidelines now recommend written action plans as part of a self-management approach in asthma, but should include other components such as education, monitoring and regular practitioner review\textsuperscript{464}.

There is now a body of evidence supporting use of combination ICS and short-acting reliever medication in a single inhaler, not only as regular therapy but on an as-required, symptom-driven basis\textsuperscript{465}. Papi et al. conducted a six-month, double-blind, double-dummy, randomised parallel-group trial where four regimens were compared: 250 micrograms beclomethasone with 100 micrograms albuterol as needed (as needed combination therapy); 100 micrograms albuterol as needed (as needed short-acting therapy); 250 micrograms beclomethasone twice daily and 100 micrograms albuterol as needed (regular steroid therapy); or 250 micrograms beclomethasone and 100 micrograms albuterol in a single inhaler twice daily plus 100 micrograms albuterol as needed (regular combination therapy). The authors concluded that in patients with mild asthma, symptom-driven use of a combined ICS with a short-acting reliever, delivered in a single inhaler, is as effective as regular ICS use (either alone or as combination therapy) but with a lower cumulative dose of ICS over the six months\textsuperscript{466}. Using an as-required regimen holds promise for overcoming some of the adherence issues in asthma, particularly in those with milder asthma and infrequent symptoms where regular medication-taking can be burdensome. Use of a single inhaler also reduces treatment burden on the patient\textsuperscript{360}. Two RCTs published in 2013 also found that a combination ICS, plus a rapid-onset LABA used as maintenance and reliever treatment, significantly reduced asthma exacerbations, potentially due to increased exposure to inhaled, but not overall, corticosteroids\textsuperscript{465, 467}. With adherence to regular asthma therapies an ongoing issue, there may be a particular place in therapy for symptom-driven medication regimens in the future.
2.5.3 Adherence interventions in children with asthma

As discussed in section 2.4.3, the factors influencing adherence in children differ from adults. There is a need to develop adherence interventions for children specifically rather than translating results from adult studies to children\(^\text{468}\). The majority of adherence interventions for asthma in children are educational, with or without an accompanying behavioural or psychological intervention component, rather than being related to simplification of therapy, which have primarily been conducted in adults\(^{158, 219, 435, 469}\), or reminders\(^{446}\). Studies that have involved reminder systems in children only included older children (12–18 years) as part of a larger cohort of adults, rather than focusing on children specifically\(^{16, 449, 470}\), there are no reminder intervention studies solely in children with asthma. As such, this section will discuss only educational interventions.

2.5.3.1 Patient education

The majority of studies that have used patient education as an adherence intervention have focused on knowledge-based interventions\(^{468}\), primarily focusing on information provision through home visits, videos, books and other written information\(^{471-474}\). These have generally shown limited effectiveness on adherence\(^{468}\). Studies that include additional components beyond simple information provision, such as behavioural strategies including coaching and adherence monitoring\(^{475, 476}\), or psychological components, where attitudes and health beliefs are explored\(^{477}\), appear to have better success in adherence promotion, potentially as the underlying behaviour is targeted. Adherence interventions may be more effective when both the caregiver and child are involved, as adherence in the child is likely influenced by the caregiver and the caregiver-child relationship. Duncan et al. compared adherence between three groups aged 9–15 years: those receiving a parent-youth teamwork intervention versus asthma education versus standard care\(^{456}\). The teamwork intervention focused on sharing responsibility for asthma management between the parent and youth and taught problem-solving techniques around conflict to allow consistent parental involvement in a supportive manner. This teamwork intervention group had significantly higher adherence than the other groups, which likely resulted from the lower parent-reported conflict. This suggests that adherence in the child improved primarily due to changes in the caregiver-child relationship, and highlights the benefit of targeting both the caregiver and child when delivering adherence interventions.

Other interventions focusing on the caregiver-child relationship have involved tailoring adherence management plans to both the caregiver and child, thus influencing the behaviour of both. Burgess et al. conducted a RCT in 26 children, aged between six and 14 years, where the intervention group received feedback on their adherence and a tailored adherence management plan based on the adherence data, whilst the control group received no such feedback or management plan\(^{299}\). The intervention group had higher adherence (79% versus 58%) and greater improvements in their
forced expiratory volume in one second (FEV₁) (13.8% versus 9.8%). The increased adherence was likely a result of both adherence feedback, which was given to both the parent and child, and the physician’s tailored response to the adherence data. Together these studies suggest that multi-component interventions involving both education and another intervention type may be most effective, particularly when delivered to both the caregiver and child. The sustainability of these interventions remains unknown, though some evidence suggests that adherence gains are highest immediately post-intervention⁴⁷⁸. Further exploration into the long-term effects of these interventions is needed.

Beyond education of the patient, interventions which educate physicians with the aim of improving the provider-patient relationship and communication have also been studied. Lewis et al. found that when physicians, as well as parents and children, were educated, the physician was better able to interact with children when discussing treatments and children were able to recall more about their medication⁴⁷⁹. Other studies have shown a similar effect with lower healthcare utilisation in children whose physicians received the educational intervention⁴⁸⁰-⁴⁸². None of these studies measured adherence. Further investigation into the potential role of physician education in improving adherence is needed to understand whether adherence mediates the improvements in outcomes seen.

2.5.3.2 Conclusions

Educational interventions form the bulk of the literature relating to adherence interventions in children with asthma. Interventions which include other intervention components, such as behavioural or psychological components, and involve the healthcare team, caregiver and child, appear to be the most effective. Additional exploration into the long-term effectiveness of these interventions is needed.

2.6 Gaps in knowledge in adherence

This chapter has presented a large number of studies on adherence determinants and interventions⁴⁸³-⁴⁸⁵. Although vast literature exists, the strength of the evidence varies widely between different adherence determinants, primarily due to methodological heterogeneity. Despite the availability of EAM, many studies continue to use self-report for adherence measurement. There is a need for future studies to use objective adherence measures, preferably EAM as the ‘gold standard’ of adherence measurement. Standardisation of data collection methods will allow data to be compared across studies.

Strategies to improve adherence have also been inconsistent in their effects on adherence, and questions remain around their long term effectiveness. The sustainability of interventions needs to
be considered, as many of the most effective reported interventions are complex and labour-intensive\(^{30, 32, 486}\), thus minimising long-term feasibility. In a limited resource setting, adherence interventions need to be sustainable and practical to implement\(^{40}\). Few studies have examined the patient acceptability of adherence interventions. This is an important factor that future studies should consider as the success of an intervention long-term will be dependent on patient uptake. Certain conditions and age groups continue to be under-represented in adherence literature, such as mental health conditions and chronic pain, and children, and represent an area requiring further research attention.

Most importantly, the question remains whether improved adherence translates to improved health outcomes. Whilst there is evidence that poor adherence leads to poorer outcomes\(^{151, 487}\), many adherence interventions have failed to show benefits in outcomes despite improved adherence, or outcomes have not been measured\(^{30, 32, 445, 446, 486}\). This is a significant research gap that needs to be addressed.

There is emerging evidence that adherence support technologies, such as EMDs, provide a new and effective intervention strategy to promote adherence. The following chapters will examine the use of EMDs as an adherence intervention and consider its effect on both adherence and clinical outcomes. Asthma will be the condition of focus, though the findings may be applicable to other chronic diseases. The patient acceptability of the intervention will be addressed and questions around the practical implementation of these interventions in everyday practice will be discussed.
Chapter 3: Literature review: use of electronic adherence monitoring devices in chronic disease

EMDs have increasingly been used as part of adherence interventions, either as part of an adherence feedback intervention to the patient, or as a stand-alone intervention using a real-time reminder functionality, or both. Whilst there has been an increase in the number of studies on electronic monitoring and adherence, the results relating to their impact on clinical outcomes have not been consistent. This chapter reviews adherence intervention studies which have used EMDs in the management of chronic disease as part of an initiative to improve adherence.

3.1 The role of electronic adherence monitoring in medication adherence

Medication adherence describes the extent to which a person’s medication-taking behaviour corresponds with the treatment plan agreed with their healthcare provider\(^1\). Adherence is one of the key components bridging the gap between an efficacious clinical intervention and patient outcomes, without which outcomes show increased morbidity, mortality and overall healthcare cost\(^168,487\). Nevertheless, despite the large number of studies describing the importance of adherence particularly in chronic disease, medication adherence remains suboptimal in many chronic conditions\(^148\). Interventions that have been used to improve adherence have demonstrated only modest improvements in adherence and have been hampered by uncertain sustainability of the intervention due to the short duration of most studies, and inconsistent correlations with improved clinical outcomes\(^30,31\). With the advent of e-health and new technology solutions for other healthcare problems\(^445,488-492\), there is an increasing interest in electronic solutions for non-adherence. Such solutions have the benefit of allowing a certain amount of automation which increases the chances of sustainability of the intervention, and a potential reduction in resources needed to implement the intervention by allowing increased patient self-management\(^33,493\). There is enormous potential in this growing area, and EMDs form the leading edge of this research.

EMDs are seen as the gold standard of adherence measurement based on their objectivity and accuracy in collecting adherence data\(^493\). EMDs are increasingly being used in an extended role as adherence interventions in themselves. This approach acts in one of two ways – through acting either as a direct reminder, or by facilitating adherence feedback to the patient. There are several reviews that have examined the effectiveness of reminder functions and adherence monitoring in improving adherence\(^445,446,494\). Vervloet et al. conducted a systematic review on the effectiveness of electronic reminders on adherence\(^445\). This review evaluated a variety of electronic reminder interventions, including but not limited to EMDs, and interventions such as mobile SMS or pager systems. Only EMDs with a reminder function were included, and the review did not look at EMDs...
when used as adherence interventions via adherence feedback. Tran et al. evaluated reminder systems in asthma including both personal reminders, such as telephone calls, and electronic reminders. Other similar reviews have been undertaken, focusing specifically on EMDs in specific chronic conditions of hypertension and HIV. Both reviews suggest there is a potential role for EMDs in improving adherence and outcomes, but methodological limitations and study quality preclude definitive conclusions. The reviews highlight a need for further and more rigorous research of higher quality. Checchi et al. expanded on the above literature by conducting a review on adherence and the use of electronic medication packaging devices, defined by the authors as adherence-monitoring devices incorporated into the packaging of the medication. The review however did not assess the effect on clinical outcomes and only reviewed adherence monitors that were incorporated into the packaging holding the prescribed medication, hence studies using a device that monitored adherence to several medicines or that was incorporated outside of the medication packaging were not included.

To date, there are no reviews investigating the impact of EAM per se on medication adherence as well as clinical outcomes in chronic disease. This chapter aims to systematically review evidence on the effectiveness of EAM when used as adherence interventions as part of RCTs to improve patients’ adherence to medication and clinical outcomes.

3.2 Methodology of review

This review was conducted based on Guidelines of the Cochrane Collaboration, as described in the Cochrane Handbook of systematic reviews of interventions, version 5.1.0 (updated March 2011).

3.2.1 Study selection

The following inclusion criteria were used for the review: a) the intervention was aimed at patients prescribed long-term medication; b) the intervention was targeted at assessing the effect on adherence with prescribed medication using EAM, either directly or indirectly with the patient; c) one of the outcome measures was medication adherence, with or without an assessment of clinical outcomes; and d) the study was a RCT or a controlled clinical trial. EAM was defined as any mechanism or device that measures and records adherence electronically, regardless of the presence or absence of an electronic reminder function. For a study to be included, adherence also had to be clearly measured for all participants during the study at the patient level, rather than using a downstream measure to approximate adherence. Only randomised trials were considered for this review to ensure the highest quality of evidence was included.
Studies that used electronic monitoring purely as an adherence measurement tool, rather than as an adherence-enhancing intervention, were excluded. Studies using a within-subjects design or historical controls were excluded due to the risk of bias arising from factors other than the intervention itself, though studies using contemporary controls were included.

3.2.2 Search strategy

A systematic search of the literature was undertaken using the OVIDSP platform for Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946 to present, EMBASE 1974 to 13 March 2015, Social Work Abstracts (SWA) 1968 to March 2015, PsycINFO 1806 to May Week 4, 2015, International Pharmaceutical Abstracts (IPA) 1970 to May 2015, and EBM Reviews – Cochrane Central Register of Controlled Trials April 2015; CINAHL was searched via the CINAHL Plus portal.

Previously published reviews in a similar topic area were used to guide the search strategy and the formation of search terms. The following Boolean search was conducted for OVIDSP databases: (electronic monitoring.mp. OR electronics.sh OR remote monitoring.mp. OR monitoring device.mp. OR reminder device.mp) AND (medication adherence OR patient compliance).sh. OR patient compliance.mp. OR medication adherence.mp. OR adhere*.mp. OR complian*.mp. OR non-adhere*.mp. OR nonadhere*.mp. OR no-ncomplian*.mp. OR noncomplian*.mp) AND (intervention study.mp. OR intervention studies.sh OR randomized controlled trial.sh OR randomized controlled trial.mp. OR randomised controlled trial.mp. OR controlled clinical trial.sh OR controlled clinical trial.mp.).

A modified version of this search was used for CINAHL Plus: (monitoring device.mp. OR reminder device.mp OR electronic monitoring.mp. OR electronics.sh OR remote monitoring.mp.) AND (medication adherence OR patient compliance).sh. OR patient compliance.mp. OR medication adherence.mp. OR adhere*.mp. OR complian*.mp. OR non-adherence.mp OR nonadherence.mp OR non-compliance.mp OR noncompliance.mp OR Noncompliance (NANDA).sh OR Noncompliance of Therapeutic Regimen (Saba CCC) OR Noncompliance of Medication Regimen (Saba CCC) OR Noncompliance (Saba CCC) AND (intervention study.mp. OR experimental studies.sh OR randomized controlled trials.sh OR randomized controlled trial.mp. OR randomised controlled trial.mp. OR clinical trials.sh OR controlled clinical trial.mp.).

No language or participant type limit was applied, though the intention was to have only studies using human participants. Publication date was not restricted, and the last search of these databases was conducted on 3 June 2015. This electronic search strategy was supplemented by a
manual search of the reference lists of the identified studies and previously published reviews in a similar subject area to find other potentially relevant studies.

### 3.2.3 Study review and classification procedures

RefWorks and EndNote X7.2 were used to manage the citations. The titles and abstracts of all identified citations were screened by two reviewers (initially AC, followed by a second review by JH); full texts were obtained for any potentially eligible studies or abstracts that did not have sufficient information for review. Studies that did not meet the inclusion criteria or had reasons for exclusion at this stage of review were not reviewed further, and reasons for exclusion documented.

Studies were classified based on how the EAM was applied as an adherence intervention – either as a direct-to-patient adherence enhancing intervention (such as via an on-board reminder system or visual feedback mechanism), or via an indirect provider-to-patient interaction (such as feedback of adherence reports by the healthcare provider as part of a larger intervention), or both. Effect on adherence was further classified into categories of either significant positive overall effect, significant positive effect but only in a subgroup, or no effect. These were based on statistical significance of p < 0.05 for the main outcome of overall adherence between the two groups. Where possible, the effect size was calculated, based on the percentage difference in adherence between the two groups. Where clinical outcomes were reported, the effect was classified as significantly improved, trend towards improvement but not significant, no effect, or worsened. Patient perceptions of the intervention were also reviewed and categorised as opinions relating to the EMD directly or relating to the adherence intervention.

### 3.2.4 Data extraction

The following data from each of the studies were extracted:

- General study information (author, year of publication)
- Study design (study setting, length of study)
- Study population (disease condition, number of participants, inclusion and exclusion criteria, completion rate)
- Type of EMD used
- How adherence was measured
- Presence of blinding to adherence monitoring of EMD
- Description of the intervention and control conditions
- Outcome measures
- Adherence findings
• Clinical outcome and other findings
• Any data on patient perceptions of the EMD.

3.3 Results from the literature review

A total of 375 hits were identified from the electronic database searches, of which 247 were unique studies. After screening the titles and abstracts of these studies, 199 were excluded, leaving 48 references for inclusion. The primary reasons for exclusion were that the study did not include an adherence intervention at all (e.g. electronic monitoring was included in the study to model pharmacokinetics, or to validate an adherence measuring instrument but the study aim was not to improve adherence); or where they did, electronic monitoring was not used for the adherence intervention (with most cases using electronic monitoring only as an adherence measurement tool); or the study was not about EAM at all (see Figure 1). An additional four potential studies were identified from using a snowball method, from a search of reviews and the reference lists of other studies, giving a total of 52 studies for inclusion. The full texts of these 52 studies were obtained and reviewed for final inclusion in the review. Further analysis of these studies excluded another 16 references, leaving 36 studies which met the inclusion criteria.
Figure 1. Flowchart of study inclusion

Electronic search strategy from databases: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Psychinfo, IPA, SWA. n=375 hits

Excluded: 128 duplicates

Titles and abstract screened: n=247 studies

199 studies excluded
Reasons:
- 68 did not investigate medication adherence and electronic monitoring (out of topic)
- 60 did not include an adherence intervention
- 58 did not use electronic monitoring as an adherence intervention
- 13 were not randomised controlled trials

48 studies included

Other sources: References of reviews and snowball methodology: n=4

4 studies included

Full-text of total of 52 studies reviewed

16 studies excluded
Reasons:
- 2 did not investigate medication adherence and electronic monitoring (out of topic)
- 4 did not use electronic monitoring as an adherence intervention
- 3 were not randomised controlled trials
- 6 did not measure adherence as an outcome
- 1 had no results available yet

Total 36 studies included in this review
3.3.1 Characteristics of included studies

Table 1 describes the main characteristics of the 36 included studies published between 1990 and 2015, the majority (25 studies) of which were published in the last 10 years. The study population size ranged from 6496 to 784497 patients (median 67; lower quartile 36, upper quartile 142). The study period (not including run-in phases) varied in duration from one month498,499 to one year134,497, 500-503 (median six months; lower quartile three months, upper quartile seven months).
# Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Setting</th>
<th>Condition</th>
<th>Subjects</th>
<th>Length of study</th>
<th>Completion rate</th>
<th>Type of EMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrade et al.</td>
<td>2005</td>
<td>The Johns Hopkins Moore HIV Clinic, Baltimore, MD</td>
<td>HIV</td>
<td>64 HIV-infected males and females ≥ 18 years attending HIV clinic</td>
<td>24 weeks</td>
<td>58/64</td>
<td>Electronic verbal prompting device - Disease Management Assistance System (DMAS). Device produces a timed, programmed voice message that prompts subjects to take medication. Records dosing times and dates when response button is pressed. Data can be uploaded and printed.</td>
</tr>
<tr>
<td>Artinian et al.</td>
<td>2003</td>
<td>Congestive Heart Failure (CHF) clinic of the Detroit Veterans Affairs Medical Centre</td>
<td>CHF</td>
<td>18 outpatients from the CHF clinic aged 50 to 87 years</td>
<td>3 months</td>
<td>18/18 (drop outs not discussed so assume 100% completion)</td>
<td>Medication compliance device - Med-eMonitor linked to a Web-based monitoring system via the patient’s telephone line. Stores up to 5 medicines and has an alarm to remind patients when to take their medication, which to take, and how many. Daily reminders given about healthy lifestyle, other medicines and questions about symptoms, blood pressure, weight. Records date and time stamp of pill compartment opening and patient responses to questions. Data uploaded daily to central server - accessible by clinicians.</td>
</tr>
<tr>
<td>Burgess et al.</td>
<td>2010</td>
<td>Paediatric asthma clinic within an outer metropolitan general hospital, Australia</td>
<td>Asthma</td>
<td>26 children aged between 6 and 14 years</td>
<td>4 months</td>
<td>26/26</td>
<td>Smartinhaler - validated EMD.</td>
</tr>
<tr>
<td>Chan et al.</td>
<td>2015</td>
<td>Regional hospital ED, Auckland, NZ</td>
<td>Asthma</td>
<td>220 children aged between 6 and 15 years</td>
<td>6 months</td>
<td>213/220</td>
<td>SmartTrack EMD with audiovisual reminder function for use with preventive medication. Records date, time and number of actuations used. Has 14 different reminders that ring twice daily, stopping after the correct dose is taken or after 15 min. Reminder only goes if the correct dose is not taken within 6 hours of the set reminder time.</td>
</tr>
<tr>
<td>Charles et al.</td>
<td>2007</td>
<td>P3 research clinical trials facility, Wellington, NZ. Recruitment was from research volunteer databases, newspaper advertisements, informal contacts</td>
<td>Asthma</td>
<td>110 patients aged 12 to 65 years</td>
<td>2 week run-in period, 24 weeks after</td>
<td>90/110</td>
<td>Smartinhaler - EMD for use with pMDIs. It has an audiovisual reminder function, that emits an audible reminder (beep) at set times plus a visual cue to show patients whether they have taken their inhaler during a designated period or not (green before inhaler use; red once dose taken). Alarm stops after dose is taken or after 60 min. An electronic covert adherence log is included to record medication use, which can be uploaded to the study centre.</td>
</tr>
<tr>
<td>Christensen et al.</td>
<td>2010</td>
<td>Included by physicians in private practice or hospital ambulatories across Poland</td>
<td>Hypertension</td>
<td>784 patients aged ≥ 18 years</td>
<td>1 year (6 months with either the device or standard therapy, then crossed over to other arm for 6 months)</td>
<td>398/784 in final analysis</td>
<td>Helping Hand Data Capture device. Device has tablet blister cards and has an audiovisual reminder to remind patients once daily to take their medication. It records compliance by recording the date/time of each blister card removal.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Setting</td>
<td>Condition</td>
<td>Subjects</td>
<td>Length of study</td>
<td>Completion rate</td>
<td>Type of EMD</td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>-------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>de Bruin et al.</td>
<td>2010</td>
<td>HIV outpatient clinic of the Academic Medical Centre in Amsterdam, The Netherlands</td>
<td>HIV</td>
<td>133 patients ≥ 18 years</td>
<td>9 months (2 months baseline measurement, 3 months intervention, 4 months follow-up)</td>
<td>116/133</td>
<td>Medication Event Monitoring System (MEMS) caps - electronic caps that fit on standard pill bottles and register the date/time of each pill bottle opening. Data can be downloaded and printed from the MEMS cap to provide a detailed but comprehensible overview of medication-taking behaviour. The MEMS-viewcap used to feedback data to patients as it has a display on top.</td>
</tr>
<tr>
<td>De Geest et al.</td>
<td>2006</td>
<td>The University Hospital Basel, or Cantonal Hospital, Aarau, Switzerland</td>
<td>Renal transplant</td>
<td>18 patients ≥ 18 years</td>
<td>9 months (3 months intervention, 6 months follow-up)</td>
<td>13/18</td>
<td>Electronic bottle cap that registers data/time of bottle opening; data downloaded to a computer which generates lists and graphics of medication-taking habits.</td>
</tr>
<tr>
<td>Duncan et al.</td>
<td>2013</td>
<td>Rural, university-based hospital in the northeastern United States and an urban-based children's hospital in the Midwest</td>
<td>Asthma</td>
<td>55 participants aged 9 to 15 years</td>
<td>4 sessions of treatment over 2 months with a 3-month follow-up. Total time was 6 sessions (recruitment; 2,4,6,8 weeks; follow-up) across ~5 months</td>
<td>48/55</td>
<td>MDILog-II electronic recording device - captures date/time of inhaler dispensings and whether the participant had inhaled the medication. Attaches to the ICS canister.</td>
</tr>
<tr>
<td>Elixhauser et al.</td>
<td>1990</td>
<td>Outpatient psychiatric clinic of the St. Louis Veterans Administration Medical Center</td>
<td>Bipolar affective disorder</td>
<td>93 enrolled adult patients</td>
<td>4–8 months depending on frequency of visits set by the patient’s provider (visits could be 2- or 4-monthly)</td>
<td>67/93</td>
<td>Electronic medication monitor for use with oral medication. Involves two plastic blister sheets, each containing 21 blisters holding patient’s medication. The position of the blisters is updated every 15 minutes; if a blister is opened, the time is recorded. Data can be collected with a microcomputer. Printouts provide data on the timing of blister openings with a resolution of 15 minutes.</td>
</tr>
<tr>
<td>Erickson et al.</td>
<td>2005</td>
<td>Hypertension specialty outpatient clinic within a large university-affiliated medical centre</td>
<td>Hypertension</td>
<td>42 subjects aged ≥ 21 years</td>
<td>3 months</td>
<td>37/42</td>
<td>Medication management system (MMS). The MMS uses patient-specific information to tailor the interactive technology to each patient, and aims to enhance adherence and communication between the patient and health provider. It includes the MedManager device which stores medication, provides reminder signals through an audio alarm and visual text message to alert patients to take a dose or enter data, and collects date/time of opening of a medication well, blood pressure readings and potential symptoms of adverse effects of medication. Data are transmitted nightly to the central computer. Reports of patient medication use and clinical parameters were generated monthly and sent to the patient and physician.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Setting</td>
<td>Condition</td>
<td>Subjects</td>
<td>Length of study</td>
<td>Completion rate</td>
<td>Type of EMD</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>-------------------------------------------------------------------------</td>
<td>----------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Foster et al.</td>
<td>2014</td>
<td>General practices in Greater Sydney, Australia</td>
<td>Asthma</td>
<td>143 patients aged 14 to 65 years with moderate–severe asthma</td>
<td>6 months with just 2 study visits (enrolment, then follow-up) with telephone data collection at BL, 2, 4 and 6 months</td>
<td>129/143</td>
<td>SmartTrack EMD with audiovisual reminder function for use with preventive medication. Records date, time and number of actuations used and uploads data monthly to a secure website. Asks 3 onscreen questions about asthma control each month.</td>
</tr>
<tr>
<td>Frick et al.</td>
<td>2001</td>
<td>Sexually Transmitted Disease and Family Planning Clinics, Coast Provincial General Hospital in Mombasa - the government referral hospital for the coastal region of Kenya</td>
<td>HIV model but tested with multivitamins</td>
<td>140 women aged between 18 and 45 years</td>
<td>1 month</td>
<td>120/140 in final analysis</td>
<td>RemindRx® - Microelectronic alarmed medication vial with programmable dosage administration times that records date/time when a button on the vial is depressed. The button also serves to silence the alarm. Data could be downloaded into a computer.</td>
</tr>
<tr>
<td>Hardstaff et al.</td>
<td>2003</td>
<td>Renal and Liver Transplant Unit, Freeman Hospital, Newcastle-upon-Tyne, UK</td>
<td>Renal transplant</td>
<td>75 renal transplant adult patients</td>
<td>12 months</td>
<td>48/75</td>
<td>Smart Top bottle. These bottles have specialised lids containing a microprocessor that records date/time of bottle opening/closing. Information downloadable into a computer database.</td>
</tr>
<tr>
<td>Hermann et al.</td>
<td>2011</td>
<td>Glaucoma clinic at the University Hospital in Athens, Greece</td>
<td>Glaucoma</td>
<td>37 patients ≥ 18 years with glaucoma or ocular hypertension</td>
<td>4 weeks</td>
<td>36/37</td>
<td>EMD for use with brimonidine eye drops 0.2%. Records time/date of use by measuring bottle motion and squeezing. Device not able to be separated from the bottle.</td>
</tr>
<tr>
<td>Joost et al.</td>
<td>2014</td>
<td>Erlangen University Hospital, Germany</td>
<td>Renal transplant</td>
<td>74 renal transplant patients ≥ 18 years</td>
<td>1 year</td>
<td>67/74</td>
<td>Medication Event Monitoring System (MEMS) caps</td>
</tr>
<tr>
<td>Kozuki et al.</td>
<td>2006</td>
<td>Community mental health centres in the Pacific North-west</td>
<td>Psychotic disorders</td>
<td>30 adult patients</td>
<td>3 months</td>
<td>28/30</td>
<td>eDEM - electronic monitoring cap that records daily execution of the regimen and produces a chronology of the time the medication was taken each day. Information can be downloaded and presented on a computer screen.</td>
</tr>
<tr>
<td>Matteson-Kome et al.</td>
<td>2014</td>
<td>Mid-western outpatient Inflammatory bowel disease (IBD) clinic</td>
<td>IBD</td>
<td>6 adults ≥ 18 years</td>
<td>3 months intervention phase with a 60-day screening phase to identify non-adherent patients (&lt; 85%) = total 5 months</td>
<td>5/6</td>
<td>Medication Event Monitoring System (MEMS Track Cap –) electronic bottle cap that monitors dosing (not timing) of medication.</td>
</tr>
<tr>
<td>McKenney et al.</td>
<td>1992</td>
<td>Residence in a retirement community or attending a primary care centre, Virginia</td>
<td>Hypertension</td>
<td>70 ambulant patients ≥ 50 years</td>
<td>2 x 12-week phases</td>
<td>Phase I: 69/70 Phase II: 59/70</td>
<td>Prescript TimeCap - an electronic compliance aid consisting of a medication vial with a cap displaying the last time the cap was removed.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Setting</td>
<td>Condition</td>
<td>Subjects</td>
<td>Length of study</td>
<td>Completion rate</td>
<td>Type of EMD</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>-------------------------------------------------------------------------</td>
<td>-----------</td>
<td>---------------------------------------</td>
<td>-----------------------------------------------------</td>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Murray et al.</td>
<td>2007</td>
<td>University-affiliated, inner-city, ambulatory care practice - general medicine and cardiology practices of Wishard Health Services, Indianapolis, Indiana and Wishard Memorial Hospital</td>
<td>CHF</td>
<td>314 low-income patients ≥ 50 years with heart failure</td>
<td>12 months (9-month multi-level intervention with 3-month poststudy phase)</td>
<td>270/314</td>
<td>Medication Event Monitoring System (MEMS) V prescription container lids that recorded the time/date of each opening and closing. The MEMS cap was labelled with the same icon as the container body to allow correct matching of medicines.</td>
</tr>
<tr>
<td>Nides et al.</td>
<td>1993</td>
<td>University of California at Los Angeles and John Hopkins University</td>
<td>COPD</td>
<td>251 patients aged 35 to 60 years</td>
<td>4 months</td>
<td>205/251</td>
<td>Nebulizer Chronolog - a microprocessor device recording time and date of actuation that can be downloaded into an IBM-compatible computer.</td>
</tr>
<tr>
<td>Okeke et al.</td>
<td>2009</td>
<td>Glaucoma services of the Scheie or Wilmer Eye Institutes</td>
<td>Glaucoma</td>
<td>66 patients ≥ 18 years</td>
<td>6 months (initial 3-month observational period of which 2 months of data from week 2 to 10 were used, plus 3-month intervention period)</td>
<td>Not stated</td>
<td>Dosing aid bottle - squeezes the drop from the bottle and records the time and date of delivery.</td>
</tr>
<tr>
<td>Onyirimba et al.</td>
<td>2003</td>
<td>Asthma Center at Saint Francis Hospital and Medical Center</td>
<td>Asthma</td>
<td>30 adult patients</td>
<td>10 weeks</td>
<td>19/30</td>
<td>MDI Chronologs</td>
</tr>
<tr>
<td>Rigsby et al.</td>
<td>2000</td>
<td>Department of Veterans Affairs HIV clinic and the University of Connecticut Infectious Diseases Study Center - a community-based HIV clinical trials site in the City of Hartford Health Department in Hartford, Connecticut</td>
<td>HIV</td>
<td>55 HIV-infected adult subjects</td>
<td>12 weeks (intervention 0-4 weeks, then follow-up at weeks 8 and 12).</td>
<td>46/55</td>
<td>MEMS caps - fixed to the medication with the lowest baseline adherence in the 1-week baseline period.</td>
</tr>
<tr>
<td>Rosen et al.</td>
<td>2004</td>
<td>Primary care clinic at the VA Connecticut Healthcare System</td>
<td>Diabetes</td>
<td>79 adult patients enrolled but only 33 had lower than 80% baseline adherence and were randomised</td>
<td>4 months intervention + 3 months follow-up (no intervention, assessment only)</td>
<td>33/33</td>
<td>MEMScaps/Smart Caps</td>
</tr>
<tr>
<td>Rosen et al.</td>
<td>2007</td>
<td>HIV clinics in the greater Hartford, Connecticut area</td>
<td>HIV</td>
<td>56 adult participants</td>
<td>32 weeks</td>
<td>36/56</td>
<td>MEMS caps with downloaded data to a computer. Print out shows date and time of each bottle opening over the preceding weeks and the list of doses taken.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Setting</td>
<td>Condition</td>
<td>Subjects</td>
<td>Length of study</td>
<td>Completion rate</td>
<td>Type of EMD</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ruppar</td>
<td>2010</td>
<td>Senior centres, senior living facilities, churches in two Midwestern US cities</td>
<td>Hypertension</td>
<td>15 subjects aged 60 years or older</td>
<td>28 weeks (8-week run-in period + 8-week intervention + 12-week follow-up)</td>
<td>15/15</td>
<td>MEMS electronic medication bottle cap with a digital display that provided daily adherence feedback of date and time of opening of the bottle during the 8-week intervention.</td>
</tr>
<tr>
<td>Russell et al.</td>
<td>2011</td>
<td>Tertiary care transplant centre located in the Midwestern United States</td>
<td>Renal transplant</td>
<td>15 adult renal transplant recipients aged 21 years or older</td>
<td>9 months [3-month screening phase + 6-month intervention]</td>
<td>15/15</td>
<td>MEMS Track cap - date and time of removal of the cap from the vial,</td>
</tr>
<tr>
<td>Sabin et al.</td>
<td>2010</td>
<td>Dali Second People’s Hospital in Dali, Yunnan province, China</td>
<td>HIV</td>
<td>80 enrolled, 68 subjects ≥ 18 years old randomised</td>
<td>12 months [pre-intervention phase months 1-6 of monitoring to identify high or low adherence for stratification; intervention period months 7-12]</td>
<td>64/68</td>
<td>Med-ic - Electronic drug monitor pill bottle.</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>2003</td>
<td>Hospital-based infection disease clinic at the University of North Carolina Hospitals in Chapel Hill, NC</td>
<td>HIV</td>
<td>43 individuals ≥ 18 years</td>
<td>3 months but clinical outcomes assessed within 1 year of randomisation</td>
<td>Not stated</td>
<td>MEMS electronic monitors on medication bottles.</td>
</tr>
<tr>
<td>Sutton et al.</td>
<td>2014</td>
<td>Primary care clinics in Oxfordshire, Buckinghamshire, Suffolk, Essex, Huntingdonshire</td>
<td>Diabetes</td>
<td>226 adults ≥ 18 years</td>
<td>8 weeks</td>
<td>184/226 for adherence analysis; 193/226 for HbA1c analysis</td>
<td>TrackCap</td>
</tr>
<tr>
<td>Tashkin et al.</td>
<td>1991</td>
<td>John Hopkins University and UCLA</td>
<td>COPD</td>
<td>237 adults of a larger intervention group that received a group-based smoking cessation programme, education, counselling and NRT</td>
<td>12 weeks (4 months)</td>
<td>197/237 (40 forgot devices, missed the appointment or had malfunctioning devices)</td>
<td>Nebulizer Chronolog - small, portable electronic device housing a pMDI - records the date and time of each actuation and is read out by an IBM PC.</td>
</tr>
<tr>
<td>van Onzenoort et al.</td>
<td>2012</td>
<td>Maastricht University Hospital, Maastricht, The Netherlands and surrounding general practitioners’ practices</td>
<td>Hypertension</td>
<td>470 patients ≥18 years with mild–moderate hypertension as part of a larger HOMERUS trial</td>
<td>1 year with seven follow-up visits (a placebo run-in period of 4 weeks was also conducted before study initiation)</td>
<td>Not stated</td>
<td>MEMS V TrackCaps</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Setting</td>
<td>Condition</td>
<td>Subjects</td>
<td>Length of study</td>
<td>Completion rate</td>
<td>Type of EMD</td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------</td>
<td>----------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Velligan et al</td>
<td>2013</td>
<td>Community mental health centre from two counties in Texas</td>
<td>Schizophrenia</td>
<td>142 patients aged between 18 and 60</td>
<td>9 months after 1-month baseline assessment of adherence monitoring with the MM and pill count</td>
<td>132/142</td>
<td>Med-eMonitor (MM) - an electronic medication monitor that prompts use of medication, cues medication taking, warns patients when the wrong medication is taken or at the wrong time, records complaints and alerts staff of failures to take medication as prescribed.</td>
</tr>
<tr>
<td>Wilson et al.</td>
<td>2010</td>
<td>Two academic medical centres, a community health centre, general medicine practice and private infectious diseases practice in the US</td>
<td>HIV</td>
<td>156 adult patients</td>
<td>6 study visits (BL, visits 1–4 before a provider visit, final (6–12 weeks after 4th provider visit)</td>
<td>106/156</td>
<td>MEMS cap</td>
</tr>
<tr>
<td>Wu et al</td>
<td>2006</td>
<td>John Hopkins Moore (HIV) clinic</td>
<td>HIV</td>
<td>64 patients ≥ 18 years</td>
<td>6 months</td>
<td>48/64</td>
<td>Disease Management Assistance System (DMAS) - a prompting device that verbally reminds patients at medication times and records doses when manually pushed; also eDEM to measure adherence.</td>
</tr>
</tbody>
</table>
3.3.1.1 Health conditions

The health conditions that were investigated varied widely across eight general areas: cardiac (five hypertension\textsuperscript{497, 503-506}, two heart failure\textsuperscript{135, 502}); respiratory (six asthma\textsuperscript{36, 37, 299, 456-458}, two COPD\textsuperscript{124, 507}); neurological (one psychotic disorders\textsuperscript{508}, one bipolar affective disorder\textsuperscript{137}, one schizophrenia\textsuperscript{509}); endocrine (two diabetes\textsuperscript{142, 510}); ophthalmic (two glaucoma\textsuperscript{499, 511}); gastrointestinal (one inflammatory bowel disease\textsuperscript{496}); infectious diseases (nine HIV\textsuperscript{133, 134, 277, 498, 512-516}); organ transplants (four renal transplants\textsuperscript{500, 501, 517, 518}).

3.3.1.2 Age group

Most (33 studies) were conducted in adults, of which four were in older aged participants (≥ 50 years as specified in the studies)\textsuperscript{135, 502, 505, 506}. These four older-adult studies were all on cardiac-related conditions (hypertension or heart failure). Only three studies\textsuperscript{299, 456, 457} were conducted in children, all of which were on asthma\textsuperscript{27, 28, 30}.

3.3.1.3 Study location

The majority (22) of these studies were undertaken in the United States of America\textsuperscript{124, 133, 135, 137, 277, 456, 458, 496, 502, 504-511, 513-516, 518}, followed by the United Kingdom (two studies\textsuperscript{142, 500}), Australia (two studies\textsuperscript{37, 299}) and New Zealand (two studies\textsuperscript{36, 457}). Other countries that had one study each were: Africa\textsuperscript{498}, Amsterdam\textsuperscript{512}, China\textsuperscript{134}, Germany\textsuperscript{501}, Greece\textsuperscript{499}, Netherlands\textsuperscript{503}, Poland\textsuperscript{497} and Switzerland\textsuperscript{517}.

3.3.1.4 Healthcare setting

Most (17 studies) took place in outpatient specialty clinics, though there were some in a hospital (seven studies\textsuperscript{134, 456, 457, 500, 501, 517, 518}), primary care (four studies\textsuperscript{37, 142, 502, 510}), university (two studies\textsuperscript{124, 507}) or research (one study\textsuperscript{16}) setting; or a combination of such settings (five studies\textsuperscript{497, 503, 505, 506, 515}).

3.3.1.5 Device type

The most common (20 studies) type of EMD studied was the electronic oral medication vial – either the MEMS\textsuperscript{277, 496, 501-503, 506, 510, 512-515, 518} or similar\textsuperscript{134, 142, 498, 500, 505, 508, 517} – where the electronic cap is fitted on the standard pill bottle and registers the date and time of bottle opening. In two other studies investigating oral medicines, adherence was monitored using electronic oral medication blister cards\textsuperscript{137, 497}. The remaining studies were for specific medication formulations such as inhalers (eight studies\textsuperscript{36, 37, 124, 299, 456-458, 507}) or eyedrops (two studies\textsuperscript{499, 511}), while five studies\textsuperscript{133, 135, 504, 509, 516} used an integrated medication management system (MMS) which included recording of dosing times but also records of symptoms, reminders about lifestyle, or prompts about medication and disease control. Most of these studies, except two early studies\textsuperscript{137, 505}, used electronic monitoring to measure adherence, though this was frequently supplemented with other adherence measures such
as serum drug levels, self-report, pill counts, or adherence questionnaires, pill counts, or canister weights, or prescription refill data.

### 3.3.2 Method of adherence feedback

Studies used the adherence monitoring function of the EMD in two different ways to promote adherence. Half used the adherence data recorded by the EMDs to provide feedback of adherence behaviour via generation of adherence reports. These reports were generally given to the patient, though in two studies, these were given only to the health provider. This will be described in this section as an ‘indirect’ method of adherence feedback. Nine studies used a direct-to-patient approach, where adherence was fed back directly through audible reminders on the EMD, visual displays, or both. This method of adherence feedback will be referred to in this section as a ‘direct’ method of feedback.

Of the nine studies involving direct feedback, three provided the adherence information in real-time. ‘Real-time’ feedback describes feedback that is given as data are collected (i.e. at the time the adherence behaviour occurs, including both adherent and non-adherent behaviour). Six studies used both indirect and direct methods of adherence feedback, involving direct feedback to the patient through the device, and then indirectly via discussion of the adherence data with the patient; in four studies, this feedback was given in real-time.

The remaining three studies did not feedback adherence; these studies used the EMD solely as an adherence recorder to assess the effect of monitoring on medication-taking behaviour.

### 3.3.3 Factors affecting effectiveness of interventions

The effect of the adherence monitoring interventions on adherence and clinical outcomes are summarised in Table 2 and Section 3.3.4. Most studies were in cardiac or respiratory conditions, or HIV. Of these, asthma and hypertension were two of the most commonly studied conditions after HIV. The majority (24 studies) showed a significant improvement in adherence, though three studies noted this was lost on follow-up when the intervention was removed. Just under a third of the studies showed no intervention effect, though Andrade et al. found a significant improvement in adherence for memory-impaired patients in a subgroup analysis compared to memory-intact patients. Similarly, less than a third of the studies demonstrated statistically significant improvements in clinical outcomes. None reported any worsening of adherence as a result of the intervention, though clinical worsening was noted in two studies.
<table>
<thead>
<tr>
<th>Author</th>
<th>Condition</th>
<th>Age group</th>
<th>Length of study (months)</th>
<th>Blinded to adherence monitoring?</th>
<th>Type of EMD</th>
<th>Method of feedback</th>
<th>Real-time feedback?</th>
<th>Method of adherence measurement</th>
<th>Effect on adherence</th>
<th>Size of effect</th>
<th>Clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrade et al., 2005</td>
<td>HIV</td>
<td>Adults</td>
<td>6</td>
<td>No</td>
<td>Integrated</td>
<td>Both</td>
<td>No</td>
<td>EM, Adherence questionnaire</td>
<td>0, +</td>
<td>+15% (overall), +20% (memory-impaired)</td>
<td>+/0</td>
</tr>
<tr>
<td>Artinian et al., 2003</td>
<td>CHF</td>
<td>Older age</td>
<td>3</td>
<td>Not stated</td>
<td>Integrated</td>
<td>Direct</td>
<td>No</td>
<td>EM, Pill questionnaire</td>
<td>Not compared</td>
<td>Not available</td>
<td>+/0</td>
</tr>
<tr>
<td>Burgess et al., 2010</td>
<td>Asthma</td>
<td>Children</td>
<td>4</td>
<td>No</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM</td>
<td>++</td>
<td>+21%</td>
<td>++</td>
</tr>
<tr>
<td>Chan et al., 2015</td>
<td>Asthma</td>
<td>Children</td>
<td>6</td>
<td>Yes</td>
<td>Simple EMD</td>
<td>Direct</td>
<td>Yes</td>
<td>EM</td>
<td>++</td>
<td>+54%</td>
<td>++</td>
</tr>
<tr>
<td>Charles et al., 2007</td>
<td>Asthma</td>
<td>Adults</td>
<td>6</td>
<td>Yes</td>
<td>Simple EMD</td>
<td>Direct</td>
<td>Yes</td>
<td>EM</td>
<td>++</td>
<td>+22%</td>
<td>0</td>
</tr>
<tr>
<td>Christensen et al., 2010</td>
<td>Hypertension</td>
<td>Adults</td>
<td>12</td>
<td>Not stated</td>
<td>Simple EMD</td>
<td>Direct</td>
<td>No</td>
<td>EM, Self-report</td>
<td>0</td>
<td>+6% then -2% with crossover</td>
<td>0</td>
</tr>
<tr>
<td>de Bruin et al., 2010</td>
<td>HIV</td>
<td>Adults</td>
<td>7</td>
<td>No</td>
<td>Simple EMD</td>
<td>Both</td>
<td>Yes</td>
<td>EM</td>
<td>++, +</td>
<td>+7% (overall), +15% (&lt; 95% baseline adherence)</td>
<td>++</td>
</tr>
<tr>
<td>De Geest et al., 2006</td>
<td>Renal Transplant</td>
<td>Adults</td>
<td>9</td>
<td>No</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM</td>
<td>0</td>
<td>Not available</td>
<td>Not measured</td>
</tr>
<tr>
<td>Duncan et al., 2013</td>
<td>Asthma</td>
<td>Children</td>
<td>5</td>
<td>Yes</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM</td>
<td>++</td>
<td>+44%</td>
<td>++</td>
</tr>
<tr>
<td>Elixhauser et al., 1990</td>
<td>Bipolar</td>
<td>Adults</td>
<td>8</td>
<td>No</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>Self-report, Prescription refill, Levels</td>
<td>0</td>
<td>+3%</td>
<td>--</td>
</tr>
<tr>
<td>Erickson et al., 2005</td>
<td>Hypertension</td>
<td>Adults</td>
<td>3</td>
<td>Not stated</td>
<td>Integrated</td>
<td>Direct</td>
<td>No</td>
<td>EM, Adherence questionnaire</td>
<td>0</td>
<td>Not available</td>
<td>+</td>
</tr>
<tr>
<td>Foster et al., 2014</td>
<td>Asthma</td>
<td>Adults</td>
<td>6</td>
<td>Yes</td>
<td>Simple EMD</td>
<td>Both</td>
<td>Yes</td>
<td>EM</td>
<td>++</td>
<td>+27%</td>
<td>+</td>
</tr>
<tr>
<td>Frick et al., 2001</td>
<td>HIV</td>
<td>Adults</td>
<td>1</td>
<td>No</td>
<td>Simple EMD</td>
<td>Direct</td>
<td>No</td>
<td>EM, Pill count, Self-report</td>
<td>++</td>
<td>+46%</td>
<td>Not measured</td>
</tr>
<tr>
<td>Hardstaff et al., 2003</td>
<td>Renal Transplant</td>
<td>Adults</td>
<td>12</td>
<td>No</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM</td>
<td>0</td>
<td>Not available</td>
<td>Not measured</td>
</tr>
<tr>
<td>Hermann et al., 2011</td>
<td>Glaucoma</td>
<td>Adults</td>
<td>1</td>
<td>Yes</td>
<td>Simple EMD</td>
<td>N/a</td>
<td>N/a</td>
<td>EM</td>
<td>0</td>
<td>-7% (BD dosing), +3% (TDS)</td>
<td>Not measured</td>
</tr>
<tr>
<td>Joost et al., 2014</td>
<td>Renal Transplant</td>
<td>Adults</td>
<td>12</td>
<td>No</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM, Pill count, Self-report, Q</td>
<td>++</td>
<td>+16%</td>
<td>0</td>
</tr>
<tr>
<td>Kozuki et al., 2006</td>
<td>Psychotic disorders</td>
<td>Adults</td>
<td>3</td>
<td>Not stated</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM, Drug levels, Pill count</td>
<td>++</td>
<td>+20%</td>
<td>+</td>
</tr>
<tr>
<td>Matteson-Kome et al., 2014</td>
<td>Inflammatory Bowel Disease</td>
<td>Adults</td>
<td>3</td>
<td>Not stated</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM</td>
<td>0</td>
<td>Not available</td>
<td>Not measured</td>
</tr>
<tr>
<td>Author</td>
<td>Condition</td>
<td>Age group</td>
<td>Length of study (months)</td>
<td>Blinded to adherence monitoring?</td>
<td>Type of EMD</td>
<td>Method of feedback</td>
<td>Real-time feedback?</td>
<td>Method of adherence measurement</td>
<td>Effect on adherence</td>
<td>Size of effect</td>
<td>Clinical effect</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------</td>
<td>-----------</td>
<td>--------------------------</td>
<td>----------------------------------</td>
<td>-------------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>-------------------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>McKenney et al., 1992</td>
<td>Hypertension</td>
<td>Older age</td>
<td>6</td>
<td>Yes</td>
<td>Simple EMD</td>
<td>Direct</td>
<td>Yes</td>
<td>Pill count</td>
<td>++</td>
<td>+17%</td>
<td>++</td>
</tr>
<tr>
<td>Murray et al., 2007</td>
<td>CHF</td>
<td>Older age</td>
<td>12</td>
<td>Not stated</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM, Prescription refill, Self-report</td>
<td>++, 0 on f/u</td>
<td>+11%</td>
<td>++</td>
</tr>
<tr>
<td>Nides et al., 1993</td>
<td>COPD</td>
<td>Adults</td>
<td>4</td>
<td>Yes</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM, Self-report, Canister Weights</td>
<td>++</td>
<td>+20%</td>
<td>Not measured</td>
</tr>
<tr>
<td>Okeke et al., 2009</td>
<td>Glaucoma</td>
<td>Adults</td>
<td>3</td>
<td>No</td>
<td>Simple EMD</td>
<td>Direct</td>
<td>No</td>
<td>EM, Self-report</td>
<td>++</td>
<td>+22%</td>
<td>0</td>
</tr>
<tr>
<td>Onyirimba et al., 2003</td>
<td>Asthma</td>
<td>Adults</td>
<td>2.5</td>
<td>No</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM</td>
<td>++</td>
<td>+34%</td>
<td>0</td>
</tr>
<tr>
<td>Rigsby et al., 2000</td>
<td>HIV</td>
<td>Adults</td>
<td>3</td>
<td>Not stated</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM, Drug levels</td>
<td>++, 0 on f/u</td>
<td>Not available</td>
<td>0</td>
</tr>
<tr>
<td>Rosen et al., 2004</td>
<td>Diabetes</td>
<td>Adults</td>
<td>8</td>
<td>No</td>
<td>Simple EMD</td>
<td>Both</td>
<td>Yes</td>
<td>EM, Self-report</td>
<td>++</td>
<td>+15%</td>
<td>0</td>
</tr>
<tr>
<td>Rosen et al., 2007</td>
<td>HIV</td>
<td>Adults</td>
<td>7</td>
<td>Not stated</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM, Self-report, Drug levels</td>
<td>++</td>
<td>+32%</td>
<td>++</td>
</tr>
<tr>
<td>Ruppar, 2010</td>
<td>Hypertension</td>
<td>Older age</td>
<td>5</td>
<td>Not stated</td>
<td>Simple EMD</td>
<td>Both</td>
<td>Yes</td>
<td>EM</td>
<td>++, 0 on f/u</td>
<td>+80%*</td>
<td>++</td>
</tr>
<tr>
<td>Russell et al., 2011</td>
<td>Renal Transplant</td>
<td>Adults</td>
<td>6</td>
<td>Not stated</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM</td>
<td>++</td>
<td>Not available</td>
<td>Not measured</td>
</tr>
<tr>
<td>Sabin et al., 2010</td>
<td>HIV</td>
<td>Adults</td>
<td>6</td>
<td>No</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM, Self-report</td>
<td>++</td>
<td>+12%</td>
<td>+/0</td>
</tr>
<tr>
<td>Smith et al., 2003</td>
<td>HIV</td>
<td>Adults</td>
<td>3</td>
<td>No</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM</td>
<td>++</td>
<td>+59%</td>
<td>+</td>
</tr>
<tr>
<td>Sutton et al., 2014</td>
<td>Diabetes</td>
<td>Adults</td>
<td>2</td>
<td>No</td>
<td>Simple EMD</td>
<td>N/a</td>
<td>N/a</td>
<td>EM, Adherence questionnaire</td>
<td>0</td>
<td>Not available</td>
<td>+</td>
</tr>
<tr>
<td>Tashkin et al., 1991</td>
<td>COPD</td>
<td>Adults</td>
<td>4</td>
<td>Yes</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM, Self-report, Canister Weights</td>
<td>++</td>
<td>+26%</td>
<td>Not measured</td>
</tr>
<tr>
<td>van Onzenoort et al., 2012</td>
<td>Hypertension</td>
<td>Adults</td>
<td>12</td>
<td>No</td>
<td>Simple EMD</td>
<td>N/a</td>
<td>N/a</td>
<td>EM, Pill count</td>
<td>0</td>
<td>+2%</td>
<td>0</td>
</tr>
<tr>
<td>Velligan et al., 2013</td>
<td>Schizophrenia</td>
<td>Adults</td>
<td>9</td>
<td>Not stated</td>
<td>Integrated</td>
<td>Both</td>
<td>No</td>
<td>EM, Pill count</td>
<td>++</td>
<td>+19%</td>
<td>0</td>
</tr>
<tr>
<td>Wilson et al., 2010</td>
<td>HIV</td>
<td>Adults</td>
<td>3</td>
<td>Not stated</td>
<td>Simple EMD</td>
<td>Indirect</td>
<td>No</td>
<td>EM, Self-report</td>
<td>0</td>
<td>+2%</td>
<td>0</td>
</tr>
<tr>
<td>Wu et al., 2006</td>
<td>HIV</td>
<td>Adults</td>
<td>6</td>
<td>Not stated</td>
<td>Integrated</td>
<td>Direct</td>
<td>No</td>
<td>EM</td>
<td>++</td>
<td>+20%</td>
<td>-</td>
</tr>
</tbody>
</table>

*++ (significant overall), + (significant subgroup) or 0 (no effect)
++ (significant improvement), + (trend in improvements), +/0 (improvement in some parameters but no effect on others), 0 (no effect), - (trend towards worsening), -- (significant worsening)
EM = Electronic monitoring
3.3.3.1 Effect of condition on effectiveness

Of the eight studies conducted on respiratory conditions, all were noted to have a positive effect on adherence, with a relatively large overall effect size (median 27%, lower quartile 22%, upper quartile 37%) and half showing improvements in outcomes\textsuperscript{36, 37, 124, 299, 456-458, 507}. Similarly, all but one study on HIV showed improvements in overall adherence\textsuperscript{133, 134, 277, 498, 512-514} or in a subgroup\textsuperscript{516} (median 18%, lower quartile 11%, upper quartile 36%). The one study that did not show an effect targeted adherence feedback to the healthcare provider, rather than the patient, whereas the other studies had the patient as the focus of the intervention. Wilson et al. also note the lack of effect was likely mediated by the ineffective physician-patient interactions arising from the adherence data rather than ineffectiveness of adherence data per se\textsuperscript{515}. Effects on clinical outcomes were again varied, with only three studies reporting significantly improved, or a trend towards improved, clinical outcomes\textsuperscript{512-514}. These studies tended towards larger effect sizes and longer study durations.

Studies on other conditions, such as cardiac-related and mental health conditions, showed more mixed results. The seven cardiac studies showed positive results in three studies, all of which were in an older age population\textsuperscript{502, 505, 506}, but the effect did not persist in two studies\textsuperscript{502, 506} when the intervention was removed. There was no effect on adherence reported in the other three studies on adults\textsuperscript{497, 503, 504} and adherence between groups was not analysed in one study\textsuperscript{135}. Over half reported clinical improvements\textsuperscript{502, 504-506}. The differences in effect on adherence and outcomes did not appear to bear any relationship with whether the treatment was used for primary or secondary prevention of cardiovascular disease. Conflicting results were seen in the three studies examining mental health conditions, with two studies showing improved adherence for psychotic disorder\textsuperscript{508} and schizophrenia\textsuperscript{509}. The study that did not find a difference suffered from poor study design, as patients in both the intervention and control groups effectively received an active intervention – patients in this study were randomised to either feedback of their adherence to lithium, based on electronic monitoring and lithium levels, or feedback based on lithium levels alone\textsuperscript{137}. As both groups received feedback and discussion about their medication-taking, any differences seen in adherence were likely diluted by the improvements in adherence in the ‘standard care’ arm. Future studies should ensure comparator groups are true ‘controls’ to ensure robustness of the study design. None of the studies in mental health demonstrated significantly improved clinical outcomes\textsuperscript{508, 509}; one demonstrated worsened outcomes\textsuperscript{137}. Kozuki et al. investigated the use of visual adherence feedback therapy from an electronic monitoring medication cap accompanied with psychodynamic counselling, and showed a trend towards improved positive and negative symptom scores but this did not reach statistical significance\textsuperscript{508}. Adherence improved post renal transplant in two\textsuperscript{501, 518} of the four studies for renal transplant; however clinical effect was not measured, and in the one study by Joost et al. that did assess outcomes, in terms of transplant rejections, transplant
function and quality of life, there was no effect\textsuperscript{501}. The relationship between other health conditions and effects on adherence and outcomes are less clear due to the small number of studies for conditions such as diabetes\textsuperscript{142, 510}, glaucoma\textsuperscript{499, 511} and inflammatory bowel disease\textsuperscript{496}. None of the studies of these latter conditions showed any significant benefits in surrogate markers of disease control despite two demonstrating improvements in adherence\textsuperscript{510, 511}.

3.3.3.2 Effect of age on effectiveness

From the study data, the effect of age on adherence and clinical outcomes appeared to be associated. All the studies that compared adherence between children\textsuperscript{299, 456, 457} or older aged adults\textsuperscript{502, 505, 506} who received an electronic monitoring intervention, against those who did not, had significant benefits on adherence and outcomes. These studies are however limited to only two health conditions – respiratory\textsuperscript{299, 456, 457} and cardiac\textsuperscript{502, 505, 506} – so the results could be a factor of the condition studied as well as age.

3.3.3.3 Effect of study duration on effectiveness

Duration of the intervention did not appear to be related to the intervention effects. The majority of studies (25 studies) were six months or less\textsuperscript{36, 37, 124, 133-135, 142, 277, 299, 456-458, 496, 498, 499, 504-508, 511, 514-516, 518}; of these, over 70% (18/25) had significant effects on adherence (median 22%, lower quartile 19%, upper quartile 39%)\textsuperscript{36, 37, 124, 133, 134, 277, 299, 456-458, 498, 505-508, 511, 514, 518} and one had effects in a subgroup\textsuperscript{516}. Five demonstrated significant clinical benefits\textsuperscript{299, 456, 505, 506, 519}. In contrast, over half of the studies (6/11) with a longer study duration showed significant effects on adherence but of a lower overall effect size (median 11%, lower quartile 6%, upper quartile 16%)\textsuperscript{501, 502, 509, 510, 512, 513}, of which three showed clinical benefits\textsuperscript{502, 512, 513}.

It appears that studies which are shorter show greater benefits on adherence with a larger effect size than studies of a longer duration (median improvement 22% versus 11% respectively). The effect on clinical outcomes is overall unclear since only a small number demonstrated clinical benefit. This is similar to the findings reported by Vervloet et al.\textsuperscript{445} where studies with a longer follow-up period were less likely to show an effect on adherence. It is known that adherence diminishes with time\textsuperscript{48, 520}, and initial benefits seen in adherence may not be sustained long-term as the novelty of new interventions wear off. There is a need for future studies to address whether the benefits seen with adherence monitors persist in the longer term.

3.3.3.4 Effect of blinding to adherence monitoring function on effectiveness

This review looked at whether participants who were blinded to the adherence monitoring function of the device had better adherence and clinical outcomes. Many studies (14/36) did not report on blinding status\textsuperscript{133, 135, 277, 496, 497, 502, 504, 506, 508, 509, 513, 515, 516, 518}. Those that did document blinding status were generally not blinded (14/22) and participants were aware of the adherence monitoring
function. Only eight studies blinded participants to the adherence monitoring function of the device. Of these, seven (88%) had significant improvements in adherence versus only nine of the 14 (64%) without blinding. Median improvements in adherence reported with blinded studies were generally higher than non-blinded studies, though there was significant overlap (blinded: median 24%, 19%, 31%; non-blinded: median 16%, 10%, 28%). This corresponds with the pattern observed in clinical effect, with a greater proportion of blinded studies (4/8) showing improvements in outcomes compared to non-blinded studies (4/14). The greater improvements in adherence and clinical outcomes seen in blinded versus non-blinded studies may be due to the Hawthorne effect—patients aware of monitoring may have better adherence, which may raise the adherence in the control groups, thus minimising the difference in adherence, and correspondingly clinical outcomes, between the groups.

3.3.3.5 Effect of adherence feedback method on effectiveness

The method used to feedback adherence (indirect versus direct; in real-time or not) did not appear to be associated with the effectiveness of the intervention on adherence, with the majority of studies reporting statistically significant improvements in adherence independent of whether the intervention was administered directly or indirectly; use of both methods, however, appeared to offer more consistent improvements than either direct or indirect alone. The percentage of studies reporting significant improvements in adherence were similar across direct and indirect intervention types, with 67% (6/9) of direct studies and 72% (13/18) of indirect studies reporting significant effects. Those that utilised both direct and indirect methods appeared to have a more consistent effect on adherence with all studies showing a positive effect on overall, or if not overall then subgroup, adherence. Effect sizes across all types were similar (direct: median 22%, 19%, 34%; indirect: median 20%, 12%, 32%; both: median 17%, 15%, 25%).

Clinically, the effect is attenuated but still present, with 33% of direct (3/9) and indirect (6/18) studies showing significant clinical improvements or a trend towards improvement. Comparatively, half of the studies utilising both methods showed improved, or a trend towards improved, clinical benefits. With regards to the relationship between adherence and outcomes, it appears that, overall, of those studies that do show an improvement in adherence, approximately half demonstrate corresponding improvements in clinical outcomes. It is noteworthy though that a sizeable portion did not measure clinical outcomes, particularly in the studies involving indirect interventions, where a third did not report on clinical outcomes.
Real-time feedback appeared to play an important role in mediating adherence as all seven studies that utilised real-time feedback had positive improvements in adherence\(^{36, 37, 457, 505, 506, 510, 512}\) (median 22%, lower quartile 16%, upper quartile 41%), with associated clinical benefits, except in two studies\(^{36, 510}\) which showed no change in clinical outcomes. Of the 26 studies that did not use real-time feedback, approximately two-thirds (17/26) still showed significant improvements in adherence; just under half of those (7/17) had improved, or showed a trend towards improved, clinical outcomes.

The majority of studies used a simple EMD with only five studies utilising an integrated MMS involving either a direct-to-patient approach or both indirect and direct methods. None of these five used real-time feedback. The results on adherence and outcomes are mixed, with half showing no effect on adherence but a trend towards some clinical benefit\(^{504, 516}\), and the other showing significant positive effect on adherence but not on clinical outcomes\(^{133, 509}\). Either way, the clinical effect is, at best, only a trend towards improvement, with none of these five studies reporting any significant changes in clinical outcomes.

### 3.3.4 Summary of relationships between intervention characteristics and clinical outcomes

There were only eight studies that showed statistically significant improvements in clinical outcomes\(^{299, 456, 457, 502, 505, 506, 512, 513}\). Three of these were in asthma in children\(^{299, 456, 457}\), three in cardiac conditions in the older age population\(^{502, 505, 506}\), and the remaining two in HIV\(^{512, 513}\). All demonstrated significant improvements in adherence, with effect sizes ranging from 7%\(^{512}\) to 80%\(^{506}\) (median 27%, lower quartile 16%, upper quartile 47%), though it should be noted that the large effect seen in the study by Ruppar is partly mediated by the large difference in baseline adherence (41%) between the two groups, prior to any intervention. All of these studies utilised a simple monitoring device rather than an integrated device. These studies varied in duration from 4\(^{299}\) to 12 months\(^{502}\), and involved a mix of both direct and indirect use of electronic monitoring to the patient, real-time feedback and blinding to the adherence monitoring function. The lack of a consistent theme in these aspects suggests there is no direct link between the way that the adherence intervention is delivered and the clinical outcome, though conversely the ten studies that had no effect on outcomes tended towards a lack of blinding and real-time feedback, with the majority (eight studies) not feeding back adherence data in real-time to the patient. Though there were mixed reports on adherence effect, the effect sizes observed were generally smaller, ranging from 2%\(^{503, 515}\) to 34%\(^{458}\) (median 16%, lower quartile 6%, upper quartile 22%) than that reported for studies showing a positive clinical effect (median 27%, lower quartile 16%, upper quartile 47%).

Five studies showed a trend towards clinical improvement but did not reach statistical significance. Again, these were a mix of study duration, method of adherence intervention delivery, blinding
status and use of real-time feedback. Interestingly, not all showed improvements in adherence, with two studies\textsuperscript{142, 504} showing no significant effect on adherence overall but a positive trend towards significant improvement in clinical outcomes. The study by Erickson et al. used an electronic device for medication management in patients with hypertension\textsuperscript{504}. This showed a trend towards improved adherence, but as adherence was high in both groups, the difference did not reach statistical significance but seemed to be sufficient to translate to improvements in blood pressure. Likewise, Sutton et al. conducted their study in adults with diabetes and found higher adherence and lower HbA1c in the intervention group; again, baseline adherence was high, which may have reduced the chances of detecting increases in adherence\textsuperscript{142}. Both studies also used medication adherence questionnaires for adherence measurement, and reported on changes in adherence scores rather than percentage adherence. Use of adherence questionnaires tends to overestimate adherence by \textasciitilde15\%\textsuperscript{522} which may reduce the ability to detect changes in adherence via this method.

Three studies\textsuperscript{134, 135, 516} showed improvements in some parameters but no effect on others, and two\textsuperscript{133, 137} showed a negative effect on clinical outcomes, though in these studies, disease control was not the outcome measured. Eight studies did not assess clinical effect at all\textsuperscript{124, 496, 498-500, 507, 517, 518}. These eight were of shorter duration (six months or less).

### 3.3.5 Patient perceptions of the intervention

Eleven studies included questions to ascertain patient perceptions of and satisfaction with the adherence intervention. Seven of these assessed usability of the actual device\textsuperscript{133, 135, 456, 498, 509, 511, 512} though one study did not report the results\textsuperscript{511}; four focused on the acceptability of the adherence feedback and discussion with health providers\textsuperscript{506, 510, 517, 518}. Of the studies that reported patient perceptions relating to the EMD itself, perceptions were found to be negative in a large proportion of patients in four\textsuperscript{133, 135, 509, 512} of the six studies. In the study by Velligan et al., which compared the effect of medication support delivered through weekly home visits by a case worker versus support from an electronic medication manager, overall patient satisfaction scores were higher in the group receiving support from healthcare staff rather than from the device. A significantly higher proportion of patients (38\% in the EMD group versus 5\% in the case worker group) held negative opinions about the intervention involving the device, primarily about the device’s beeps\textsuperscript{509}. Similarly, Wu et al. noted from anecdotal feedback that the EMD was too large and too loud, which resulted in unwelcome questions and possible revelation of the patient’s HIV condition\textsuperscript{133}. In contrast, the medication vial used in the Frick et al. study included a button that silenced the alarm – patient perceptions of the EMD here were much more positive, with 99\% stating they would use the vial again and 97\% finding the alarm helpful\textsuperscript{498}. Artinian et al. reported more mixed results, where
approximately half enjoyed the reminders and felt it helped them stay on schedule with their doses; but a significant portion (44%) hated the device and felt their lives were regulated by the monitor and that it was a nuisance. The usability of the device was also an issue, with 44% having technical difficulties with getting the medicines out from the device or reading the screen\textsuperscript{135}. De Bruin et al. noted that patients preferred the device to have multiple compartments and a smaller, pocket-sized box for daytime doses\textsuperscript{512}.

In contrast, patient perceptions of the adherence intervention itself tended to be more positive than for the EMD\textsuperscript{512}. Patients and health providers generally found reviewing and discussing adherence data the most beneficial aspects of the intervention and “looked forward” to receiving their adherence information\textsuperscript{506, 510 517}. The adherence feedback did not make patients feel uncomfortable\textsuperscript{510}, nor did they find it to be a burden on their time\textsuperscript{518}.

It is noteworthy that although the majority did not set out to obtain information about patient perceptions, four studies attributed patient drop-outs and non-participation in the study to issues with device acceptability by patients\textsuperscript{497, 501, 504, 512}. Joost et al. reported 17 of 129 patients did not want to participate when informed about the project due to the use of the MEMS device, and another three out of 74 patients withdrew after the study start as they did not want to use the device\textsuperscript{501}. Similarly, over 50% of patients chose not to use the device in the study by Christensen et al.\textsuperscript{497} and two out of the 42 enrolled patients dropped out of the Erickson et al. study due to a lack of interest in using the device\textsuperscript{504}. De Bruin et al. had trouble with initial recruitment into the study as 14% of patients refused to be included due to concerns about the size of the device and 6% had fears it would disturb their routine. Yet another 5% later refused to continue in the study as they found the device big and impractical to use and, at study end, another 5% had dropped out for the same reasons\textsuperscript{512}. Training was also briefly discussed in one study as a factor to consider when implementing new technology in a clinical setting. Sabin et al. reported that the device required a “moderate” degree of training and practice which lasted a full day, though sustaining use of the technology thereafter was not found to be burdensome\textsuperscript{134}.

Beyond patient perceptions relating to the device, two studies reported negative clinical outcomes associated with the adherence monitoring. In a study of patients with bipolar affective disorder, higher rates of anxiety, depression and somatism were reported by those who were monitored compared to those who were not\textsuperscript{137}. Wu et al. compared quality of life scores of 64 adult HIV patients who received a disease management assistance system (DMAS) device to the scores of those who did not, and reported a trend towards worsened quality of life with the device\textsuperscript{133}; no differences were noted with disease control.
3.4 Discussion

This literature review highlights the potential for use of EMDs in chronic disease. The majority (70%) of the studies included in this review demonstrated significant improvements in adherence across a range of ages and conditions, from cardiac, respiratory, psychiatric to infectious diseases, over 25 years of publications. The age group of the study population seems to be a factor mediating clinical response to the intervention, with positive effects in both adherence and clinical outcomes noted in the two extremes of the age range – in children and older age. One possible explanation for this effect could be related to the rates of unintentional non-adherence in these age groups. In children, unintentional non-adherence has been reported to be particularly high with forgetfulness being cited as one of the primary reasons for non-adherence in children. Children also tend to show greater improvements in outcomes when adherence is increased than do adults. In older adults, memory failure and cognitive difficulties have been shown to play a key role in non-adherence, which can increase the risks of unintentional non-adherence. Interestingly, Andrade et al. found that use of a prompting device with audiovisual reminders improved adherence significantly in those that were memory-impaired but not in those who had intact memory. Perhaps EMDs are most effective for this particular type of adherence – unintentional non-adherence – and the variability in effectiveness seen across studies actually arises from a dilution of intervention effects by the intentional non-adherers in the study populations. Aspects of the effect of age may also be mediated by the condition being researched, as all the childhood studies were in asthma, and the older age ones were in cardiac conditions (hypertension and heart failure). These conditions have a higher adherence-outcome relationship, where increases in adherence are more likely to be linked with improvements in disease control. The effectiveness of the intervention seen in these age groups may therefore be a result of the health condition being more responsive to changes in adherence, rather than age itself. Indeed, asthma and hypertension were the two most commonly studied conditions, which is not surprising as they represent areas where adherence is more strongly related to outcomes and, as such, adherence interventions are more likely to make a therapeutic difference.

Many studies in this review used EMDs as part of indirect adherence interventions, where adherence data was fed back to the patient in the form of a graphical print-out or other visual display, and discussed as part of a counselling session identifying barriers to adherence, and solutions to these. Yet our review appears to show that direct feedback to the patient from the device is an equally important component to include in the intervention. When direct-to-patient versus indirect methods were compared, studies that included a direct patient-device interaction appeared to fare better: 100% of those studies reported improved adherence versus 70% of those that used the indirect or direct method alone, and 50% showed clinical benefits versus 33% of those
that did not use both. The way in which EMDs are used appears to affect the effectiveness of the adherence intervention.

Several other themes were identified from the review that indicate the aspects of electronic monitoring that are important for effective adherence enhancement. Adherence feedback that occurs in real-time directly to the patient appears more successful in promoting adherence. Those showing adherence and clinical benefits tended to include real-time feedback, and those that had no effect, did not. All studies that included real-time feedback reported significant improvements in adherence, and nearly all demonstrated improvements in clinical outcomes. The two studies\(^{36, 510}\) that did not were in patients with near optimal disease control and who were recruited by advertisement. Rosen et al. investigated the use of electronic monitoring in patients with diabetes; the baseline HbA1c for the active and control groups were 7.5 ± 0.9% and 8.3 ± 1.3% respectively (normal 5.6–7.5%) which was effectively normal in the active group and only slightly out of range in the control\(^{510}\). Similarly, Charles et al. used an electronic device with an audiovisual reminder function for adults with asthma; median asthma control scores were 0.5 in both groups indicating well-controlled asthma (scores below 0.75 indicated well-controlled on a 0 to 6 scale\(^{524}\)). It is difficult to demonstrate improvements in already high levels of disease control, which may explain the lack of effect in these two studies. It is known from behavioural psychology that a behaviour is most effectively reinforced if the feedback is immediate and relevant\(^{525}\). Feedback of a patient’s adherence behaviour is therefore more likely effective if the stimulus, such as an audible reminder or visual display or indicator of when the last dose was taken, is delivered in real-time.

There is a suggestion that use of an integrated medication management approach is not effective, with none of the five studies showing significant clinical effect. This finding was unexpected, as complex interactions involving more than one element are usually more effective\(^{32}\). These interactions may have had a paradoxically negative effect due to the high complexity of the electronic system used, which frequently required patient interaction with the device and may therefore have provided too much disruption to patients’ lives. Indeed, qualitative feedback from these studies all shared negative themes about the devices, with patients complaining that they were intrusive and a “nuisance”\(^{133, 135}\) and rating satisfaction poorly\(^{509}\). This may have affected patient uptake of the intervention, leading to poor effectiveness. All studies also did not use real-time feedback. Conversely, three studies looked at the use of adherence monitoring alone, without any patient involvement or feedback of adherence to assess the impact of the actual electronic monitor on behaviour. These studies showed minimal effect on adherence and outcomes\(^{142, 499, 503}\), emphasising the importance of the feedback aspect of electronic monitoring in improving adherence. On the other hand, it also highlights the potential for these devices to be solely used for
measuring adherence, such as in a clinical trial, as the device itself seems to have minimal impact on behaviour.

Although many studies reported significant improvements in medication-taking, few were able to show corresponding benefits in clinical outcomes. Those that did demonstrate clinical improvements tended to be those that also reported adherence effects of a greater magnitude. It is possible that a minimum threshold of percentage adherence change is needed before any clinical change can be achieved. Whilst there are plenty of studies highlighting the association between adherence and clinical outcomes\textsuperscript{151, 167}, it is not known whether the relationship is a linear, exponential or logarithmic one, and the relationship is likely to change depending on the disease, medication and patient. This review found that, on average, only half of those interventions that improve adherence translate to corresponding improvements in clinical outcomes. More importantly, the review also found that many studies, whilst demonstrating robust methodologies around adherence research, did not measure clinical outcome data or where data were measured, the outcomes were not relevant to the condition studied. In the Elixhauser et al. study, which reported a significantly negative effect on clinical outcomes\textsuperscript{137}, the study was conducted in patients with bipolar affective disorder where lithium adherence was the main objective of the intervention. However, the clinical outcome studied was not one clearly correlated with lithium adherence in patients with bipolar disorder. Lithium is the mainstay of treatment in bipolar for prevention of manic relapses, so one could expect that a validated measure of mania symptoms, such as the Young Mania Rating Scale\textsuperscript{526} or Bech-Rafaelsen Mania Scale\textsuperscript{527}, would have been a more appropriate clinical outcome, rather than a general psychological symptom questionnaire. Moreover, the Symptom Questionnaire chosen was originally developed primarily to measure distress and hostility rather than clinical response to lithium or disease control in bipolar disorder\textsuperscript{528}.

Similarly, even in conditions where markers of disease control are easily measured and validated disease control questionnaires exist, there is a wide variability in the measures used and outcomes studied. These studies, such as ones in asthma\textsuperscript{36, 37, 299, 456-458}, heart failure\textsuperscript{135, 502}, hypertension\textsuperscript{497, 503-506} or diabetes\textsuperscript{142, 510}, tend to routinely report clinical outcomes but the outcomes reported on differ. In the six asthma studies alone, six different asthma control measures were used, ranging from validated questionnaires such as the Asthma Control Test (ACT)\textsuperscript{37, 457} to an unspecified “symptom questionnaire”\textsuperscript{299}. Likewise in HIV, where symptom questionnaires are less relevant and objective laboratory measures are the mainstay of disease monitoring, some studies included only viral load\textsuperscript{277, 515}, whereas others included viral load and CD4 count. The lack of standardisation in outcome measures across the same disease state makes inter-study analyses and comparisons difficult. We have improved vastly in the way we measure adherence, which is reflected in the methods used in these studies to collect adherence data. None used self-report alone, and
electronic monitoring – the gold standard in adherence measurement$^{493}$ – was consistently used across nearly all but two studies$^{137, 505}$. Many used more than one objective adherence measure. Whilst we have become very adept at handling adherence data, there is now a more urgent and relevant need to focus on what really matters – patient-related outcomes. For research to focus on health outcomes in the future, there is perhaps a need to identify clear and easily measured markers of disease control which can be applied consistently across different research studies and clinical settings. Adherence should not be a target by itself, but considered to be a means to achieve therapeutic outcomes. Future adherence studies should all aim to include clinical outcomes as an endpoint, as achievement of 100% adherence is meaningless if patients are not deriving the clinical benefits required.

Lastly, there is a need to consider the patient at the receiving end of all these interventions. Only a few studies reported on patient acceptability and feasibility of these interventions. Those that did found patient perceptions of the devices were negative, but perceptions about the adherence interventions themselves were positive, particularly relating to the feedback of the adherence data and opportunity for interaction with the health provider. Issues relating to the loudness of the reminder and device size appear to be common themes amongst the feedback that need to be considered in future adherence interventions involving EMDs. Devices where patients have the ability to silence reminders may be more acceptable to them. Training is a factor that will also need to be taken into account, particularly as EMDs evolve and more EMDs become available for use. These results highlight the importance of including feasibility and patient acceptability measures in future intervention studies, as for interventions to even have a chance of being successful, they must be used by the patient and health providers.

### 3.5 Conclusion

In summary, this review has found that EMDs do have the potential to improve medication adherence in chronic disease. Whether these improvements translate into benefits for clinical outcomes is less clear. There appear to be particular factors relating to the population, disease and intervention itself that play key roles in dictating the effectiveness of the EMD-based intervention. Children or older aged adults appear to respond better to such interventions, and those disease states where there is a clear adherence-outcome relationship seem to demonstrate clinical benefits more consistently, at least for surrogate markers of disease control. The lack of standardised outcome measures that reliably and accurately reflect disease control impedes the ability for definitive conclusions to be drawn around the effect of EMDs on clinical outcomes. Interventions that involve direct-to-patient adherence feedback in real-time using simple EMDs appear to be most effective. Whilst there are signals in the literature that indicate the effectiveness of EMDs as
adherence interventions, much remains unanswered about what, who and how interventions should be delivered, which need to be addressed by well-conducted studies. Future research should focus on the effect on clinical outcomes using standardised and validated tools; the sustainability of improvements in the medium to long term; and the patient acceptability of such interventions.
Chapter 4: Electronic monitoring devices in research and practice: a review

This chapter presents a clinical commentary review on the role of EMDs in the research and clinical setting. It provides an overview of currently available EMDs and the evidence supporting their use in adherence studies. This was published in the Journal of Allergy and Clinical Immunology: In Practice, which is the companion journal of Journal of Allergy and Clinical Immunology. Since its publication in 2013, it has been cited by 17 publications.

Title:

Adherence monitoring and e-health: how clinicians and researchers can use technology to promote inhaler adherence in asthma.

Journal:

Journal of Allergy and Clinical Immunology: In Practice 2013; Vol 1: pages 446-54

Authors:

Amy Hai Yan CHAN, Helen REDDEL, Andrea APTER, Michelle EAKIN, Kristin RIEKERT, Juliet FOSTER.

Contributions:

Amy CHAN was involved in the conception of the paper, literature review, co-ordination of the paper write-up, data collection on different devices, manuscript write-up and review for submission for publication

Helen REDDEL was involved in the literature review, manuscript write-up and review for submission for publication

Andrea APTER was involved in the literature review, manuscript write-up and review for submission for publication

Michelle EAKIN was involved in the literature review, data collection on different devices, manuscript write-up and review for submission for publication

Kristin RIEKERT was involved in the literature review, manuscript write-up and review for submission for publication

Juliet FOSTER was involved in the conception of the paper, literature review, co-ordination of paper write-up, manuscript write-up and review for submission for publication
4.1 Abstract

In the last decade, rapid technological developments have advanced EMDs (EMDs) for asthma inhalers beyond simple recording of actuations to providing adherence promotion features and detailed information about patterns of medication use. This article describes currently available EMDs, discusses their utility and limitations in assessing adherence, and describes the potential for EMD-based adherence promotion interventions in clinical settings. To date, the main use of EMDs has been in clinical research. In selected populations, simple EMD-based adherence interventions, delivered either through clinician-to-patient feedback about medication use, or by direct-to-patient reminders for missed doses, can significantly improve adherence. Further work is now needed to determine the impact of EMDs on clinical outcomes, and their cost-effectiveness and feasibility for different clinical settings, including in disadvantaged populations. If this evidence can be provided, the use of EMDs could expand into the management of asthma in populations with high healthcare costs, such as severe asthma. In the future, medication monitoring could help distinguish poor treatment response from poor adherence, guide prescribing decisions and prompt providers to discuss barriers to adherence; and electronic health records may provide the gateway for integrating medication use monitoring into digital chronic care management.

4.2 Paper I: Adherence monitoring and e-health: how clinicians and researchers can use technology to promote inhaler adherence in asthma

4.2.1 Medication adherence in asthma is suboptimal

Patient adherence with therapy is the necessary link between effective treatment and improved patient outcomes. However, recent asthma studies using objective measures show significant underuse of controller therapy in children (25–76% of prescribed doses) and adults (1%–93%)\(^{29}\). At a population level, poor adherence contributes to greater asthma morbidity including increased symptoms, more frequent oral steroid courses, lower lung function, poorer quality of life, greater healthcare utilisation and higher asthma-related mortality\(^{11, 12, 23, 530}\). For these reasons, patient adherence is a top priority area for research\(^{264, 531}\) and clinical practice\(^{89}\).

4.2.2 Why are electronic monitoring devices for inhalers needed?

Medication-use-monitoring can provide important information for patients, researchers and health professionals, with the aim of facilitating improved adherence and improving treatment prescribing, but available monitoring methods vary in quality. Patient self-report and clinician assessments of medication adherence are notoriously unreliable\(^{107, 124, 521}\). Assessment from canister weight or dose counter is limited by undetectable dose-dumping, i.e. multiple actuations to conceal poor adherence\(^{124, 532}\). Increasingly, clinicians in some health systems such as health maintenance
organisations are able to obtain real-time or retrospective pharmacy records showing when medications were dispensed. Dispensing data can provide an estimate of maximum overall inhaler use in a given period\cite{533}, but few countries have complete dispensing registers, and, unlike EMDs\cite{534}, these records cannot confirm timing of use and have limited sensitivity to change in adherence patterns. For example, despite regular dispensing of controller medication, a patient may take large amounts during symptomatic periods then nothing for weeks. EMDs capture this level of detail by recording the time and date of every puff, providing precise, personalised data to support the adherence promotion strategies of patients, researchers and health professionals.

In this paper, we review the state-of-the-art of EMDs for inhaled medications. We describe the features, reliability and limitations of currently available EMDs, review evidence for their effectiveness in monitoring and promoting adherence, discuss emerging roles for EMDs, and identify the changes needed to move electronic monitoring from the research arena into clinical practice.

4.2.3 Features and reliability of currently available electronic monitoring devices

4.2.3.1 Electronic monitoring device features and functions

Most currently available EMDs (Table 1) are designed for pMDIs. Because of the wide variation in inhaler design, the majority of EMDs only function with one specific inhaler type. Most EMDs are retro-fitted to commercial inhalers, with only two electronic nebulizers (not used routinely for asthma) having integrated adherence monitoring. With some EMDs, data collection may be concealed; ethical issues should always be considered in this context\cite{136}.
**Table 1. The features and reliability of currently available electronic monitoring devices**

<table>
<thead>
<tr>
<th>Device name</th>
<th>Manufacturer</th>
<th>Device compatibility</th>
<th>Description</th>
<th>Actuation recording</th>
<th>Data transfer</th>
<th>Reliability/ accuracy</th>
<th>Features / limitations</th>
<th>Device Cost*</th>
<th>Re-usable#</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Commercially available EMDs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthmapolis[5, 535]</td>
<td>Asthmapolis, Midwest</td>
<td>Standard pMDI</td>
<td>Disposable adapter cap that mounts onto the end of a canister of a standard pMDI. Combines a GPS tracking device with a mobile smartphone application.</td>
<td>Uses GPS to determine time &amp; location of inhaler use. Lights on device shows actuation recording, charging &amp; battery level. Device can store &gt;100,000 logs</td>
<td>Data stored on device can be sent to a remote server or computer via a USB port or Bluetooth to cellphone. Usage patterns can be provided to patients via weekly email and portal reports.</td>
<td>No published data available</td>
<td>1. Battery life 2-3 days; Device recharges with a wall charger or USB power source; 2. Easily transferable to a new canister – does not modify drug delivery or actuation; 3. Engages patients via text reminders and education content; 4. Able to track rescue inhaler usage when and where it happens</td>
<td>$230 per year</td>
<td>Yes</td>
</tr>
<tr>
<td>Doser[107, 536-538]</td>
<td>Meditrac, Inc., Hudson, MA</td>
<td>Standard pMDI. Compatible with use of a spacer but not Haleraid.</td>
<td>A round, flat device secured to the top of a pMDI canister. Has a small LCD screen to view results</td>
<td>When pressure is applied to actuate the inhaler, an electromechanical switch records the actuation. Records total daily use (number of puffs each day) for up to 30 days.</td>
<td>Data can be read from the device screen but cannot be uploaded. History of actuations is obtained by scrolling through the display.</td>
<td>Actuation recording accuracy 94% to 97%[36, 120]; failure rate 63/301[107], 2/101[120], 8%[120]; 1. Has covert and overt modes so feedback on usage can be displayed or hidden; 2. Stores data for only 30 days; 3. Data cannot be uploaded; 4. Counts down to when inhaler is empty; 5. Beeps when fewer than 20 actuations remain in canister; 6. Detects actuations more than 1 second apart, therefore cannot detect puffs performed in quick succession; 7. May not fit some newer pMDIs; 8. Battery lasts 13 months; 9. FDA approved device</td>
<td>US$28 per unit</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Smartinhaler Tracker[35, 36, 120]</td>
<td>Nexus6, Auckland, NZ</td>
<td>pMDI; different Smartinhaler mouldings for different medications; inhaler cap may not necessarily fit</td>
<td>Monitoring device situated in a plastic case into which the inhaler canister is placed</td>
<td>Incorporates a switch which is activated when canister is depressed recording time &amp; date stamp of actuation. Stores up to 1600 logs</td>
<td>Date may be uploaded to a computer via a serial cradle &amp; serial communication link. Web-based programme used to set up the device.</td>
<td>Actuation recording accuracy up to 100%[36, 120]; Failure rates of 0/10[120], 13/99[120], 2/101[120], 9%[120], 1.9%[120]; 1. Records time and date of actuation; 2. Can incorporate an audiovisual reminder for missed doses &amp; provide visual feedback on inhaler use 3. Time stamp has a resolution of seconds. 4. USB or cellphone upload available on request</td>
<td>US$120 per device</td>
<td>Yes; potential issues with blocking of nozzle</td>
<td></td>
</tr>
<tr>
<td>Device name</td>
<td>Manufacturer</td>
<td>Device compatibility</td>
<td>Description</td>
<td>Actuation recording</td>
<td>Data transfer</td>
<td>Reliability/accuracy</td>
<td>Features / limitations</td>
<td>Device Cost*</td>
<td>Re-usable#</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------</td>
<td>----------------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>---------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>SmartTrack</td>
<td>Nexus 6, Auckland, NZ</td>
<td>pMDI; different SmartTrack mouldings for different medications</td>
<td>Monitor fits around a pMDI. Has a LCD screen to display time, date, battery level &amp; other user feedback as desired</td>
<td>Records time and date of actuation by optical sensor (no mechanical parts). Able to record actuations with a time and date stamp with a resolution of seconds. Stores up to 3200 logs.</td>
<td>Optional remote data upload by SIM card to secure website available or upload manually to computer via a docking station and USB cable. Option to communicate with Smartinhaler Live software</td>
<td>Mean accuracy of actuation logs reported to be 97 to 99%. Reminders were 100% accurate. Failure 1/10.</td>
<td>Uses a standard AAA battery; Optional features include 1. Visual and/or audio adherence feedback (overt &amp; covert modes selections); 3. Graphical and numerical adherence data can be viewed/uploaded from secure website or on desktop software; 4. Audio reminders tailored to weekday &amp; weekend routine; 5. Personalised ringtone selection; 6. Battery installation/removal logging; 7. Audio reminder on/off logging; 8. Security screw to ensure inhaler cannot be taken out during monitoring</td>
<td>US$220</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Custom-built EMDs**

| Device linking Turbuhaler with a pneumotachograph | AstraZeneca, Sodertalje, Sweden | Budesonide Turbuhaler dry powder inhaler | The Turbuhaler is connected in line with the pneumotachograph via a spacer, consisting of an adapter and sealing cap. Any flow generated via inhalation is detected by the Data Storage Spirometer (DSS) | A DSS records the peak inspiratory flow via the device each time a dose of medication is inhaled. The DSS consists of a pneumotachograph and computer | After each inhalation and exhalation, values are shown on the DSS display, and are uploaded at study visits | Missing data due to malfunction of the DSS reported on 2.5% of the study days during the treatment period | Records date and time of inhalations Assesses peak inspiratory flow. Reduces handling errors with the turbuhaler | Data not available | Yes |

<p>| Diskus Adherence Logger, DAL | Daniel Bogen, PhD Philadelphia, Pa. Not in commercial production | Diskus (Accuhaler) dry powder inhaler | Attaches externally to the patient’s Diskus – consists of 3 subsystems: a data collection module which detects doses, an interface module to allow uploading to a computer, and computer software to initialize the data collection | Senses motion of the dose delivery lever of the Diskus and records date and time of lever motion. Operates via an electromagnetic system. | Adherence data able to be uploaded onto a computer via a USB port and connecting cable | 1. Expected battery life of 5.8 months; 2. Time logs accurate to one minute; 3. No interference with normal inhaler function | Available through collaboration with D Bogen | Yes |</p>
<table>
<thead>
<tr>
<th>Device name</th>
<th>Manufacturer</th>
<th>Device compatibility</th>
<th>Description</th>
<th>Actuation recording</th>
<th>Data transfer</th>
<th>Reliability/accuracy</th>
<th>Features / limitations</th>
<th>Device Cost*</th>
<th>Re-usable#</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCA study device(^a)</td>
<td>Trinity Centre for Bioengineering, Trinity College, Dublin</td>
<td>Diskus dry powder inhaler</td>
<td>Device that stores an audio recording of each inhaler event. Software program checks time/date of audible steps in inhaler use</td>
<td>Adherence device that records an audio signal with each inhaler use</td>
<td>Database of audio recordings of inhalations generated. Data are transferred from device to PC for local processing.</td>
<td>5% (unpublished)</td>
<td>Detects actuation and inhalation</td>
<td>Not commercially available</td>
<td>Data unavailable</td>
</tr>
<tr>
<td>Nebulizer EMDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adaptive aerosol delivery (AAD) nebulizer system(^a)(^b)(^c)</td>
<td>Philips Respironics, Chichester, England</td>
<td>Nebulized medications; not currently used in routine asthma care</td>
<td>Jet nebulizer connected to a Patient Logging System (PLS).</td>
<td>The processor collects pressure data from the nebulizer via a sensor and analogue-to-digital converter, which is stored on a memory chip</td>
<td>Data able to be downloaded from PLS to a computer. Compatible with the I-neb insight Online system allowing uploading of data onto a server to provide remote access to data by clinician</td>
<td>12.8% of PLS units malfunctioned in one study(^d)</td>
<td>Records date and time of each nebulizer treatment and cumulative inhalation time. Gives visible and audible feedback signals to indicate when dose delivery is complete. Monitors amount of drug delivered per treatment</td>
<td>Data not available</td>
<td>Yes</td>
</tr>
<tr>
<td>Akita(^e)</td>
<td>Activaero GmbH, Gemunden, Germany</td>
<td>Nebulized medications; not currently used in routine asthma care</td>
<td>Nebulizer system including smart card technology to record adherence and breathing data. The smart card is an electronic microchip that transfers information to the AKITA control unit.</td>
<td>Saves data onto a microchip (Smart Card)</td>
<td>Data can be transferred to a computer for analysis</td>
<td>Data unavailable</td>
<td>Provides information on: number of breaths per treatment; duration of treatment; timing of inhalation; inhaled drug dose (overall vs. seven-day dose). Inhalation with AKITA can be adapted to the patient</td>
<td>Data not available</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note: The SmartDisk, SmartTurbo (manufacturer: Nexus6), Turbohaler Inhalation Computer (manufacturer: Smartmist), MicroDose with Smartinhaled Live (MicroDose Therapeutx Inc. and Nexus6) and the Electronic Diskhaler are not included in this table due to limited data/early developmental status.

Discontinued devices that are no longer available, including the MDI Log, MDI Chronolog and Nebulizer Chronolog are also not included.

*Device cost does not include cost of medication itself where relevant, or the cost of data transfer services or web maintenance for remote monitoring.

#Re-usable by same patient with replacement medication.
EMD functionality is no longer limited to actuation recording. Some devices record inspiratory flow data (e.g. the Turbuhaler/pneumotachograph device) which may be useful for exploring relationships between inhaler technique and poor outcomes in patients with good adherence, although it cannot substitute for a face-to-face check of inhaler skills\(^5\). Some EMDs offer interactive features such as customisable ringtone reminders for promoting adherence (e.g. SmartTrack\(^5\))\(^5\) and direct data uploading to a secure website or via Bluetooth connection to a cellphone (e.g. Asthmapolis\(^5\), which also allows Global Positioning System (GPS) tracking; Figure 1). Remote data uploads reduce data loss and allow patients and/or providers to monitor adherence data without the need for clinic visits.

**Figure 1. Images of some electronic monitoring devices discussed in this paper**

![Images of some electronic monitoring devices](image)

<table>
<thead>
<tr>
<th>Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthmapolis device</td>
</tr>
<tr>
<td>Doser device</td>
</tr>
<tr>
<td>INCA device</td>
</tr>
<tr>
<td>Smartinhaler device</td>
</tr>
<tr>
<td>Smarttrack device</td>
</tr>
<tr>
<td>Diskus Adherence Logger (DAL) device</td>
</tr>
</tbody>
</table>

### 4.2.3.2 Accuracy and reliability of electronic monitoring devices

As with any technology, accuracy and reliability are important considerations. Under laboratory conditions, EMD recording accuracies compared with written diaries are 90% or higher, and close to 100% for newer devices (Table 1). Reported failure rates, for example due to device malfunction, vary between 0 to 21%. However, the rapidity of technological development means that published performance data becomes quickly superseded.
4.2.4 The role of electronic devices in monitoring adherence with asthma inhalers

At a population level, research shows that stopping treatment can leave patients at serious risk but understanding patients’ patterns of inhaler use may become paramount since recent evidence suggests that intermittent or as-needed controller use may be as effective as regular regimens for some patients. EMDS produce detailed data about temporal changes in patterns of inhaler use even over relatively short time periods and can support the identification of patients who may benefit from intermittent regimens. Since improved adherence is most likely to benefit those with the poorest adherence, EMDS may allow identification of patients requiring more intensive interventions. If used reliably, EMDS can also help clarify the relationship between patient attitudes and adherence, explain heterogeneity in treatment response, and plot the time course of adherence change.

4.2.5 The role of electronic monitoring devices in adherence promotion in asthma

Two different approaches have been used for EMD-based adherence promotion studies: health professional-to-patient discussion based on EMD data, and direct-to-patient EMD reminders for missed doses. Relatively few publications exist, but early data are promising.

4.2.5.1 Face-to-face adherence feedback studies when utilising electronic monitoring devices

Objective, personalised, feedback data on patterns of medication use, provided by EMDS, can open discussions between the health professional and patient, and provided feedback is given sensitively and with respect for the patient’s autonomy, it can facilitate shared decision making and optimise treatment routines.

A number of trials, from 2–18 months’ duration, have examined the use of adherence feedback as a strategy to improve asthma patients’ adherence, either alone or in conjunction with a behavioural intervention. Feedback generally took the form of reviewing printouts of inhaler use, with constructive and positive discussion and suggestions, problem-solving or goal-setting sessions. The impact of adherence feedback on asthma outcomes such as asthma control and ED visits across these studies was inconsistent. Most studies demonstrated improvement in adherence during the feedback intervention. One exception was a study which compared asthma education with adherence feedback plus problem-solving amongst disadvantaged inner city adults with moderate to severe asthma, in which electronically-monitored adherence did not differ between groups. This may have been due to complex issues which are difficult to address in disadvantaged populations.

Limitations of existing studies include high adherence in some control groups, possibly due to self-selection of motivated volunteers in research environments, free medication and/or frequent study...
visits. Awareness of adherence monitoring may inflate adherence, and although early evidence suggests that this lasts for only around seven days, more data are needed. Collection of run-in EMD adherence data would be beneficial, to ensure baseline adherence is comparable between randomisation groups and to allow monitoring awareness to subside. Adherence tends to decrease over time in research studies, so although adherence may be significantly higher in the intervention group at study end, the long-term duration of effect is uncertain. These limitations may impact the generalisability of study findings to clinical settings.

4.2.5.2 Direct-to-patient adherence reminder interventions using electronic monitoring devices

Direct-to-patient reminders about medications can help patients with chronic illness to establish medication-taking routines and increase engagement with self-management. Two published RCTs have investigated the effectiveness of inhaler reminders for improving adherence. In one six-month study in adults with asthma, the EMD beeped for up to an hour if the dose was not taken by a patient-determined time, and a light changed colour once the dose was taken. Adherence over weeks 13–24 was significantly higher in the reminder group compared with the control group (93% vs 74%, p<0.0001). The second study, in children, of eight-week duration and reported only in an abstract, had twice-daily inhaler reminders that rotated through 14 different ringtones (cow mooing, movie themes etc.). Median adherence in the last two weeks of the study was significantly higher in the reminder group (92.0% vs 51.5%, p<0.0001). Neither study showed significant differences in asthma outcomes.

These studies are limited by a lack of baseline adherence data, and relatively high adherence in control groups, perhaps reflecting selection bias. They suggest the potential for reminders to positively change adherence behaviour, but much more evidence from longer pragmatically-designed trials is needed to assess the clinical impact, especially in real-world practice populations.

4.3 Discussion

With the rapid development of communications technology, and increasing awareness of the importance of patient-centred care, interest in remote monitoring of chronic illnesses is growing among physicians and consumers. Technology in EMDs for inhaled asthma medications have advanced, with devices now offering customisable reminder systems, internet/cellphone applications, inspiratory flow recording, GPS tracking, and feedback to health professionals and patients via web-based interfaces, email and/or text messages. However, more evidence is needed to establish their feasibility and cost-effectiveness for use in clinical practice, and to clarify the populations and clinical contexts in which they may improve asthma outcomes or reduce healthcare costs.
EMDs have a unique role in monitoring adherence and investigating related health outcomes, by providing information about the pattern of medication use that is unobtainable from other methods. This is important in light of recent evidence that intermittent use could be as effective as regular ICS use for asthma control in some patients. In addition, EMDs can contribute to adherence promotion, either through direct reminders or as part of a behavioural intervention, with benefits remaining up to two years, although benefits may not be sustainable once feedback is removed. EMD intervention studies have been conducted in a variety of populations, ranging from research volunteers to inner-city minorities with major socio-economic disadvantage, but there is still a paucity of studies outside research settings which can assess acceptability and feasibility in real-life practice. Most EMD intervention studies to date have not been able to demonstrate changes in clinical asthma outcomes, or have been unable to link improved adherence with better health outcomes. This may partly relate to the brevity of the interventions; differing asthma phenotypes requiring differing treatment intensities; inappropriate prescribed doses; a potential lag of several months between poor adherence and negative asthma outcomes; ‘ceiling’ or threshold effects on response to ICS; and the tendency for improved adherence in the lead-up to an exacerbation. Population-based evidence tends to support the relationship between poor adherence and poorer asthma outcomes, but the current evidence from intervention studies remains weak.

### 4.3.1 What are the evidence gaps?

Existing EMD studies have essentially represented proof-of-concept for their use in adherence monitoring and promotion. Most have been conducted in research environments with technical support for device checking and data handling, with trained clinicians having time to deliver appropriate counselling. Feasibility data are needed from normal clinical settings, because significant barriers to implementation of adherence feedback interventions may be concealed in research studies in which patients and clinicians are actively recruited and reimbursed for participation. Patients, particularly those from disadvantaged populations, may fail to attend clinic visits and lose EMDs, and healthcare professionals may lack the resources and time to review patients’ adherence data and provide counselling. Longer term, larger studies are needed to determine whether adherence improvements can be sustained, and to demonstrate which feedback interventions can reliably improve asthma outcomes to ensure these relatively costly interventions produce useful outcomes beyond the research setting.

At the present time a key barrier to implementation of adherence interventions is the lack of evidence for sustained improvements in asthma outcomes. Longer, larger or more targeted studies may show clinical benefit in those patients for whom poor adherence drives poor asthma control, so
EMD research will be important for facilitating the identification of patients who would benefit from adherence interventions.

4.3.2 What are the most promising areas for use of Electronic Monitoring Devices?

The greatest potential use for EMDs in coming years appears to lie in three main areas: personal patient-driven use, clinical management of difficult-to-treat asthma, and clinical research.

Recent surveys\textsuperscript{560} indicate a substantial appetite for personal patient-driven health monitoring in populations aware of e-health and technological developments. Several EMD manufacturers report engaging in direct-to-patient marketing; and their customers use EMDs as dose counters, to monitor controller medication use, or to set inhaler reminders. This market is likely to largely comprise patients with high health literacy\textsuperscript{565} and to exclude disadvantaged and minority populations, but its existence may facilitate progress on hardware and software design and connectivity issues.

In clinical practice, the most promising indications for EMDs lie in the management of severe asthma\textsuperscript{564}, which is associated with high health costs. In particular, EMD data could help identify asthma that is poorly-controlled due to poor adherence with ICS\textsuperscript{529}. They could generate cost savings by better informing prescribing of expensive add-on therapies, such as biological agents, where the EMD cost may be less than one month’s treatment. EMD data could prompt discussion of adherence barriers, and identify who might benefit from flexible ICS dosing strategies\textsuperscript{529,566}.

However, feasibility issues in populations with diverse medical and social problems, complicated by poverty and low health literacy, must be investigated, including the patient’s ability and willingness to use EMDs and appropriately engage with interventions, and the design of acceptable feedback strategies\textsuperscript{552}.

Asthma is an area of major health disparity. The worst asthma outcomes and adherence are seen amongst those who have difficulty obtaining even basic medical care and are unlikely to have access to EMD interventions\textsuperscript{567,568}. Benefits to these populations from EMD utilisation will mostly likely stem from the information gathered from EMD research to inform public health initiatives targeting these disparities.

In research, use of EMDs may allow greater insight into heterogeneity of treatment response to controller medications and risks associated with over-use of reliever medications\textsuperscript{467}; particularly in real-life rather than select populations. Other high priorities for research include identifying the impact of pattern of inhaler use e.g. regular/irregular/intermittent\textsuperscript{23,380,554} on adverse events (e.g. overuse when symptomatic) – particularly in early phase trials of inhaled medications-and clinical asthma outcomes.
4.3.3 Limitations of current EMDs

Healthcare consumers need to be aware of potential pitfalls in using new gadgets. There is only a small range of reliable EMDs, particularly for dry powder inhalers, and some devices are vulnerable to changes in inhaler design. EMDs need to be reliable and user-friendly, but technology develops quickly, and it may not be feasible to publish performance data for every model; standardised QC processes, prior to issue to patients and after return, are necessary to identify faults and reduce the risk of device failure\textsuperscript{34, 552}. Other current limitations include the cost of the device and data transfer services\textsuperscript{564}; and the diverse software and web platforms used by different manufacturers, which make it difficult to assess adherence across available medications. EMD data can be complicated to synthesize. Manufacturers are increasingly offering analytic options within their software, but there is a need for standardised evidence-based adherence metrics to facilitate consistent analysis and reporting. Finally, EMD data are only useful if the EMDs are used as intended by patients; however, people may share medications and break, lose, or tamper with the EMD rendering the data less useful.

4.3.4 Moving EMDs from research into clinical practice – what is needed?

EMDs are considered to be too complicated and expensive to incorporate into routine clinical practice\textsuperscript{552}, but with rapidly improving technology, the cost and complexity should decrease while reliability increases. Cost may be offset by savings seen with improved asthma outcomes, particularly in severe asthma where the cost of increased healthcare is extremely high\textsuperscript{564}. Other barriers to use of EMDs in the clinic include the lack of reimbursement for devices, staff time, training and patient counselling\textsuperscript{552}. A useful model may be the reimbursement of continuous glucose monitors for juveniles with diabetes, where increasing research evidence for effectiveness is leveraging insurance coverage\textsuperscript{569}.

Given the existing evidence for effectiveness of EMD-based interventions in improving adherence, and the limitations identified above, further well-designed studies are needed to strengthen this evidence, particularly to clarify the link between improved adherence and improved asthma outcomes. Large scale implementation studies, in a range of populations and health contexts are needed, for a robust examination of their cost-effectiveness, feasibility and acceptability. Such evidence would potentially support EMD interventions as a reimbursable clinic-based or self-management activity.

Initial implementation data from the Cincinnati Children’s Hospital Medical Center, where adherence feedback is routinely delivered in a specialised adherence unit for adolescents, show that it is feasible to utilise EMD data within these specialist appointments and that the approach is accepted well by patients and families\textsuperscript{569}. However, more EMD studies are needed to build an
evidence base around the most effective feedback formatting. Further, it is plausible that conflict situations may arise if the patient’s self-reported adherence does not concord with feedback data. In research studies using EMD feedback, staff were trained in non-threatening, supportive adherence communication\textsuperscript{124, 157, 299, 458, 530, 558}, and had time for such counselling. Development of suitable tools and training for clinical settings will also be needed, both for optimal device management and to facilitate health professional-patient communication. Health professionals should already have many communication skills needed to facilitate conversations about medication adherence, but formalized training is often necessary to understand when and how to use specific skills most effectively; indeed, in a recent meta-analysis the odds of patient adherence were 1.62 times higher in patients of trained than of untrained physicians\textsuperscript{61}.

Governments and healthcare organisations must ensure that budgets, systems and staff are ready for an increasingly digital environment, in order to take advantage of this new era of personalised healthcare management\textsuperscript{561}, and the introduction of electronic health records may provide a gateway. Data from EMDs may be interfaced with electronic records to allow seamless transition of care between different health settings, development of management plans personalised for the patient based on their adherence data and promote patient autonomy over their own healthcare. In the meantime, EMDs already offer stand-alone adherence monitoring, PC software, and internet applications which can be used by clinicians and researchers to better support and understand patients’ asthma self-management. More research is needed to identify the clinical contexts in which this can be both feasible and cost-effective.
Chapter 5: Factors to consider when using electronic monitoring devices in research and practice

This section discusses the practical factors to consider when using EMDs in research and practice, including when, what and how to test for accuracy and reliability of EMDs. It includes a framework for testing EMDs which was published as a paper in the Journal of Allergy and Clinical Immunology: In Practice. This framework was applied to the in-vitro testing of two different EMDs. The results of this testing are described in this section which were presented as a poster and later published as a conference proceeding, and paper in the Journal of Allergy and Clinical Immunology of which I am a co-author.

Title:
Using electronic monitoring devices to measure inhaler adherence: a practical guide for clinicians

Journal:
Journal of Allergy and Clinical Immunology: In Practice 2015: Vol 3: pages 335-349.

Authors:
Amy Hai Yan CHAN, Jeff HARRISON, Peter BLACK, Edwin MITCHELL, Juliet FOSTER

Contributions:
Amy CHAN was involved in the paper conception, literature review, collection of data on different devices, development of testing frameworks and checklists and how to troubleshoot problems found, co-ordination of paper write-up, manuscript write up and review for submission for publication

Jeff HARRISON was involved in the development of testing frameworks, manuscript write-up and review for submission for publication

Peter BLACK contributed to the original study conception regarding need for testing of electronic monitoring devices and development of original test frameworks

Edwin MITCHELL was involved in the development of testing frameworks, manuscript write-up and review for submission for publication

Juliet FOSTER was involved in the paper conception, literature review, development of testing frameworks and checklists and how to troubleshoot problems found, manuscript write up and review for submission for publication
5.1 Abstract

Use of EMDs for inhalers is growing rapidly due to their ability to provide objective and detailed adherence data to support clinical decision-making. There is increasing potential for EMD use in clinical settings, especially as cost-effectiveness is realised and device costs reduce. However, it is important for clinicians to know about the attributes of different EMDs so they can select the right device for their patients and understand the factors which impact the reliability and accuracy of the data EMDs record. This paper gives information on where to obtain EMDs, describes device specifications and highlights useful features for the clinician and patient, including user feedback data. We discuss the benefits and potential drawbacks of data collected by EMDs and provide device users with a set of tools to optimise the use of EMDs in clinical settings; such as advice on how to carry out brief EMD checks to ensure data quality and device reliability. New EMDs on the market require pre-testing before use by patients. We provide information on how to carry out EMD pre-testing in the clinic and patient’s homes, which can be carried out by health professionals or in collaboration with researchers or manufacturers. Strategies for interpreting and managing common device malfunctions are also discussed.

5.2 Paper II: Using electronic monitoring devices to measure inhaler adherence: practical guide for clinicians

5.2.1 Introduction

Despite effective medications for asthma and chronic obstructive pulmonary disease, adherence with inhalers is often suboptimal\textsuperscript{102, 570, 571}. In asthma, poor adherence with preventive treatment is associated with reduced quality of life and increased asthma symptoms, oral steroid use, hospitalisation and mortality\textsuperscript{10-12, 530, 572, 573}. Over-use of rescue medication is also an important issue, associated with poorer health status and mortality\textsuperscript{573-576}.

It is difficult to accurately measure inhaler use in clinical settings since the most commonly utilised measurement methods suffer from subjectivity, poor reliability and lack of precision\textsuperscript{107, 122}. Physician judgment of patient adherence is inaccurate\textsuperscript{506, 577, 578}, patient self-report is unreliable and over-estimated\textsuperscript{107, 578}, and proxy measures such as prescription refill data\textsuperscript{382} may not indicate ingestion and are vulnerable to recording bias, due to the use of multiple pharmacies or stockpiling\textsuperscript{107, 579}. Access to reliable adherence data could benefit clinicians and patients by better informing healthcare decisions, for example by distinguishing poor treatment response from suboptimal adherence - thus avoiding unnecessary dose escalations or add-on therapies\textsuperscript{529} – or by enabling the clinician to evaluate the effect of a regimen change or an adherence enhancing intervention.
An ideal measure of adherence should be objective, accurate, and unobtrusive to minimise impact on patient behavior\textsuperscript{141} and allow reliable data collection in real-world settings. EMDs address more of these requirements than other methods\textsuperscript{538}. EMDs have been expensive in the past, but prices are falling as the technology becomes more commonplace\textsuperscript{580}, with EMDs already within the $100–$500 unit price estimated to facilitate wider uptake of monitoring devices in healthcare settings\textsuperscript{581, 582}. Digital remote monitoring is becoming established in healthcare and is likely to increase rapidly in the future, with research increasingly supporting the cost-effectiveness of such interventions\textsuperscript{581, 583, 584}. In 2006, structured billing codes were approved by the Centers for Medicare and Medicaid Services (CMS) for analysis of remote data from implantable cardiac devices\textsuperscript{585}, and monitoring and assessment of continuous positive airway pressure adherence in obstructive sleep apnoea is a requirement for Medicare and other payers to provide ongoing reimbursement\textsuperscript{586}.

While EMDs are considered to be the ‘gold standard’ adherence measurement method for inhaled treatments\textsuperscript{507, 579}, available EMDs for inhalers vary in function, capability, robustness, accuracy and reliability\textsuperscript{119, 120, 125, 539, 541, 543, 545, 552}. To optimise the use of these devices, clinicians need to be well-informed about the range of different devices, their potential adherence support functions, and their potential pitfalls and benefits to ensure that clinical decision making is enhanced by their use. Devices may become damaged during shipping or storage or in patient’s homes. Brief, simple, standardised device checks prior to dispensing and after return of devices from patients can ensure data accuracy and minimise data loss. When a brand new EMD comes onto the market it may have limited reliability data available, so clinicians should consider running lengthier and more thorough device checks\textsuperscript{34, 587} prior to use in patients. However, there is currently little guidance in the literature on how to carry out brief or extended checks of EMDs or how to interpret collected data\textsuperscript{552}.

This paper describes the range of available EMDs for inhalers, user-feedback and useful device features and specifications for the clinical setting. It provides practical guidance on how to carry out simple, standardised device checks based on existing literature, and offers practical strategies for identifying, minimising and managing EMD malfunctions if and when they occur.

### 5.2.2 Available EMDs

#### 5.2.2.1 FDA approved EMDs

Table 1 provides detailed information on the useful clinical attributes (e.g. features, functions, battery life, storage capacity) of available EMDs and Table 2 summarises factors to consider when clinicians and patients use devices in terms of device acceptability (e.g. user-feedback) and regulatory considerations. At the time of writing, a number of EMDs for pMDIs have been approved by the US Food and Drug Administration (FDA). The oldest of the FDA approved devices is the Doser
which is the least expensive and the most basic (Tables 1 and 2; Figure 1). It records the number of daily actuations but does not record the time of each puff, and it is not possible to download adherence data, which is read from the device screen. The Doser’s memory capacity (maximum 30 days) is significantly less than the other EMDs for pMDIs, but it may be a suitable choice where budget is low, where short monitoring periods between face to face visits is planned and where the number of actuations per day is a sufficient measure of adherence. The SmartTouch (recently re-branded, formerly SmartTrack) and the Propeller sensor are more sophisticated devices which record the date and time of each actuation, provide real-time adherence data, by uploading remotely to a webpage or app, and feature on-board reminders for missed doses customisable to the patient’s regimen or daily routine, to prompt optimal adherence. The SmartTouch also has an on-board colour screen and the Propeller sensor has a GPS which tracks the location of inhaler use. Patients and clinicians can access detailed adherence data from these devices and use it to discuss current adherence, barriers and strategies for improving future adherence\textsuperscript{564}. 
<table>
<thead>
<tr>
<th>Device name</th>
<th>Battery life</th>
<th>Storage capacity</th>
<th>Remote upload</th>
<th>Manufacturer software</th>
<th>Medication reminder option</th>
<th>Patient feedback option</th>
<th>Online EMD information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propeller sensor</td>
<td>Not rechargeable - battery lasts 18 months after which device needs to be replaced</td>
<td>Up to 3900 events</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doser</td>
<td>13 months</td>
<td>Stores 30 days of data in memory</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smartinhaler Tracker</td>
<td>Minimum 24 Weeks</td>
<td>~3000 events</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device name</td>
<td>Useful features for clinical practice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SmartTrack</strong></td>
<td>Rechargeable via USB port; lasts 1 - 3 months from full charge depending on usage. Battery level displayed on screen and website145</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syncs medication usage information from device to manufacturer's SmartinhalerLive.com platform via the Smartinhaler Connection Centre through Bluetooth, SIM card and external aerial or USB upload to PC, smartphone or tablet. Manual upload also possible146</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smartinhaler platform: EMDs link into central SmartinhalerLive cloud platform via Smartphone app or SmartKey device.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optional, customisable twice-daily audio reminders which ring for up to 15 minutes, or another set duration, until the pMDI is actuated - personalised to routine, frequency and time of day; different reminder tunes available. Reminders can be switched off or cancelled individually. &quot;Flight&quot; option available for reminders when travelling147</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Customisable feedback options with on-board user interface to view medication usage and change EMD settings; graphical or numerical adherence data available via secure website148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimal - contact details listed on the manufacturer website for enquiries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SmartTouch</strong></td>
<td>Two versions available depending on EMD type: Rechargeable type via USB port; lasts 1 - 3 months from full charge depending on usage; Non-rechargeable type has a minimum 1 year battery life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syncs medication usage information from device to manufacturer's SmartinhalerLive.com platform via the Smartinhaler Connection Centre through Bluetooth or USB upload to PC, smartphone or tablet.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smartinhaler platform: EMDs link into central SmartinhalerLive cloud platform via Smartphone app or SmartKey device.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optional customisable twice-daily audiovisual reminders available via Smartinhaler App or embedded into the EMD on request - weekday and weekend reminders. LED indicator to indicate usage and battery level.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Customisable feedback options; graphical or numerical adherence data available via the manufacturer's Smartinhaler Live platform</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimal - contact details listed on the manufacturer website for enquiries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SmartDisk</strong></td>
<td>Rechargeable via USB port; lasts 2 - 3 months from full charge depending on usage.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syncs via Bluetooth to SmartinhalerLive via Smartinhaler App or USB upload to PC, smartphone or tablet to SmartinhalerLive via the Smartinhaler Connection Centre.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smartinhaler platform: EMDs link into central SmartinhalerLive cloud platform via Smartphone app or SmartKey device.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Twice daily audio reminders customisable for weekdays and weekends; LED indicator shows usage and battery level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Customisable feedback options; graphical or numerical adherence data available via the manufacturer's Smartinhaler Live platform</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimal - contact details listed on the manufacturer website for enquiries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SmartTurbo</strong></td>
<td>Lasts minimum of 1 year. Not rechargeable.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syncs via Bluetooth to SmartinhalerLive via Smartinhaler App or USB upload to PC, smartphone or tablet to SmartinhalerLive via the Smartinhaler Connection Centre.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smartinhaler platform: EMDs link into central SmartinhalerLive cloud platform via Smartphone app or SmartKey device.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reminder option available via Smartinhaler App or embedded in the device (on request). LED indicates usage and battery level.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Customisable feedback options; graphical or numerical adherence data available via the manufacturer's Smartinhaler Live platform</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimal - contact details listed on the manufacturer website for enquiries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device name</td>
<td>Useful features for clinical practice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SmartFlow</strong></td>
<td>Rechargeable via USB port; lasts 2 months from full charge depending on usage.</td>
<td>Up to 125 actuations</td>
<td>Syncs via USB upload to PC. No wireless or Bluetooth capability.</td>
<td>Smartinhaler platform: EMD links into SmartinhalerLive cloud platform via Smartinhaler Connection Centre via USB</td>
<td>LED indicates usage and battery level but no formal medication reminders</td>
<td>Customisable feedback options; graphical or numerical adherence data available via the manufacturer’s Smartinhaler Live platform</td>
<td>Minimal - contact details listed on the manufacturer website for enquiries</td>
</tr>
<tr>
<td><strong>SmartMat</strong></td>
<td>Rechargeable via USB port; lasts 2-3 months from full charge depending on usage.</td>
<td>Up to 4000 logs</td>
<td>Syncs via Bluetooth to SmartinhalerLive via Smartinhaler App or USB upload to PC, smartphone or tablet to SmartinhalerLive via the Smartinhaler Connection Centre.</td>
<td>Smartinhaler platform: EMD links into SmartinhalerLive cloud platform via Smartinhaler Connection Centre</td>
<td>LED indicates usage and battery level but no formal medication reminders</td>
<td>Customisable feedback options; graphical or numerical adherence data available via the manufacturer’s Smartinhaler Live platform</td>
<td>Minimal - contact details listed on the manufacturer website for enquiries</td>
</tr>
<tr>
<td><strong>SmartSpray</strong></td>
<td>Rechargeable via USB port; lasts minimum of 1 year from full charge depending on usage.</td>
<td>Up to 4000 logs</td>
<td>Syncs via USB upload to PC. No wireless or Bluetooth capability.</td>
<td>Smartinhaler platform: EMD links into SmartinhalerLive cloud platform via Smartinhaler Connection Centre via USB</td>
<td>LED indicates usage and battery level but no formal medication reminders</td>
<td>Customisable feedback options; graphical or numerical adherence data available via the manufacturer’s Smartinhaler Live platform</td>
<td>Minimal - contact details listed on the manufacturer website for enquiries</td>
</tr>
</tbody>
</table>

*Information sourced from references as cited; where no reference is given, the information has been provided to authors the respective manufacturers as at October 2014. To the authors’ knowledge, information included in the table is correct at the time of writing - please contact your local manufacturer for updated information.

LED: Light-emitting diode

#The Smartinhaler range (excluding the Smartinhaler Tracker) produced by Nexus 6 Ltd all have the following core features / specifications: 1. Usage data showing date and time of last use can be uploaded for review by the clinician; 2. Communicates with SmartinhalerLive which shows medication usage reports, charts, graphs, device reports - option to generate automatic email reports; 3. Different account types for patient vs clinician; 4. Can integrate into other health information systems and track lung function; 5. Available as English, German, French, Spanish; 6. Device clock drifts by up to 20 minutes after 1 year with no uploads; 7. Operates between 0 to 40 degrees Celsius at 15% - 95% humidity.
<table>
<thead>
<tr>
<th>Device name</th>
<th>EMD use considerations for clinicians (clinician feedback; simplicity of use by clinicians)</th>
<th>EMD use considerations for patients (patient experience and feedback)</th>
<th>Regulatory considerations and privacy law compatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propeller sensor</td>
<td>1. Real-time objective data with time / location of use remotely available via a secure provider dashboard; 2. Health provider can customise alerts and patient notifications to intervene with patients who are worsening; 3. &gt;84% of health providers report benefits to patients and clinical care**</td>
<td>1. Actuation detection mechanism tuned and bench tested to match the forces required to actuate a range of pMDIs; 2. 99% patient satisfaction with device, 94% satisfied with information provided by the platform; 92% found device easy to use**</td>
<td>FDA-approved device and mobile apps. Compatible with the HIPAA privacy laws - patient can choose to share as much or as little information with their clinician, friends and family regarding their usage.</td>
</tr>
<tr>
<td>Doser</td>
<td>1. Relatively cheaper than other EMDs - more affordable but fewer functions available; 2. Currently available model less prone to EMD faults / data losses than older models as reported in the literature; 3. Short memory of events (only last 30 days) and inability to download information makes data more cumbersome; 4. Shows date, but not time of actuation, so cannot provide information about adherence patterns; 5. Maximal daily dose displayable is “99” due to two-digit window.</td>
<td>1. Young children with small fingers may have difficulty pressing the device with enough force to register a puff; 2. Difficulty with registering “double-puffing” or puffs that are done in quick succession as device only records one actuation per second - however this does prevent spurious recording arising from an unsteady hand; 3. Plastic ring structure at bottom of device can prevent delivery of full medication dose; 4. Patient device training identified as necessary to reduce errors; 5. Actuations that occur when the Doser is depressed on the side rather than the centre may be not be recorded; 6. Device is small and compact so easily portable; 7. Doser device can fall off - the need to re-attach can lead to spurious actuations; 7. Spurious actuations can arise during set up and transportation.</td>
<td>FDA approved; no information on privacy law compatibility</td>
</tr>
<tr>
<td>SmartInhaler Tracker</td>
<td>1. Adherence data accessible via a web-based programme displaying adherence as a report / graph, which may be downloaded into a standard spreadsheet; 2. Each device gives a timestamp to each event to a resolution of seconds; 3. Computer software has a TEST function to check device functionalities.</td>
<td>1. Shape similar to that of a standard pMDI; 2. Spurious actuations can occur on canister insertion into the device, though canisters fit firmly and do not fall out; 3. For doses actuated in quick succession, all are given the same time stamp to the second, correlating to the time of the first actuation; 4. The device will not detect actuations achieved by gentle depression of the canister which do not activate the detection switch leading to under-recording; 5. Incorrect date / time logs and data uploading issues have occurred; 6. Potential issues of nozzle blockage affecting medication delivery - may require frequent device replacement; 7. Broken switches and hardware faults have been reported; 8. Qualitative patient feedback available from one study – feedback included that “recording dosing time made (me) more conscious of taking (my) medicine” and “knowing someone is going to check the (dosing) times makes you comply”.</td>
<td>No information on regulatory approval or privacy law compatibility available</td>
</tr>
<tr>
<td>SmartTrack®</td>
<td>1. Data uploads can be automated with email reporting option to minimise risk of data loss. One study reported on clinicians’ perceptions of the usefulness of the EMD - average rating was high: mean score 80 / 100 with higher scores indicating increasing usefulness.</td>
<td>1. On-board LED screen shows date, time of last use and number of doses used in last 24 hours; 2. Some functions impaired when battery is low; 3. Some patients report that reminders ring too regularly and are annoying at times, and device is bulky to handle; 4. Older patients may need additional training on use of the LEDs screen when first using the EMD; 5. One study reported on patient acceptability – average rating of ‘how easy it is to use the EMD to take medication’ was high: mean score 6/100 with lower scores indicating greater ease of use.</td>
<td>FDA approved; no information on privacy law compatibility</td>
</tr>
<tr>
<td>SmartTouch®</td>
<td>On-board colour screen available which can be customised to show medication usage charts, adherence metrics and patient questionnaires</td>
<td>On-board colour touch screen shows date, time of last use and total doses used in last 24 hours</td>
<td>FDA approved – cleared as a prescribable inhaler with a handful of intended uses: in clinical trials; in clinical practice, and for patient self-management; no information on privacy law compatibility</td>
</tr>
<tr>
<td>Device name</td>
<td>EMD use considerations for clinicians (clinician feedback; simplicity of use by clinicians)</td>
<td>EMD use considerations for patients (patient experience and feedback)</td>
<td>Regulatory considerations and privacy law compatibility</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>SmartDisk*</td>
<td>Nil additional features to basic “Smart” features</td>
<td>On-board colour touch screen shows date, time of last use and total doses used in last 24 hours</td>
<td>No information on regulatory approval or privacy law compatibility available</td>
</tr>
<tr>
<td>SmartTurbo*</td>
<td>Nil additional features to basic “Smart” features</td>
<td>Nil additional features to basic “Smart” features</td>
<td>No information on regulatory approval or privacy law compatibility available</td>
</tr>
<tr>
<td>SmartFlow*</td>
<td>Records and stores information about the flow rate the patient uses when inhaling the medication.</td>
<td>Nil additional features to basic “Smart” features</td>
<td>No information on regulatory approval or privacy law compatibility available</td>
</tr>
<tr>
<td>SmartMat*</td>
<td>Nil additional features to basic “Smart” features</td>
<td>Nil additional features to basic “Smart” features</td>
<td>No information on regulatory approval or privacy law compatibility available</td>
</tr>
<tr>
<td>SmartSpray*</td>
<td>Nil additional features to basic “Smart” features</td>
<td>Nil additional features to basic “Smart” features</td>
<td>No information on regulatory approval or privacy law compatibility available</td>
</tr>
</tbody>
</table>

*Information sourced from references as cited; where no reference is given, the information has been provided to authors the respective manufacturers as at October 2014. To the authors’ knowledge, information included in the table is correct at the time of writing – please contact your local manufacturer for updated information.

~Personal communication

LED: Light-emitting diode

HIPAA: The Health Insurance Portability and Accountability Act of 1996 privacy laws

FDA: US Food and Drugs Administration

#The Smartinhaler range (excluding the Smartinhaler Tracker) produced by Nexus 6 Ltd all have the following core features / specifications: 1. Usage data showing date and time of last use can be uploaded for review by the clinician; 2. Communicates with SmartinhalerLive which shows medication usage reports, charts, graphs, device reports – option to generate automatic email reports; 3. Different account types for patient vs clinician; 4. Can integrate into other health information systems and track lung function; 5. Available as English, German, French, Spanish; 6. Device clock drifts by up to 20 minutes after 1 year with no uploads; 7. Operates between 0 to 40 degrees Celsius at 15% - 95% humidity.
Figure 1. Images of currently available electronic monitoring devices and details on where to obtain supply, development status, mechanism of actuation detection and inhaler compatibility*

<table>
<thead>
<tr>
<th>Device name</th>
<th>Manufacturer name and website address</th>
<th>EMD development status (New / Established)*</th>
<th>Mechanism for detecting inhaler use</th>
<th>Inhaler compatibility</th>
<th>Device image</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propeller sensor</td>
<td>Propeller Health, Madison, WI <a href="http://propellerhealth.com/">http://propellerhealth.com/</a> (Previously branded as Asthmapolis until September 2013)</td>
<td>New</td>
<td>Exact mechanism information not available; transmission of collected data to smartphone is via a secure, low-power, wireless radio protocol (Bluetooth Low Energy).</td>
<td>Standard pMDIs: the canister needs to sit outside of the housing to allow sensor attachment to top of canister. A silicon sleeve allows for easy fitting to almost all pMDIs. Compatible with spacers.</td>
<td><img src="image" alt="" /></td>
</tr>
<tr>
<td>Doser</td>
<td>Meditrack Products, Easton, MA <a href="http://www.doser.com/">http://www.doser.com/</a></td>
<td>Established</td>
<td>Electromechanical switch – completes circuit when depressed</td>
<td>Standard pMDIs: the canister needs to sit outside of the housing to allow sensor attachment to top of canister. Not compatible with some pMDIs e.g. ipratropium, cromolyn, nedocromil – canister may not actuate effectively if attached to these(^{120, 539}). Compatible with spacers and does not interfere with drug delivery(^{539}).</td>
<td><img src="image" alt="" /></td>
</tr>
<tr>
<td>Smartinhaler Tracker</td>
<td>Nexus6, Auckland, NZ <a href="http://www.smartinhaler.com/">http://www.smartinhaler.com/</a></td>
<td>Established; Currently rebranded to Smart Touch (New EMD – see below)</td>
<td>Physical switch(^{\text{TM}})</td>
<td>Standard pMDI: the canister fits into the EMD casing which is moulded for the canister</td>
<td><img src="image" alt="" /></td>
</tr>
<tr>
<td>Device name</td>
<td>Manufacturer name and website address</td>
<td>EMD development status (New / Established)^</td>
<td>Mechanism for detecting inhaler use</td>
<td>Inhaler compatibility</td>
<td>Device image</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------</td>
<td>---------------------------------------------</td>
<td>-------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>--------------</td>
</tr>
</tbody>
</table>
| SmartTrack   | Nexus6, Auckland, NZ
http://www.smartinhaler.com/ | Established; Currently rebranded to Smart Touch (New EMD – see below) | Optical sensing**                   | Standard pMDIs: EMD wraps around existing plastic housing so compatibility not dependent on position of canister in relation to plastic housing. Product datasheet only specifies compatibility with GlaxoSmithKline pMDIs. Able to be used with Volumatic spacers*. | ![Image]      |
| SmartTouch   | Nexus6, Auckland, NZ
http://www.smartinhaler.com/ | New                                         | Information not provided by manufacturer | Standard pMDIs: EMD wraps around existing plastic housing so compatibility not dependent on position of canister in relation to plastic housing. Product datasheet lists different EMDs available for different pMDIs. Different colours and types available for specific pMDI types. | ![Image]      |
| SmartDisk    | Nexus6, Auckland, NZ
http://www.smartinhaler.com/ | New                                         | Information not provided by manufacturer | Accuhalers - product datasheet only lists compatibility with GSK preventer Accuhalers (i.e. not for use with GSK Ventolin® Accuhaler) | ![Image]      |
| SmartTurbo   | Nexus6, Auckland, NZ
http://www.smartinhaler.com/ | New                                         | Information not provided by manufacturer | Dry Powder Inhalers. Product datasheet lists compatibility with AstraZeneca DPIs (Symbicort®, Pulmicort® and Bricanyl®) | ![Image]      |
<table>
<thead>
<tr>
<th>Device name</th>
<th>Manufacturer name and website address</th>
<th>EMD development status (New / Established)*</th>
<th>Mechanism for detecting inhaler use</th>
<th>Inhaler compatibility</th>
<th>Device image</th>
</tr>
</thead>
</table>
| SmartFlow   | Nexus6, Auckland, NZ  
http://www.smartinhaler.com/ | New                                         | Information not provided by manufacturer | Boehringer Ingelheim Berodual pMDI | ![SmartFlow image](image1.png) |
| SmartMat    | Nexus6, Auckland, NZ  
http://www.smartinhaler.com/ | New                                         | Information not provided by manufacturer | Boehringer Ingelheim Respimat® SMI | ![SmartMat image](image2.png) |
| SmartSpray  | Nexus6, Auckland, NZ  
http://www.smartinhaler.com/ | New                                         | Information not provided by manufacturer | Boehringer Ingelheim Berodual LS | ![SmartSpray image](image3.png) |

*Information sourced from references as cited; where no reference is given, the information has been provided to authors the respective manufacturers as at October 2014. To the authors’ knowledge, information included in the table is correct at the time of writing - please contact your local manufacturer for updated information.

*New development status refer to EMDs entering the market with limited independent published data on its performance and use

pMDI – pressurised metered dose inhaler
Table 3. Common EMD malfunctions and their management

<table>
<thead>
<tr>
<th>Problem</th>
<th>Possible causes</th>
<th>Suggested action</th>
</tr>
</thead>
<tbody>
<tr>
<td>The number of puffs recorded by the EMD is greater than the number of puffs actuated (“over-recording”)</td>
<td>The EMD has responded to an external stimulus that has activated the recording function of the EMD.</td>
<td>Report the fault and return the device to the manufacturer for test and repair or replacement.</td>
</tr>
<tr>
<td>The number of puffs recorded by the EMD is less than the number of puffs actuated (“under-recording”)</td>
<td>The energy source powering the EMD is faulty, leading to a failure to record events.</td>
<td>Check battery connection – intermittent connection / disconnection events may lead to intermittent data recording. Report the fault and if not resolved return the device to the manufacturer for test and repair.</td>
</tr>
<tr>
<td></td>
<td>Insufficient force used to lead to detection of the actuation (e.g. for switch-activated EMD for pMDIs).</td>
<td>Check actuation technique to identify patients who are unable to use enough force to depress pMDIs (e.g. young children or the elderly). Check EMD compatibility with other devices that the patient may be using e.g. spacer, Haleraid®. Report the fault to the manufacturer.</td>
</tr>
<tr>
<td></td>
<td>The standard threshold for detection of puffs has been set too high, leading to loss of sensitivity of actuation detection.</td>
<td>Report the fault and return the device to the manufacturer for test and repair or replacement.</td>
</tr>
<tr>
<td>The EMD has failed to record any data</td>
<td>An incompatible inhaler type has been used with the EMD.</td>
<td>Check device compatibility specifications and ensure patient has received adequate EMD training e.g. on compatible inhalers and fitting the inhaler correctly to the device</td>
</tr>
<tr>
<td></td>
<td>The energy source (e.g. internal battery) powering the EMD has been depleted or is absent.</td>
<td>Charge battery prior to dispensing, provide battery chargers, or battery charging docking stations to patients. Check expected battery life with the manufacturer prior to purchasing the device for your clinic. Consider more frequent EMD replacement / charging. Replacement devices can be mailed to patients familiar with the EMD.</td>
</tr>
<tr>
<td>The EMD has failed to record any data (continued)</td>
<td>The circuitry responsible for powering the EMD is malfunctioning.</td>
<td>Check battery levels and charge the device. Check for loose connections or parts or physical damage (e.g. water damage). Report the fault and if the problem persists, return the device to the manufacturer for test and repair or replacement.</td>
</tr>
<tr>
<td></td>
<td>The internal memory capacity for data storage is full.</td>
<td>Check the maximum storage capacity (number of events / days stored) with the manufacturer, and ensure it meets intended needs, prior to purchasing the device for your clinic. If the device allows data upload, upload data onto an external server to free up device memory.</td>
</tr>
<tr>
<td>The EMD has recorded the correct number of puffs but the time / date is incorrect</td>
<td>The clock for the EMD is incorrect.</td>
<td>If the device has a screen, check if the screen time matches an external time source (e.g. your computer). Check the disparity in the log. If the disparity is consistently one hour then the EMD may have incorrectly adjusted for daylight saving. Check the battery connection. If the battery is loose, or has been removed by the user, the clock may stop or be incorrect. Re-set time or send the device to the manufacturer for reset. If issues persist, report the fault and return the device to the manufacturer for test and repair or replacement.</td>
</tr>
<tr>
<td>The EMD will not switch on</td>
<td>Battery empty.</td>
<td>Charge the battery if possible, or send the device to the manufacturer for battery replacement and reset.</td>
</tr>
<tr>
<td>The energy source powering the EMD is faulty.</td>
<td>Check the battery and charger connection. If possible, replace with a new energy source / battery. Report the fault and return the device to the manufacturer for test and repair or replacement.</td>
<td></td>
</tr>
<tr>
<td>The power button on the EMD is faulty.</td>
<td>Check if the other buttons / functions work on the device. Report the fault and return the device to the manufacturer for test and repair or replacement.</td>
<td></td>
</tr>
</tbody>
</table>
5.2.2.2 Non FDA approved EMDs

EMDs for other inhalers, such as for the Accuhaler and Turbuhaler, are relatively new products (manufacturer: Nexus6 Ltd, Auckland, NZ) which do not yet have FDA, or other country-specific regulatory approval and no published data on their accuracy and reliability (Table 2). We recommend contacting the manufacturer for an update on EMD performance and approval for your location as the situation may have changed since this paper was written.

5.2.3 Regulation and insurance for EMDs

EMDs currently fall under the FDA’s ‘low risk’ category of medical devices and are therefore subject to less regulatory control than other medical devices such as powered wheelchairs and pacemakers; however regulatory control differs between countries and approval bodies and can change with time. At present, there is an increasing call for medical devices and their associated applications, such as smartphone apps, to be regulated and patients and clinicians are likely to feel more confident using a regulatory approved device. Before purchasing devices, manufacturers should be asked to provide status and evidence of appropriate regulatory approval(s) for use in the target patient population and location. Manufacturers should also provide buyers with information about the compliance of their product with local privacy laws, such as the Health Insurance Portability and Accountability Act 1996 (HIPAA) in the US (Table 2).

As government agencies such as the Department of Veterans Affairs begin to adopt e-health solutions and medical devices, consumer demand increases, and cost-effectiveness is demonstrated, insurers are likely to increase coverage for a wider range of monitoring devices and services. Regulatory approval may become increasingly relevant in the context of insurance cover, and the need to demonstrate the cost-effectiveness of adherence monitoring is important for securing reimbursement for EMDs. Data are beginning to emerge. For example, the cost of a program that improves controller adherence by 50% could be as low as USD130 per person annually to be cost-effective. EMDs are already around this price range and the reducing cost of technology and increasing competition will reduce their price further. To achieve cost-neutrality at present, monitors may need to be reserved for patients with more severe asthma and / or high use of healthcare resources.

5.2.4 Using EMDs in clinical settings

Electronic monitoring has been used in clinical settings as part of adherence-promoting interventions to provide accurate, objective and detailed information on adherence patterns, without significant disruption to patients’ natural medication-taking behaviour. When used appropriately, EMD data can be a powerful tool to engage patients in active discussions about their
unique medication-taking behaviours, beliefs about their disease and attitudes to their prescribed treatment\textsuperscript{37, 493, 510, 512, 530, 569}. The patient’s general views on monitoring as well as the perceived usability of the chosen device should be discussed to encourage participation in the decision to use this technology and ascertain potential barriers to sustained use\textsuperscript{595}. Independent published data on patient and clinician satisfaction with EMDs is available for some devices (see Table 2). Other data may be obtainable directly from manufacturers.

To facilitate patient engagement, the information provided by the EMD must be accurate and reliable. It is also important to train the patient on how to use the EMD prior to issue, to maximise data reliability. Training should include: how to insert/remove the inhaler from the EMD; inhalers compatible/not compatible with the EMD; use of any EMD menu system, app or website; and appropriate EMD storage, such as keeping the EMD away from direct sunlight and water, and removing the EMD from pockets before putting clothes in the laundry.

Clinical staff using the EMD should be trained on how to use the EMD, how to undertake routine device checks, and what to do if a device fails any of the checks (see Table 3). The checking process should be simple enough to be followed by any staff member who has had basic training on how to use the EMD, and need not be limited to clinical personnel. The following, separate, storage containers should be set up for new EMDs received from the manufacturer: ‘checked and passed’; ‘checked and failed’; ‘not checked’. A similar system can be established for used devices requiring re-use by the same patient, with precautions to prevent cross-contamination and to manage device-patient allocation. A basic electronic database can be set up, for example in an electronic spreadsheet, to track the location of the EMD and its patient allocation. Some manufacturers provide software or applications to assist with EMD checking and management (see Table 1).

5.2.5 Implementing EMD checks

EMD faults can lead to poor data quality, data retrieval problems or data loss\textsuperscript{119, 124, 507, 596}. To check for any damage acquired in the storage or shipping process or during patient use, a brief EMD check is recommended prior to issue of the EMD to the patient and immediately after return from the patient to ensure the EMD is recording accurately and that collected data are correct.

The following section provides practical guidance on how to implement such EMD checks in a standardised way. Such standardisation simplifies the process and, if needed, allows comparison of results within and between devices.

5.2.5.1 How to carry out brief EMD checks

The existing literature on EMD testing has focused on the types of tests needed for new EMDs entering the market, rather than brief EMD checks for more established devices (Figure 1).
However, the underlying principles are much the same. The key recommended tests are for accuracy of single and multiple actuation recording\textsuperscript{121, 125, 507, 539}. Checks for accuracy of single actuation recording requires actuation of the inhaler once, while simultaneously recording the time and date in a paper diary. This is usually done three to four times in succession. EMD records are subsequently checked against the paper diary. Checks for multiple actuation recording differ from single actuation in that multiple, closely-spaced, sequential actuations are carried out (10 to 300 actuations can be used for testing\textsuperscript{545}) to ensure that the device can reliably record a behaviour known as ‘dose-dumping’\textsuperscript{71}. Dose-dumping is a series of deliberate multiple actuations usually occurring prior to clinic visits in an attempt to disguise poor adherence. Dose-dumping data points can be easily seen in a printout or graph of a patient’s adherence record, and on the Doser may be indicated by an unusually large daily count of puffs made close to an appointment. These data points need to be removed from the adherence record to correctly gauge the patient’s adherence.

Checks of other clinically important device functions may also be important. For instance, if an EMD has failed to deliver adherence reminders as expected, a patient’s adherence may not improve, so it is advisable to check the performance of reminder functions in a random sample or all devices\textsuperscript{543}.

Checks for physical damage and power source performance are recommended. A quick inspection of the physical state of the EMD is a simple, important check that can identify any damage or loose parts which may cause a safety issue or impede device functionality\textsuperscript{54}. A check of the EMD power source will ensure that the device is powering correctly and that the power level is sufficient to last for the duration of use. It can also help troubleshoot EMD data inaccuracies as recording errors or data loss can occur when EMD power is unstable, low or absent\textsuperscript{125, 542, 596}.

On the basis of this literature and our own experience with implementing EMD checks we have developed a simple checklist of recommended factors to include when performing brief device checks (see Table E1 and Appendix A1 below). Recommended checks, prior to issue and after return from the patient, fall into three categories: 1. physical check of the device; 2. accuracy of actuation recordings and other functions; and 3. power source check. A laboratory is not needed to carry out EMD checks; any space with a small storage area for devices, a computer, desk and chair is sufficient.

5.2.5.2 Interpreting EMD check results

It is helpful to set a threshold for “pass” or “failure” for each checking step to determine the degree of acceptable variation between the EMD and the paper record of the checks done. This will mostly be determined by the manufacturer’s EMD specifications, but also by the clinician’s and/or patient’s reason for adherence measurement and how important a particular function is for the intended purpose. For some functions, such as actuation recording, only near 100% reliability will be
acceptable, whereas recording of other functions such as time of battery removal may be less stringent if they provide non-essential data.

5.2.5.3 Trouble shooting common EMD malfunctions

Table 3 describes common EMD malfunctions and provides recommendations on how to manage them. The most commonly reported EMD failures are inaccurate time recordings of performed actuations\textsuperscript{34, 125, 537, 596} or incorrect numbers of actuation recordings (i.e. missing or extra recordings)\textsuperscript{34}. “Time-drift” can occur if the EMD has not made contact for a period of time with an external time source (e.g. a server or computer) which automatically synchronises with Coordinated Universal Time (UTC). A moderate degree of time drift may not necessarily be a reason to mistrust the adherence data from an EMD, particularly if the degree of time drift is known from the manufacturer’s specifications. For example, a time drift of plus one hour may not affect the interpretation of adherence data, although actuations taken just after 2300 hours would theoretically be recorded as occurring the next day. Some older EMDs have impacted on medication delivery due to clogging of the EMD nozzle\textsuperscript{541, 596}. Although EMD actuation recording is not affected, this can lead to inaccurate patient dosing records as the EMD will have recorded actuations which the patient may not have been able to take due to poor medication delivery.

Battery depletion or failure can lead to data loss, inaccurate actuation recordings, failure of data upload or EMD failure\textsuperscript{125, 542, 596}, though newer EMDs appear to have improved battery life\textsuperscript{541}. Battery failure may occur due to deliberate or inadvertent removal of the power source by the patient-user or excessive power consumption due to simultaneous use of multiple functions on the EMD (e.g. continuously sounding reminders during a data upload). Some devices, such as the SmartTouch and Propeller Sensor, can register low power or battery removal which may be recorded on data printouts. Other possible explanations for EMD malfunctions or recording inaccuracies are outlined in Table 3.

5.2.5.4 Explaining and managing EMD malfunctions

Over- and under-recording of actuations may occur in different ways. For example, an EMD that detects actuations using an optical system may falsely record actuations in the presence of external beams of light if the wavelength triggers the actuation detection mechanism. In EMDs relying on a physical method for actuation detection, failure to record an actuation may indicate that insufficient force was used during actuation (Table 3). Elderly, frail or pediatric patients may perform weaker actuations so it may be important to ask manufacturers if the EMD has been tested in a broad population of people representing a variety of actuation techniques. While one can assume to some extent that actuation detection malfunctions have been identified and addressed by manufacturers
during the development process, it is helpful to note and report any potentially unrecognised sources of error.

A blank event record, or the recording of a high number of multiple actuations in rapid succession, may be a sign of battery failure or malfunction of the EMD memory. Multiple actuations caused by battery failure can usually be differentiated from dose-dumping since battery failure usually results in a high number of actuation recordings far in excess of the ‘maximum number of actuations recordable in one second’ described in the manufacturer’s specification. Data uploading issues can occur with low battery power, but this may also be caused by connection port malfunction or due to water damage to electronics used for connectivity e.g. Bluetooth, USB. A common cause of water damage is leaving the EMD in clothing and washing in a washing machine.

5.2.6 Working with newly developed EMDs

Potential buyers cannot assume that EMDs newly available on the market have undergone the prototype and pre-production testing needed to ensure adequate reliability, though as the market grows, it is likely that new EMDs will increasingly be delivered patient-ready to the clinician or researcher. However, at present, before using any new EMD, we recommend running a series of detailed checks either in your clinic, in collaboration with researchers or the manufacturer, to ensure that adequate checks, similar to those discussed in the next paragraphs, have been carried out. Clinicians can increasingly contribute to the design and production of EMDs by providing feedback to manufacturers and researchers about their needs when using EMDs in practice.

Two phases of checks are recommended for new EMDs before using them for the first time in patients: 1. “clinic-based checks” which can be done in a clinic and “patient-based checks” which need to be performed in the homes of a small number of patients.

5.2.6.1 Clinic-based checks of a new EMD

During “clinic-based checks”, any errors in EMD function are checked under controlled conditions. These checks are similar to brief EMD checks but are more detailed and include checks for storage capacity, EMD-inhaler fit and compatibility (Figure 1), and device robustness, as well as checks for physical damage or faults and accuracy of inhaler actuation recording and other relevant functions. Further information on “clinic-based checks”, including a checklist of recommended tests and guidance on interpreting test results, can be found below (Appendix A1 and Tables E2 and E3).

5.2.6.2 Patient-based checks of a new EMD

Prior to patient use, any new EMD should undergo “patient-based checks” with patients to ensure suitability and reliability, but also acceptability, of the EMD in the target population. Ease of EMD handling, likelihood of tampering and EMD robustness should be checked. A small number of
patients should be asked to record the date and time of every actuation taken over a few days in a paper diary (Figure 2), for comparison with the EMD record upon device return. On return of the EMD, patient feedback should be sought about the acceptability of the EMD and ease of use, for example via structured questionnaires or interviews. Specific details on how to carry out patient-based checks can be found below (Appendix A1 and Table E4).
Figure 2. Example of a patient actuation diary

**Monday**

Please fill in below, all the prescribed puffs you take today

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Time 1st puff taken</th>
<th>Time 2nd puff taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td>__ : ___ / puff not taken</td>
<td>__ : ___ / puff not taken</td>
</tr>
<tr>
<td>PM</td>
<td>__ : ___ / puff not taken</td>
<td>__ : ___ / puff not taken</td>
</tr>
</tbody>
</table>

Please fill in below, any extra puffs you take today

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Time puff taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM / PM</td>
<td>__ : ___</td>
</tr>
<tr>
<td>AM / PM</td>
<td>__ : ___</td>
</tr>
<tr>
<td>AM / PM</td>
<td>__ : ___</td>
</tr>
<tr>
<td>AM / PM</td>
<td>__ : ___</td>
</tr>
</tbody>
</table>

**Tuesday**

Please fill in below, all the prescribed puffs you take today

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Time 1st puff taken</th>
<th>Time 2nd puff taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td>__ : ___ / puff not taken</td>
<td>__ : ___ / puff not taken</td>
</tr>
<tr>
<td>PM</td>
<td>__ : ___ / puff not taken</td>
<td>__ : ___ / puff not taken</td>
</tr>
</tbody>
</table>

Please fill in below, any extra puffs you take today

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Time puff taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM / PM</td>
<td>__ : ___</td>
</tr>
<tr>
<td>AM / PM</td>
<td>__ : ___</td>
</tr>
<tr>
<td>AM / PM</td>
<td>__ : ___</td>
</tr>
<tr>
<td>AM / PM</td>
<td>__ : ___</td>
</tr>
</tbody>
</table>
5.3 Summary

There is increasing potential for EMD use in clinical settings, especially as costs reduce and user-interfaces become simpler for clinicians and patients\textsuperscript{493}. EMDs appear feasible and effective for improving patients’ inhaler adherence in primary and secondary care settings\textsuperscript{37, 512}, although more data on the cost-effectiveness of monitoring is needed to secure EMD reimbursement. Clinic staff need to be prepared to carry out brief standardised checks of EMDs to ensure data quality and reliability. This paper has provided a starting guide for health professionals on the attributes and user acceptability of different EMDs, and how to implement brief device checks in established EMDs or more detailed evaluation of new devices, based on published methodology. Device checking processes can be carried out in clinic settings and should be simple enough for clinic personnel to do after receiving basic device training. Clear procedures should be in place for storage of devices and for responding to device failures. Informed clinicians can select appropriate EMDs for their patients and implement reliable EMD checking processes to allow confident interpretation of their patient’s adherence data to inform clinical decisions.
5.4 Appendix A1: Detailed testing of new EMD devices

Newly available EMDs require rigorous checks to ascertain acceptable EMD function and accuracy\(^{34}\). Two types of checks, i.e. “clinic-based checks” (checks that can be done in the clinic) and “patient-based checks” (checks that need to be done with patients), are recommended for new EMDs before using them for the first time\(^{121}\).

5.4.1 Evaluating new EMDs in the clinic office setting

A laboratory is not needed to carry out checks for new EMDs; any space with a small storage area for devices, a computer, desk and chair is sufficient to provide controlled conditions. During “clinic-based checks”, systematic errors in EMD functionality can be checked under controlled conditions. A checklist of parameters to assess in a new EMD, as described below, can also be found in Tables E2 and E4.

5.4.1.1 Physical checks

An initial physical check for loose parts or cracks should be carried out\(^{34}\), with a focus on device joints, compartment / ports for the power source and overall finish. A quick once-over of the physical state of the EMD is a simple, important, check that can identify any damage or loose parts which may cause a safety issue or impede device functionality\(^{34}\).

5.4.1.2 EMD-inhaler compatibility

Poor or incorrect EMD-inhaler fit can lead to data inaccuracies. Before using a particular EMD, it is important to obtain information about EMD-inhaler compatibility from the manufacturer. Most EMDs are for pMDIs and although these may appear to fit a range of inhalers, some will only provide reliable data for a specific pMDI. Breath-actuated or dry powder devices generally require specifically designed EMDs. Other issues to consider include compatibility with inhaler aids such as the Haleraid\(^{®}\) or spacers, and the presence of dose-counters, which may alter the shape of the pMDI. EMD set up can be simple or complex, with some EMDs fitted by the user and others requiring specialized set up by the manufacturer\(^{121, 537}\). The ease of set up can affect patient acceptability of use and should be considered by the clinician when choosing an EMD for the patient.

5.4.1.3 Actuation recording accuracy

Given its essential purpose, actuation recording accuracy of the EMD is one of the most important tests to carry out. EMDs will record, at minimum, the number of doses taken over a set period. More sophisticated EMDs will provide a time and date log for each dose taken\(^{507}\). Before checking the actuation recording accuracy on an EMD, it is important to understand the method of detection.
used by the EMD as this can influence other factors, such as inhaler compatibility, power consumption and type of faults encountered. Devices generally use one of three methods. *Physical* detectors use a pressure sensor or switch to record an actuation\textsuperscript{507}. *Optical* devices detect actuations via interruption of energy beams or specific wavelengths of light, whereas others use an *electromagnetic* system where actuations are monitored via the position of a lever as sensed by magnets\textsuperscript{545}. Table 1 and Figure 1 in the main manuscript lists currently available EMDs and their specifications, including their method of detection.

Actuation recording should be checked by actuating the inhaler and keeping a paper diary of the date and time of each actuation. A detailed description of recommended actuation accuracy checks is shown in Table E3 as a guide; clinicians may wish to adopt an abbreviated version for more established EMDs (Table E1). An independent time source, not the EMD clock, should be used to ascertain the time of each check carried out. A different, validated EMD\textsuperscript{120, 539}, or canister weight at baseline and after each actuation\textsuperscript{119, 596} can be used as a second independent check. Different actuation patterns should be tested to mimic real patient use, such as over- and under-use and periods of no use as well as usual regimes, e.g. two puffs twice daily\textsuperscript{12}.

Recording of multiple actuations or “dose dumping” should be tested. Dose-dumping usually occurs prior to clinic visits in an attempt to disguise poor adherence. Dose dumping can be defined by setting an arbitrary threshold of a number of puffs in succession (a minimum of 10 and a maximum of 300 have been used in the literature\textsuperscript{545}) and comparing the EMD record with the paper record. It is important to check actuation recording logs carefully. A faulty EMD may record spurious ‘extra’ actuations or fail to record executed manoeuvres (see Table 3 above).

5.4.1.4 **Accuracy of other functions**

Contemporary EMDs can provide medication reminders. Reminder systems are more complex than simple digital alarm clocks because they are usually designed to ring only when an actuation / dose have been missed within a certain window. Reminders can be checked by setting the reminder for a specific time then, after failing to actuate the device, checking the accuracy of the reminder ring time relative to the reminder time set on the EMD using an external time source. Other useful tests include checking that reminders stop in response to actuation if the EMD is programmed to do so. We recommend checking reminder function on at least two different occasions e.g. morning and evening.

Other contemporary EMD functions may include adherence feedback (e.g. via an on-board screen), recording of reminder on/off, inhaler or power source removal/insertion and inhaler shaking and inhalation. These functions should be checked by performing the appropriate action and recording
feedback and/or the date and time of each action in a paper diary. The EMD log should then be compared with the paper diary for any discrepancies.

5.4.1.5 Storage/memory capacity

EMDs have a pre-specified limit on data storage capacity, either defined by a maximum number of days of data or by a maximum number of events\(^{539}\). If the maximum storage threshold is reached, the EMD will be unable to record any further events. It is important to obtain information about EMD storage capacity, as this will dictate the frequency of EMD replacement and/or data uploading by the clinician or patient.

5.4.1.6 Robustness

Robustness requirements may depend on the target population, e.g. EMDs used by children may be more likely dropped or handled roughly. It is important that the EMD records inhaler removal and insertion and if not, that tamper-proofing strategies are used to prevent inhaler removal between clinic visits.

Environmental conditions may influence the reliability of the EMD. EMD specifications should be checked with the manufacturer such as: temperature and humidity range within which the EMD can function, water- or splash-proofing, tolerance to sunlight exposure (for optical EMDs) and the maximum external force the device can tolerate e.g. when dropped from a height or placed under an object.

5.4.1.7 Energy/power source

EMDs are usually powered by a single use or rechargeable battery and rely on regular battery replacement or recharging to function. EMD power consumption rates should be checked with the manufacturer to ensure adequate power for the duration of intended use. Generally, the greater the number of functions active on an EMD, the greater the energy use, so power usage will be increased under conditions of high-activity (e.g. reminders ringing constantly) compared to conditions of low-activity (e.g. audiovisual functions disabled). Some EMDs have internal auxiliary (back-up) batteries and the extent to which these protect data integrity if the main battery becomes empty or faulty should be ascertained from the manufacturer. For longer duration monitoring it may be necessary to adjust the frequency of clinic visits to facilitate charging. Table E3 describes battery testing in more detail.

5.4.1.8 Re-usability

Some EMDs are disposable or specified for single use only, whereas others may be used within the same patient over several months\(^{537}\). Re-usability may introduce difficulties such as keeping track of
device damage or patient tampering over long periods of use. Remote data uploading, which is a common feature of contemporary EMDs (Table 1), may be useful in these circumstances.

### 5.4.2 Patient-based checks of the new EMD

It is useful to record battery life before and after patient-based checks to check power consumption\(^{543}\). It may be useful to obtain patient feedback on the device during the patient-based checks as well; the degree of patient satisfaction with the EMD will affect patient uptake and duration of use. Usability testing provides information about the participants’ subjective assessment of the EMD. This can be done via interview, rating scales and/or questionnaires to collect quantitative and qualitative data\(^{543}\).

Providing participants with a thorough demonstration of the EMD, clear instructions, and reinforcing that the aim of the field test is to study EMD performance rather than the participant’s medication use, may optimise reporting of device faults. Explain clearly to participants that the EMD should be used in a normal manner, simulating “real-life”. A checklist of steps for patient-based checks of new EMDs is available in Table E4.

**Table E1. Brief EMD performance checklist**

- Physical check (e.g. check for loose parts, cracks)
- Accuracy of functions
  - Actuation recording accuracy
    - Single actuation recording
      Perform four actuations. Make a simultaneous, written record of the date and time (to the second)* of each actuation in a paper diary and subsequently compare the diary and EMD record.
    - Multiple actuation recording
      Perform a set of actuations in quick succession, to mimic “dose dumping” (e.g. 10 puffs). Make a simultaneous, written record of the date and time (to the second)* of the first and last actuation in the set of actuations in a paper diary and subsequently compare the diary and EMD record.
  - Accuracy of other essential functions
    - Check core functions for the intended use (e.g. reminder function should be checked if the EMD is used by the patient primarily for its reminder function) by performing the chosen manoeuvres(s) once. Make a
simultaneous, written record of the date and time (to the second)* of each manoeuvre in a paper diary and subsequently compare the diary to the EMD record.

- Energy source (check battery level and recharge or replace battery)
  - The energy source powering the EMD should be fully charged, and its charge status checked and recorded prior to issue and on return from the patient.

Table E1 footnote:

*Use a single external time source (even if the EMD has an on-board clock).
Table E2. Clinic-based checks – a checklist of parameters to check in a new inhaler EMD†

- Physical check of EMD – loose parts, cracks
- EMD compatibility – choice of inhaler type / brand
- Accuracy of functions
  - Actuation recording accuracy*
    - Actuation detection method – clinician should become acquainted with the specific mechanism used by the new EMD to identify reliability risks and perform checks that are appropriate for the EMD detection method
      - Physical detection method?
      - Optical detection method?
      - Electromagnetic detection method?
      - Other detection method?
    - Usual dosing
    - Under / over-dosing
    - No usage
    - Dose dumping
  - Accuracy of other functions
    - Reminder (time, type, duration, response to actuations)
    - On-board screen / buttons
    - Inhaler insertion and removal
    - Power source connection and removal
    - Inhaler shaking
    - Inhalation
    - Other key functions (see device specifications)
- Energy / power source
  - Life of power source*
- Storage / memory capacity
- Robustness
- Child safety
- Tampering
- Durability under different conditions (temperature, humidity, wet / dry, light / dark, drop test)

- Re-usability
- Regulation and approval

Table E2 footnote:

†The creation of a standard device checking record is recommended which lists each checking procedure to be carried out on each EMD. The form should include fields for recording the device number, the overall result of the series of checking procedures (e.g. pass / fail) and a comments section for explaining the overall result of the checks.

*See Table E3 for a more detailed description of actuation recording accuracy and power source / battery life tests.
Table E3. Recommended actuation recording accuracy and battery life checks

1. Set up the EMD as per manufacturer’s instructions and record baseline battery life.

2. It is important to emulate normal inhaler use as closely as possible when performing EMD checks, for example, shaking pMDIs (while attached to the EMD) prior to actuation.

3. **PHASE 1 ACTUATION RECORDING ACCURACY CHECKS**
   - Perform a series of actuations at different times of the day for a period of several days. Make a simultaneous, written record of the date and time (to the second)* of each actuation in a paper diary†. If the inhaler has a dose counter, record the counter number or weigh the canister before and after each actuation, to provide an additional record of the number of actuations made.
   - Perform at least one series of fast sequential actuations (e.g. 10 puffs) to check how the device records dose dumping. Make a simultaneous, written record of the date and time (to the second)* of the first and last actuation in the set of actuations in a paper diary, and record the counter number or weigh the canister before and after the set of actuations.
   - Compare the diary, dose counter, canister weight and EMD records to determine if the device has passed or failed phase 1 tests.

4. **PHASE 2 ACTUATION RECORDING ACCURACY CHECKS**
   - A patient use simulation checking procedure¶ of normal prescribed regimens (e.g. two puffs AM and PM) as well as under-, over-, and no use (e.g. 0 to 20 puffs per day) should be conducted over a number of sequential days (e.g. seven days). Make a simultaneous, written record of the date and time (to the second)* of each actuation in a paper diary, record the counter number or weigh the canister before and after each actuation.
   - Compare the diary, dose counter, canister weight and EMD records to determine if the device has passed or failed phase 2 tests.

5. **BATTERY LIFE CHECKS**
   - Check the battery life in a subset of devices over several days, and check no data are lost due to low or empty batteries.
If possible, carry out a longer battery life check for 30-90 days in three devices (one each with high, low and zero daily use e.g. actuations, screen use and / or data uploads) to test longer-term battery life and / or internal back up battery problems.

Table E3 footnote:
*Use a single external time source (even if the EMD has an on-board clock). The EMD clock should be synchronised with the external time source at baseline to provide a gold standard comparison with device logs.
†The creation of a standard device checking record is recommended which lists each checking procedure to be carried out on each EMD. The form should include fields for recording the device number, the overall result of the series of checking procedures (e.g. pass / fail) and a comments section for explaining the overall result of the checks.
¶Where relevant, apply a pharmacy dispensing label to a proportion of inhalers to check for any effects on EMD data recording.
Table E4. Patient-based checks – a checklist of parameters to check in a new inhaler EMD

Patient-based checks should ideally be a minimum of seven days duration, to provide sufficient data, and should include the following:\textsuperscript{539, 543}:

1. Set up the device as per the manufacturer’s instructions.
2. Carry out a brief performance check (Table E1) of the EMD as close as possible prior to the patient visit, or if the EMD is new, a full office-based check may be required (see online repository Appendix A1, Tables E2 and E3).
3. At the baseline visit, attach the EMD to the inhaler. Record the dose counter number on the inhaler, if available, or the weight of the canister.
4. At the baseline visit, train the patient on EMD use (e.g. inhaler compatibility, appropriate storage to avoid water damage). Provide a clear instruction manual and a physical demonstration of the EMD functions. Ask the patient to demonstrate the functions and correct any errors. Remind the patient to use the device and their inhaler normally to check its capacity to withstand normal wear and tear.
5. At the baseline visit (and also at follow-up) record patient-reported ease of use. Where appropriate check EMD compatibility with any other inhaler aids the patient usually uses e.g. a spacer or Haleraid®.
6. At the baseline visit, provide the patient with a simple actuation diary (Figure 2) and demonstrate how to use it. Show example time and date record produced by the EMD to reinforce the need for accuracy (e.g. time recordings to the second). Encourage accuracy by stating “Your diary entries gives us accurate data which we use to check how well the device records each puff” and “It is much better to leave a diary entry blank than to fill in an estimate or guess later”. Record the date and end time of the baseline visit so that any manoeuvres made during the visit can be identified.
7. At the follow-up visit, record the dose counter number (if available), or weigh the canister (for pMDIs) and carry out a return EMD performance check. Record the date and start time of the follow-up visit so that any manoeuvres made during the visit can be identified and excluded.

At the follow-up visit, upload EMD data and compare it with the patient diary and any dose-counter / weight records. Ask the patient to clarify any discrepancies. Avoid leading the patient by concealing the full details of any disparity initially. Normalize discrepancies to encourage the patient to report events as openly as possible.
5.5 In-vitro validation testing of a simple electronic adherence monitoring device, the Smartinhaler

This results of in-vitro validation testing of a simple EMD, the Smartinhaler, were presented as a poster at the Australasian Pharmaceutical Science Association Annual Conference 2009 and published in their conference proceedings. This device was the initial prototype device which is a simple actuation recorder, recording the time and date of dosing, without any other on-board functionalities. The accuracy of its recording function alone and in the presence of accessories commonly used with inhalers such as spacers and dispensing labels was investigated.

**Title:**

In-vitro validation testing of electronic adherence monitoring devices

**Conference proceedings:**


**Authors:**

Amy Hai Yan CHAN, Maye HAMED, Juliet FOSTER, Jeff HARRISON, Peter BLACK

**Contributions:**

Amy CHAN was involved in the literature review, study conception and development of testing framework for device, data collection, results analysis, creation of poster and presentation of poster at conference

Maye HAMED was involved in data collection and review of testing framework

Juliet FOSTER was involved in the development of testing frameworks, results analysis and review of poster for submission and presentation

Jeff HARRISON was involved in the original study conception regarding need for testing of electronic monitoring devices and development of test frameworks, results analysis and review of poster for submission and presentation

Peter BLACK conceived of the original study regarding need for testing of electronic monitoring devices and development of test frameworks, and was involved in data collection, results analysis and review of poster for submission and presentation
5.5.1 Abstract

Objective: Medication adherence is an essential aspect of asthma management. Many patients experience poor asthma control due to poor adherence. Monitoring adherence is notoriously difficult due to unreliability of self-reporting and occurrence of dose dumping by patients. The Smartinhaler® is an objective EMD for pMDIs which records a date and time stamp for every actuation. Although previously validated for use with other pMDI medications, the Smartinhaler® has not yet been validated with Vannair® (a combination eformoterol and budesonide therapy delivered via pMDI), which has unique dimensions from standard pMDI canisters. This study was therefore undertaken to validate use of a modified version of the Smartinhaler® adapted for Vannair®.

Methods: Accuracy of data recording, effect on data recording of canister removal and application of dispensing labels, identification of dose-dumping, appearance, spacer compatibility, and ease of uploading to computer software (Respiratory Research Analyser®) were examined. A standardised protocol was followed where each device was actuated two times, twice daily over a 48-hour period. This was followed by a dose dumping test where 30 doses were actuated consecutively in fast succession. A total of three devices were tested. At the end of testing, data were uploaded from the Smartinhaler® and compared to the known number and timing of actuations recorded in a paper diary.

Results: Data recording was accurate with the exception of two extra recordings on two occasions. Removal and replacement of the canister and presence of a dispensing label on the Smartinhaler® did not affect recordings. Recording of dose dumping was 100% accurate. The Smartinhaler® was compatible with Vannair® with or without a spacer. No problems were encountered with data uploading.

Discussion: Adherence monitoring by the Smartinhaler® with Vannair® had acceptable accuracy, with an overall accuracy rate of 98% for recording all actuations including dose dumping. The Smartinhaler® is compatible with Vannair® and can be used to objectively measure adherence.

5.5.2 In-vitro validation testing of electronic adherence monitoring devices

5.5.2.1 Background

Medication adherence is an essential aspect of asthma management. Regular use of ICS have been shown to reduce symptoms and exacerbations, improve lung function and prevent hospital admissions. However, many patients experience poor asthma control due to poor adherence. Studies report average adherence rates of ~50%. Monitoring adherence is notoriously difficult due to unreliability of self-reporting and occurrence of dose dumping by patients. There are
various methods for measuring adherence, of which use of electronic monitors is the most accurate and objective method\textsuperscript{107}.

Various adherence monitoring devices have been developed – these include the Doser CT, MDI Log, MDI-CM, Turbohaler Inhalation Computer and Smartmist. The most commonly used devices are the Doser CT and MDI Log. A comparison is shown in the table below.

Table 4. Comparison of Doser CT with MDI Log

<table>
<thead>
<tr>
<th>Doser CT</th>
<th>MDI Log</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy</strong> ~94.3%</td>
<td><strong>Accuracy</strong> ~90.1%</td>
</tr>
<tr>
<td>Records number of actuations daily for 45 days</td>
<td>Records number, date and time of actuation</td>
</tr>
<tr>
<td>Reported failure rate ~8% to 21%</td>
<td>Reported failure rate ~9%</td>
</tr>
<tr>
<td>No written record of adherence</td>
<td>Data can be downloaded</td>
</tr>
<tr>
<td>Does not indicated whether inhalation occurred</td>
<td>Can detect inhalation &amp; inhaler shaking.</td>
</tr>
<tr>
<td>US$30</td>
<td>US$300</td>
</tr>
</tbody>
</table>

\textit{The Smartinhaler®}

The Smartinhaler® is an EMD for pMDIs developed in New Zealand. It offers the advantage of recording a date and time stamp for every actuation, and the data can be downloaded to a computer to provide a written record, similar to the MDI Log. Although it cannot detect inhalation, previous studies have shown a high accuracy rate, in particular in its ability to detect dose dumping\textsuperscript{120}. It is also less expensive, with each costing ~US$150. Although previously validated with other pMDI medications, the Smartinhaler® has not been validated with Vannair® (a combination of eformoterol and budesonide delivered via pMDI), which has unique dimensions from standard pMDI canisters. This study was undertaken to validate use of a modified Smartinhaler® adapted for Vannair®.

5.5.2.2 Aims

To validate use of the Smartinhaler® with Vannair® medication

Specifically:

- To test its physical compatibility with Vannair®
- To determine the accuracy of recordings by the monitoring system

5.5.2.3 Methods

A protocol was developed where several parameters were tested over 48 hours with Vannair 200/6. A total of three Smartinhalers® were tested, of which one had a dispensing label applied to the outer casing to test if the presence of a label would affect data recording. The following tests were conducted:
Visual test
Each device was examined for defects. The Smartinhaler® has a LED light on the side which flashes when the canister is depressed. This was tested in the visual testing phase.

Spacer-device fit test
Each Smartinhaler® was checked for fit with a volumatic spacer and compared to a normal pMDI.

Validity testing
Each Smartinhaler® was actuated two times, twice daily over 48 hours. Two actuations were done in the morning (0301 to 1200 hours) and two in the evening (1201 to 0300). The date and time of each actuation was recorded in a paper diary. Following this, the Smartinhaler® was actuated thirty times in quick succession and the date and time of the first and last actuation recorded. Data was uploaded at the end of testing using the Respiratory Research Analyser® software. The data recorded by the Smartinhaler® was then compared to the known number and timing of actuations in the paper diary.

5.5.2.4 Results
Visual test
No defects were noted in the Smartinhaler® devices. The LED light on all three devices were fully functional, flashing five times with each actuation of the device.

Spacer-device fit test
The modified Smartinhaler® had a good fit with the spacer with no interference with normal pMDI functioning.

Validity testing
The date and time of each actuation recorded was accurate and showed good concordance with the paper diary. Two of the three Smartinhalers® had 100% accuracy. The third device recorded two extra actuations on two separate occasions. It was noted that the canister was difficult to depress at those times and the plume produced was not a full plume. Recording of dose dumping was 100% accurate in all three devices. Presence of a dispensing label did not affect data recording.

5.5.2.5 Discussion
Adherence monitoring by the Smartinhaler® with Vannair® had acceptable accuracy, with an overall accuracy rate of 98% for all actuations including dose dumping. This is higher than what has been previously reported with other devices. The only inaccuracy that occurred was the recording of two extra actuations with one device. This may have occurred as the canister was difficult to press which may have led to an incomplete or haphazard actuation that was logged as two separate events rather than one. No problems were noted with the other two devices. Although only three devices
were tested, this small validation study suggests that the Smartinhaler® is compatible with Vannair® and can be used to objectively measure adherence.

5.6 Paper III: Six-month in vitro validation of a metered-dose inhaler electronic monitoring device: Implications for asthma clinical trial use

The accuracy of recording of another EMD, the Smartinhaler Tracker, was investigated over 24 weeks to determine its accuracy when used over prolonged periods to guide use in a clinical trial and practice setting. This was published as a Letter to the Editor in the Journal of Allergy and Clinical Immunology, which has an impact factor of 11.476, and has since been cited 21 times.

**Title:**

Six-month in vitro validation of a metered-dose inhaler electronic monitoring device: Implications for asthma clinical trial use

**Journal:**

Journal of Allergy and Clinical Immunology 2012: Vol 130: pages 1420-2.

**Authors:**

Mitesh PATEL, Janine PILCHER, Amy CHAN, Kyle PERRIN, Peter BLACK, Richard BEASLEY

**Contributions:**

Mitesh PATEL was involved in the literature review, study conception and design, development of testing frameworks, data collection, results analysis and interpretation, manuscript write-up and review for submission for publication

Janine PILCHER was involved in the literature review, study design, results analysis and interpretation, manuscript write-up and review for submission for publication

Amy CHAN was involved in the development of testing framework, manuscript write-up and review for submission for publication

Kyle PERRIN was involved in the literature review, study conception and design, results analysis and interpretation, manuscript write-up and review for submission

Peter BLACK was involved in the original study conception regarding need for testing of electronic monitoring devices and development of test frameworks
Richard BEASLEY was involved in the literature review, study conception and design, development of testing frameworks, data collection, results analysis and interpretation, manuscript write-up and review for submission for publication.

Measuring adherence to inhaled asthma medication and patterns of use of both maintenance and reliever therapies is of importance in research and clinical settings. Medication usage can be recorded by electronic monitors, and a variety of such monitors have been developed over the past 20 years. Prior validation studies for a number of electronic monitors are limited by their short-term nature.

The Smartinhaler Tracker (Nexus6 Limited, Auckland, NZ) is an EMD for use with pMDIs. It consists of a plastic pMDI casing into which a standard pMDI medication canister can be inserted; the casing incorporates a battery and a switch, which is triggered by depression of the canister during inhaler actuation. Each actuation results in a date and time log (to the nearest second) that is stored on the monitor and can be downloaded onto a computer or uploaded to a Web-based server via a USB computer connection and dedicated software. The Smartinhaler has previously been validated for use in short-term laboratory studies, but no data exist on the accuracy of the monitors over prolonged periods.

The aim of the present study was to determine the in vitro accuracy of the Smartinhaler in recording pMDI actuations over a 24-week period of use. The findings were considered in relation to the use of electronic monitors in a clinical trial setting to provide guidance for clinical trial conduct utilising these, and other similar devices, to maximise data integrity.

A total of 22 Smartinhaler monitors were included in this study. Half were loaded with Vannair (AstraZeneca, Auckland, NZ) (budesonide/eformoterol 200/6 μg per actuation) medication canisters and half with Ventolin (GlaxoSmithKline, Auckland, NZ) (salbutamol 100 μg per actuation) medication canisters. Testing was undertaken at 0, 8, 16, and 24 weeks under standardised conditions. Monitor data were compared with a written diary. The key elements of monitor function that were tested are displayed in Table 5 and summarised below.
Table 5. Monitor functions tested over the 24-week period

<table>
<thead>
<tr>
<th>Monitor function tested</th>
<th>Week 0</th>
<th>Week 8</th>
<th>Week 16</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reset*</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Loading with medication canister†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial screen of monitor‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low use actuations§</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>High use actuations‖</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actuation time and date</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Upload of data to Web site</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Preview of data¶</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Erroneous actuation check during 8-wk period without use</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Storage of electronic data for an 8-wk period</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Accuracy of monitors in recording actuations after 8 weeks of no use</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Comparison of uploaded Web site data with diary data</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Comparison of computer backup data with diary data</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Monitor clock accuracy over 8 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitor battery charge</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

* Data cleared from monitor memory and clock synchronised with computer.
† The monitor was actuated during every canister reload to ensure correct insertion.
‡ Initial screen comprised of two actuations performed twice per day for two days (n = 176 actuations).
§ Low use actuations comprised of two actuations performed twice per day on a total of seven days over the 24-week period (n = 560 actuations).
‖ High use actuations comprised of eight actuations performed three times per day on a total of three days over the 24-week period (n = 1440 actuations).
¶ Visual inspection of data on monitor without uploading of data to website.

Monitors were actuated as follows:

Initial screen: Two actuations separated by 10 to 20 seconds, repeated once at least two hours later, for two days. This pattern was chosen to act as an initial screen to identify malfunctioning devices early in the testing process.

Low use: Two actuations separated by 10 to 20 seconds, repeated once at least two hours later on the same day. This pattern was chosen to reflect maintenance or “low” reliever medication use.

High use: Eight actuations, each separated by 10 to 20 seconds, repeated on two other occasions on the same day. This pattern was chosen to reflect “high” reliever medication use.

In addition, checks of data retention and recording of spurious logs during periods without use were made. Monitor clock accuracy, battery charge, and data transfer were also assessed. The results of the 24-week testing for all 22 monitors are detailed in Table 6.
Table 6. Results of testing process

<table>
<thead>
<tr>
<th>Monitor function tested</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitors completing full testing period, n (%)</td>
<td>20 (91)*</td>
</tr>
<tr>
<td>Overall accuracy in recording number of actuations over 24 weeks (%)</td>
<td>2170 recorded of 2176 actuations performed (99.7)</td>
</tr>
<tr>
<td>Accuracy during low use† (%)</td>
<td>554 recorded of 560 actuations performed (98.9)</td>
</tr>
<tr>
<td>Accuracy during high use† (%)</td>
<td>1440 recorded of 1440 actuations performed (100)</td>
</tr>
<tr>
<td>Accuracy at week 24 (%) vs accuracy at weeks 0-16† (%)</td>
<td>Week 24: 716 recorded of 720 actuations performed (99.4)</td>
</tr>
<tr>
<td></td>
<td>Weeks 0-16: 1278 recorded of 1280 actuations performed (99.8)</td>
</tr>
<tr>
<td>Accuracy of recording actuation time and date‡ (%)</td>
<td>2160 actuations accurate of 2176 performed (99.3)</td>
</tr>
<tr>
<td>No. of extra actuations recorded (% of total)</td>
<td>8 extra actuations§ (0.37)</td>
</tr>
<tr>
<td>No. of monitors in which extra or missed actuations occurred during testing</td>
<td>2 Ventolin Smartinhalers</td>
</tr>
<tr>
<td>No. of erroneous actuations during 8 weeks without use</td>
<td>0</td>
</tr>
<tr>
<td>Data retention for 8 weeks (%)</td>
<td>100</td>
</tr>
<tr>
<td>Accuracy after 8 weeks of no use (%)</td>
<td>716 recorded of 720 actuations performed (99.4)</td>
</tr>
<tr>
<td>Accuracy of website data (%)</td>
<td>100</td>
</tr>
<tr>
<td>Accuracy of computer backup of data (%)</td>
<td>100</td>
</tr>
<tr>
<td>Mean (SD) monitor clock accuracy (mm:ss)‖</td>
<td>05:10 (00:52)</td>
</tr>
<tr>
<td>Battery charge at week 24</td>
<td>Full charge for all monitors</td>
</tr>
</tbody>
</table>

* One Vannair and one Ventolin monitor failed during Week 0 initial screen.
† Accuracy in recording the number of actuations performed.
‡ Accommodating clock drift.
§ Four during testing period and four outside of testing period (at the time of computer connection).
‖ Estimate of discrepancy between monitor clock and actual time occurring over eight weeks.

Two monitors (9%) failed during the initial screen, as they recorded incorrect date or time logs, and were subsequently removed from further testing. In two other monitors, six actuations (0.28% of total) were not recorded during low use testing. One of these monitors also recorded four extra actuations erroneously (0.18% of total); three of these logs were during low use testing. Four actuations were recorded at the time of computer connection (e.g. preview or upload), outside of the testing period. An estimate of mean (SD) time drift between the actual time and the Smartinhaler clock time was 5 minutes 10 seconds (52 seconds) over an eight-week period.

The overall accuracy in recording the number of actuations was 99.7%. Accommodating the drift in monitor clock over time, the overall accuracy in recording date and time was 99.3%. Monitors were 100% accurate in retaining stored electronic logs for an eight-week period, during which the monitors were not used. No additional logs were recorded during this period.

This study has demonstrated that the Smartinhaler electronic monitor is an accurate device for measuring inhaled asthma medication use over a 24-week period, in a strictly controlled laboratory.
setting. The information gained from this validation process also highlights the need for clinical trial protocols to identify malfunctioning devices, both before and during patient use.

An important part of this validation process was to relate the findings from this in vitro study to the conduct of clinical trials utilising these or similar devices. Our study emphasises the importance of putting into place adequate checks to screen for faulty monitors prior to patient use. An initial abbreviated QC protocol (for instance, two actuations, with a further two performed at least two hours later) is suggested. It was also noted that four extra recorded actuations occurred outside of the testing period, around the time of connection of the monitor to the computer. Data recorded on the day of the study visit could be removed from the final database, to reduce the chance of erroneous actuations being included in the analysis. This may also have the effect of removing “dose-dumping” data from the analysis, as “dose-dumping” is more likely to occur on the day of the study visit.

As this study did not assess “real-world” use of the monitors, there is a potential for malfunction during “real-life” use by patients. For example, because of its electronic components, the monitor may also be vulnerable to the effects of moisture or other environmental factors.

Within-trial testing, such as checks of actuation accuracy and battery life, is advocated to identify and retrieve malfunctioning devices or corrupted data.

In conclusion, we have demonstrated that the Smartinhaler is accurate in recording and retaining pMDI actuation data during a six-month in vitro validation process, provided initial pre-use checks are performed. Our testing process may also be relevant to researchers utilising other electronic adherence monitors. Using the information from this validation, systems may be incorporated into study protocols when using electronic monitors in a clinical trial setting, to safeguard data acquisition and minimise erroneous data collection.
Chapter 6: Using electronic monitoring devices to improve adherence and asthma outcomes – a randomised controlled trial

This chapter presents the results of a six-month RCT investigating the effect of an EMD with an on-board audiovisual reminder function on adherence to preventive treatment and asthma outcomes. These results were published as a paper in The Lancet Respiratory Medicine, which has a partial (1 year) impact factor of 9.629, and was selected as Editor’s Choice. The accompanying editorial by Szefer602 highlighted that, based on our results, there is potential for use of these devices in clinical care beyond a research environment to assure that optimum response is obtained from existing therapies, and potentially to prevent relapses after severe asthma exacerbations, as seen from the significant improvement in asthma control in our study.

Title:

The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial

Journal:

The Lancet Respiratory Medicine 2015: Vol 3: Pages 210-19

Authors:

Amy Hai Yan CHAN, Alistair STEWART, Jeff HARRISON, Carlos CAMARGO Jr, Peter BLACK, Edwin MITCHELL.

Contributions:

Amy CHAN was involved in the literature review, study design, data collection, results analysis and interpretation, manuscript write-up and review for submission for publication

Alistair STEWART was involved in the literature review, study design, results analysis and interpretation, manuscript write-up and review for submission for publication

Jeff HARRISON was involved in the results analysis and interpretation, manuscript write-up and review for submission for publication

Carlos CAMARGO Jr was involved in the results analysis and interpretation, manuscript write-up and review for submission for publication

Peter BLACK was involved in the literature review, study conception and design
Edwin MITCHELL was involved in the literature review, study conception and design, results analysis and interpretation, manuscript write-up and review for submission for publication.

6.1 Abstract

6.1.1 Background

Suboptimum adherence to preventive asthma treatment is associated with substantial morbidity and mortality, yet adherence often remains poor. We aimed to investigate whether use of an inhaler with audiovisual reminders leads to improved adherence and asthma outcomes in school-aged children who presented to the ED with an asthma exacerbation.

6.1.2 Methods

We did a RCT in patients aged 6–15 years who attended the regional ED in Auckland, New Zealand with an asthma exacerbation and were on regular ICS. Using a simple, unrestricted block randomisation with block sizes of 200, we randomly assigned patients to receive an EMD for use with their preventer inhaler with the audiovisual reminder functions either enabled to support adherence to ICS (intervention group) or disabled (control group). Participants were followed up every two months for six months. The primary outcomes were adherence to preventive ICS and number of days absent from school for any reason. Asthma control was assessed as a secondary outcome. All analyses were done in the intention-to-treat population. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12613001353785.

6.1.3 Findings

The study took place between May 10, 2010, and Feb 26, 2012. We randomly assigned 220 patients, 110 to the intervention group and 110 to the control group. Median percentage adherence was 84% (10th percentile 54%, 90th percentile 96%) in the intervention group, compared with 30% (8%, 68%) in the control group (p<0.0001). The proportion of days absent from school for any reason was 1.9% (10th percentile 0.0%, 90th percentile 7.9%) in the intervention group and 1.7% (0.0%, 8.6%) in the control group. The change in asthma morbidity score from baseline to six months was significantly greater in the intervention group than in the control group (p=0.008), with a reduction of 2.0 points from a mean baseline score of 9.3 (SD 2.2) to 7.3 (2.1) in the intervention group, compared with a reduction of 1.2 points from a baseline of 9.2 (2.5) to 8.0 (2.2) in the control group.
6.1.4 Interpretation

Use of an EMD with an audiovisual reminder led to significant improvements in adherence to ICS in school-aged children with asthma. This intervention could be beneficial for the improvement of asthma control in patients for whom poor asthma control is related to poor adherence.

6.2 Paper IV: The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial

6.2.1 Introduction

Asthma is one of the most common chronic diseases in childhood\(^9,603,604\). Suboptimum adherence to long-term preventive asthma treatment, such as ICS, is associated with substantial morbidity and mortality\(^11,12\), and adherence remains poor\(^102,103,107,304\). Various interventions have been tried to improve adherence, but have shown only small benefits\(^32,486\). Additionally, studies of adherence interventions in children with asthma are scarce, and many of those that have been done were underpowered to detect differences in clinical asthma outcomes or used subjective methods to monitor adherence\(^91\).

In the past 15 years, EMDs have been introduced for both objective adherence monitoring\(^302\) and as an adherence aid via reminder systems\(^445,493\). EMDs are regarded as the gold standard in adherence monitoring because of their objectivity and their ability to provide detailed information about patterns of treatment use. Three RCTs to investigate EMD-based reminder interventions in asthma have been reported\(^35-37\). In all of these studies, adherence was improved in the reminder group compared with the control groups, but none showed significant differences in clinical asthma outcomes. Possible explanations for these findings include the recruitment of motivated volunteers, use of higher overall doses of ICS than what the patient might clinically need for asthma control\(^36,37\), and low participant numbers\(^35\). Whether the improvements seen in adherence with audiovisual reminders translate into improvements in asthma outcomes therefore remains unknown.

In this study, we aimed to investigate the effect of an EMD with an audiovisual reminder on adherence to ICS and asthma outcomes in school-aged children who attended the ED with an asthma exacerbation.

6.2.2 Methods

6.2.2.1 Study design and participants

In this RCT, children and adolescents aged 6–15 years who attended the regional ED in Auckland, New Zealand, with a suspected diagnosis of asthma exacerbation were screened for eligibility.
Patients with a diagnosis of acute asthma and who were on treatment or needed treatment with twice-daily ICS were eligible for inclusion. Patients with a diagnosis of a chronic lung disease other than asthma, those with congenital heart disease, those who lived outside the Auckland catchment area, and those with a diagnosis of a severe chronic medical disorder that causes impaired immunity or increased morbidity were excluded. Patients treated with other asthma drugs, including LABAs and theophylline, were eligible for inclusion.

The New Zealand Northern Y Regional Ethics Committee (NTY/08/12/116) and all relevant district health boards (DHBs) provided ethical approval for the study. We obtained verbal and written informed consent from the parent or guardian of all participants.

6.2.2.2 Randomisation and masking

Using a simple, unrestricted block randomisation with block sizes of 200, we randomly assigned patients to receive an EMD for use with their preventer inhaler with the audiovisual reminder functions either enabled to support adherence to ICS (intervention group) or disabled (control group). The study statistician (AWS) provided the randomisation group to investigators in opaque, sealed envelopes, which were opened by investigators and research assistants in consecutive order to allocate participants to their randomisation group. Envelopes were sealed to investigators, and research assistants did not know the next allocation group. Use of preventer and reliever inhalers was covertly monitored in both treatment groups with two different EMDs. Participants were unaware of the adherence monitoring function of either device, but were informed that the reliever monitoring device was to be used with their reliever inhaler to enable investigators to know when the drug was running out. This covert monitoring method was done in accordance with previously suggested guidelines and was approved by the New Zealand Northern Y Regional Ethics Committee.

6.2.2.3 Procedures

Investigators and research assistants identified potential participants from daily ED attendance sheets on the basis of their documented reason for attendance. Patients who attended the ED for shortness of breath, viral illness, stridor, wheeze, asthma, cough, respiratory distress, difficulty breathing, pneumonia, increased work of breathing, croup, upper respiratory tract infection, or whose documented reason for attendance was unwell, review, or had no listed reason had their hospital records reviewed further to determine eligibility. Only patients identified as attending the ED for an asthma exacerbation were contacted to determine eligibility and enrolment. Information about the study was provided via telephone, email, or both to the patients, their parents or caregivers, or both.
Patients who consented were randomly assigned to receive the EMD for use with their preventive inhalers (SmartTrack; Nexus6, Auckland, NZ; Figure 1) with the audiovisual function enabled (intervention) or disabled (control). The SmartTrack device is approved by the US FDA. The device records the date, time, and number of actuations used and has 14 different ringtone reminders that ring twice daily, stopping once the correct dose is taken or after 15 min. If the correct dose is taken within six hours before the set reminder time, the reminder does not go off. A visual display shows the date and time of the most recent use. We checked all devices before and after issue to participants using standard QC procedures, involving key checks of the device’s adherence monitoring and audiovisual reminder functions, similar to the procedures described previously543.

Figure 1. SmartTrack inhaler

Photo courtesy of Nexus6, Auckland, NZ.

Patients were enrolled four weeks after their most recent ED attendance to allow for asthma stabilisation. We provided participants with fluticasone propionate inhaled treatment. Those already prescribed other types of ICS were switched to an equipotent fluticasone dose with their general practitioners’ permission for consistency in ICS type and formulation. Participants on both an ICS and LABA were switched to a combination fluticasone propionate and salmeterol xinafoate inhaler. Salbutamol sulfate (also known as albuterol) was available as reliever treatment when needed, delivered via a separate EMD (Smartinhaler Tracker; Nexus6) which also monitors use.

Participants were followed up for six months, with follow-up visits taking place every two months, either at home or in The University of Auckland clinic (Auckland, NZ). During these visits, we obtained information about the number of days patients were absent from school and whether or not their parents or caregivers were absent from work for one day or more during the study period, as well as the reasons for these absences; asthma symptoms and exacerbations since the previous visit; unscheduled doctor, emergency clinic, or hospital visits; and any changes in drug treatments or lifestyle. We also measured lung function and assessed inhaler technique. Participants were encouraged at these visits to only use the inhalers provided by the investigators; when patients had
other inhalers, these were collected. If participants needed additional reliever inhalers, they were replaced with monitored relievers.

We collected all EMDs to be cleaned and to have their data downloaded at each two-month visit, and new devices were issued to patients, or where there were existing devices previously issued to the same patient, these were reissued. Devices were cleaned after collection in preparation for reissue at the next follow-up visit to the same participant. These follow-up visits were in addition to any usual asthma care that was in place before study participation. The duration and frequency of these follow-up visits were limited to minimise the effects of investigator contact on adherence behaviour.

6.2.2.4 Outcomes

Primary outcomes were adherence to preventive ICS and number of days absent from school for any reason. Adherence was defined as the proportion of preventer doses taken relative to the number of doses prescribed. This proportion was calculated by measurement of the degree of deviation from the prescribed dose up to the prescribed dose (i.e. non-adherence, up to a maximum of 0% non-adherence) and subtracting from one (i.e. 100% adherence). This method was chosen so that the effects of overdosing and dose dumping would not affect final adherence calculations. We also compared adherence in the morning (from 0000 h to 1200 h) with that in the afternoon or evening (from 1201 h to 2359 h). We obtained the number of days absent from school from parental report, calculated as a proportion of total number of possible school days for each participant to take into account the different number of school holiday days for each participant and time period.

Secondary outcomes were changes in asthma control (as measured by change in Asthma Morbidity Score (AMS) and Childhood Asthma Control Test (c-ACT) score), lung function (percentage of predicted FEV₁), ED attendance, whether or not parents or caregivers were absent from work for one day or more, number of participants with one or more asthma exacerbations, and number of days of reliever use.

We assessed asthma control with the AMS at baseline and at six months, and with the c-ACT at baseline and at all follow-up visits (i.e. at two, four, and six months). The AMS assesses asthma morbidity on the basis of parental responses to four questions about the child’s asthma, with higher scores indicating greater morbidity. This score was developed in New Zealand and uses both traditional and new measures of asthma morbidity to produce a composite score. Since its development, the AMS has been used in other studies and has been used as the basis for the development of other questionnaires designed to measure morbidity. The c-ACT is a seven-item, validated questionnaire for children aged 4–11 years, based on the ACT. It assesses asthma
control on the basis of child and caregiver responses about asthma symptoms and activity limitations, with a higher score reflecting better control\(^{608}\).

Lung function (FEV\(_1\) and forced vital capacity) were tested with a hand-held spirometer (Micro Plus; Micro Medical, Rochester, UK) at each follow-up visit (two, four, and six months) and three measurements of each parameter were recorded at each visit. Participants were advised to withhold salbutamol use for at least four hours before each study visit if possible. Data for ED attendance, numbers of days absent from work by parents or caregivers, and number of patients with asthma exacerbations were obtained from parental report and hospital records where available. Reliever use was defined as the proportion of days on which the reliever was used relative to the number of days spent in the study for each participant.

Safety was assessed from reports from study participants of adverse events related to the device. Investigators and research assistants monitored for adverse events at each follow-up visit via direct questioning for any health changes in participants suggestive of an adverse event.

6.2.2.5 Statistical analysis

The sample size was based on power calculations done for the primary endpoints of days absent from school for any reason and adherence, as well as the secondary endpoint of asthma control as measured by the AMS. We aimed to ensure that enough participants were recruited for the study to have a power of 80% to detect a clinically meaningful difference in these three endpoints at a significance level of 0.05. To detect a reduction in number of days absent from school from 19.5 to 13.5 days (based on a standardised total number of 193 available school days per year), 84 patients per group would be needed; to detect an absolute difference in adherence of 10%, 51 patients per group would be needed; and to detect a 30% reduction in AMS, 100 patients per group would be needed. Therefore, we aimed to recruit 110 participants in each group, to allow for a 10% loss to follow-up.

We used a generalised linear mixed-model regression to assess adherence, reliever use, and asthma exacerbations with participants as a random effect and time modelled by use of an autoregressive covariance matrix, a logistic link function, and binomial distribution. Fixed effects were treatment group, time (two, four, and six months), and their interaction. Adherence, reliever use, and exacerbations were measured for each two-month period. This mixed-model regression was not affected by missing data. For days absent from school, we used Mann-Whitney U tests to compare the groups with data for the entire six months.

We assessed c-ACT score and lung function using a similar model to that used for adherence data, with the normal distribution and identity link. These two measures had their baseline values as fixed effects. We used a \(\chi^2\) test to analyse the proportions of participants who attended the ED and the
proportions of caregivers with one or more days absent from work during the study period. Medians and 10th and 90th percentiles are given as estimates of the treatment group parameters, unless otherwise indicated, since the data are asymmetrically distributed and often bounded.

The null hypothesis for all analyses was that there was no difference between the treatment groups. All comparisons of the treatment groups used two-sided tests with a significance level of 0.05. Analyses of all primary and secondary outcomes were done for the intention-to-treat population with IBM SPSS Statistics (version 22) and SAS (version 9.2). There was no separate safety population.

This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12613001353785.

6.2.2.6  Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. AHYC, AWS, EAM, and JH had full access to all the data in the study and AHYC had final responsibility for the decision to submit for publication.

6.2.3  Results
2045 patients aged 6–15 years were admitted to the Auckland regional ED with a possible asthma diagnosis during the 21-month recruitment period (May 10, 2010, to Feb 26, 2012), of whom 656 were eligible for further contact and assessment. After exclusions, 220 participants were enrolled and randomly assigned, 110 to each group (Figure 2). At the end of the study, five participants from the control group and two from the intervention group had withdrawn (overall retention 97% [213/220]). 694 reminder devices (SmartTrack) and 697 reliever devices (Smartinhaler Tracker) were issued during the study, of which 16 (2%) reminder devices and 65 (9%) reliever devices were not returned. Complete data were available from the remaining 678 (98%) reminder devices and 632 (91%) reliever devices.
Baseline characteristics of enrolled patients are shown in Table 1. These were well balanced between groups. The characteristics of the population of patients who presented to the ED with asthma symptoms (n=656) from which the study sample was taken was similar to the study population in terms of age, sex, deprivation index, and ethnic origin (Section 6.4, Appendix Table 1).

No adverse events related to the intervention were identified or reported during the study.
### Table 1. Baseline characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Intervention group (n=110)</th>
<th>Control group (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years</td>
<td>8.9±2.5</td>
<td>8.9±2.6</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>55 (50)</td>
<td>58 (53)</td>
</tr>
<tr>
<td>Height – cm</td>
<td>138.9±15.7</td>
<td>137.6±15.9</td>
</tr>
<tr>
<td>Age at diagnosis – years</td>
<td>3.2±2.4</td>
<td>3.4±2.3</td>
</tr>
<tr>
<td>Baseline Asthma Morbidity Score</td>
<td>9.3±2.2</td>
<td>9.2±2.5</td>
</tr>
<tr>
<td>Baseline Childhood Asthma Control Test</td>
<td>18.8±4.4</td>
<td>18.8±4.2</td>
</tr>
<tr>
<td>score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline % Forced Expiratory Volume in 1 second (predicted)</td>
<td>92±17</td>
<td>90±17</td>
</tr>
<tr>
<td>Deprivation Index⁺</td>
<td>6.1±2.7</td>
<td>6.1±2.7</td>
</tr>
<tr>
<td>Weight – kg</td>
<td>38.3±18.7</td>
<td>36.5±16.1</td>
</tr>
<tr>
<td>Ethnicity – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>42 (38)</td>
<td>41 (37)</td>
</tr>
<tr>
<td>Māori</td>
<td>6 (5)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Pacific Peoples</td>
<td>25 (23)</td>
<td>21 (19)</td>
</tr>
<tr>
<td>Asian</td>
<td>19 (17)</td>
<td>20 (18)</td>
</tr>
<tr>
<td>MELAA∞</td>
<td>2 (2)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (15)</td>
<td>11 (10)</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ±SD.

⁺Deprivation index based on the NZDep2006 Score. This is an indicator of socioeconomic deprivation of the area where the individual resides. Scores are derived from census data on income, home ownership, employment, qualifications, family structure, housing, access to transport and communications. Scores are reported as deciles, ranging from 1 to 10, with 1 representing areas that are least deprived, and 10 being the areas that are most deprived.

∞Middle Eastern / Latin American / African

Median percentage adherence was 84% in the intervention group (10th percentile 54%, 90th percentile 96%), compared with 30% in the control group (8%, 68%; p<0.0001). A higher proportion of participants in the intervention group than in the control group had greater than 70% adherence (Figure 3). The control group had better adherence in the evening than in the morning at all three timepoints (two, four, and six months), whereas in the intervention group, adherence was better in the morning than in the evening (p=0.0003; Section 6.4, Appendix Figure 1).
Overall adherence fell in both groups over time, with no difference in the rate of decline between the two (p=0.10; Section 6.4, Appendix Figure 2). Mean percentage adherence at two, four, and six months was 91%, 84%, and 79%, respectively, for the intervention group, compared with 40%, 33%, and 27%, respectively, for the control group.

We noted no difference in the proportion of parent-reported number of days absent from school between the two groups, either for any reason or for asthma. Over the six months of the study, the median proportion of days absent from school for any reason was 1.9% (10th percentile 0.0%, 90th percentile 7.9%) in the intervention group and 1.7% (0.0%, 8.6%) in the control group (90th percentile is equivalent to 15.3 days per year for the intervention group and 16.6 days per year for the control group, based on a standard school year; p=0.99). Median proportion of days absent from school because of asthma was 0.0% (0.0%, 2.9%; 90th percentile equivalent to 5.6 days per year) for the intervention group and 0.0% (0.0%, 3.9%; 90th percentile equivalent to 7.5 days per year) for the control group (p=0.096).

The change in AMS from baseline to six months was significantly greater in the intervention group than in the control group (p=0.008), with a reduction of 2.0 points from a mean baseline score of 9.3 (SD 2.2) to 7.3 (2.1) in the intervention group, compared with a reduction of 1.2 points from a baseline of 9.2 (2.5) to 8.0 (2.2) in the control group. We noted no interaction between treatment group and time for the c-ACT score (p=0.25); however, the difference between groups was significant at all timepoints (two, four, and six months; p<0.0001), with the intervention group scoring higher by an overall average of 1.57. Both groups showed the greatest improvement in c-
ACT score at two months, with the score plateauing at four and six months. We noted no interaction between the c-ACT score and time (table 2).

For reliever use, the median percentage of days on which a reliever was used was 9.5% (10th percentile 1.1%, 90th percentile 32.8%) in the intervention group and 17.4% (2.4%, 49.2%) in the control group (p=0.002). We noted a non-significant (p=0.054) interaction over time, with the control group slightly reducing their reliever use over the duration of the study (19.6% [10th percentile 0.0%, 90th percentile 56.0%] at two months, 14.0% [0.0%, 61.3%] at four months, and 9.8% [0.0%, 51.1%] at six months), whereas use in the intervention group increased slightly (6.7% [0.0%, 36.1%] at two months, 5.5% [0.0%, 40.0%] at four months, and 10.5% [0.0%, 39.0%] at six months).

We noted no interaction between treatment group and time for lung function, as measured by change in FEV1 (% predicted; p=0.76). The small difference between groups (1.26%) was not significant (p=0.38), although we noted improvement with each study visit in both groups, with mean % FEV1 (predicted) increasing from a baseline value of 92% (SD 17) to 101% (16) at six months in the intervention group and from 90% (18) to 97% (16) in the control group (p=0.0003; table 2).

We noted no differences in the proportions of participants with one or more ED attendance for asthma-related causes (ten [9%] of 110 in the intervention vs 13 [12%] of 110 in the control group; p=0.509), respiratory-related causes (four [4%] of 110 vs two [2%] of 110; p=0.408), or any causes (21 [19%] of 110 vs 25 [23%] of 110; p=0.507). Forced vital capacity data was not used in the analysis.

Table 2. Change in Childhood-Asthma Control Test scores, lung function and exacerbations*

<table>
<thead>
<tr>
<th>Visit</th>
<th>Childhood Asthma Control Test score</th>
<th>Lung function (%FEV1(predicted))</th>
<th>Parental-reported exacerbations (% with ≥ 1 exacerbation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n=110)*</td>
<td>Intervention (n=110)*</td>
<td>Control (n=110)*</td>
</tr>
<tr>
<td>Baseline</td>
<td>18.8 ±4.2</td>
<td>18.8 ±4.5</td>
<td>89.5 ±17.8</td>
</tr>
<tr>
<td>2 months</td>
<td>21.4 ±3.5</td>
<td>23.4 ±3.0</td>
<td>95.0 ±15.5</td>
</tr>
<tr>
<td>4 months</td>
<td>21.6 ±4.1</td>
<td>22.9 ±3.2</td>
<td>94.0 ±18.7</td>
</tr>
<tr>
<td>6 months</td>
<td>21.4 ±4.2</td>
<td>22.7 ±3.7</td>
<td>97.2 ±15.8</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td>0.38</td>
<td></td>
</tr>
</tbody>
</table>

*Plus-minus values are means ±SD. FEV1 denotes forced expiratory volume in 1 second.

*For n=108 for the intervention group at two, four, and six months; n = 108 for the control group at two months; and n=105 for the control group at four and 6 months; or as indicated in the table denominator, where n/N is represented. Numbers are less than 110 due to participant withdrawals, as described in the Results.
We noted no difference in the proportion of caregivers who had one or more days absent from work for any reason (45 [41%] of 110 in the intervention group vs 36 [33%] of 110 in the control group; p=0.142) or for asthma in the participant (18 [16%] of 110 vs 13 [12%] of 110; p=0.167). For parent-reported asthma exacerbations, we noted a significant interaction between treatment group and the three observation periods (0–2 months, 2–4 months, and 4–6 months; p=0.015), suggesting a treatment effect particularly within the first two months of use of the EMD. The intervention group had a significantly lower proportion of parent-reported asthma exacerbations than the control group, with seven (6%) of 108 participants in the intervention group versus 26 (24%) of 108 participants in the control group having one or more exacerbation reported in the first two months. This difference was not seen at four months (17 [16%] of 108 in the intervention group vs 16 [15%] of 104 in the control group) or at six months (17 [16%] of 106 vs 17 [17%] of 102). Note the denominators here are less than 110 because of patient withdrawals or missing data in participants who were not administered the questionnaire.

6.2.3.1 Panel: Research in context

Systematic review

We searched MEDLINE, Embase, PubMed, and the Cochrane library for articles published in any language up to Sept 24, 2014, using the terms “asthma” AND “adherence” AND “reminder*”. We identified 212 publications across the four databases. Of these publications, only four were reports of RCTs in which reminders were used as an intervention to improve adherence to asthma treatment. Two of these studies assessed an inhaler device with an incorporated reminder, one investigated the use of fortnightly phone calls, and the fourth was a small RCT (n=26) that assessed the use of text message reminders for adults with asthma. In all of these studies, the intervention group that received the reminder had improved adherence compared with the control group. However, none of the studies showed significant differences in asthma control, or asthma outcomes were not measured. All four of these previous trials were done in participants aged at least 12 years and did not include younger children. An unpublished study in 40 children, available only as a conference abstract and located via personal communication, investigated an inhaler device with an incorporated reminder but also showed no differences in asthma outcomes due to the small sample size.

Interpretation

To our knowledge, this is the first RCT to investigate the use of an EMD with an audiovisual reminder in children and adolescents, and was powered to detect differences in adherence and asthma outcomes. The results show that use of an EMD reminder can lead to improvements in treatment adherence, asthma control, and reliever use, although we did not note any effect on absences from school. The improvement in asthma control was significant and was sustained throughout the six-
month trial. The large improvements in adherence seen in this population of children and adolescents recruited from the ED suggest that a reminder intervention could be especially useful in patients with very poor adherence, such as those who present to EDs with asthma, and in children and adolescents in whom non-adherence is mainly related to forgetfulness.

6.3 Discussion

To our knowledge, this is the first and largest randomised controlled study powered to detect the effect of reminders from an EMD on both adherence and asthma outcomes among children and adolescents. Use of an EMD with an in-built audiovisual reminder significantly improved adherence in school-aged children with asthma, with corresponding improvements in several indicators of asthma control, although we did not note any effect on absences from school (see panel).

Although three previous studies of EMD reminders for preventive asthma treatment showed improvements in adherence, none of them were powered to detect differences in asthma outcomes, showing only non-significant improvements in some parameters such as exacerbations, but not in overall asthma control. Furthermore, the only other study to have been done in children and adolescents included only 40 participants studied over eight weeks. The small sample size and short duration meant that it was underpowered to show differences in outcomes between groups. Additionally, whereas most previous intervention studies in children have used subjective methods to measure adherence, in our study the use of both preventer and reliever treatments was objectively monitored via the EMDs, thus improving the reliability and validity of the results.

The improvement in adherence seen in the intervention group in our study was significant, and of a greater size than previously reported, with a difference in adherence between the intervention and control groups of more than 50 percentage points. This improvement could be caused both by the simple presence of the reminder and by the real-time feedback provided by the device, since the reminder only ceased when the correct dose was taken or after 15 min, with the screen displaying the date and time of the most recent dose taken.

The larger improvement seen in our study could also be due to the control group population having lower baseline adherence than the control groups in the other studies. Previous studies used volunteers as their controls, who would probably have been highly motivated and more adherent than our participants, who were recruited from EDs and are therefore representative of patients with poor asthma control, poor adherence, and previous ED attendance. The most recent study recruited patients from primary care, where controls received usual care from their primary care physician. The control group showed substantial improvements in their asthma control, which might have diluted the effect of the intervention on asthma outcomes. Another possibility is that...
children and adolescents respond better than adults with reminder interventions since simple forgetfulness is the most commonly reported reason for non-adherence in this age group. Indeed, the second largest adherence difference reported (41 percentage points) with EMD reminders was in a study of children and adolescents. We also investigated the effect of the reminders on patterns of inhaler use. Despite the ability of EMDs to provide valuable information about adherence patterns, no previous studies have included data for the effect of reminder interventions on morning versus evening adherence. In fact, this outcome has seldom been investigated in any asthma studies. Although the intervention improved adherence significantly in both the morning and the evening, the effect seemed to be more pronounced for the morning doses. The control group showed better evening adherence across all timepoints, as has been noted previously. The reminder seemed to change this pattern by improving the morning adherence to a level similar to or better than that in the evening, and slowing the fall in adherence with time. The reminder might therefore be especially effective for morning adherence in patients who miss doses because of forgetfulness and busy morning routines.

Consistent with the improved adherence, we noted significant improvements in the intervention group across several asthma outcomes. Asthma control improved significantly, with most benefits occurring in the first two months of the study. Adherence tends to decrease over time in all patients, and this pattern was seen across both groups. The pattern with asthma control followed the pattern of adherence, suggesting that the improvements in asthma outcomes were related to improved adherence. Based on the reported minimally important difference of three points for the ACT score, only the intervention group had a large enough improvement to be regarded as clinically significant, with an improvement of more than three points across all time periods. Improvements were also seen in the control group, as has been reported elsewhere. This finding of improvement in the control group could be partly caused by participating in a clinical trial and by the natural progress of asthma after discharge from hospital.

We also noted improvements in the number of asthma exacerbations and reliever use in the intervention group. The reduction in exacerbations was not sustained beyond two months, possibly because of a fall in adherence to a level below that needed to prevent exacerbations. Indeed, there seems to be a dose-response relation between the use of ICS and prevention of asthma exacerbations, and good adherence to ICS is needed to prevent exacerbations. Risk of re-exacerbation is high after ED attendance, when adherence to ICS drops to 50% within the seven days after discharge from hospital. Use of ICS in the immediate post-discharge period prevents subsequent exacerbations. The intervention might therefore be most beneficial during this initial high-risk period. Reliever use is associated with poor asthma control, mortality, and future exacerbations, and the reduced reliever use in the intervention group compared with the control
group in our study is consistent with increased adherence to ICS, resulting in improved asthma control. The difference in reliever use between the two study groups seemed to narrow with time. Speculatively, this finding might be partly due to a higher use of non-monitored relievers by the control group than by the intervention group, which might have occurred because the control group patients were more likely to require reliever treatments (based on their asthma control results) so theoretically had a higher likelihood of obtaining non-monitored relievers from their general practitioner or emergency clinics. Therefore, actual reliever use might have been underestimated in the control group. Unfortunately, we could not identify the exact numbers of participants who used non-monitored relievers, since this information was only available when provided by the participant.

The absence of differences in other outcome measures is similar to the results of other reminder studies. We did not identify differences in hospital attendance and number of days absent from school and work; these outcomes were much less frequent than previously reported, meaning that our study was underpowered to detect differences despite our initial power calculations. This issue was compounded by the fact that the likelihood of hospital attendance is low even in patients who stop regular ICS treatment, compared with those who continue to use it. The number of days absent from school might have been underreported because parental reports tend to underestimate school absence. Although we chose number of days absent from school as a primary outcome because it is one of the highest indirect health costs associated with childhood asthma, the association between asthma control and school attendance is not clear. Although in some studies school absenteeism is increased in children with asthma, no difference was seen in another study. No studies have been reported in which increased use of ICS has been shown to improve school attendance.

One limitation of the measurement methods used in our study was the absence of a validated asthma control measure across the age range of our study population. The c-ACT is validated for children aged 4–11 years, whereas the age range of our participants extended to 15 years. However, since asthma control is based on several parameters, no single outcome measure can be used as the determinant of asthma control. The outcomes used as markers of control in this study all showed numerical improvements in the same direction, which suggests that use of an audiovisual reminder intervention improves adherence and asthma outcomes. Further research with larger study populations might be able to detect more significant differences in school absence and hospital attendance. Although baseline adherence is likely to be poor in a population of patients presenting to the ED with asthma, the clinical benefit in this group might be underestimated in our study because of the effect on the overall estimates of those patients with better adherence (e.g. first presentations to the ED). For this reason, a run-in phase to determine baseline adherence would be useful to allow investigation of the true change in adherence. Because most of the
improvements seen in our study occurred in the first two months, a question exists about the sustainability of the benefits seen. Long-term sustainability could be affected by habituation to the reminder, particularly if the reminder is automated. Real-time reminders that occur only when treatment is missed, or variable reminders that occur at different frequencies or use different ringtones, might reduce the risks of habituation. The reminder used in this study was only activated if the correct dose had not been taken on time. This setup and the ringtone variety might have reduced the risk of habituation over the six months of the study. A study with a longer research period is needed to investigate the effects of reminder frequency and variability on long-term adherence.

Additional factors such as cost and ease of use need to be taken into account when EMDs are used in clinical practice. The device used in this study is compatible with any metered-dose inhaler and feedback on its use so far has been positive; patients in the intervention group in this study were more likely than those in the control group to state that they better remembered to take their treatment with the device (data not shown). The ratio of costs to benefits also needs to be taken into account—the acquisition costs of EMDs for inhalers have traditionally been high, although costs will probably fall with increasing use, technological advancement, and expansion of available options on the market. The cost associated with EMDs is accrued at the start of treatment, whereas the benefits of costs saved from improved adherence and better treatment outcomes would occur over the longer term. In a recent review, Golay examined the pharmacoeconomic dimensions of poor adherence to preventive asthma treatment and concluded that interventions that improve adherence might confer cost-effectiveness benefits, although more research is needed. Until such work is done, these initial results suggest that audiovisual reminders do have a role in asthma management, particularly in populations with poorly controlled asthma, for whom the benefits of improved symptom control will probably outweigh the one-off cost of the device. In a poorly adherent population such as patients who present to the ED with asthma, the effect of such a reminder intervention is likely to be the greatest.
6.4 Appendix

Appendix Table 1. Baseline characteristics of patients aged 6–15 years presenting to ED with asthma*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Population numbers (n=560)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – year</td>
<td>8.8±2.6</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>315 (56)</td>
</tr>
<tr>
<td>Deprivation Index*</td>
<td>6.1±2.7</td>
</tr>
<tr>
<td>Ethnicity – no. (%)</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>209 (37)</td>
</tr>
<tr>
<td>Māori</td>
<td>90 (16)</td>
</tr>
<tr>
<td>Pacific Peoples</td>
<td>126 (23)</td>
</tr>
<tr>
<td>Asian</td>
<td>117 (21)</td>
</tr>
<tr>
<td>MELAA∞</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (0.5)</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ±SD

†n = 560 as data not available for 96 patients

*Deprivation index based on the NZDep2006 Score

∞Middle Eastern / Latin American / African

Appendix Figure 1. Morning (AM) versus evening (PM) percentage adherence over time by group*  

*Top and bottom of bars represent 25th and 75th percentiles. Percentage adherence depicted as medians as described in text.
Appendix Figure 2. Change in percentage adherence over time

![Graph showing change in percentage adherence over time with error bars for Intervention and Control groups. The y-axis represents percentage adherence, and the x-axis represents time in months (2 month, 4 month, 6 month). The graph shows a decline in adherence over time for both groups, with error bars indicating variability.]
Chapter 7: Performance and acceptability of electronic monitoring devices in children

For adherence interventions to be effective, their use must be sustained – a factor dependent on patient preference and uptake. It is important to consider user acceptability of any intervention to ensure sustainability yet assessment of the performance, reliability and patient acceptability of new adherence strategies is often lacking. This section reports on the performance and patient-reported acceptability of the EMD used in the RCT that demonstrated improvements in adherence and asthma outcomes with use of this device.

**Title:**

Electronic adherence monitoring device performance and patient acceptability: a randomized control trial

**Journal:**

Pediatric Research 2016 *submitted*

**Authors:**

Amy Hai Yan CHAN, Alistair STEWART, Jeff HARRISON, Peter BLACK, Edwin MITCHELL, Juliet FOSTER

**Contributions:**

Amy CHAN conceptualized and designed the study and data collection instruments, coordinated and supervised data collection, drafted the initial manuscript, analysed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Alistair STEWART designed the study and the data collection instruments, analysed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Jeff HARRISON designed the study and data collection instruments, supervised data collection, analysed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Peter BLACK conceptualized and designed the study and the data collection instruments, and supervised data collection.

Edwin MITCHELL conceptualized and designed the study and the data collection instruments, supervised data collection, analysed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.
Juliet FOSTER designed the study, analysed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

7.1 Abstract

**Background**: To investigate the performance and patient acceptability of an inhaler EMD in a real-world childhood asthma population.

**Methods**: Children 6 to 15 years presenting with asthma to the hospital ED and prescribed ICS were included. Participants were randomised to receive a device with reminder features enabled or disabled for use with their preventer. Device QC tests were conducted. Questionnaires on device acceptability, utility and ergonomics were completed at six months.

**Results**: A total of 1,306 QC tests were conducted; 84% passed pre-issue and 87% return testing. The most common failure reason was actuation under-recording. Acceptability scores were high, with higher scores in the reminder than non-reminder group (median, 5th–95th percentile: 4.1, 3.1-5.0 versus 3.7, 2.3-4.8; p<0.001). Most (>90%) rated the device easy to use. Feedback was positive across five themes: device acceptability, ringtone acceptability, suggestions for improvement, effect on medication use, and effect on asthma control.

**Conclusion**: This is the first study to investigate EMD performance and acceptability in children using quantitative and qualitative measures. Results indicate satisfactory reliability, although failure rates of 13-16% indicate the importance of QC. Favourable acceptability ratings support the use of these devices in children.

7.2 Paper V: Electronic adherence monitoring device performance and patient acceptability: a randomized control trial

7.2.1 Introduction

Adherence to preventive therapy is essential for reducing morbidity in childhood asthma, yet adherence remains suboptimal. EMDs are increasingly used to deliver adherence interventions and provide objective adherence data, but EMDs vary in their accuracy and reliability and there is little data available on patient acceptability. Implementation of standardised testing is recommended to evaluate the validity of EMD data collected and measurement of patient-reported EMD acceptability is advised to identify feasibility issues. However, there is scant research on EMD performance and even fewer studies on patient acceptability in real world populations.
The SmartTrack EMD (Nexus 6 Limited, NZ; Figure 1) is an EMD for pMDIs. This device has increasingly been used in adherence research\textsuperscript{37, 457, 543} as it has features that are not available on older EMDs, like the Doser\textsuperscript{628}. These include remote data upload capability, real-time adherence feedback via an on-board screen and multiple customisable functions including customised reminder times and ringtones\textsuperscript{628}.

**Figure 1. SmartTrack\textsuperscript{®} electronic monitoring device**

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{smarttrack_device.png}
\caption{Left: Angled view showing open SmartTrack with Universal Serial Bus charging port bottom right. Centre: Front view with pressurised metered dose inhaler in-situ. Right: Side view showing on-board buttons and a light-emitting diode screen displaying date / time of last taken dose.}
\end{figure}

Whilst this device has been used in several published studies, there is currently little knowledge about the reliability of this device in a real world setting and how patients respond to its use. In one 6-day study, SmartTrack data recording accuracy was reported at 99% and ease of use scores were high in adults with asthma\textsuperscript{543}. There is little data on patient acceptability beyond this short study, and no published data at all in children. Lack of long-term EMD performance and acceptability data in real world settings\textsuperscript{542, 543}, particularly in children\textsuperscript{34, 125, 493, 538, 539}, may impede EMD implementation in clinical settings, since use will only be sustained if patients are comfortable with using them and if devices perform reliably.

The SmartTrack EMD was recently used in a RCT in 220 children aged 6 to 15 years, presenting with an asthma exacerbation to the regional ED in Auckland, New Zealand\textsuperscript{457}. The objective of this paper is to assess the performance and patient acceptability of the SmartTrack EMD, when used for six months in a trial investigating the effects of a reminder EMD on adherence and asthma outcomes in children.
7.2.2 Methods

7.2.2.1 Patients and trial design

This trial was undertaken in children aged 6 to 15 years, presenting with asthma to the regional ED in Auckland, New Zealand (Australian New Zealand Clinical Trials Registry no. ACTRN12613001353785). The full study design and methods are described in detail elsewhere\(^4\). All participants with a physician-diagnosis of asthma and prescribed regular, twice-daily ICS were eligible. Exclusion criteria included diagnosis of chronic lung disease other than asthma, congenital heart disease, residence outside the Auckland area or diagnosis of a severe chronic medical condition leading to impaired immunity or increased morbidity\(^4\). All participants received the EMD attached to their preventer inhaler; half were randomised to receive the EMD with audiovisual functions enabled (reminder group) and half disabled (non-reminder group). Each participant was followed up for six months. Face-to-face visits occurred every two months, where investigators collected the EMD for performance checking and data upload and participants completed questionnaires. Asthma control was assessed using the AMS\(^6\) and c-ACT\(^6\). Written informed consent was provided by the child’s parent or guardian, and written assent obtained from children.

7.2.2.2 The electronic monitoring device

The SmartTrack EMD delivered twice-daily reminders for missed doses (Figure 1). Reminder times were set by investigators prior to each visit, as per participant preference. The reminder sounded until the correct dose was taken or for a maximum of fifteen minutes, and did not sound if the correct dose was taken in the six hours preceding the set reminder time. One of fourteen different ringtones played each time in a cyclical pattern. The EMD recorded the date and time of each actuation, ringtone initiation and sound, and pMDI or battery removal and insertion; this was stored until data upload. Adherence data was determined from these EMD records. The EMD battery compartment and pMDI entry door were secured using security screws to minimise participant tampering.

Each participant was issued with an EMD at the first visit and shown how to use the device. The EMD was replaced at every visit. Participants were told that the study was investigating the effect of a reminder inhaler on asthma; the adherence monitoring function was not disclosed, as per established ethical guidelines\(^1\), to avoid interference with usual behaviour.

7.2.2.3 EMD quality control testing

All devices were checked prior to issue and after return from participants according to a standardised QC procedure (Table S1)\(^6\), carried out by one of three trained investigators. Any inaccuracies or faults were documented, and affected devices returned to the manufacturer for analysis, repair and data retrieval.
### Table S1: Table summarising SmartTrack electronic monitoring device quality control tests conducted prior to issue and after return from participants

<table>
<thead>
<tr>
<th>QC test component</th>
<th>Pre-issue QC testing(^a)</th>
<th>Return QC testing(^b) Non-reminder group</th>
<th>Return QC testing(^b) Reminder group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual check for any external damage</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Security screw(^c) insertion and removal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device reset(^d)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>pMDI removal and installation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assign device to test patient(^e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actuate two puffs</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>USB cable insertion and removal</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Preview(^f) and upload data</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Check device identification number(^g) matches software</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Check battery strength(^h)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Check EMD screen is enabled in reminder mode</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Check EMD screen clock for accuracy, allowing for time-drift(^i,(^b)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Set reminders for two puffs twice-daily dosing</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Actuate two puffs within 6-hour window before reminder due - check reminder does not sound</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Check next reminder sounds on time</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Check reminder sound recorded correctly</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Actuate one puff (under-dosing)(^j)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Check reminder continues to sound with under-dosing</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Check reminder stops on completion of correct dosing</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Check reminder duration of next reminder</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Check dose dumping recording (actuate five puffs)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Switch EMD to non-reminder mode</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Check actuation recording (actuate one then two puffs at least five minutes apart) in non-reminder mode</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Check dose dumping (actuate five puffs) in non-reminder mode</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Check EMD screen is disabled in non-reminder mode</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

EMD - electronic monitoring device; QC – quality control; pMDI - pressurised metered dose inhaler
\(^a\) QC tests performed prior to issue of the device to participant; all tests were checked for accuracy of recording of time / date (± 2 minutes allowance for internal clock time drift), type of manoeuvre and number of events conducted
\(^b\) QC tests performed after collection of the device from participant; all tests are checked for accuracy of recording of time / date (± 15 minutes allowance for internal clock time drift over two months), type of manoeuvre and number of events conducted
\(^c\) Security screws holding device door and battery compartment
\(^d\) Reset cleared data from the device memory and synchronised the internal clock with the connected computer
\(^e\) 'Test patient' was a set up in the device software for the purpose of QC testing
\(^f\) Preview allowed viewing of data stored on the device without data upload
\(^g\) Each device had a unique device identification number which was labelled externally and readable on computer connection
\(^h\) Battery strength could be checked on device software (for all devices) and on the EMD screen (for reminder EMDs)
Test for under-dosing was only possible if participant dose was prescribed two puffs or greater. If participant was prescribed one puff twice-daily, this test was omitted.

**QC testing before patient use – ‘pre-issue’ QC testing**

Standardised pre-issue QC tests included checks for physical damage, integrity of the security screws and functional and recording accuracy of: actuations, pMDI insertion and removal, and reminders (Table S1). Actuation recording accuracy was checked using varying patterns of puffs at different times of the day to mimic correct, over-, under- and zero dosing. Reminders were checked for accuracy of reminder timing, duration and response to under- and correct dosing. The EMD could be set to reminder or non-reminder mode. Tests were conducted in both modes on each device. Investigators also carried the EMD in pockets or bags in between active testing to mimic real-life use.

**QC testing after patient use – ‘return’ QC testing**

Return QC tests, similar to pre-issue tests, were carried out immediately after collecting the device from the participant to retain pre-return device conditions. A shorter return test, omitting audiovisual testing, was done on non-reminder EMDs.

**QC testing pass threshold**

Devices “passed” testing if all manoeuvres were recorded with 100% event and time accuracy. At baseline an allowance of ±2 minutes was made for internal clock time drift, and ±15 minutes after the two-monthly visits. Reasons for QC test failure were documented and classified into categories. Where more than one reason occurred, the primary reason for failure was reported.

**7.2.2.4 EMD acceptability and ringtone rating score**

Participants completed a questionnaire about device acceptability at study end. The 7-item questionnaire was scored on a 5-point semantic differential scale (1=strongly disagree, 5=strongly agree) which asked about topics such as ease of use, usefulness for medication reminding, and device size. Total score was the average score of the 7 items; item 7 (using my new asthma inhaler in front of other people is embarrassing) was negatively worded so scores were reversed prior to calculating total score. Participants using a reminder EMD completed an 8th question asking how much they liked the reminder sounds and extra questions on ringtone preference [14 ringtones were rated on a 4-point Likert scale (0 = very bad, 3 = very good)], device size [too big, just right, too small] and whether the device was easy to hold [yes, no]. All questionnaires were completed by the child without assistance from the parent or caregiver. Where assistance was needed with interpretation and completion of the questionnaires, this was provided by the researcher. There was also an option of providing written feedback about the device via a free-text comments field at the end of the paper questionnaire which the participant or caregiver could complete, or through
verbal feedback to the investigators either at or between visits via telephone. Ethics approval was obtained from the New Zealand Northern Y Regional Ethics Committee (NTY/08/12/116) and DHBs.

7.2.2.5 Statistical analysis

Descriptive statistics were calculated for patient demographics and acceptability scores. The mean number of faults per participant and acceptability scores were compared in reminder and non-reminder patients using the Mann-Whitney U test. To determine whether there was any association between asthma control and adherence with acceptability scores, univariate analyses were conducted using a general linear model with the variables as covariates. The Friedman test was used to compare ringtone ratings. P-values of less than 0.05 indicated statistical significance. Analyses were undertaken on the intention to treat population using IBM SPSS Statistics (version 22).

7.2.3 Results

As described previously\textsuperscript{467}, of 656 patients initially identified as potentially eligible, 253 were ineligible on further assessment, 41 could not be contacted, 57 declined participation, 82 had already been assessed for eligibility and three excluded for other reasons. The remaining 220 participants were enrolled and 110 participants randomised to each group – the reminder EMD group versus the non-reminder group. The participant flow diagram is shown in Figure 2, with baseline characteristics summarised in Table 1.

Figure 2. Participant flow diagram for inclusion of participants in the clinical trial
Table 1. Baseline participant characteristics by trial randomisation group

<table>
<thead>
<tr>
<th>Randomised group</th>
<th>Reminder n = 110</th>
<th>Non-reminder n = 110</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.9 (2.5)</td>
<td>8.9 (2.6)</td>
</tr>
<tr>
<td>Male sex, no. (%)</td>
<td>55 (50)</td>
<td>58 (53)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>138.9 (15.7)</td>
<td>137.6 (15.9)</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>3.2 (2.4)</td>
<td>3.4 (2.3)</td>
</tr>
<tr>
<td>Asthma Morbidity Score</td>
<td>9.3 (2.2)</td>
<td>9.2 (2.5)</td>
</tr>
<tr>
<td>Childhood Asthma Control Test</td>
<td>18.8 (4.4)</td>
<td>18.8 (4.2)</td>
</tr>
<tr>
<td>Forced Expiratory Volume in 1 second (% predicted)</td>
<td>92 (17)</td>
<td>90 (17)</td>
</tr>
<tr>
<td>Deprivation Index*</td>
<td>6.1 (2.7)</td>
<td>6.1 (2.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>38.3 (18.7)</td>
<td>36.5 (16.1)</td>
</tr>
<tr>
<td>Ethnicity, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>42 (38)</td>
<td>41 (37)</td>
</tr>
<tr>
<td>Māori</td>
<td>6 (5)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Pacific Peoples</td>
<td>25 (23)</td>
<td>21 (19)</td>
</tr>
<tr>
<td>Asian</td>
<td>19 (17)</td>
<td>20 (18)</td>
</tr>
<tr>
<td>Middle Eastern/Latin American /African</td>
<td>2 (2)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (15)</td>
<td>11 (10)</td>
</tr>
</tbody>
</table>

All values are mean (SD) or n (%). See also Table 1, section 6.2.3
Deprivation index based on the NZDep2006 Score. This is an indicator of socioeconomic deprivation of the area where the individual resides. Scores are derived from census data on income, home ownership, employment, qualifications, family structure, housing, access to transport and communications. Scores are reported as deciles, ranging from 1 to 10, with 1 representing areas that are least deprived, and 10 being the areas that are most deprived.

7.2.3.1 EMD performance

There were four categories of device failure: data recording, reminder, battery or upload faults. Pre-issue QC tests were conducted on 628 devices, of which 527 (84%) passed (Table 2). The majority of failures were due to data recording inaccuracies (67%), followed by reminder faults (17%).
### Table 2. Pre-issue and return quality control testing results

<table>
<thead>
<tr>
<th>Quality Control Testing</th>
<th>Passed</th>
<th>Failed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-issue quality control testing</strong> (n=628 devices)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passed</td>
<td>527 (84%)</td>
<td></td>
</tr>
<tr>
<td>Failed(^a)</td>
<td>101 (16%)</td>
<td></td>
</tr>
<tr>
<td><strong>Recording inaccuracies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Actuation under-recording</td>
<td>55 (81%)</td>
<td></td>
</tr>
<tr>
<td>- Actuation over-recording</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>- Inaccurate event recording(^b)</td>
<td>10 (15%)</td>
<td></td>
</tr>
<tr>
<td><strong>Reminder faults</strong></td>
<td>68 (67%)</td>
<td></td>
</tr>
<tr>
<td>- Erroneous sounding outside pre-set times</td>
<td>4 (24%)</td>
<td></td>
</tr>
<tr>
<td>- Failure of the reminder to sound at set times</td>
<td>13 (76%)</td>
<td></td>
</tr>
<tr>
<td><strong>Battery faults</strong></td>
<td>7 (7%)</td>
<td></td>
</tr>
<tr>
<td>- Short battery life</td>
<td>2 (29%)</td>
<td></td>
</tr>
<tr>
<td>- Battery removal / insertion leading to loss of device function</td>
<td>4 (57%)</td>
<td></td>
</tr>
<tr>
<td>- Battery removal and insertion leading to loss of data</td>
<td>1 (14%)</td>
<td></td>
</tr>
<tr>
<td><strong>Upload faults</strong></td>
<td>7 (7%)</td>
<td></td>
</tr>
<tr>
<td>- Failure of the device to connect to the computer</td>
<td>3 (43%)</td>
<td></td>
</tr>
<tr>
<td>- Inappropriate events occurring during upload(^c)</td>
<td>4 (57%)</td>
<td></td>
</tr>
<tr>
<td><strong>Return quality control testing</strong> (n=678 devices)(^d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passed</td>
<td>591 (87%)</td>
<td></td>
</tr>
<tr>
<td>Failed</td>
<td>87 (13%)</td>
<td></td>
</tr>
<tr>
<td><strong>Recording inaccuracies</strong></td>
<td>83 (95%)</td>
<td></td>
</tr>
<tr>
<td>- Actuation under-recording</td>
<td>81 (98%)</td>
<td></td>
</tr>
<tr>
<td>- Erroneous event recording(^b)</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Reminder faults</strong></td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>- Erroneous sounding of the reminder outside pre-set times</td>
<td>1 (50%)</td>
<td></td>
</tr>
<tr>
<td>- Failure of reminder to stop</td>
<td>1 (50%)</td>
<td></td>
</tr>
<tr>
<td><strong>Battery fault leading to data loss</strong></td>
<td>2 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Faults occurring during pre-issue quality control testing that were not categorised: one device had the same identification number as a device already issued; another device was an incorrect model with extra features supplied in error by the manufacturer.

\(^b\) E.g. Inhaler removal erroneously recorded as an actuation, recording a battery removal that did not happen.

\(^c\) E.g. Reminder sounding upon upload.

\(^d\) Physical damage – a broken battery case in three devices and unresponsive buttons and a blank display screen in one device – was observed in four devices on return.

During the study, 694 devices were issued (an average of three devices per participant; a new device at baseline, two- and four-month visits); 16 (2%) were not returned at study completion. Return QC testing was carried out on the remaining 678 devices, of which 591 (87%) passed. Of the 87 (13%) that failed, data recording inaccuracies accounted for the majority (95%) of failures. Physical damage was observed in four EMDs. The mean ± SD number of device faults per participant did not differ between the two groups (intervention: 0.45±0.79 versus control: 0.34±0.62; p=0.33).
**7.2.3.2 EMD acceptability scale**

Ninety-eight per cent (108/110) of participants in the reminder group and 95% (104/110) in the non-reminder group completed the acceptability questionnaire. Scores in both groups (mean ≥4.4) indicated that the majority were happy to continue using the EMD (Table 3).

**Table 3. Electronic monitoring device acceptability scores by trial randomisation group**

<table>
<thead>
<tr>
<th>Question</th>
<th>Reminder group</th>
<th>Non-reminder group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel happy to continue using my Smart inhaler</td>
<td>4.5 (3.0,5.0)</td>
<td>4.4 (3.0,5.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>2. It is easy to remember when to take my new asthma inhaler</td>
<td>4.4 (3.0,5.0)</td>
<td>3.5 (1.0,5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3. Knowing when to take my asthma medication is easy</td>
<td>4.5 (3.0,5.0)</td>
<td>3.5 (1.2,5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4. I feel more in control of my asthma now</td>
<td>4.3 (2.4,5.0)</td>
<td>3.8 (2.0,5.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>5. I would tell my friends who also have asthma about my new inhaler</td>
<td>3.7 (1.0,5.0)</td>
<td>3.2 (1.0,5.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>6. My asthma inhaler fits easily in my bag or pocket</td>
<td>3.9 (2.0,5.0)</td>
<td>3.8 (1.2,5.0)</td>
<td>0.79</td>
</tr>
<tr>
<td>7. Using my new asthma inhaler in front of other people is embarrassing</td>
<td>2.6 (1.0,5.0)</td>
<td>2.3 (1.0,5.0)</td>
<td>0.26</td>
</tr>
<tr>
<td>8. I like the sounds my inhaler makes</td>
<td>4.0 (1.0,5.0)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**TOTAL SCORE (Q 1 – 7)**

|                           | 4.1 (3.1, 5.0) | 3.7 (2.3,4.8) | <0.001 |

All values mean (5th, 95th percentile). Questions were scored: 1=strongly disagree, 5=strongly agree.

N less than 110 due to patient withdrawals (2 reminder group, 5 non-reminder group) and incomplete questionnaires (3 reminder group, 4 non-reminder group).

*a*Unreversed scores; *b*Total score was the average score of questions 1 to 7; question 7 scores were reversed prior to calculating the total score.

The total mean acceptability score was higher in the reminder than non-reminder group (P<0.001).

A number of individual items were scored significantly higher in the reminder group including: ease of remembering and knowing better when to take their asthma medication (Reminder: mean 4.4 (5th, 95th percentile: 3.0, 5.0) vs. non-reminder 3.5 (1.0, 5.0); p<0.001). Of particular note, patients who received reminders reported feeling more in control of their asthma (Reminder: 4.3 (2.4, 5.0) vs. non-reminder: 3.8 (2.0, 5.0), p=0.001). These improvements in perceived medication-taking and perceived asthma control in the reminder group corresponded with actual improvements in objective measures of asthma control and adherence; the details of which are reported elsewhere. There was no relationship between acceptability scores and clinical outcomes of adherence or asthma control, as assessed by the AMS and ACT at the final six-month visit.
7.2.3.3  **Ringtone ratings**

Of the 110 reminder EMD users, 104 (95%) completed the ringtone ratings questionnaire. There was a significant difference in the ratings of 14 different ringtones ($\chi^2(13) = 185, P < 0.001$). The highest ratings were for popular culture ringtones like “The Simpsons”, which had a median rating of 3 (25th-75th percentile: 2-3). The lowest median ratings were for animal sound ringtones like “Donkey”, which received a rating of 2 (25th-75th percentile: 0.25-2).

7.2.3.4  **Device ergonomics**

One hundred of the 110 (91%) reminder EMD users completed the question on device handling, and 99 (90%) completed the question on device size. Ninety-four percent (94/100) agreed the device was easy to hold; 6% (6/100) disagreed. For device size, 81% (80/99) rated the device “just right”, 16% (16/99) “too big” and 3% (3/99) “too small”.

7.2.3.5  **Feedback about the EMD**

Additional qualitative feedback on the device was provided by 44 individuals (24 children, 20 caregivers; 41 unique participant IDs). Of these individuals, 22 provided written, 21 verbal and 1 both written and verbal feedback. Feedback was predominantly positive and could be classified into five themes: EMD acceptability, ringtone acceptability, suggestions for EMD improvement, effect of EMD on medication use and effect of EMD on asthma control (Table 4).

<table>
<thead>
<tr>
<th>Table 4. Feedback on the electronic monitoring device from participants or their caregivers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feedback and themes</strong></td>
</tr>
<tr>
<td><strong>Participant gender, age</strong></td>
</tr>
<tr>
<td><strong>Electronic monitoring device acceptability</strong></td>
</tr>
<tr>
<td>“Liked it [EMD] but depends on ringtones”</td>
</tr>
<tr>
<td>“Like it [EMD], want to keep using it”</td>
</tr>
<tr>
<td>“Love the device”</td>
</tr>
<tr>
<td>“It is awesome”</td>
</tr>
<tr>
<td>“Love the ... little device”</td>
</tr>
<tr>
<td>“[My child] has liked using the ringtone SmartTrack”</td>
</tr>
<tr>
<td>“Device is handy”</td>
</tr>
<tr>
<td><strong>Ringtone acceptability</strong></td>
</tr>
<tr>
<td>“I really like the ringtones!”</td>
</tr>
<tr>
<td>“Like the alarms!”</td>
</tr>
<tr>
<td>&quot;Love the alarms&quot;</td>
</tr>
<tr>
<td>“Feel ringtones helpful”</td>
</tr>
<tr>
<td>“Cool. Sometimes annoying like in holidays when want to sleep in”</td>
</tr>
<tr>
<td>&quot;The only reason I don't like the ringtones is because in the mornings I wake up with a fright”</td>
</tr>
<tr>
<td>“Not everybody likes the sounds there are!”</td>
</tr>
<tr>
<td>“The music is loud and it wakes my friends up when I take it to their house”</td>
</tr>
<tr>
<td>Feedback and themes</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>“The reminders are still keeping the kids entertained, but perhaps a change of</td>
</tr>
<tr>
<td>ringtones next time might be a good idea. Being the holidays the 7am reminder</td>
</tr>
<tr>
<td>can be bit early sometimes, so bit more flexibility with the times maybe a useful</td>
</tr>
<tr>
<td>feature.”</td>
</tr>
<tr>
<td>“Device doesn’t stop ringing. If I had a choice, I wouldn’t use the device again.</td>
</tr>
<tr>
<td>Would definitely be turning the reminders off at the end of the study”</td>
</tr>
<tr>
<td><strong>Suggestions for electronic monitoring device improvement</strong></td>
</tr>
<tr>
<td>“Add more monkeys”</td>
</tr>
<tr>
<td>“Make skins! [different coloured or patterned outer casings]”</td>
</tr>
<tr>
<td>“Maybe make the ringtones a bit longer”</td>
</tr>
<tr>
<td>“Device is plain - needs colour”</td>
</tr>
<tr>
<td>“Want better tunes”</td>
</tr>
<tr>
<td>“I would like to choose my own tune please”</td>
</tr>
<tr>
<td><strong>Effect of electronic monitoring device on medication use</strong></td>
</tr>
<tr>
<td>“I’ll remember to take my inhaler more often”</td>
</tr>
<tr>
<td>“Wake up call is good – don’t forget the meds”</td>
</tr>
<tr>
<td>“Easy remembering the inhaler”</td>
</tr>
<tr>
<td>“I really like how it has alarms with different tunes and I don’t forget to take</td>
</tr>
<tr>
<td>the orange [preventer] inhaler”</td>
</tr>
<tr>
<td>“Still needs to remind him (participant) to take inhaler, the ringtone sounds but</td>
</tr>
<tr>
<td>he just ignores it. It more reminds me (the parent) to tell him”</td>
</tr>
<tr>
<td>“[Participant is] doing well, reminders work especially during holidays when</td>
</tr>
<tr>
<td>routine goes.”</td>
</tr>
<tr>
<td><strong>Effect of electronic monitoring device on asthma control</strong></td>
</tr>
<tr>
<td>“Not using [reliever] inhalers much anymore – asthma feels controlled”</td>
</tr>
<tr>
<td>“Noticed [my child] seem to be less coughy [sic] this year than last year”</td>
</tr>
<tr>
<td>“[My child’s] asthma is better than ever”</td>
</tr>
<tr>
<td>“[My child is] a changed boy since taking his preventer regularly. Plays sports,</td>
</tr>
<tr>
<td>more energy, hardly coughs at all. [The parent] tells everyone how good the</td>
</tr>
<tr>
<td>device is”</td>
</tr>
</tbody>
</table>

ªReported by caregiver

Some children reported finding the reminders intrusive due to ringtone type, volume, or reminder time but most responded favourably, describing reminders as helpful for medication-taking. Many caregivers perceived improvements in their child’s asthma control as a result of EMD use.

### 7.3 Discussion

We believe this is the first study to report on both EMD performance in children and quantitative and qualitative measures of patient acceptability of an EMD. As use of EMDs grows, it becomes increasingly important to determine how and if patients are able to engage with these devices, and particularly if EMDs are feasible and practical for use in younger age groups, and what unique factors need to be considered. There is however little data on performance and patient
acceptability of EMDs in children. Our study reports on the performance of an EMD when used by
children, and more importantly is the first to demonstrate the high acceptability of EMDs by
children. Although the study specifically investigated the SmartTrack EMD in children presenting to
the ED with asthma (i.e. a population at high-risk of non-adherence), these methods and results are
applicable to other EMDs as well as other age groups in terms of factors to consider when assessing
acceptability and designing an EMD for patient use.

7.3.1 EMD performance

Recording accuracy of the SmartTrack EMD was similar to previously reported, and device failure
rates were within the maximum 10-20% considered feasible for research settings\textsuperscript{543}. Our QC failure
rates were lower than previously reported in a SmartTrack validation study among adults (20–
25\%)\textsuperscript{542}; but aligned with rates reported for other more established EMDs, such as the Doser (0–
21\%)\textsuperscript{107, 119, 539}, MDI/Chronolog (10–53\%)\textsuperscript{125, 539, 596, 629} and Smartinhaler (0–20\%)\textsuperscript{120, 542, 553}. In the
present study the SmartTrack EMD was used for longer and included more participants than the
adult validation study\textsuperscript{543}, thus likely providing more representative performance data. Further, the
devices were used in children recruited from ED, providing
the first acceptability data in a population
whose adherence and asthma control was poor\textsuperscript{611, 612}, and where the device was challenged by real-
life conditions, such as rough handling. In such populations, adherence monitoring may provide the
most benefit, thus suggesting our performance results are generalisable to the population where
EMDs are most needed\textsuperscript{457}.

7.3.2 Limitations – EMD performance

Although our failure rate aligns with that of other available EMDs, it remains a small but significant
percentage which may need to be lower to encourage device implementation in clinical settings.
Until then, QC testing before and after participant use is recommended\textsuperscript{628}; however testing may not
be practical or feasible in limited-resource settings due to the time required for testing. Our
requirement for 100\% accuracy on all tested functions was exacting and may not have been
necessary or realistic. At the start of the trial in 2010, the SmartTrack was a new device which
lacked reported performance data; shorter tests may become more appropriate as reliable
performance data are reported. Indeed, the SmartTrack has now been employed successfully in
other published trials\textsuperscript{17, 457}.

7.3.3 EMD acceptability

Previous research on EMD performance has focused predominantly on accuracy and reliability\textsuperscript{120, 125,}
\textsuperscript{537, 541, 542, 596} and lacks data on user acceptability, which is key to sustained patient use. Only one
previous study has reported on patient acceptability but was limited to a single question on general utility. In the present study, we aimed to extend knowledge on device acceptability by creating an acceptability questionnaire which explored a variety of criteria, including attitudes to device use in public, responses to device features and ergonomic factors such as size and ease of handling.

After six months of use, participants reported good acceptability for the EMD, including being willing to continue use (in both groups) and rating the reminder EMD favourably for medication reminding and knowing when to take medication. The reminder group also reported feeling significantly more in control of their asthma than participants without reminders. These results suggest that a reminder EMD not only improves actual medication adherence and clinical asthma control (data reported elsewhere), but it may correspondingly improve perceived control of asthma (Table 3), which is a psychological concept associated with self-efficacy and personal responsibility. This could be particularly significant and signals further research, since greater perceived control of asthma has been associated with improved health status and decreased future risk of severe exacerbations requiring emergency healthcare utilization.

Ratings on device size and ease of handling were encouraging. Most (94%) rated the EMD as easy to hold and only a small proportion (16%) reported EMD size as “too big”. The large size of the SmartTrack EMD has been noted previously, however EMDs are likely to become more compact with time. Indeed the re-branded version of the SmartTrack EMD (SmartTouch) appears to have addressed this by utilising a smaller and softer casing. EMD designers should consider these ergonomic factors when developing devices, particularly for those who may find device size problematic, such as children.

Participants rated the ringtone options favourably, with a preference for popular culture ringtones, such as “The Simpsons”, and a lower preference for loud, abrupt or harsh ringtones, and animal sounds. Such reminder preferences should be considered by EMD designers to optimally engage patients.

Qualitative feedback was generally positive across all categories – including EMD and ringtone acceptability and positive effects on medication use and asthma control. Children also made some useful suggestions such as adding customised ringtones and device skins. This extends previous data in adults, and indicates acceptability across a wider age range.

7.3.4 Limitations – EMD acceptability

The acceptability questionnaire provided novel data from children but was not validated. Young children can have difficulty comprehending the language used in questionnaires, parental answers may not serve as an accurate proxy, and older children may refuse to complete questionnaires
or provide inaccurate answers\textsuperscript{632}. Although we report a high questionnaire completion rate (>95%), further validation testing in other young populations and with other EMDs is recommended. Whilst this questionnaire was designed for the SmartTrack EMD and was answered by children, we specifically included questions generalisable to other EMDs and other age groups\textsuperscript{628} such as assessing satisfaction with continued use, effects on medication management and attitudes to use in public (Table 3).

7.3.5 Conclusions

This study is the first to report on both EMD performance in children and patient acceptability using quantitative and qualitative measures. Performance was consistent with that of other EMDs, indicating similar feasibility. Despite this, there remains a small but significant failure rate which needs to be addressed prior to use in a clinical setting. This study reinforces the practical approach and resources needed for QC testing and its key role for enhancing the integrity of adherence data. This work advances previous EMD research by exploring patient-reported acceptability, using a combination of quantitative and open-text qualitative methods. The SmartTrack EMD was found to be highly acceptable to this population of children, highlighting the potential for use in other children. Further research combining EMD reliability and acceptability assessments is recommended to ensure a wider and successful uptake of EMDs in research and clinical settings, and to allow standardised comparison between different EMDs.
Chapter 8: Factors affecting medication adherence in school aged children to inhaled corticosteroids

Although many studies have investigated factors associated with medication adherence, few have focused on adherence barriers in children, and even less have used objective adherence measures – in particular EAM – to evaluate the relationship between adherence and potential determinants of adherence. This chapter uses the electronically measured adherence data in the control arm of the RCT described in Chapter 6 to examine a range of potential adherence barriers and their relationship to medication-taking in a group of children presenting to the ED with asthma. The investigation of learning styles as a novel determinant of adherence will also be presented.

Title:
Factors associated with medication adherence in school-aged children with asthma

Journal:

Authors:
Amy Hai Yan CHAN, Alistair STEWART, Juliet FOSTER, Edwin MITCHELL, Carlos CAMARGO Jr, Jeff HARRISON

Contributions:
Amy CHAN was involved in the study conception and design, original literature search, overall study data collection, data analysis, interpretation, writing and review of the report and the decision to submit for publication

Alistair STEWART was involved in the study conception and design, original literature search, data analysis, interpretation, writing and review of the report and the decision to submit for publication

Juliet FOSTER was involved in data analysis, interpretation, writing and review of the report and the decision to submit for publication

Edwin MITCHELL was involved in the study conception and design, original literature search, data analysis, interpretation, writing and review of the report and the decision to submit for publication

Carlos CAMARGO Jr was involved in data analysis, interpretation, writing and review of the report and the decision to submit for publication
Jeff HARRISON was involved in the original literature search, data analysis, interpretation, writing and review of the report and the decision to submit for publication.

8.1 Abstract

Background: Adherence to preventive asthma treatment is poor, particularly in children, yet the factors associated with adherence in this age group are not well understood.

Methods: Adherence was monitored electronically over six-months in school-aged children, who attended a regional ED in New Zealand for an asthma exacerbation and were prescribed twice-daily ICS. Participants completed questionnaires including assessment of family demographics, asthma responsibility and learning style. Multivariable analysis of factors associated with adherence was conducted.

Results: One hundred and one children (mean age 8.9, range 6-15 years, 51% male) participated. Median preventer adherence was 30% of prescribed (25th percentile 17%, 75th percentile 48%). Four explanatory factors: female sex (+12% adherence), Asian ethnicity (+19% adherence), living in a smaller household (-3.0% adherence per person in the household), and younger age at diagnosis (-2.7% for every later year of diagnosis) (all P<0.02) were identified.

Conclusion: In school-aged children attending ED for asthma, males and non-Asian ethnic groups were at high risk for poor ICS adherence and may benefit most from intervention. Four factors explained a small proportion of adherence behaviour indicating the difficulty in identifying adherence barriers. Further research is recommended in other similar populations.

8.2 Paper VI: Factors associated with medication adherence in school-aged children with asthma

8.2.1 Introduction

Asthma is one of the most common chronic conditions in childhood\(^9\). Adherence with preventive medication remains poor in this age group (≤16 years)\(^{48,91}\). Poor adherence with ICS is associated with morbidity\(^{365}\) and mortality\(^{12}\). Interventions to improve adherence have shown benefits on adherence, however effects are inconsistent, even when using similar strategies\(^{468}\). In order to develop effective childhood interventions, it is important to investigate the unique adherence barriers children face\(^{394}\), as these are different to adults\(^{365,394}\). There are few studies in children which aim to understand these barriers, and even fewer interventional studies which aim to improve adherence in children\(^{468,633}\). Previous research investigating adherence barriers in childhood have used inconsistent methodology, with data on adherence factors being collected from either the child, a proxy (e.g. parent) or both. Adherence measures commonly used such as self-report or
pharmacy claims data are subject to bias. Electronic monitoring provides the most objective measure of adherence monitoring, however only a few studies have used electronic monitoring to provide adherence data to investigate adherence barriers. Of the studies that have used electronic monitoring, these have tended to focus on a narrow set of adherence barriers such as psychological factors or asthma knowledge, or used data collected only over a short duration. Morton et al. recently reviewed the literature around adherence in childhood asthma. The authors reported a paucity of studies investigating adherence barriers in children, and that future studies investigating adherence in children with asthma should use electronically monitored adherence data. There is therefore a need to examine a range of adherence barriers unique to children using objective adherence data.

Learning style is one adherence factor that has not been previously examined. Learning style has been linked with a patient’s understanding of health information and subsequent medication-taking behaviours and responses to interventions. Although there is no current literature examining this relationship, learning style may influence adherence. For example, individuals with an aural learning style may benefit more from an auditory intervention such as reminders, than those with alternative learning styles.

We previously conducted a RCT investigating the effects of audiovisual reminders on medication adherence and asthma outcomes in children with asthma. The present study uses the objectively measured adherence data from the RCT to: a) identify the adherence barriers unique to children, particularly in those at high-risk of non-adherence; and b) examine the relative importance of these factors for non-adherence, including the novel concept of learning style as a factor associated with adherence.

8.3 Material and methods

8.3.1 Study subjects and design

The RCT investigated the effect of a reminder on adherence to preventer treatment and asthma outcomes, as described previously. Briefly, 220 children between 6 and 15 years were recruited from the regional ED in Auckland, New Zealand. Inclusion criteria were: current diagnosis of asthma; current treatment or those started on treatment at ED with a twice-daily ICS; no comorbid congenital heart disease, chronic lung disease (other than asthma) or severe chronic medical condition leading to increased morbidity; and residence inside the Auckland area.

Patients were enrolled after a minimum of four weeks had elapsed since hospital attendance, and followed prospectively for six months, with two-monthly follow-up visits by study investigators. Patients were randomly allocated to the intervention (n=110) or control (n=110) group. All received
an EMD for use with their preventer inhaler. The intervention group had the reminder function enabled; this was disabled in the control group. Information on asthma control was collected at each visit, and at study end participants and their caregiver completed a series of questionnaires to assess variables associated with adherence. Verbal and written informed consent was obtained from the child’s parent or caregiver, and ethics approval from the New Zealand Northern Y Regional Ethics Committee (NTY/08/12/116) and DHBs. The trial was registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12613001353785.

8.3.2 Adherence measurement

ICS adherence was objectively measured by an EMD (SmartTrack; Nexus 6 Ltd, Auckland, NZ) recording date, time and number of doses taken. An on-board screen displayed the date and time of the last dose. Participants were unaware of the device adherence monitoring function. This covert monitoring method followed published ethical guidelines as discussed previously by Rand et al.\textsuperscript{136} and was accordingly approved by the regional ethics committee. At the end of the study, participants and their general practitioner, or other asthma healthcare provider, were offered access to the study results and a copy of the published paper. Adherence was defined as median percentage of the daily prescribed dose taken.

8.3.3 Analysis of factors associated with adherence

Caregivers (parent or guardian) of participants completed self-report questions on demographics and the primary caregiver’s highest educational qualification (none (not finishing secondary school), secondary, tertiary, or postgraduate). Participant ethnicity was obtained from their NZ National Health Index number. Deprivation was assessed, using NZDep2006 Deprivation Index (1=least deprived, 10=most deprived area) of the area the participant lived in.\textsuperscript{638} Caregivers self-reported household size (number of people usually living in the household) and family status (single / divorced / separated / widowed / married / de facto (cohabitating) / extended family or whanau [Māori concept of an extended family or community of families living together]). Information on the caregivers’ experience of the health system and healthcare access was collected using the following questions (scored yes/no): “Do you feel you can discuss concerns with the health professional who looks after the child’s asthma?”; “Have you ever delayed or avoided picking up medications due to cost?”; “Have you ever delayed or avoided seeing the doctor due to cost?”; “Is your doctor easy to access?” and “Is your local pharmacy easy to access?”.

Age at diagnosis was obtained by caregiver self-report. Asthma control was measured using two validated questionnaires – the c-ACT (0=worst control, 27=best control)\textsuperscript{608} completed by the child and caregiver and the AMS\textsuperscript{605} (17=maximal morbidity, 4=lowest morbidity) completed by the
caregiver. Caregivers answered questions about side effects (scored yes/no): “Does the child complain of, or have, any side effects from their medications?” and the type of healthcare professional following up their child’s asthma, outside of the two-monthly investigator-initiated visits (asthma nurse, specialist, general physician (family doctor), no usual care follow-up received or other). Asthma responsibility was evaluated using the 10-item Asthma Responsibility Questionnaire completed by the caregiver. This assesses how responsibility is shared for ten asthma management tasks. Each item is scored from 1 (parent is completely responsible) to 5 (child is completely responsible); total score 10=maximum parent responsibility, 50=maximum child responsibility. The child’s asthma knowledge was assessed using the child-reported 24-item questionnaire (0=worst knowledge, 26=best knowledge) validated for primary school-aged children.

Children completed the VARK Learning Styles Inventory for Younger People which identified each participant’s learning style preference (visual (V), aural (A), read/write (R), and kinaesthetic (K) or various combinations of these) based on the Standard Scoring System. As this questionnaire was for children aged 12 years or older, the language was modified for the reading skills of our population of 6 to 15 year olds. Results were categorised into two groups for analysis: those with an aural learning style preference (Aural group) versus no aural learning style preference (Non-aural group).

8.3.4 Statistical analysis

Descriptive statistics were used to describe the study population. All statistical tests were performed at the 0.05 level of significance (two-tailed) using IBM SPSS Statistics (version 22) or SAS version 9.3.

8.3.4.1 Factors associated with adherence

Unadjusted analysis

To avoid interference from the intervention, only data from the control group of the trial was used as the analytical cohort to analyse factors associated with adherence. Unadjusted analyses on 20 variables were conducted in this analytical cohort using a general linear model.

All possible subsets regression

To determine the factors associated with adherence, an all possible subsets regression was conducted. This multivariable regression technique was chosen over the traditional stepwise regression, as it tests all possible subsets of potential variables. This allows models that have similar predictive value to be identified and compared, rather than selecting just one model. Binary variables with low numbers in one outcome group i.e. [<25% of participants in one outcome group]
were not included in the multivariable regression. Participants with complete data across all remaining variables were used for the multivariable analysis. The remaining variables were included in the model and multiple subsets of variables generated, ranging from single-variable models to models using all remaining variables. By examining the five best models at each level, alternative variable combinations were assessed, including whether the addition of other variables to the model led to a masking of effect. The model accounting for the greatest variance (maximum $R^2$) whilst still consisting of only significant ($P<0.05$) variables was selected.

Data were then analysed using an alternative model as a sensitivity analysis, by performing the all subsets regression with the variables that had missing data removed (rather than removal of participants with missing data).

**Effect of aural learning styles**

Analysis of the effect of aural learning styles on adherence was conducted using a general linear model. Data from both the intervention and control groups were used as participants with an aural learning style may not only be more responsive to an auditory adherence intervention, but may also be more responsive to adherence advice from health providers, which is often delivered verbally.

### 8.4 Results

Of the 110 participants forming the analytical cohort, nine did not complete the questionnaires, leaving 101 for analysis. Overall adherence was low (median adherence 30% (25th percentile 17%, 75th percentile 48%)). Table 1 shows the characteristics of the analytical cohort (n=101) and describes the unadjusted analyses of factors associated with adherence.
Table 1. Characteristics of participants in the analytical cohort and unadjusted analyses of 20 factors associated with adherence (n = 101³)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of participants or mean (SD)</th>
<th>Effect size</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Change in adherence with change in 1 unit of independent variable (95% CI), or median (% adherence (upper and lower quartiles)*</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>8.9 (2.7)</td>
<td>-1.5% per year (-3.2–0.2%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>52</td>
<td>26 (15, 43)</td>
<td>0.05</td>
</tr>
<tr>
<td>- Female</td>
<td>49</td>
<td>40 (19, 60)</td>
<td></td>
</tr>
<tr>
<td>Qualification of primary caregiver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- None</td>
<td>8</td>
<td>36 (11, 42)</td>
<td>0.81</td>
</tr>
<tr>
<td>- Secondary School</td>
<td>22</td>
<td>28 (15, 53)</td>
<td>0.81</td>
</tr>
<tr>
<td>- Tertiary</td>
<td>45</td>
<td>26 (12, 47)</td>
<td></td>
</tr>
<tr>
<td>- Postgraduate</td>
<td>22</td>
<td>42 (21, 51)</td>
<td></td>
</tr>
<tr>
<td>- Missing</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Māori</td>
<td>10</td>
<td>19 (13, 44)</td>
<td>0.002*</td>
</tr>
<tr>
<td>- European</td>
<td>39</td>
<td>26 (17, 43)</td>
<td></td>
</tr>
<tr>
<td>- Pacific Peoples</td>
<td>20</td>
<td>28 (13, 40)</td>
<td></td>
</tr>
<tr>
<td>- Middle Eastern / Latin American / African</td>
<td>4</td>
<td>35 (5, 68)</td>
<td>0.002*</td>
</tr>
<tr>
<td>- Asian</td>
<td>19</td>
<td>47 (30, 83)</td>
<td></td>
</tr>
<tr>
<td>- Other</td>
<td>9</td>
<td>31 (21, 46)</td>
<td></td>
</tr>
<tr>
<td>Deprivation Index*</td>
<td>6.0 (2.7)</td>
<td>+0.002% per deprivation scale (-1.7%–1.7%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Number of people in household</td>
<td>4.8 (1.9); n = 98²</td>
<td>-3.4% per person added to household (-5.8– -0.1%)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Family status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Single (Single parent / divorced / separated / widowed / single)</td>
<td>35</td>
<td>26 (15, 47)</td>
<td>0.39</td>
</tr>
<tr>
<td>- Not single (De facto / extended whanau / married)</td>
<td>65</td>
<td>32 (18, 49)</td>
<td></td>
</tr>
<tr>
<td>- Missing</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Able to discuss concerns with the healthcare professional looking after the child's asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>8</td>
<td>24 (6, 49)</td>
<td>0.68</td>
</tr>
<tr>
<td>- Yes</td>
<td>92</td>
<td>31 (17, 48)</td>
<td></td>
</tr>
<tr>
<td>- Missing</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed picking up medications due to cost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>78</td>
<td>31 (16, 48)</td>
<td>0.87</td>
</tr>
<tr>
<td>- Yes</td>
<td>21</td>
<td>26 (16, 49)</td>
<td></td>
</tr>
<tr>
<td>- Missing</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed seeing the doctor due to cost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>69</td>
<td>31 (16, 54)</td>
<td>0.28</td>
</tr>
<tr>
<td>- Yes</td>
<td>30</td>
<td>28 (16, 46)</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Number of participants or mean (SD)</td>
<td>Effect size Change in adherence with change in 1 unit of independent variable (95% CI), or median (%) adherence (upper and lower quartiles)*</td>
<td>p-value</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ease of access to doctor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>10</td>
<td>37 (18, 52)</td>
<td>0.91</td>
</tr>
<tr>
<td>- Yes</td>
<td>90</td>
<td>30 (17, 48)</td>
<td></td>
</tr>
<tr>
<td>- Missing</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ease of access to pharmacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>2</td>
<td>20 (7, -)</td>
<td>0.37</td>
</tr>
<tr>
<td>- Yes</td>
<td>99</td>
<td>30 (17, 48)</td>
<td></td>
</tr>
<tr>
<td>Age at asthma diagnosis</td>
<td>3.3 (2.3)</td>
<td>-1.7% per year (-3.7%–0.3%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Childhood-Asthma Control Test</td>
<td>18.8 (4.2); n=100^a</td>
<td>+0.9% per 1 point on the c-ACT (-0.2%–2.0%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Asthma Morbidity Score</td>
<td>9.2 (2.6); n =100^g</td>
<td>-0.3% per 1 point on the AMS (-2.1%–1.5%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Medication side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>91</td>
<td>29 (17, 48)</td>
<td>0.84</td>
</tr>
<tr>
<td>- Yes</td>
<td>10</td>
<td>33 (11, 46)</td>
<td></td>
</tr>
<tr>
<td>Type of healthcare provider involved in routine follow-up asthma care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- None (no follow-up)</td>
<td>2</td>
<td>72 (60, -)</td>
<td>0.003*</td>
</tr>
<tr>
<td>- General Practitioner</td>
<td>74</td>
<td>26 (12, 43)</td>
<td></td>
</tr>
<tr>
<td>- Specialist</td>
<td>5</td>
<td>31 (23, 61)</td>
<td></td>
</tr>
<tr>
<td>- Asthma Nurse</td>
<td>15</td>
<td>51 (15, 85)</td>
<td></td>
</tr>
<tr>
<td>- Multiple providers</td>
<td>5</td>
<td>46 (26, 61)</td>
<td></td>
</tr>
<tr>
<td>Asthma Responsibility Questionnaire</td>
<td>23.7 (8.1)</td>
<td>-0.2% per 1 point of ARQ (-0.7%–0.4%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Asthma Knowledge Test</td>
<td>19.1 (2.7)</td>
<td>+0.7% per 1 point of AKT (-1.0%–2.4%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Learning styles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Aural</td>
<td>64</td>
<td>29 (17, 48)</td>
<td>0.76</td>
</tr>
<tr>
<td>- Non-aural</td>
<td>30</td>
<td>30 (14, 49)</td>
<td></td>
</tr>
<tr>
<td>- Missing</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Deprivation index based on the NZDep2006 Score (Scores are reported as deciles: 1 = least deprived; 10 = most deprived). This is an indicator of socioeconomic deprivation of the area where the individual resides. Scores are derived from census data on income, home ownership, employment, qualifications, family structure, housing, access to transport and communications.

^Numbers are less than 101 for some parameters due to missing data from participants who did not completed the relevant questionnaire(s). Percentages are not shown as N is very close to 100.

Median % adherence for total sample (n=101): 30% (25th percentile 17%, 75th percentile 48%)

*Bolded text indicated effect size

### 8.4.1 Unadjusted analyses of factors associated with adherence

Only 3 out of 20 variables examined were significantly associated with adherence to preventive treatment (Table 1). These were ethnicity (Asian ethnicity most adherent), living with a lower
number of people in the household, and type of healthcare provider involved in asthma follow-up (those with no asthma follow-up by their own healthcare provider had better adherence, though that outcome group had only two participants). Younger age, female sex and a younger age at diagnosis were of borderline significance.

8.4.2 Multivariable analysis of factors associated with adherence

The following variables, which had very low numbers in one outcome group compared to the other, were not included in the analysis: whether or not the caregiver could discuss concerns with their asthma healthcare provider, whether or not the caregiver had ever delayed picking up medicines due to cost, whether or not the caregiver had easy access to the doctor, or pharmacy, presence or absence of medication adverse effects in the child, and lack of follow-up for the child’s asthma by their own healthcare provider. After removal of these variables, 87 of the 101 participants in the analytical cohort had complete data across all variables and were included in the multivariable analysis.

The all subsets regression selected a subset of four factors that together explained 30% of the variance in objective adherence ($R^2=0.33$; adjusted $R^2=0.30$) (Table 2). Addition of all the other predictor variables accounted for only an additional 14% in variance ($R^2=0.47$; adjusted $R^2=0.29$) and included variables that were not statistically significant. The multivariable analysis found those of Asian ethnicity, female sex, living with a lower number of people in the household and having a younger age at diagnosis were more likely to adhere to treatment. Lack of asthma follow-up by their own healthcare provider was also significant, but as there were only two participants who did not have follow-up (Table 1; median adherence 72%), this was not included in the model. These two participants had high adherence. There was no indication that any variables were masked by the presence of other variables. The sensitivity analysis produced very similar results confirming the results of the all subsets regression described above.
Table 2. Multivariable regression analysis with objective adherence as independent variable (n=87)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect size Change in adherence with change in 1 unit of independent variable (S.E.)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>12% (4%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Asian ethnicity</td>
<td>19% (5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of people in the household</td>
<td>-3.0% per person (1%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age at asthma diagnosis</td>
<td>-2.7% per year (0.9%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

8.4.3 Effect of aural learning styles

There was no relationship between aural learning style and adherence in either the control (analytical cohort for this study) (aural 29% vs non-aural 30%, P=0.76) or in intervention (reminder) group (aural 85 % vs non-aural 88%, P=0.34).

8.5 Discussion

This study investigated factors associated with adherence in children presenting to a regional ED with an asthma exacerbation. Electronically monitored adherence was poor with median adherence being 30%, a rate similar to other studies in children at high-risk of non-adherence but lower than the average reported adherence from studies using electronic monitoring and when compared to other developed Western countries. We examined a number of factors that have previously been associated with adherence, such as ethnicity and asthma knowledge; as well as factors not previously investigated such as learning style. Of the variables examined in this study, only a few were significantly associated with adherence.

Ethnicity had a strong association with adherence, with Asian participants having the highest overall adherence (47%). The reason for this is unclear. There is little literature available on adherence for ethnic groups in New Zealand beyond Māori, Pacific and European populations. Education studies in Australia show that Asian students are more compliant with orders from teachers than other ethnic groups due to respect and perceived dominance of the teacher. The healthcare provider-patient relationship may be associated with a similar respectful or submissive response which may enhance adherence. Māori children had the poorest adherence (median adherence 19%), followed closely by New Zealand European (26%) and Pacific Peoples (28%). From studies in mild to moderate asthmatics, Māori and Pacific children show poorer asthma control than other ethnic groups due to under-treatment and poor adherence with preventive treatment. The ethnic differences in our study were therefore unexpected, as although adherence rates for New Zealand...
Europeans were higher than Māori children, they were lower than that of other minority ethnic groups. The participants in our study attended ED for asthma and therefore represent those with the poorest asthma control and adherence. This suggests that the effect of ethnicity may be different in those with poorly controlled asthma and at high-risk of non-adherence, but more research is needed to confirm this. We note that the adherence rate in our population of high-risk children was particularly low when compared to populations recruited from outpatient clinics, and more similar to those recruited from tertiary centres or hospitals. Indeed in adults, Krishnan et al. reported a drop in ICS use to approximately 50% within a week of hospital discharge after an asthma exacerbation. This highlights the potential vulnerability of patients presenting to tertiary care settings and importance of considering the contribution of this as a potential marker of poor adherence. The high-risk nature of a population presenting to ED with asthma may override the usual effects of other adherence determinants, such as ethnicity, as seen in our study.

Female sex was significantly associated with better adherence in our study. The relationship between sex and adherence is inconsistent in the literature, with many studies showing no association. Only one study has reported an association between female sex and higher adherence in adult asthma. In other chronic conditions, female sex has been linked with poorer adherence in adolescents. Mental health and coping strategies may mediate the relationship between sex and adherence, but we did not measure psychological factors.

No clear relationship was found between socioeconomic status, determined by NZDep scores, and adherence. Some studies have reported a lack of correlation between adherence and general socioeconomic status, family income or qualifications of the primary caregiver, though others report low adherence rates in those with poor socioeconomic status. Compared to studies that report higher overall adherence, the population in our study did tend towards higher deprivation scores (mean deprivation 6 out of 10). We found a significant relationship between household size and adherence – a factor seldom studied in asthma. Kyngas found that adherence improved with increasing number of siblings and similarly Lieu et al. reported better adherence in larger families. Our study found the opposite effect, with larger household size associated with poorer adherence. It is possible that larger families present more competing demands, thus limiting the time available to manage a child’s asthma and increasing forgetfulness – a key reason for non-adherence in childhood asthma. This negative effect of family size on adherence may be more pronounced in our study as over half of the participants were younger than eight years old. Previous studies have demonstrated that younger children have the majority of their medicines managed by their parents, which may contribute to poorer adherence with increased household size. This is also supported by the negative relationship seen between asthma responsibility scores and
adherence, where adherence decreased with increasing child responsibility for their own asthma management, though the relationship did not reach statistical significance.

The relationship between age at diagnosis and adherence is unclear; the few studies investigating this relationship have not found any association\textsuperscript{59,646}. Our study found age at diagnosis was a significant factor, with a reduction in adherence of 3\% per increasing year of age at diagnosis. There was a corresponding non-significant trend between age of the child and adherence, with adherence being worse in older children, similar to previous findings\textsuperscript{48,107,365,649,652}. This may in part explain the association between age of diagnosis and adherence. The association between increased age and worsened adherence might also explain the overall low adherence seen in this population. Most previous studies that have reported higher adherence have included much younger age range, from as young as 15 months\textsuperscript{91}. Disease duration may play a role as those with a younger age of onset have more opportunity for habit formation for medication adherence\textsuperscript{653}. Conditioning may lead children, or their parents, to believe that asthma is a long-term condition, requiring long-term preventive treatment, and as a result, lead to better adherence. Indeed, adherence is higher in those that believe asthma is a long-lasting condition\textsuperscript{319}.

This is the first study investigating the impact of learning style on adherence. A link between the two is plausible given that learning style is associated with behaviour\textsuperscript{636,637}, but no association was found in either the group receiving the auditory intervention or control. This may be due to the difficulties in characterising learning styles in children as younger children tend to have multimodal learning styles rather than a single learning modality\textsuperscript{641}. The lack of a validated tool for assessing learning style in the younger age groups in our study may have also limited the accuracy of determining the child’s learning style. Although a relationship between learning styles and adherence was not found, there is a possibility that interventions that are tailored to an individual’s learning style may be more successful. The literature supports those interventions that are personalised to an individual\textsuperscript{91,633}; future research should investigate the usefulness of incorporating learning style into the intervention tailoring process.

Of the factors that were investigated, only four were found to be significantly associated with adherence. These factors however still only explained 30\% of the variance in adherence seen. Although a wide range of adherence determinants were examined, we did not investigate the effect of illness perceptions\textsuperscript{171,392,654-657} or medication beliefs\textsuperscript{311,316,318,321,652,658,659}, which are thought to be more powerful determinants of adherence\textsuperscript{171} than sociodemographic and clinical factors in adults.

In children, Drotar and Bonner’s review of studies investigating the factors associated with adherence in children reports that parental, and to a lesser extent child, beliefs demonstrate significant relationships with adherence\textsuperscript{414}. Medication beliefs and illness perceptions were not measured in our study but future research should include them in order to develop a clearer
understanding of the extent to which these may explain adherence behaviour in children with poorly controlled asthma and to investigate how these may interact with the adherence determinants identified in our study.

The generalisability of our study results may be limited by data collection in a single centre and country. Nevertheless, our study population were representative of the total population presenting to ED with asthma, as previously described, and included a wide range of ethnic and socioeconomic groups. Due to missing data, we excluded 14 participants from the multivariable analysis, which could lead to selection bias. However, bias as a result of this exclusion is unlikely as our sensitivity analysis, where variables with missing data were excluded rather than participants, showed similar results. Questionnaires were administered in the presence of research personnel, which may have affected the reliability of the data collected. A small number of participants chose not to complete some questions, but the numbers with missing data were low and unlikely to affect our results. The application of these findings to the design of adherence interventions may be limited, as the adherence determinants identified are largely non-modifiable. Nevertheless, our findings add important information to the literature on factors that contribute to poor adherence in children, particularly in those with poorly controlled asthma. As the factors identified from our study are easily quantifiable, they may be used to help prioritise those at greatest need for intervention. Our work sets a platform for further research into how potentially modifiable adherence determinants, such as medication beliefs, may be related to non-modifiable factors such as ethnicity or duration/experience in managing asthma, and how these non-modifiable factors may serve as proxies for identifying those who are most at risk of poor adherence.

In summary, female sex, Asian ethnicity, smaller household size and younger age at diagnosis were strongly associated with better preventive medication adherence in children with poorly controlled asthma requiring presentation to a regional ED. These factors explained only 30% of the variation in adherence, highlighting the difficulty of identifying adherence barriers in this age group. There was no association between adherence and learning styles. Further research in other ED populations is needed. Given the combination of poor adherence and high risk for life-threatening asthma in children presenting to ED, there is an urgent need to identify the specific adherence barriers and develop effective interventions for this population of children.
Chapter 9: Discussion

9.1 Overview of discussion

This chapter forms the conclusion to the thesis and provides an overview of the results that have arisen from this research, considers the strengths and limitations and discusses the implications of the study findings on the direction of future research.

It begins with a reminder of the research context in which this research was developed, and a review of the main study findings and what these add to our current knowledge. This is then followed by a critical appraisal of the study methodology and its strengths and limitations. The questions raised by this research are then discussed, and current gaps in the literature highlighted.

9.2 The research context and review of study findings

Asthma is a major public health concern globally, across both high- and low-income countries\(^7\). In New Zealand, the rates of poorly controlled asthma are particularly high, with a quarter to a third of New Zealand children having current wheeze, of which approximately 40% have severe asthma symptoms\(^9\). Whilst there have been reductions in the prevalence of these symptoms in New Zealand, the magnitude of the improvements are relatively small and the reported lifetime prevalence of asthma is on the rise\(^8,15,660\). Poorly controlled asthma leads to a significant burden of disease on society, through direct healthcare costs resulting from increased morbidity and hospitalisations, to indirect costs arising from days off school and work by caregivers\(^621\). There is a need to address this largely manageable chronic disease, as although significant morbidity continues to affect many with asthma, it need not be the case as there are effective treatments available, the most important of which are ICS\(^5\). The issue lies with the way that medicines are taken, rather than a lack of available treatments. Much of the value of these treatments is not realised as the medication is not taken as prescribed. This poor ICS adherence leads to poor outcomes\(^10,11,23\) and an increased risk of death\(^12\), and underpins much of the poor asthma control that is still seen to this day.

Although adherence has long been recognised as a barrier to achieving optimal asthma control, strategies to improve adherence have so far been disappointing\(^297\). Most have shown only modest benefits on adherence and the effect on clinical outcomes has been inconsistent\(^81\). There is an urgent need to consider newer technologies as solutions to poor adherence, to ensure that the full benefits of ICS are recognised and patients are given the best chance of having their asthma controlled.
This research evaluated use of an innovative technology – an EMD with an audiovisual reminder function – as an adherence intervention, and investigated its effect on adherence and asthma outcomes in children presenting to ED with asthma. The study found that those who received the intervention had much better adherence than those who did not, with a difference of more than 50 percentage points in adherence between the two groups – a difference of greater magnitude than previously reported. Median percentage adherence was 84% in the intervention compared with 30% in the control group, equating to a 180% increase in adherence. Correspondingly, there was a significant reduction in reliever usage, with the intervention group requiring reliever treatment on only 9.5% of study days compared with 17.4% in the control group; a reduction in reliever use of 45%. General measures of asthma control, such as wheeze, cough and night time awakenings, as well as activity limitation for both the child and family, were also significantly improved with the intervention.

Despite the importance of medication adherence to asthma outcomes, there are surprisingly few adherence intervention studies in children with asthma, and even fewer investigating EMDs specifically. To date, there have only been three RCTs investigating the use of EMDs with audiovisual reminder function as adherence interventions in asthma\textsuperscript{35-37}. Although these studies reported improved adherence with the EMD intervention, none were large enough to show significant benefits in asthma outcomes. This study is therefore the first and largest RCT powered to detect the effect of a reminder EMD on both adherence and outcomes, and the first and only published study to investigate the use of reminder EMDs in children. Whilst reminder EMDs have been shown to be beneficial for adherence in adults with asthma\textsuperscript{37}, there have been no other published studies in children. The only study in this age group is available only as a conference abstract, and was small (40 children) and of short duration (8 weeks), and therefore underpowered to show differences in outcomes\textsuperscript{35}.

The effectiveness of the EMD on adherence is likely mediated by both the audiovisual reminder on the EMD, and the real-time adherence feedback, as the reminder was only activated if the correct dose had not been taken by the set time, and ceased when the correct dose was taken. This simple reminder-feedback process was easy to implement and well-received by the children and families in the study, with positive feedback on measures of patient acceptability, ease of use of the device, and effect on medicine use and asthma control. Interestingly, those who received the EMD with the reminder function enabled, felt it was easier to remember when to take their inhalers, and felt more in control of their asthma. Not only did the use of the EMD lead to improvements in objectively measured adherence and validated measures of asthma control, the device improved the patient’s perception of their own medicine-taking and asthma control.
The research highlighted that poor asthma adherence continues to be problematic, with an average adherence of 30% in this high-risk group of children with asthma. This adherence is lower than the 50% usually reported in children\textsuperscript{10, 102} and is more in line with the adherence reported for disadvantaged and minority populations\textsuperscript{567, 661, 662}. This likely reflects the high-risk nature of this population presenting to ED with an asthma exacerbation. It is known that prior ED attendance is associated with poor adherence and outcomes\textsuperscript{611, 612}. This study therefore demonstrates the promising effects of an EMD when used in a population that represents those with the poorest adherence and asthma control, in which the greatest benefits are likely to be gained from adherence interventions. The research also found that those who are male, of non-Asian ethnicity, who live with a greater number of people in their household and were diagnosed at a later age, tend to have the poorest adherence. This group is likely to derive the most benefits from adherence interventions, yet are the ones that are least likely to be able to access these interventions. By identifying these adherence risk factors, there is potential for future interventions to be targeted to these high-risk groups to help with resource allocation and public health planning in limited resource settings. Practical aspects to be considered when implementing EMD interventions into practice have been outlined at the start of this thesis, and add to the body of literature that guide the movement of interventions from research to practice.

9.3 Appraisal of study methodology

The main study in this thesis was conducted as a RCT. Participants were administered questionnaires at the end of the study to gather their feedback on the usability and acceptability of the intervention, and to identify factors that may be associated with adherence. Patients were recruited prospectively after four weeks had elapsed from ED attendance, and followed up every two months for six months. Using the risk of bias tool from the Cochrane Handbook for Systematic Reviews of Interventions\textsuperscript{663}, which assesses bias arising from selection, detection, attrition, reporting and other sources, the overall bias was low. This is discussed further in the study strengths and limitations below.

9.3.1 Study strengths

9.3.1.1 Randomised controlled trial design

This study employed a RCT study design as the ‘gold standard’ in the hierarchy of evidence for determining the effects of a therapeutic intervention\textsuperscript{664, 665}. Through randomisation, the effects of confounding factors and potential sources of bias are minimised and both known and unknown factors that might influence the end outcome are controlled.
9.3.1.2 Sample size

To date, this is the largest RCT undertaken for investigating EMDs in asthma and was powered to detect both changes in adherence and clinical outcomes. The study sample size was based on power calculations for the endpoints of days absent from school (all reasons), adherence and asthma control (measured by the AMS). The sample size was chosen to ensure the study would have a power of 80% to detect a clinically meaningful difference in all three endpoints at a significance level of $p < 0.05$. To detect a reduction in number of days absent from school from 19.5 to 13.5 days (based on a standardised total number of 193 available school days per year), 84 patients per group were required; to detect an absolute difference in adherence of 10%, 51 patients per group were required; and to detect a 30% reduction in AMS, 100 patients per group were required. The final number recruited was 220 participants which exceeded the target of 200 needed and allowed for a 10% loss to follow-up, which did not occur. Of the three other studies\textsuperscript{35-37} that have investigated reminder EMDs in asthma, the population sizes were 40\textsuperscript{35}, 143\textsuperscript{37}, and 110\textsuperscript{36}. This study is therefore the largest conducted ($N = 220$) with a predetermined, calculated sample size that was large enough to detect clinically significant outcomes. The previous studies were otherwise underpowered to detect differences in outcomes and only noted trends in improvement in certain outcomes such as lung function\textsuperscript{36} or asthma exacerbations\textsuperscript{37}.

9.3.1.3 Use of a personalised dose regimen

Charles et al. conducted a study in 110 adults and found a significant improvement in adherence from 74% to 93% with the reminder EMD intervention but no changes in asthma control, as measured by the Asthma Control Questionnaire and PEF rates. The study used a fixed dose ICS regimen where all participants were prescribed a daily dose of fluticasone propionate 500 micrograms to ensure maximal medication benefits. However, the authors recognised that most of the clinical benefits can be achieved at a lower daily dose of 100 to 250 micrograms\textsuperscript{666,667} and that use of the higher dose may have masked any clinical differences that might have arisen as a result of changes in adherence between the groups. Our study did not specify a fixed dose ICS regimen, but instead continued the patient on their original doses which had been clinically determined by their asthma provider at the point of entry to the study. All patients were switched to the same ICS – fluticasone propionate – to enable comparisons but were changed to equipotent doses of their original ICS regimen. This prevented a masking effect from using higher than required ICS doses.

9.3.1.4 Study duration

The 4-week window used in our study between the time of ED attendance and time of enrolment allowed asthma stabilisation to occur prior to study recruitment. On average, it takes 7 to 10 days for symptoms and lung function to stabilise after an asthma exacerbation\textsuperscript{668}. Enrolling patients too early after an exacerbation can lead to overestimation of the effectiveness of an intervention as
baseline measures are worse than usual. Furthermore, interventions can initially be effective due to a ‘novelty effect’ for participants and changes in behaviour can be lost once this effect wears off. Matsuddi et al. discussed this phenomenon of novelty for text messaging interventions, referring to a one- to two-month period in which technological interventions could have a ‘novelty effect’ post-implementation. The authors proposed a minimum study duration of three months to allow true effects of interventions to be observed. A six-month study duration was therefore chosen for our study to minimise these novelty effects resulting from the new EMD. This allowed participants to revert to their usual routines and baseline behaviour so the true effects of the intervention could be observed in a natural environment.

9.3.1.5 Blinding of adherence monitoring function to participants
Participants were not informed of the adherence monitoring function of the EMDs, but were informed that their different reliever device was to enable investigators to know when the medication was running out. This covert adherence monitoring was done in accordance with previous ethical guidelines, to minimise the Hawthorne effect on behaviour, as patients may act differently if they are aware of the observation. Indeed, our literature review highlighted that studies that blind participants to the monitoring function of the EMD seem to report different results to those that are non-blinded. A study conducted last year reported that monitored patients tend towards better adherence, thus monitoring itself appears to have some effect on behaviour beyond the intervention being studied.

9.3.1.6 Similar conditions for intervention and control groups
Both groups received the EMD which ensured the only difference in the intervention group was the presence of the audiovisual reminder. This differs from other studies where only the intervention group received the EMD, whilst the control group received standard packaging without electronic monitoring. Studies that utilise this design often require two different adherence measures as whilst the intervention group has adherence recorded electronically via the EMD, the control group does not as they are not using the EMD. This limits the reliability of the conclusions drawn as the data are not comparable between the two groups; or where the same adherence measurement method is used, this is often not the gold standard of electronic monitoring. In our study, both groups received the same physical intervention (EMD), so performance bias was minimised – although it was not possible to blind the participants and research personnel from awareness of which intervention group the participant was allocated to, both received the same devices, which would minimise any behaviour change that might result from the presence of the physical device.
9.3.1.7  Adequate blinding at point of randomisation and allocation (minimal selection bias)

A simple, unrestricted block randomisation method was used to randomly assign patients to each group. The randomisation sequence was generated by the study statistician, independent of the research personnel who had contact with the participants. These randomisation groups were provided to investigators in opaque, sealed envelopes which were processed by a research assistant from another research group. These envelopes were opened by research personnel in consecutive order to allocate participants to their randomisation group and remained sealed until the next participant needed to be allocated. This method ensures that selection bias is minimised and the use of a restricted random allocation method helps to achieve greater equivalence between treatment groups.  

9.3.1.8  Minimal loss to follow-up (minimal attrition bias)

There were only seven participants (3% drop-out) that withdrew before study end. This low percentage of loss to follow-up ensures that biases resulting from attrition are kept to a minimum. Where data were missing due to malfunction or loss of the device, the entire period of data was withdrawn, ensuring adequate adjustment of both the numerator (number of doses taken) and the denominator (prescribed doses for the study period).

9.3.1.9  Objective measures of adherence

The vast majority of intervention studies in the past have used subjective adherence monitoring methods, such as parental report or medication diaries, or proxy adherence measures such as pharmacy refill records. Data from these measures are less reliable than from EMDs. This study used EMDs for adherence data collection in both the intervention and control groups, which is considered to be the ‘gold standard’ adherence measuring method.  

9.3.1.10  Recruitment of participants from ED

Participants were recruited after presentation to the regional ED with an asthma exacerbation. The recruitment of this study sample from the population which is most likely to need adherence interventions, and to benefit from them, most increases the applicability and relevance of these results. As the study was conducted in the population that is most likely to end up using the intervention, the data is more representative than that obtained from volunteer databases or by advertisement. Furthermore, these patients are often excluded from studies due to the difficulties with research participation and follow-up, since they often represent those with the poorest adherence in society. The participation and follow-up rates were however surprisingly high in this study, with ~69% (220/321) of eligible patients enrolling into the study and ~97% (213/220) completing it, thus representing the eligible study population well. Furthermore, the baseline characteristics of the final enrolled sample were found to be well matched to the characteristics of
the population presenting to ED (Section 6.4, Appendix Table 1) therefore increasing the
generalisability of these results to other children presenting to ED with asthma.

9.3.1.11 Patient acceptability of the intervention assessed

Our study formally assessed patient acceptability and usability of the EMD, via both quantitative and
qualitative methods, to ensure feasibility of the intervention. As addressed in our literature review,
few studies collect patient acceptability data; and where collected, this is often not measured
formally. Assessing patient uptake of an intervention is crucial as patients are the end users and are
ultimately the target population of adherence interventions. Regardless of the effectiveness of an
intervention in a research setting, an intervention is of limited use if patients do not use it.

9.3.2 Study limitations

9.3.2.1 Blinding of outcome assessment not possible (detection bias)

Due to the nature of the intervention, it was not possible to blind outcome assessors from
knowledge of which intervention a participant was allocated to. However, this is in line with other
similar studies using EMD-based interventions, and bias was kept to a minimum by using objective
adherence measures that cannot be altered, such as the EMD records of adherence, and using
validated measures of asthma outcomes, such as the ACT.

9.3.2.2 Lack of validated outcome measures for the enrolled study population

Our study population spanned a wide age range, which included younger children and adolescents
(aged 6 to 15 years). This posed issues when choosing validated outcome measures to use, as many
measures are validated either for younger children, usually up to 12 years – or older children. For
example, the c-ACT was originally validated for 4 to 11 year olds, and the VARK learning styles
questionnaire for younger people was for a lower limit of 12 years old. We considered using two
separate measures for these outcomes – such as using the child version of the VARK for those below
12 years old, then using the questionnaire for younger people in those 12 years and older –
however, this would have introduced inconsistencies in the results beyond the effect of the
intervention. As such, the measurement tool that was most appropriate for the study population
was chosen, though the limitation of using a tool that is not validated for some ages is
acknowledged. A similar issue arose with choosing which dataset to use as reference values for
spirometry, as there were considerations of both the age range and variety of ethnicities in our
population. The dataset from Asher et al. could have provided ethnicity specific reference data for
Māori/Pacific versus European ethnicities. However, this only covers 6 to 13 year olds so there
would be a need to switch to another set of reference values for the 14 to 15 year olds. As such, a
decision was made to use the Stanojevic dataset. This dataset, although based on European
children, was able to give us a seamless reference over the entire age range.
9.3.2.3 Potential under-representation of minority populations

Despite the high study participation rate, and the similar baseline characteristics between the enrolled study population and the population presenting to ED with asthma, there remains some differences between the two groups that have the potential to affect the generalisability of the results. Notably, the group that presented to ED with asthma consisted of 16% Māori; however, the final enrolled population only had 5% Māori in the intervention group and 10% in the control. This under-representation of Māori in research is commonly encountered and needs to be addressed in future studies. Although our study attempted to encourage Māori participation through consultation with local Māori research committees and undertaking the research in a culturally sensitive manner, such as conducting follow-up visits at the Marae, we still encountered a low Māori participation rate. Furthermore, although the trial was randomised, the number of Māori in the intervention group was half that of the control. This may affect the generalisability of the findings to the Māori population; future studies may need to stratify randomisation by ethnicity and/or set a minimum percentage enrolment target for Māori to ensure Māori are adequately represented.

9.3.2.4 Inadequate sample size for detection of changes in hospitalisations

Whilst this study demonstrated significant improvements in asthma control, exacerbations and reliever use, no improvements were seen for ED utilisation. The sample size was too small to detect changes in ED utilisation as the frequency of these events was lower than expected. Data from a recent systematic review by Rank et al. found no significant difference in ED visits and hospitalisations among those who stop regular ICS treatment compared to those who continue treatment and noted that ED visits and hospitalisations were infrequent events even among those who stop ICS. Williams et al. discussed the difficulties with quantifying the relationship between ICS adherence and asthma outcomes, and recognised that ED visits and hospitalisations are infrequent events which make detection of an association difficult. Given the infrequency of these events, no outcome differences were observed between the study groups with our sample size and study duration. Studies in larger samples with a longer duration of follow-up will be needed to detect a difference in these events.

9.3.2.5 Lack of assessment of baseline adherence

There was no run-in phase in our study to determine baseline adherence prior to enrolment into the study. This would have been useful as the impact of the intervention may have been diluted by those with already high adherence rates, and many adherence studies have recruited only those who have poor baseline adherence. However, as prior adherence is likely to predict future adherence, it is likely that our study population had poor baseline adherence as this correlates with ED attendance. Moreover, those with the poorest adherence are likely to benefit most from interventions that improve adherence, so the impact of this intervention is
likely to be the greatest with this population presenting to ED, even though baseline adherence was not measured. Despite the potential inclusion of adherent patients in the study, our findings still showed improvements in adherence of a much greater magnitude than previously reported; limiting the sample to just those who have poor adherence would only magnify, not diminish, this effect.

9.3.2.6 Missing data and faulty devices

Of the 694 devices issued during the study, 2% were not returned and 13% did not pass return QC testing. Although the data loss rate was low, and was managed by excluding the period with missing data, a significant percentage failed return QC testing, which may affect data reliability. The primary reason for failure was actuation under-recording which would lead to under-estimation of adherence. This would be preferable to overestimation of adherence, but either way, as the study was randomised and the chances of this error occurring in the intervention group are not expected to be greater than in the control, it is unlikely to affect the conclusions drawn from the study.

9.3.2.7 Use of non-monitored inhalers

Participants were noted to possess non-monitored inhalers, particularly relievers, as an extra inhaler at school or for the holidays. This was managed as much as possible at each research visit by encouraging participants to use only the inhalers provided by the investigators and actively asking if participants had multiple inhalers. Where extra inhalers were identified by investigators, these were collected and replaced with monitored inhalers. All inhaled asthma medication were also provided by the researchers during the study which helped to reduce the need for participants to obtain their own (non-monitored) medication. We do not expect the rates of non-monitored medication usage to be different between the groups; nevertheless, there is a small chance that the control group may have had more opportunities to obtain reliever inhalers as they reported a higher exacerbation rate, which may have resulted in more visits to healthcare facilities and potential opportunities to obtain extra medication. This would however have led to an underestimation of reliever use in the control group, which means the intervention impact may in reality have been even greater.

9.3.2.8 Use of only one adherence measurement method

Our study utilised only electronic monitoring to measure adherence. More recent adherence studies have used two or more methods to double-check the reliability and accuracy of the different measures and potentially allow standardisation between measures. As described above, there were issues encountered with some of the EMDs and inclusion of a secondary adherence measure may have increased data accuracy and minimised data loss.

9.3.2.9 Lack of monitoring of inhalation

As with all currently available EMDs, the EMD used in our study recorded only time and date of actuations rather than inhalations. However, as this was a randomised study, we do not expect the
rates of actual inhalation to be different between the groups, and the measure of actuations was therefore an appropriate proxy measure in our study.

9.3.2.10  Use of self-reported data for some outcomes

Several outcomes, such as days off school and work, were assessed by self-report which is likely less reliable due to recall bias, subjectivity, information bias and response biases\textsuperscript{676}. All of these questionnaires were also administered in the presence of the investigators which may have led to inaccurate answers due to a social desirability bias\textsuperscript{677}. We originally intended to confirm this data with an objective source such as school records of absences. Unfortunately, data recorded by school were organised as number of half days absent per term, and schools were unable to give number of days absent for the participant for the time they were in the study. For other measures, such as family and socioeconomic data, it was not possible to use a second objective confirmation measure, as is the case in other similar studies\textsuperscript{13, 106, 300}.

9.3.2.11  Lack of feedback from health providers

Whilst our study obtained feedback from the patients and families regarding the intervention, we did not measure feasibility and acceptability of the intervention for health providers. Our study aim was to measure the effect of the EMD-based adherence intervention on patients rather than assessing feasibility or uptake. However, as this study has provided data on effectiveness, there is now a need for future studies to determine feasibility of implementing this intervention in a real-world practice setting and obtain feedback from health providers on its implementation and sustainability.

9.4  Implications of results – direction for future studies

The results from this trial reinforce that for preventive medicines to realise their full potential, they must be taken regularly. The research highlights the importance of a partnership between medicines and adherence support technologies in ensuring that the effectiveness of medicines seen in clinical trials is demonstrated even in a non-controlled clinical environment. This is the first of such studies to demonstrate improvements in adherence and clinical outcomes with an EMD-based intervention in asthma. The improvements in asthma control observed were significant; and are particularly relevant to New Zealand, given the high prevalence of poor asthma control relative to other countries\textsuperscript{9}. This marks a point in asthma history where the management of childhood asthma might change, with a more focused approach on improving adherence rather than changing medication. It paves the way for other similar research to follow. There are several learnings from this research that will shape the design of future adherence interventions: 1) EMD-based interventions appear to be most effective when they involve adherence feedback in real-time directly to the patient; 2) EMD-based reminders on-board the medication may be pivotal to
effectiveness; 3) real-time reminders that occur only when a dose is missed, and that vary from one
to the next may be helpful, particularly where non-adherence results from unintentional forgetting;
4) adherence interventions have the greatest benefits in those with poor adherence; and 5) a
minimum degree of change in adherence may be required before improvements in clinical outcomes
are observed. The study also found that in a New Zealand setting, those who are of female sex,
Asian ethnicity, living in a smaller household and who had a younger age of diagnosis tend to have
better adherence.

Moving forward, the research raises questions about the applicability of these findings to other
chronic airways diseases such as bronchiectasis, as well as other chronic diseases where medication
adherence is problematic. Data from the WHO recognises adherence problems to be ubiquitous
across most chronic conditions, with an average reported adherence rate of 50%\textsuperscript{40}. Current research
on EMDs in other chronic conditions, such as hypertension\textsuperscript{497, 505, 506}, diabetes\textsuperscript{142, 510, 678} or HIV\textsuperscript{134, 512-514}, suggest that benefits are likely for adherence – but a consistent benefit on clinical outcomes is
yet to be shown. This study was targeted also at a particular population – children presenting to ED
with poor disease control – who are seen as a high-risk population for non-adherence. Whether the
same benefits would be seen in children with better, but still suboptimal, adherence, such as those
managed by primary care, or in other age groups such as adults, is not known. As people get older,
the factors dictating their health behaviours can change and there may be a more complex interplay
of factors mediating adherence\textsuperscript{57, 316, 358}. Whether this intervention can be successful in a similar
high-risk group, but of older age, remains unknown.

Questions around how best to increase the accessibility of this adherence intervention to those who
need it most, but are the least likely to be able to access it, will need to be answered. The barriers
that prevent this research from moving into practice will need to be addressed before this
intervention can be taken up in a clinical setting. The study has provided a good starting platform on
which to conduct further research to provide insight into application to a wider patient population,
and has identified factors associated with poor adherence, in whom such an intervention would
benefit most. If further research is able to show cost-effectiveness and benefits in other
populations, this intervention may change the face of healthcare and chronic disease management
beyond asthma.

9.5 Conclusion

This series of papers and chapters have formed a journey of discovery around the role of EMDs in
adherence management in asthma. Together, these findings highlight the effectiveness of an EMD
with audiovisual reminder function on adherence with ICS and asthma outcomes in school-aged
children with asthma. These findings reinforce that those with the poorest adherence benefit most
from adherence interventions, with significant improvements in outcomes seen in this high-risk group of children presenting to hospital with asthma. The intervention had high patient acceptability and usability. There is now potential for this to move from a research to a clinical practice setting, though issues around cost-effectiveness will need to be addressed, particularly around effects on hospitalisation and unscheduled healthcare utilisation. In a limited health resource setting, this intervention may need to be targeted at those at highest risk of non-adherence. These findings mark the beginning of a potential change in asthma management, where adherence support technologies and medication partner together to deliver the best possible health outcomes.
Appendices

Appendix A: Participant information sheet

SCHOOL OF MEDICAL SCIENCES
Faculty of Medical and Health Sciences

PARTICIPANT INFORMATION SHEET
Effect of an Inhaler with Ringtones in Children with Asthma.

Amy Chan
School of Pharmacy
University of Auckland
Phone Number: (021) 164 2473

Liz Garratt
Respiratory Research Group
University of Auckland
Phone Number: (021) 345 250 or (09) 923 1289

Sherron Keebone
Respiratory Research Group
University of Auckland
Phone Number: (021) 104 5543 or (09) 923 1289
Introduction

We would like to invite you and your child to take part in this study. The information in this leaflet explains the reason for doing this study. When you have read it carefully you will have the opportunity to ask questions. Taking part in this study is completely voluntary. If you do not wish to take part in this study it will not disadvantage future medical care for your child and if you do take part you are free to withdraw your child from the study at any time.

What is the reason for doing this study?

Asthma is due to inflammation in the lungs. The most effective treatment for asthma is inhaled steroids. If used regularly these medicines reduce inflammation in the lungs and this leads to fewer symptoms, fewer asthma attacks and less need to use reliever medicines (such as Ventolin). These medicines also have the advantage of being safe with few side effects. The most widely used inhaled steroid is Flixtotide (also known as fluticasone). The aim of this study is to see if a Flixtotide inhaler that includes an alarm which sounds twice a day to remind one to use the inhaler leads to better control of asthma than a Flixtotide inhaler that doesn’t contain the alarm.

Who is able to take part in this study?

Your child is able to take part in the study if they:

- have asthma
- are between the ages of 6 and 15 years of age
- are already on treatment with an inhaled steroid
- has visited a Hospital Emergency Department with an attack of asthma
- normally reside in the Auckland area

Your child will not be able to take part in the study if they have:

- Other forms of lung disease (other than asthma) e.g. bronchiectasis or cystic fibrosis.
- Congenital heart disease

There may be other reasons that your child cannot take part that the investigators will inform you about.

What does the study involve?

Your child’s participation in the study will be for 6 months. You and your child will be seen on five occasions. We will come and visit you at home unless you prefer to be seen at Medical School instead. Each study visit will take approximately one hour.
When you are first seen the study will be explained to you and you will have the opportunity to ask questions about the study. If you are happy for your child to participate in the study you will be asked to sign a consent form agreeing to take part in the study. If at all possible we would like your child not to use their reliever medicine for 4 hours before the study visit.

We will measure your child’s height and weight and a test for lung function will be performed. This measures the amount of air that they can blow out in a single breath. After this we will ask your child to inhale two puffs of Ventolin (releiver medicine) and we will repeat the blowing test. We will then ask them to complete a questionnaire called the Asthma Control Test (ACT) that will assess how your child’s asthma affects their life. We will also check that your child is using their inhaler correctly. During the study we will provide your child with all the inhalers that they need for treatment of their asthma.

You will be assigned to one of the two study groups by chance (like flipping a coin). One group will be provided with a Flixotide inhaler containing an alarm that will ring twice a day to remind your child to use the inhaler. The alarm consists of a series of different ringtones, with a different ringtone for each morning and evening of the week. The other group will receive the same inhaler but without the ringtones.

If your child is using a Beclzone or Pulmicort inhaler they can still able to take part in the study if you are happy for them to switch to the equivalent dose of Flixotide. We will also provide a Ventolin inhaler for them to use during the study. If they are on treatment with Seretide or Symbicort inhaler we will provide a Seretide inhaler (instead of a Flixotide inhaler) to use in the study. If you have concerns about switching inhalers, you should contact your GP to discuss this.

The second visit will be two months after the first visit. We will ask your child to do blowing tests before and after inhaling Ventolin (releiver medicine) and we will get you to complete the ACT again. We will collect the study inhaler that your child has been using and issue you with a new study inhaler.

The third visit will be two months after the second visit. This visit will be similar to the second visit.

The final visit will be two months after the third visit and will be similar to the two previous visits except that your child will be able to keep the Flixotide (or Seretide) inhaler they have been using. Alternatively
if your child is in the group without the ringtones and you would like an inhaler with ringtones we will be happy to provide you with this.

At the end of the study we will write a letter to your General Practitioner with the results and any recommendations about treatment for your child.

You will be issued with a card to confirm your child’s participation in the study. This card should be presented at the time of any medical treatment received during your participation in the trial.

What are the benefits of taking part in this study?
It is possible that your child’s asthma will improve during the study but there is no guarantee that this will happen. You may benefit from having your asthma monitored more closely and may learn more about this disease through your contact with the investigators.

What are the discomforts and risks of taking part in this study?
The lung function tests (testing the amount of air you can blow out) may cause some study subjects to feel lightheaded or dizzy.

Participation in the Study
Participation in this study is entirely voluntary; you are not obliged to take part. Your treatment and the attitude of your doctor towards you will not be affected should you decide not to take part in this study. Refusal to participate will not affect your treatment.

If you decide to take part, you will need to sign to say that you have given your consent to participate. If you agree to participate, you may nevertheless withdraw from the study at any time.

Financial Considerations
You will not incur any costs from participating in this study. If you prefer to come to the Medical School for study visits, the costs of travelling to and from Medical School for study visits will be reimbursed. During the study your child will be provided with inhalers for their asthma at no charge. There will be no other monetary payments for participation in this study.

Confidentiality
No one, except you, the study co-ordinator and study doctor will know that you are participating in the study, unless you choose to inform them. During the study, the records related to the study will be
securely stored and will only be accessed by the study investigators. The study records will be kept on file for 15 years after the study finishes.

Coding will be utilized throughout this study to protect the identity of participants – this includes all raw data collection sheets and associated documents. Tools used to cross reference codes back to the participant will be securely stored in a separate location. No material that will identify you personally will be used in any reports or publications that result from this study.

Results of the Study
When the results of the study are available they will be published in a medical journal. If you wish, you can be provided with the results of the study when they are available.

Compensation for Injury or Negligence
In the unlikely event of a physical injury as a result of participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation Act.

If your claim is accepted by ACC, you might still not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

Contact Information
If you have any questions about the study you should contact one of the investigators.

Amy Chan
School of Pharmacy
University of Auckland
Ph: (021) 164 2473
Liz Garrett
Respiratory Research Group
University of Auckland
Phone Number: (021) 345 250 or (09) 923 1289

Sherron Kneebone
Respiratory Research Group
University of Auckland
Phone Number: (021) 104 5343 or (09) 923 1289

Prof. Ed Mitchell
Dept of Paediatrics
University of Auckland
Ph: (09) 923 6431
Statement of Approval
This study has received ethical approval from the Northern Y Ethics Committee.

For Maori Health Support:

Auckland District Healthboard: Please contact Mata Forbes, RGON. Co-ordinator / Advisor, Maori Health Services, Auckland District Health Board, Auckland Hospital, Grafton.
Mobile 021 548432, Tel: 09 5074949 extn 7292.

Waitemata District Healthboards: Please contact Mo Wai Te Ora Maori Health Services, Waitemata DHB, North Shore Hospital, Takapuna. Tel: (09) 486 8958 extn 2458.

If you have any queries or concerns regarding your rights as a participant in this study you may wish to contact the Health Advocates Trust on 0800 555 050 (For Northland to Franklin).
Appendix B: Child participant information sheet

Who do we need?
Lots of kids have problems keeping their asthma under control. We are asking kids with asthma who are 6 to 15 years old (and their parents) to help us with our project.

Asthma Project
You will have been sent some information about our asthma study. After reading about it, you can call us if you have any questions or if you are interested in taking part. If you say “yes” we will need to come and see you at for 4 visits. These visits take about 1 hour.

Why do we need your help?
We want to find out if a new type of inhaler is better at treating your asthma than the one you have been using. The inhaler has different ringtones (like a mobile phone) and rings twice a day to remind you to use the inhaler.
Some children will be given the inhaler with ringtones during the study. Others will use an ordinary inhaler during the study but will get an inhaler with ringtones at the end of the study. During the study you can help by answering some questions and doing some blowing tests to check out your lungs. All the information is put into a computer which helps us to see if the new inhaler is better.
By the way...all the stuff you tell us is kept private.

What happens?
When you come and see us we will:
★ Ask you about your asthma
★ Ask you about your inhalers
★ Listen to your chest
★ Get you to do a questionnaire
★ Measure your height and weight
★ Get you to blow into a machine to see how well your lungs are working - this is like blowing up a balloon and can make you feel a little dizzy

Remember you don’t have to take part, and if you say no it won’t change how you are looked after

If you think it is OK to be in the study you can write it here...
I agree to help in your study ____________________
(write your name here)

Thanks for thinking about it
Appendix C: Consent form

CONSENT FORM

Name of Study: Effect of an inhaler with ringtones in children with asthma.

Investigators: Amy Chan, Maye Hamed, Peter Black, Ed Mitchell.

<table>
<thead>
<tr>
<th>Language</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>I wish to have an interpreter.</td>
</tr>
<tr>
<td>Maori</td>
<td>E hiahia ana ahau ki tetahi kanuwakaamaori/ka whaka paihia korero.</td>
</tr>
<tr>
<td>Cook Island</td>
<td>Ka inangaro au i tatai tangata tino ra.</td>
</tr>
<tr>
<td>Fijian</td>
<td>Au gadreva me ilahi e vaikadeva rose ini sa.</td>
</tr>
<tr>
<td>Niuean</td>
<td>Fi a menako au ke fakaapo e taha tagata fakahoko koko kupu.</td>
</tr>
<tr>
<td>Samoan</td>
<td>Ou te mana'o le i i e se fa'ametalei upu.</td>
</tr>
<tr>
<td>Tokelauan</td>
<td>Ko eu e fofo'ou ki he tino ke fakasili te fagaena Peletenisi ki he faganu o na motu o te Pahetika</td>
</tr>
<tr>
<td>Tongan</td>
<td>Oku ou fiesa'u ha fakatonulea.</td>
</tr>
</tbody>
</table>
I have heard and understood an explanation of the research project that my child has been invited to take part in.

I have been given, and I have read, a written explanation of what is asked of us, and I have had an opportunity to ask questions and to have them answered.

I understand that taking part in the study is voluntary and that if we do not wish to participate my child’s health care will not be affected in any way.

I understand that our participation in this study is confidential and that no material that could identify us will be used in any reports on this study.

I have had time to consider whether to take part.

I am happy for my child to switch inhalers where necessary in order to take part in the study.

I know whom to contact if I have any questions about the study.

I consent to take to my child taking part as a subject in this research.

Full Name: __________________________________________

Signed: __________________________ Date: ________________

I agree to my General Practitioner being notified about my involvement in this study:

Yes ☐ No ☐
I would like to know the results of the study

Yes [ ] No [ ]

Name of Researchers:
Amy Chan
Tel: 021 164 2473

Mary Hamed
Tel: 021 540 335

Peter Black
Tel: 923 9797 or Locator 93 4674

Ed Mitchell
Tel: 923 6431

Project explained by: __________________________

Project Role: __________________________

Signature: __________________________

Date: __________________________
HAS YOUR PATIENT BEEN ADMITTED FOR ASTHMA??

They may be eligible to have RINGTONE reminders for their asthma inhalers!

We are running a trial to see if using inhalers with RINGTONES as reminders to take medication will help improve asthma & reduce hospital admission.

If your patient has ASTHMA, is aged between 6-15 yr & require inhaled steroid treatment, consider them for the RINGTONES trial!

All medications will be provided free for the trial.

Questions?

Contact the study coordinators:

Amy Chan – a.chan@auckland.ac.nz
Maye Hamed – m.hamed@auckland.ac.nz or (09) 9239805
Appendix E: Letter to General Practitioner

SCHOOL OF MEDICAL SCIENCES
Faculty of Medical and Health Sciences

THE UNIVERSITY OF AUCKLAND
85 Park Road, Grafton
Auckland, New Zealand
Telephone 64 9 373 7599
Facsimile 64 9 373 7030
Email:

The University of Auckland
Private Bag 92019
Auckland, New Zealand

INFORMATION SHEET FOR GENERAL PRACTITIONERS (GPs)

Effect of an Inhaler with Ringtones in Children with Asthma

Dear Dr: ____________________________

Re: ____________________________ (NHI: ____________________________)

Your patient has been contacted by our respiratory research group following their attendance at Starship Children’s Emergency Department for asthma. Their family has consented on their behalf to enter a clinical trial, which is looking at the use of ringtone reminders in children with asthma. The ringtone device wraps around their regular preventer and rings twice daily to remind the child to take their inhalers. The study aims to determine if the use of ringtone reminders can improve medication adherence and asthma outcomes. We will be following up their asthma every 2 months for a total of 6 months. During this time, all asthma medications will be provided to the patient at each follow-up visit.
Attached is the participant information sheet for your perusal.

If you have any questions about the study, please feel free to contact one of the investigators listed below. Professor Ed Mitchell is the principal investigator.

With kind regards,

Amy

Amy Chan
Study co-ordinator
Respiratory Research Group
Faculty of Medical & Health Sciences
University of Auckland
Private Bag 92019
Grafton
Auckland, New Zealand
Ph: +64 9 373 7599 extn 86139
Email: a.chan@auckland.ac.nz
Appendix F: Investigator checklist

<table>
<thead>
<tr>
<th></th>
<th>Visit One (Baseline)</th>
<th>Visit Two</th>
<th>Visit Three</th>
<th>Visit Four</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHECKLIST FOR INVESTIGATORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Please tick the appropriate box below if task completed &amp; make comments as needed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EQUIPMENT LIST PRIOR TO EACH VISIT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scales</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stadiometer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spare Smart Tracks – two with ringtones ON, two with ringtones OFF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spare salbutamol inhalers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spacers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical CRF forms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laptop + spirometer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow up VISITS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Written consent obtained</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check accuracy of contact details at each visit for next visit follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check inhaler technique</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check baseline height and weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Issue new Smart Track+ spacer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Issue participant card confirming</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task</td>
<td>Details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child’s participation in study and providing contact details of</td>
<td>Investigator</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrange follow-up visit – 1 month ± 1 week (to change canister and</td>
<td>check for any device failure). Arrange time/ date and place.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrange follow-up visit – about 2 months ± 1 week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remind participants to withhold salbutamol for 4 hours prior to</td>
<td>next visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remind participants they will need to change canisters after 1</td>
<td>month as medication will run out by then</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remind participants to contact investigators ASAP if Smart Track is</td>
<td>lost or malfunctions, or when battery reaches 1 bar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Address any feedback or concerns.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reimburse patient as appropriate for travel costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collect used Smart Track</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For participants in control group, activate ringtones + visual</td>
<td>display in Smart Track if desired. Participants in intervention group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>can keep their Smart Track as desired.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Obtain consent to contact GP in writing about the trial results.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Contact GP in writing, detailing results of tests conducted during study and any recommendations about the child’s treatment if consent obtained.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ALL FOLLOW UP VISITS**

- Remind participant 1 week and the day before ALL visits to confirm study visit
- Record date/time of reminder below and method of reminder:
  - Reminder 1 (date/time): _/_ _/_ _/_
  - Reminder method:
  - Reminder 2 (date/time): _/_ _/_ _/_
  - Reminder method:
<table>
<thead>
<tr>
<th><strong>ONE-MONTH Check-up visit</strong> (in person visit – further monthly checks at 3 and 5 months can be over phone if canister changing technique satisfactory)</th>
<th><strong>Please tick if task completed</strong></th>
</tr>
</thead>
</table>
| 1 week reminder of visit done? | Date/time of reminder: __/__/__ __:__  
Reminder method: |
| 1 day reminder of visit done? | Date/time of reminder: __/__/__ __:__  
Reminder method: |
| Record date / time of 1 month study visit | Date/time of 1-month visit: __/__/__ __:__ |
| Check Smartinhaler fully charged and still functional. Note any problems in comments section. | |
| Remind participants to contact investigators ASAP if Smartinhaler is lost or malfunctions, or when battery reaches 1 bar. | |
| Take back old canister, issue new canister | |
| Demonstrate how to change canister and ask participant to show how to do this correctly for later changes (at 3 and 5 months). | |
| Is canister changing technique ok? | |
| Remind participant not to use salbutamol for 4 hours prior to next visit | |
| Confirm date / time of next visit and note this on the eCRF | |

**LOSS TO FOLLOW UP**

Reasons for loss to follow up recorded


Appendix G: Data collection forms

VISIT ONE – Initial screening assessment at CED

1) Patient details

Screening Number

Date of attendance at CED

Time of assessment at CED

2) Demographics

Surname of participant

First name of participant

Date of Birth

Age

Gender

NHI

Documented ethnicity 1

Documented ethnicity 2

Documented ethnicity 3

<table>
<thead>
<tr>
<th>Ethnic Group code</th>
<th>Ethnic Group code description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>European nor further defined</td>
</tr>
<tr>
<td>11</td>
<td>New Zealand European</td>
</tr>
<tr>
<td>12</td>
<td>Other European</td>
</tr>
<tr>
<td>21</td>
<td>New Zealand Maori</td>
</tr>
<tr>
<td>30</td>
<td>Pacific Island not further defined</td>
</tr>
<tr>
<td>31</td>
<td>Samoan</td>
</tr>
<tr>
<td>32</td>
<td>Cook Island Maori</td>
</tr>
<tr>
<td>33</td>
<td>Tongan</td>
</tr>
<tr>
<td>34</td>
<td>Niuean</td>
</tr>
<tr>
<td>35</td>
<td>Tokelauan</td>
</tr>
<tr>
<td>36</td>
<td>Fijian</td>
</tr>
<tr>
<td>37</td>
<td>Other Pacific Island</td>
</tr>
<tr>
<td>40</td>
<td>Asian not further defined</td>
</tr>
<tr>
<td>41</td>
<td>Southeast Asian</td>
</tr>
<tr>
<td>42</td>
<td>Chinese</td>
</tr>
<tr>
<td>43</td>
<td>Indian</td>
</tr>
<tr>
<td>44</td>
<td>Other Asian</td>
</tr>
<tr>
<td>51</td>
<td>Middle Eastern</td>
</tr>
<tr>
<td>52</td>
<td>Latin American / Hispanic</td>
</tr>
<tr>
<td>53</td>
<td>African</td>
</tr>
<tr>
<td>54</td>
<td>Other</td>
</tr>
<tr>
<td>99</td>
<td>Not stated</td>
</tr>
</tbody>
</table>
3) Physical parameters from ED (to 1 decimal place)
Weight from ED (kg) 0

Collection of further patient information

4) Assessment details

Screening Number from previous screening assessment
Date of assessment
Time of assessment
Type of assessment: Phone / In Person
Has participant info sheet been given? [ ]
How was the participant info sheet handed out? In person / Email / Post / Other
If given via 'Other' method, pls specify:

5) Inclusion criteria (please tick the following where applicable):
Aged between 6 and 15 years
Diagnosis of acute asthma
On treatment with ICS or starting ICS treatment
Does participant meet all of the inclusion criteria above? [ ]

6) Exclusion criteria (please tick the following which apply):
Other diagnosis of chronic lung disease (bronchiectasis, CF, bronchopulmonary dysplasia)
Congenital heart disease
Severe intellectual disability
Insufficient English to participate in study
Primary place of residence not in Auckland area
Does the participant have any exclusion criteria? [ ]

7) If the participant meets all inclusion criteria and has no exclusion criteria obtain consent and assign randomisation number. Exclude if participant has any exclusion criteria.
Verbal consent obtained? [ ]
8) Once verbal consent obtained, arrange date / time of first physical visit.

Date of 1st physical visit
Time of 1st physical visit
Place of Visit One
If visit is conducted on the ward, pls specify which ward

9) Assign randomisation number once written consent obtained.

Assign devices for all inhaled medications (ICS, SABA, LABA, combination).

Randomisation number
Randomised group
Not Randomised?
Device number issued (ICS)
Device number issued (SABA)
Device number issued (LABA)
Device number issued (Combination)
Spacer issued?

10) Record participant's primary caregiver details below:

First name of primary caregiver
Surname of primary caregiver
Relationship of primary caregiver to participant
If 'Other' relationship, pls specify nature of relationship
Does primary caregiver usually have the most contact with the participant?

Street number / address of primary caregiver
Suburb
City
Daytime phone
Evening phone
Mobile
Is primary caregiver happy to be called at work?
Email address
How would the primary caregiver like to be contacted?
What is the best time to contact?

Home Ph / Work Ph / Cellph – call / Cellph – Txt / Email
11) The primary caregiver may wish to identify someone else as a secondary contact should they be unavailable. Obtain details of secondary contact below (optional).

<table>
<thead>
<tr>
<th>First name of secondary caregiver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surname of secondary caregiver</td>
</tr>
<tr>
<td>Relationship of secondary caregiver to participant: Mother / Father / Sibling / Relative / Other</td>
</tr>
<tr>
<td>If 'Other' relationship, pls specify nature of relationship</td>
</tr>
<tr>
<td>Street number/address of secondary caregiver</td>
</tr>
<tr>
<td>Suburb</td>
</tr>
<tr>
<td>City</td>
</tr>
<tr>
<td>Auckland</td>
</tr>
<tr>
<td>Daytime phone</td>
</tr>
<tr>
<td>Evening phone</td>
</tr>
<tr>
<td>Mobile</td>
</tr>
<tr>
<td>Is secondary caregiver happy to be called at work?</td>
</tr>
<tr>
<td>Email address</td>
</tr>
<tr>
<td>How would the secondary caregiver like to be contacted? Home Ph/ Work Ph/ Cellph – call / Cellph – Txt / Email</td>
</tr>
<tr>
<td>What is the best time to contact?</td>
</tr>
</tbody>
</table>

12) Obtain details of the ethnicity that the participant identifies with - more than one can be chosen

<table>
<thead>
<tr>
<th>Self-defined ethnicity 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-defined ethnicity 2</td>
</tr>
<tr>
<td>Self-defined ethnicity 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnic Group code</th>
<th>Ethnic Group code description</th>
<th>Ethnic group re-defined as per Census categories 2013 – Level 1 classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>European nor further defined</td>
<td>European</td>
</tr>
<tr>
<td>11</td>
<td>New Zealand European</td>
<td>European</td>
</tr>
<tr>
<td>12</td>
<td>Other European</td>
<td>European</td>
</tr>
<tr>
<td>21</td>
<td>New Zealand Maori</td>
<td>Maori</td>
</tr>
<tr>
<td>30</td>
<td>Pacific Island not further defined</td>
<td>Pacific Peoples</td>
</tr>
<tr>
<td>31</td>
<td>Samoan</td>
<td>Pacific Peoples</td>
</tr>
<tr>
<td>32</td>
<td>Cook Island Maori</td>
<td>Pacific Peoples</td>
</tr>
<tr>
<td>33</td>
<td>Tongan</td>
<td>Pacific Peoples</td>
</tr>
<tr>
<td>34</td>
<td>Niuean</td>
<td>Pacific Peoples</td>
</tr>
<tr>
<td>35</td>
<td>Tokelauan</td>
<td>Pacific Peoples</td>
</tr>
<tr>
<td>36</td>
<td>Fijian</td>
<td>Pacific Peoples</td>
</tr>
<tr>
<td>37</td>
<td>Other Pacific Island</td>
<td>Pacific Peoples</td>
</tr>
<tr>
<td>40</td>
<td>Asian not further defined</td>
<td>Asian</td>
</tr>
<tr>
<td>41</td>
<td>Southeast Asian</td>
<td>Asian</td>
</tr>
<tr>
<td>42</td>
<td>Chinese</td>
<td>Asian</td>
</tr>
<tr>
<td>43</td>
<td>Indian</td>
<td>Asian</td>
</tr>
<tr>
<td>44</td>
<td>Other Asian</td>
<td>Asian</td>
</tr>
<tr>
<td>51</td>
<td>Middle Eastern</td>
<td>MELAA</td>
</tr>
</tbody>
</table>
13) Obtain details of the participant’s GP and school below:

Name of GP

Street number / address of GP

Suburb

City

Telephone of GP

Name of school attended

Suburb of school

Phone number of school

14) Measure the patient’s height and weight and record below (to 1 decimal place):

Measured Height (cm)

Measured Weight (kg)
Baseline Questionnaire

15) Asthma history and baseline questionnaire

15 a) How many attacks of wheezing have you had in the last 12 months?
   None / 1-3 / 4-12 / 12+ / Don’t know / Missing

15 b) In the last 12 months, how often on average has sleep been disturbed due to wheezing?
   Never woken with wheeze / Less than 1 night per wk/ One or more nights a week / Don’t know / Missing

15 c) In the last 12 months, has wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?
   Yes / No / Don’t know / Missing

15 d) In the last 12 months, has your chest sounded wheezy during or after exercise?
   Yes / No / Don’t know / Missing

15 e) In the last 12 months, have you had a dry cough at night, apart from a cough associated with a cold or chest infection?
   Yes / No / Don’t know / Missing

16) Past medical history of participant

Please list details of participant’s past medical history below:

Please list details of any allergies or intolerances below:


17) **Medication history** - please list all current regular and PRN (when required) medications used in last 4 weeks

17 a) **Asthma medications - Inhaled corticosteroid (ICS):** please select from the following:

<table>
<thead>
<tr>
<th>Name of ICS</th>
<th>Strength of ICS</th>
<th>Dose</th>
<th>Frequency</th>
<th>Tick if PRN use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone Metered Dose Inhaler</td>
<td>☐</td>
<td></td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Fluticasone Accuhaler</td>
<td>☐</td>
<td></td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Budesonide Turbuhaler</td>
<td>☐</td>
<td></td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Beclomethasone Metered Dose Inhaler</td>
<td>☐</td>
<td></td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Beclomethasone Autohaler</td>
<td>☐</td>
<td></td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

17 b) **Asthma medications - short-acting beta agonist (SABA):** please select from the following:

<table>
<thead>
<tr>
<th>Name of SABA</th>
<th>Strength of SABA</th>
<th>Dose</th>
<th>Tick if PRN use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol Metered Dose Inhaler</td>
<td>100 mcg</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Terbutaline Turbuhaler</td>
<td>250 mcg</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

17 c) **Asthma medications - long-acting beta agonist (LABA):** please select from the following:

<table>
<thead>
<tr>
<th>Name of LABA</th>
<th>Strength of LABA</th>
<th>Dose</th>
<th>Frequency</th>
<th>Tick if PRN use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol Metered Dose Inhaler</td>
<td>25 mcg</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Eformoterol Turbuhaler</td>
<td>6 mcg</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
17d) Asthma medications - combination (ICS + LABA) inhaler: please select from the following:

<table>
<thead>
<tr>
<th>Name of combination inhaler</th>
<th>Strength</th>
<th>Dose</th>
<th>Frequency</th>
<th>Tick if PRN use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbicort Turbuhaler</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seretide Metered Dose Inhaler</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seretide Accuehaler</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Does patient have own spacer?  
Does patient use their spacer?
If patient does not use their spacer, please specify why:

17e) Other asthma medications - please list any other medications used by participant for asthma below (eg theophylline, montelukast, ipratropium, cromoglycate). Include dose, strength and frequency:

17f) Other medications - please list all other medications taken by the participant, including prescription, OTC, herbal and complementary medicines. Include dose, strength and frequency for all:
### Baseline – Asthma Assessment

**Randomisation number**

<table>
<thead>
<tr>
<th>18) Lung Function Tests - need two reproducible blows with &lt;5% variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of last use of salbutamol</td>
</tr>
<tr>
<td>Time of last use of salbutamol (24hr clock)</td>
</tr>
</tbody>
</table>

**18 a) Pre-bronchodilator test**

- **Time of assessment (24hr clock)**
- **FEV1 (actual)**
- **FEV1 (predicted)**
- **FEV1 (\%)**
- **FVC (actual)**
- **FVC (predicted)**
- **FVC (\%)**
- **FEV1/FVC ratio**
- **PEF**

**18 b) Administer 4 x puffs of 100 micrograms of salbutamol (total 400 mcg) via spacer.**

*Wait 15 mins before repeating spirometry - conduct questionnaire while waiting.*

**18 c) Post-bronchodilator test**

- **Time of assessment (24hr clock)**
- **FEV1 (actual)**
- **FEV1 (predicted)**
- **FEV1 (\%)**
- **FVC (actual)**
- **FVC (predicted)**
- **FVC (\%)**
- **FEV1/FVC ratio**
- **PEF**
### 19) Asthma Morbidity Score (ask parent)

19a) Rate severity asthma in general over the last year  
- Very mild=1  
- Mild=2  
- Moderate=3  
- Severe=4  
- Very severe=5

19b) How often has asthma stopped participation in child’s activities?  
- Never=1  
- Sometimes=2  
- Often=3  
- Very often=4

19c) How often has the child’s asthma stopped family activities?  
- Never=1  
- Sometimes=2  
- Often=3  
- Very often=4

19d) How often did you (the parent) feel frightened because of the child’s asthma?  
- Never=1  
- Sometimes=2  
- Often=3  
- Very often=4

### 20) Childhood asthma control test: Child to answer

20a) How is your asthma today  
- Very bad=0  
- Bad=1  
- Good=2  
- Very good=3

20b) How much of a problem is your asthma when you run, exercise or play sport?  
- It’s a big problem, I can’t do what I want to do=0  
- It’s a problem and I don’t like it=1  
- It’s a little problem but it’s okay=2  
- It’s not a problem=3

20c) Do you cough because of your asthma?  
- Yes, all of the time=0  
- Yes, most of the time=1  
- Yes, some of the time=2  
- No, none of the time=3
20d) Do you wake up during the night because of your asthma?
   - Yes, all of the time=0
   - Yes, most of the time=1
   - Yes, some of the time=2
   - No, none of the time=3

21) **Childhood asthma control test: Parent to answer**

21a) During the last 4 weeks, how many days did your child have any daytime asthma symptoms?
   - Not at all=5
   - 1-3 days=4
   - 4-10 days=3
   - 11-18 days=2
   - 19-24 days=1
   - Everyday=0

21b) During the last 4 weeks, how many days did your child wheeze during the day because of asthma?
   - Not at all=5
   - 1-3 days=4
   - 4-10 days=3
   - 11-18 days=2
   - 19-24 days=1
   - Everyday=0

21c) During the last 4 weeks, how many days did your child wake up during the night because of asthma?
   - Not at all=5
   - 1-3 days=4
   - 4-10 days=3
   - 11-18 days=2
   - 19-24 days=1
   - Everyday=0
### FOLLOW UP VISIT ONE

#### Patient Information

<table>
<thead>
<tr>
<th>Field</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomisation number</td>
<td></td>
</tr>
<tr>
<td>Date of visit 2</td>
<td></td>
</tr>
<tr>
<td>Time of visit 2</td>
<td></td>
</tr>
<tr>
<td>Place of visit 2</td>
<td>Home / FMHS / CED / Ward</td>
</tr>
<tr>
<td>If visiting participant on ward, pls specify which ward:</td>
<td></td>
</tr>
<tr>
<td>Caregiver providing information (first name)</td>
<td></td>
</tr>
<tr>
<td>Caregiver providing information (surname)</td>
<td></td>
</tr>
<tr>
<td>Relationship of caregiver to participant</td>
<td>Mother / Father / Sibling / Relative / Other</td>
</tr>
<tr>
<td>If &quot;other&quot; relationship, please specify relationship type</td>
<td></td>
</tr>
</tbody>
</table>
23) Medication changes since baseline visit (TWO months ago) (include medicines added / altered / stopped)

Were there any changes made to their medications since their last visit?  

What changes were made to their medications? Please give details below:

<table>
<thead>
<tr>
<th>Medication name</th>
<th>Purpose for use</th>
<th>Dose</th>
<th>Frequency</th>
<th>Start date</th>
<th>Stop date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

24) Other changes

Has the participant had any new medical diagnoses since the last visit (two months ago)?  

Please give details of any new diagnoses below:  

Has the participant had any other significant lifestyle changes since the last visit?  

Please give details of any significant lifestyle changes of note below:  

Yes / No / Don’t know / Missing
25) **Asthma Assessment at Follow up Visit ONE**

25 a) Have you had any attacks of wheezing in the last months?  
   If YES - state number of attacks:

25 b) In the last month, has your sleep been disturbed by wheezing?  
   If YES - state number of nights:

25 c) In the last month, has wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?

25 d) In the last month, has your chest sounded wheezy during or after exercise?

25 e) In the last month, have you had a dry cough at night, apart from a cough associated with a cold or chest infection?

26) **Days lost from school**

Please state the number of days lost from school in the last month

   Number of days off for ASTHMA:

   Number of days off for OTHER conditions:

27) **Days lost from work (caregiver)**

Please state number of days lost from work by caregiver in last month

   Number of days off for child's ASTHMA:

   Number of days off for OTHER illness in the child:

   Number of days off for CAREGIVER'S illness:

   Number of days off for other reasons:

   Please specify 'other' reasons for days off work (generally only, specific details not needed):
28) Exacerbations - please give details of exacerbations (requiring additional visits to healthcare provider (GP/ED), or additional course of steroids or antibiotics) below:

Have you had any exacerbations since the last visit? [Yes / No / Don’t know / Missing]

If YES - please fill in details in the table below:

<table>
<thead>
<tr>
<th>Date of exacerbation</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Date of resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GP = doctor visit</td>
<td>R = Resolved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A and E = after hours clinic</td>
<td>N = Not resolved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CED = ED attendance</td>
<td>S = Resolved with sequelae</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HOSP = admitted to hospital</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- (Checkmark indicates action taken or outcome resolved)
29) Lung Function Tests - need two reproducible blows with <5% variability

- Date of last use of salbutamol
- Time of last use of salbutamol (24hr clock)

29 a) Pre-bronchodilator test

- Time of assessment (24hr clock)
- FEV1 (actual)
- FEV1 (predicted)
- FEV1 (%)
- FVC (actual)
- FVC (predicted)
- FVC (%)
- FEV1/FVC ratio
- PEF

29 b) Administer 4 x puffs of 100 micrograms of salbutamol (total 400 mcg) via spacer.

Wait 15 mins before repeating spirometry - conduct questionnaire while waiting.

29 c) Post-bronchodilator test

- Time of assessment (24hr clock)
- FEV1 (actual)
- FEV1 (predicted)
- FEV1 (%)
- FVC (actual)
- FVC (predicted)
- FVC (%)
- FEV1/FVC ratio
- PEF
### 30) Childhood asthma control test: Child to answer

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>30a) How is your asthma today</td>
<td>- Very bad=0</td>
</tr>
<tr>
<td></td>
<td>- Bad=1</td>
</tr>
<tr>
<td></td>
<td>- Good=2</td>
</tr>
<tr>
<td></td>
<td>- Very good=3</td>
</tr>
<tr>
<td>30b) How much of a problem is your asthma when you run, exercise or play sport?</td>
<td>- It’s a big problem, I can’t do what I want to do=0</td>
</tr>
<tr>
<td></td>
<td>- It’s a problem and I don’t like it=1</td>
</tr>
<tr>
<td></td>
<td>- It’s a little problem but it’s okay=2</td>
</tr>
<tr>
<td></td>
<td>- It’s not a problem=3</td>
</tr>
<tr>
<td>30c) Do you cough because of your asthma?</td>
<td>- Yes, all of the time=0</td>
</tr>
<tr>
<td></td>
<td>- Yes, most of the time=1</td>
</tr>
<tr>
<td></td>
<td>- Yes, some of the time=2</td>
</tr>
<tr>
<td></td>
<td>- No, none of the time=3</td>
</tr>
<tr>
<td>30d) Do you wake up during the night because of your asthma?</td>
<td>- Yes, all of the time=0</td>
</tr>
<tr>
<td></td>
<td>- Yes, most of the time=1</td>
</tr>
<tr>
<td></td>
<td>- Yes, some of the time=2</td>
</tr>
<tr>
<td></td>
<td>- No, none of the time=3</td>
</tr>
</tbody>
</table>

### 31) Childhood asthma control test: Parent to answer

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>31a) During the last 4 weeks, how many days did your child have any daytime asthma symptoms?</td>
<td>- Not at all=5</td>
</tr>
<tr>
<td></td>
<td>- 1-3 days=4</td>
</tr>
<tr>
<td></td>
<td>- 4-10 days=3</td>
</tr>
<tr>
<td></td>
<td>- 11-18 days=2</td>
</tr>
<tr>
<td></td>
<td>- 19-24 days=1</td>
</tr>
<tr>
<td></td>
<td>- Everyday=0</td>
</tr>
<tr>
<td>31b) During the last 4 weeks, how many days did your child wheeze during the day because of asthma?</td>
<td>- Not at all=5</td>
</tr>
<tr>
<td></td>
<td>- 1-3 days=4</td>
</tr>
<tr>
<td></td>
<td>- 4-10 days=3</td>
</tr>
<tr>
<td></td>
<td>- 11-18 days=2</td>
</tr>
<tr>
<td></td>
<td>- 19-24 days=1</td>
</tr>
<tr>
<td></td>
<td>- Everyday=0</td>
</tr>
<tr>
<td>31c) During the last 4 weeks, how many days did your child wake up during the night because of asthma?</td>
<td>- Not at all=5</td>
</tr>
<tr>
<td></td>
<td>- 1-3 days=4</td>
</tr>
<tr>
<td></td>
<td>- 4-10 days=3</td>
</tr>
<tr>
<td></td>
<td>- 11-18 days=2</td>
</tr>
<tr>
<td></td>
<td>- 19-24 days=1</td>
</tr>
<tr>
<td></td>
<td>- Everyday=0</td>
</tr>
</tbody>
</table>
32) Adverse events - please give details below:

Have any adverse events been noted since the last visit? 

<table>
<thead>
<tr>
<th>Sign or symptom of ADE</th>
<th>Date of onset</th>
<th>Outcome</th>
<th>Date of resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R = Resolved</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR = Not resolved</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>S = Resolved with sequelae</td>
<td></td>
</tr>
</tbody>
</table>

33) Additional comments noted at follow-up visit (including details of sequelae if appropriate). If all satisfactory, issue new devices.

Does patient use spacer? 

If spacer not used, please specify why:

Device number issued (ICS) 
Device number issued (SABA) 
Device number issued (LABA) 
Device number issued (Combination)
FOLLOW UP VISIT TWO

34) Patient Information

Randomisation number

Date of visit 3

Time of visit 3

Place of visit 3: Home / FMHS / CED / Ward

If visiting participant on ward, pls specify which ward:

Caregiver providing information (first name)

Caregiver providing information (surname)

Relationship of caregiver to participant: Mother / Father / Sibling / Relative / Other

If "other" relationship, please specify relationship type

35) Medication changes since baseline visit (TWO months ago) (include medicines added / altered / stopped)

Were there any changes made to their medications since their last visit? [ ]

What changes were made to their medications? Please give details below:

<table>
<thead>
<tr>
<th>Medication name</th>
<th>Purpose for use</th>
<th>Dose</th>
<th>Frequency</th>
<th>Start date</th>
<th>Stop date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
36) Other changes

Has the participant had any new medical diagnoses since the last visit (two months ago)?

Please give details of any new diagnoses below:

Has the participant had any other significant lifestyle changes since the last visit?

Please give details of any significant lifestyle changes of note below:

Randomisation number

37) Asthma Assessment at Follow up Visit TWO

37 a) Have you had any attacks of wheezing in the last months?
   If YES - state number of attacks:

37 b) In the last month, has your sleep been disturbed by wheezing?
   If YES - state number of nights:

37 c) In the last month, has wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?

37 d) In the last month, has your chest sounded wheezy during or after exercise?

37 e) In the last month, have you had a dry cough at night, apart from a cough associated with a cold or chest infection?

38) Days lost from school

Please state the number of days lost from school in the last month

   Number of days off for ASTHMA:

   Number of days off for OTHER conditions:
38) Days lost from work (caregiver)

Please state number of days lost from work by caregiver in last month

Number of days off for child’s ASTHMA: 
Number of days off for OTHER illness in the child: 
Number of days off for CAREGIVER'S illness: 
Number of days off for other reasons: 

Please specify 'other' reasons for days off work (generally only, specific details not needed):

39) Exacerbations - please give details of exacerbations (requiring additional visits to healthcare provider (GP/ED), or additional course of steroids or antibiotics) below:

Have you had any exacerbations since the last visit? √

If YES - please fill in details in the table below:

<table>
<thead>
<tr>
<th>Date of exacerbation</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Date of resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
40) Lung Function Tests - need two reproducible blows with <5% variability

Date of last use of salbutamol

Time of last use of salbutamol (24hr clock)

40a) Pre-bronchodilator test

Time of assessment (24hr clock)

FEV1 (actual)

FEV1 (predicted)

FEV1 (%)

FVC (actual)

FVC (predicted)

FVC (%)

FEV1/FVC ratio

PEF

40b) Administer 4 x puffs of 100 micrograms of salbutamol (total 400 mcg) via spacer. Wait 15 mins before repeating spirometry - conduct questionnaire while waiting.

40c) Post-bronchodilator test

Time of assessment (24hr clock)

FEV1 (actual)

FEV1 (predicted)

FEV1 (%)

FVC (actual)

FVC (predicted)

FVC (%)

FEV1/FVC ratio

PEF
### 41) Childhood asthma control test: Child to answer

41a) How is your asthma today
- Very bad=0
- Bad=1
- Good=2
- Very good=3

41b) How much of a problem is your asthma when you run, exercise or play sport?
- It’s a big problem, I can’t do what I want to do=0
- It’s a problem and I don’t like it=1
- It’s a little problem but it’s okay=2
- It’s not a problem=3

41c) Do you cough because of your asthma?
- Yes, all of the time=0
- Yes, most of the time=1
- Yes, some of the time=2
- No, none of the time=3

41d) Do you wake up during the night because of your asthma?
- Yes, all of the time=0
- Yes, most of the time=1
- Yes, some of the time=2
- No, none of the time=3

### 42) Childhood asthma control test: Parent to answer

42a) During the last 4 weeks, how many days did your child have any daytime asthma symptoms?
- Not at all=5
- 1-3 days=4
- 4-10 days=3
- 11-18 days=2
- 19-24 days=1
- Everyday=0

42b) During the last 4 weeks, how many days did your child wheeze during the day because of asthma?
- Not at all=5
- 1-3 days=4
- 4-10 days=3
- 11-18 days=2
- 19-24 days=1
- Everyday=0

42c) During the last 4 weeks, how many days did your child wake up during the night because of asthma?
- Not at all=5
- 1-3 days=4
- 4-10 days=3
- 11-18 days=2
- 19-24 days=1
43) Adverse events - please give details below:

Have any adverse events been noted since the last visit?  

<table>
<thead>
<tr>
<th>Sign or symptom of ADE</th>
<th>Date of onset</th>
<th>Outcome</th>
<th>Date of resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>S</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

44) Additional comments noted at follow-up visit 2 (including details of sequelae if appropriate). If all satisfactory, issue new devices.

Does patient use spacer?  
If spacer not used, please specify why:  

Device number issued (ICS)  
Device number issued (SABA)  
Device number issued (LABA)  
Device number issued (Combination)
FOLLOW UP VISIT THREE (FINAL)

45) Patient Information

Randomisation number

Date of final visit 4

Time of final visit 4

Place of final visit 4 [Home / FMHS / CED / Ward]

If visiting participant on ward, pls specify which ward:

Caregiver providing information (first name)

Caregiver providing information (surname)

Relationship of caregiver to participant [Mother / Father / Sibling / Relative / Other]

If "other" relationship, please specify relationship type

46) Medication changes since baseline visit (TWO months ago) (include medicines added / altered / stopped)

Were there any changes made to their medications since their last visit? [ ]

What changes were made to their medications? Please give details below:

<table>
<thead>
<tr>
<th>Medication name</th>
<th>Purpose for use</th>
<th>Dose</th>
<th>Frequency</th>
<th>Start date</th>
<th>Stop date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
47) Other changes

Has the participant had any new medical diagnoses since the last visit (two months ago)?

Please give details of any new diagnoses below:

Has the participant had any other significant lifestyle changes since the last visit?

Please give details of any significant lifestyle changes of note below:

Randomisation number

48) Asthma Assessment at Final Follow up Visit THREE

48 a) Have you had any attacks of wheezing in the last months?
   If YES - state number of attacks:

48 b) In the last month, has your sleep been disturbed by wheezing?
   If YES - state number of nights:

48 c) In the last month, has wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?

48 d) In the last month, has your chest sounded wheezy during or after exercise?

48 e) In the last month, have you had a dry cough at night, apart from a cough associated with a cold or chest infection?
49] Days lost from school

Please state the number of days lost from school in the last month:

Number of days off for ASTHMA: 
Number of days off for OTHER conditions: 

50) Days lost from work (caregiver)

Please state number of days lost from work by caregiver in last month:

Number of days off for child’s ASTHMA:
Number of days off for OTHER illness in the child:
Number of days off for CAREGIVER’S illness:
Number of days off for other reasons:

Please specify 'other' reasons for days off work (generally only, specific details not needed):

51) Exacerbations - please give details of exacerbations (requiring additional visits to healthcare provider (GP/ED), or additional course of steroids or antibiotics) below:

Have you had any exacerbations since the last visit? 
If YES - please fill in details in the table below:

<table>
<thead>
<tr>
<th>Date of exacerbation</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Date of resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>S</td>
<td></td>
</tr>
</tbody>
</table>

52] Lung Function Tests - need two reproducible blows with ≤5% variability

Date of last use of salbutamol

Time of last use of salbutamol (24hr clock)

52a) Pre-bronchodilator test

Time of assessment (24hr clock)
FEV1 (actual)
FEV1 (predicted)
FEV1 (%)
FVC (actual)
FVC (predicted)
FVC (%)
FEV1/FVC ratio
PEF
52 b) Administer 4 x puffs of 100 micrograms of salbutamol (total 400 mcg) via spacer. Wait 15 mins before repeating spirometry - conduct questionnaire while waiting.

52 c) *Post-bronchodilator test*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of assessment (24hr clock)</td>
<td></td>
</tr>
<tr>
<td>FEV1 (actual)</td>
<td></td>
</tr>
<tr>
<td>FEV1 (predicted)</td>
<td></td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td></td>
</tr>
<tr>
<td>FVC (actual)</td>
<td></td>
</tr>
<tr>
<td>FVC (predicted)</td>
<td></td>
</tr>
<tr>
<td>FVC (%)</td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td></td>
</tr>
<tr>
<td>PEF</td>
<td></td>
</tr>
<tr>
<td>53) Asthma Morbidity Score (ask parent)</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>53a) Rate severity asthma in general over the last year</strong></td>
<td></td>
</tr>
<tr>
<td>o Very mild=1</td>
<td></td>
</tr>
<tr>
<td>o Mild=2</td>
<td></td>
</tr>
<tr>
<td>o Moderate=3</td>
<td></td>
</tr>
<tr>
<td>o Severe=4</td>
<td></td>
</tr>
<tr>
<td>o Very severe=5</td>
<td></td>
</tr>
<tr>
<td><strong>53b) How often has asthma stopped participation in child’s activities?</strong></td>
<td></td>
</tr>
<tr>
<td>o Never=1</td>
<td></td>
</tr>
<tr>
<td>o Sometimes=2</td>
<td></td>
</tr>
<tr>
<td>o Often=3</td>
<td></td>
</tr>
<tr>
<td>o Very often=4</td>
<td></td>
</tr>
<tr>
<td><strong>53c) How often has the child’s asthma stopped family activities?</strong></td>
<td></td>
</tr>
<tr>
<td>o Never=1</td>
<td></td>
</tr>
<tr>
<td>o Sometimes=2</td>
<td></td>
</tr>
<tr>
<td>o Often=3</td>
<td></td>
</tr>
<tr>
<td>o Very often=4</td>
<td></td>
</tr>
<tr>
<td><strong>53d) How often did you (the parent) feel frightened because of the child’s asthma?</strong></td>
<td></td>
</tr>
<tr>
<td>o Never=1</td>
<td></td>
</tr>
<tr>
<td>o Sometimes=2</td>
<td></td>
</tr>
<tr>
<td>o Often=3</td>
<td></td>
</tr>
<tr>
<td>o Very often=4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>54) Childhood asthma control test: Child to answer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>54a) How is your asthma today</strong></td>
</tr>
<tr>
<td>o Very bad=0</td>
</tr>
<tr>
<td>o Bad=1</td>
</tr>
<tr>
<td>o Good=2</td>
</tr>
<tr>
<td>o Very good=3</td>
</tr>
<tr>
<td><strong>54b) How much of a problem is your asthma when you run, exercise or play sport?</strong></td>
</tr>
<tr>
<td>o It’s a big problem, I can’t do what I want to do=0</td>
</tr>
<tr>
<td>o It’s a problem and I don’t like it=1</td>
</tr>
<tr>
<td>o It’s a little problem but it’s okay=2</td>
</tr>
<tr>
<td>o It’s not a problem=3</td>
</tr>
<tr>
<td><strong>54c) Do you cough because of your asthma?</strong></td>
</tr>
<tr>
<td>o Yes, all of the time=0</td>
</tr>
<tr>
<td>o Yes, most of the time=1</td>
</tr>
<tr>
<td>o Yes, some of the time=2</td>
</tr>
<tr>
<td>o No, none of the time=3</td>
</tr>
<tr>
<td><strong>54d) Do you wake up during the night because of your asthma?</strong></td>
</tr>
<tr>
<td>o Yes, all of the time=0</td>
</tr>
<tr>
<td>o Yes, most of the time=1</td>
</tr>
<tr>
<td>o Yes, some of the time=2</td>
</tr>
<tr>
<td>o No, none of the time=3</td>
</tr>
</tbody>
</table>

| 55) Childhood asthma control test: Parent to answer |
55a) During the last 4 weeks, how many days did your child have any daytime asthma symptoms?
   - Not at all = 5
   - 1-3 days = 4
   - 4-10 days = 3
   - 11-18 days = 2
   - 19-24 days = 1
   - Everyday = 0

55b) During the last 4 weeks, how many days did your child wheeze during the day because of asthma?
   - Not at all = 5
   - 1-3 days = 4
   - 4-10 days = 3
   - 11-18 days = 2
   - 19-24 days = 1
   - Everyday = 0

55c) During the last 4 weeks, how many days did your child wake up during the night because of asthma?
   - Not at all = 5
   - 1-3 days = 4
   - 4-10 days = 3
   - 11-18 days = 2
   - 19-24 days = 1
   - Everyday = 0

56) Adverse events - please give details below:

Have any adverse events been noted since the last visit? [ ]

<table>
<thead>
<tr>
<th>Sign or symptom of ADE</th>
<th>Date of onset</th>
<th>Outcome</th>
<th>Date of resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R = Resolved</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR = Not resolved</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>S = Resolved with sequelae</td>
<td></td>
</tr>
</tbody>
</table>

57) Additional comments noted at final follow-up visit 3 (including details of sequelae if appropriate).
   If all satisfactory, administer patient acceptiabilty questionnaire regarding the intervention devices.

Does patient use spacer? [ ]
   If spacer not used, please specify why: [ ]

58) This is the patient’s last study visit - the investigators may contact the participant’s GP to discuss results or recommend changes to treatment. Does participant consent to this?

Has consent been obtained to allow us to contact the participant’s GP? [ ]
Appendix H: Final questionnaire

FINAL QUESTIONNAIRE  
RN: _____

The following are for statistical purposes. Please complete the following questions. If you do not wish to answer, please write N/A next to the question. Thank you.

1) What is your main occupation?

2) What income bracket does your household income fall under?
   - Less than $20,000
   - Less than $40,000
   - Less than $60,000
   - Less than $80,000
   - Less than $100,000
   - Less than $150,000
   - $150,000 or more

3) What is the highest educational qualification of the primary caregiver?
   - None
   - Secondary school qualification
   - Tertiary qualification
   - Post-graduate

4) How many people usually live at your household?

5) Who looks after the child’s asthma (health care professional)?
   - Asthma nurse
   - Asthma specialist
   - GP
   - No follow-up
   - Other: ______________________

6) Do you feel you can discuss concerns with the health professional who looks after the child’s asthma? Yes / No

7) Does the child complain of, or have, any side effects from their medications? Yes / No

8) Have you ever delayed or avoided picking up medications due to cost? Yes / No

9) Have you ever delayed or avoided seeing the doctor due to cost? Yes / No

10) Is your doctor easy to access? Yes / No

11) Is your local pharmacy easy to access? Yes / No

12) Is there any who ever smokes around the child? YES / NO
If Yes – please tick who of the following are smokers:

☐ Mother of the child  ☐ Father of the child  ☐ Other household member (state relationship)

13) Which statement below best describes your family?

☐ Sole parent – Divorced / separated / widowed / single
☐ Married
☐ De facto
☐ Extended whānau

14) Do you have any other people that help you look after your child?  Yes / No
Appendix I: Modified VARK

Randomisation number: _______

VARK
How Do I Learn Best?
Choose the answer which best explains your preference and circle the letter(s) next to it.
Please circle more than one if a single answer does not match your perception.
Leave blank any question that does not apply.

1. You like internet websites that have:
   a) things I can click on and do.
   b) music, chat and sounds.
   c) interesting information that I can read.
   d) interesting pictures and patterns.

2. You are not sure whether a word should be spelled ‘colour’ or ‘color’. You would:
   a) try and see the words in my mind and choose by how they look.
   b) hear them in my mind or out loud.
   c) find them in the dictionary.
   d) write both words on paper and choose one.

3. You want to plan a surprise birthday party for a friend. You would:
   a) invite friends and just let it happen.
   b) imagine the party happening.
   c) write out lists of what to do for the party.
   d) talk about it with your friends

4. You are going to make a special present for your family. You would:
   a) make something you have made before.
   b) talk about different ideas with my friends.
   c) look for ideas in books.
   d) find written instructions to make it.
5. You are going on a holiday with your family. How would you tell your friends what you will do on holiday? Would you:
   a) describe the things that you will do on holiday
   b) show them the map of where you are going and pictures about it.
   c) start practising the things that you may be doing on holiday (e.g., swimming)
   d) show them a list of things that you will be doing on holiday

6. You are about to buy a new toy or camera for yourself. How would you choose which one to buy? Would you
   a) try playing with it first.
   b) find out more by reading about it in a book.
   c) buy it as long as it looks good and is the latest design
   d) listen to what your friends say about it

7. Remember when you learned how to play a new computer or board game. You learned best by:
   a) watching others play it first.
   b) listening to somebody telling you how to play.
   c) looking at the pictures in the instructions.
   d) reading instructions.

8. Your teacher asks you to do a project at school after watching a school play. Would you prefer to:
   a) write about the play.
   b) act out a scene from the play.
   c) draw a picture about something that happened in the play.
   d) read a speech from the play.

9. You are need to help put a puzzle together. You would:
   a) read the instructions that come with it.
   b) phone a friend and ask how to do it.
   c) unpack the box and start putting the pieces together.
   d) follow the pictures that show how it is done.
10. You need to tell your friend how to get to your house. You would:
   a) walk with them to your house.
   b) draw a map.
   c) write down the directions.
   d) tell them the directions.

11. When you are sick you go and see the doctor. Do you prefer doctors that:
   a) show you a picture of what is wrong.
   b) give you a book to read that tells you what is wrong
   c) tell you what is wrong.
   d) show you what is wrong using a plastic model that you can play with.

12. A new movie is showing but you are not sure if it is good or not. How do you choose whether to go or not?
   a) you hear friends talk about it.
   b) you read what others say about it in books /magazines.
   c) you see a preview (trailer) of it.
   d) you go if it is similar to others you have liked.

13. Do you prefer a teacher who uses:
   a) show and tell and doing lots of things hands on (where you can touch and feel)
   b) class discussions, and talking about things in class.
   c) books and handouts / worksheets.
   d) pictures and diagrams

14. You are learning to take photos with a camera. You would like to have:
   a) examples of good and bad pictures and how to improve them.
   b) clear written instructions.
   c) a chance to ask questions and talk with your friends about it.
   d) pictures showing the camera and how to use it.
15. Your teacher wants to give you some feedback or let you know how you did in a project you did in class. Do you like:

   a) a teacher who uses examples of what you have done well.
   b) a teacher that talks about it with you.
   c) a teacher that writes comments on your project.
   d) a teacher that draws pictures on your project

16. You have to stand up and give a talk to your class. You would:

   a) draw pictures to help explain my ideas.
   b) practice what to say again and again.
   c) write out my speech and read it again and again.
   d) act it out like a play
Appendix J: Validation protocol for SmartTrack device

Device number: ________ Medication / strength: ____________ (Assign correct device type to device)

Date: ____/____/____

- Visual appearance ok?
- How many bars on the battery sign on the LED screen? 1 2 3 4
- Screws easy to place in & remove? MDI install: _______ SCREW in device. Assign device to ‘patient’
- Actuate 2 puffs: _______ _______
- Wait 10 seconds. Actuate 1 puff: _______
- Preview and UPLOAD data. How many bars does it have on the battery sign on the RRA? 1 2 3 4 5
- Scores ______ puffs / 3 puffs

RESET, assign to ‘patient’ & set reminder (for 2 puffs twice daily) to occur within the next 5 minutes
- Ensure mode is set to AUDIO/VISUAL under “Set reminders” tab. Time of set reminder: ______
- Did reminder sound on time?
- Record sound of reminder (eg Horse / Beep): __________________________
- Actuate 1 puff: _______ Wait for reminder to sound again.
- Does reminder continue after 1 puff is actuated?
- Actuate a second puff: _______
- Wait 3 minutes. Does reminder stop after two puffs are actuated?
- Dose dumping – actuate 5 puffs. Start time: _______ End time: _______
- Preview and UPLOAD data Scores ______ puffs / 7 puffs

RESET and set reminders for 2 puffs TWICE DAILY to occur in the next 5 minutes
- Ensure mode is set to AUDIO/VISUAL. Time of set reminder: ______
- Did reminder sound on time?
- Record sound of reminder (eg Horse / Beep): __________________________
- Actuate 2 puffs: _______ _______
- Wait 3 minutes. Does reminder stop after two puffs are actuated?
- Actuate 2 puffs: _______ _______ _______ Wait 10 seconds.
- Dose dumping – actuate 5 puffs. Start time: _______ End time: _______
- Preview and UPLOAD data Scores ______ puffs / 9 puffs

Set Smart Track to COVERT mode (under “Set reminders” tab)
- Check screen does not turn on when buttons are pressed
- Actuate 2 puffs: _______ _______ _______
- Wait 10 seconds, then actuate 1 puff: _______
- Wait 10 seconds
- Dose dumping – actuate 5 puffs. Start time: _______ End time: _______
- MDI remove: OUT __________
- Preview and UPLOAD. Export to Excel & write device PASS or FAIL on spreadsheet. Save under Validation.
- Turn OFF reminders at end of testing. Keep under COVERT mode for storage. Scores ______ puffs / 8 puffs

If problems are identified with inaccurate dose dumping recording, repeat a series of 2x further sets of 5 puffs:
- Dose dumping – actuate 5 puffs. Start time: _______ End time: _______
- Dose dumping – actuate 5 puffs. Start time: _______ End time: _______

- PASS (100% detection) or - FAIL
Appendix K: Re-validation protocol for SmartTrack device – Reminder group

Device number: ______ Medication / strength: ____________ Visit no: __________ Randomised number: ______

Date: ___/___/___

Please re-validate the device BEFORE previewing or uploading the device. Do the following ASAP after collection from the patient:

- Check is the visual appearance ok? How many bars on the battery on the LED screen? 1 2 3 4
- Leave inhaler in the device, and exchange for a full inhaler if empty. If inhaler not present, SCRBN: In next inhaler (this will need to be back at office then).
- Check LED screen is fully functional – clock and time of dose “last taken”. Press the buttons. Tick if ok.
- Wait for the next reminder to sound – which is next one that would have been due for the patient. Does reminder sound on time? Time of reminder: ______
- Record sound of reminder [e.g. Horse / Beeper]: ______________________
- Actuate 1 puff: ______________________

If patient was on ONE puff:
- Wait 5 minutes. Does reminder stop after the puff is actuated?

If patient was on TWO puffs, wait for reminder to sound again.
- Does reminder continue after 1 puff is actuated?
- Actuate a second puff: __________
- Wait 3 minutes. Does reminder stop after two puffs are actuated?
- Now actuate 5 puffs (dose dump). Start time: __________ End time: __________

Wait some time – then:
- Wait 10 seconds. Actuate 1 puff: __________ End time: __________
- Dose dumping – actuate 5 puffs. Start time: __________ End time: __________
- Wait 10 seconds. Actuate 1 puff: __________

When back at office:
- Preview and UPLOAD data. How many bars does it have on the battery sign on the BRA? 1 2 3 4 5
- Annotate on the UPLOAD version of the Excel spreadsheet the time and date that the device was collected from the patient so that we can differentiate our re-validation from real patient data.
- If dose dumps have failed, repeat 5 puffs: Start time: __________ End time: __________
- If failed again, repeat 5 puffs: Start time: __________ End time: __________

☐ PASS or ☐ FAIL

Annotate “PASS” or “FAIL” on the Upload version of the Excel Spreadsheet

Record failures in the “Failing devices – devices failing revalidation” spreadsheet
Appendix L: Re-validation protocol for SmartTrack device – Control group

Device number: ___________ Medication / strength: ___________ Visit no.: ___________ Randomised number: ___________

Date: __/__/___

Please re-validate the device BEFORE previewing or uploading the device. Do the following ASAP after collection from the patient:

☐ Check is the visual appearance ok?
☐ Leave inhaler in the device, and exchange for a fuller canister if empty. If inhaler not present, check the test inhaler (this will need to be back at office then).
☐ Check LED screen does not respond when buttons are pressed on the inhaler. Tick if ok.
☐ Actuate 2 puffs: ___________ ___________

☐ Wait 10 seconds. Dose dumping – actuate 3 puffs. Start time: ___________ End time: ___________
☐ Wait 10 seconds. Actuate 2 puffs: ___________ ___________

☐ Wait 10 seconds. Actuate 2 puffs: ___________ ___________
☐ Dose dumping – actuate 5 puffs. Start time: ___________ End time: ___________
☐ Wait 10 seconds. Actuate 1 puff: ___________

When back in office:
☐ Preview and UPLOAD data. How many bars does it have on the battery sign on the PPA? 1 2 3 4 5
☐ Annotate on the UPLOADED version of the excel spreadsheet the time and date that the device was collected from the patient so that we can differentiate our re-validation from real patient data.

☐ If dose dumps have failed, repeat 3 puffs:
Start time: ___________ End time: ___________

☐ If failed again, repeat 5 puffs:
Start time: ___________ End time: ___________

☐ PASS or ☐ FAIL

Annotate “PASS” or “FAIL” on the Upload version of the Excel Spreadsheet

Record failures in the “Failing devices – devices failing revalidation” spreadsheet
References

57. Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: how unintentional is it really? BMC Health Serv Res. 2012;12:98-.


82. Frieden TR, Sbarbaro JA. Promoting adherence to treatment for tuberculosis: the importance of direct observation. World Hosp Health Serv. 2007;43:30-3.


284


