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Integrating Digital Inhalers into Clinical Care of Patients with Asthma and Chronic Obstructive Pulmonary Disease

[*]Roy A Pleasants, PharmD Division of Pulmonary Diseases and Critical Care Medicine, University of North Carolina, Chapel Hill, NC USA; pleas005@email.unc.edu

Amy HY Chan, BPharm(Hons), PhD Faculty of Medical and Health Sciences, University of Auckland; a.chan@auckland.ac.nz

Giselle Mosnaim, MD, MS, NorthShore University Health System, Clinical Associate Professor at the University of Chicago Pritzker School of Medicine; gmosnaim@northshore.org

Richard W.Costello, MD Royal College of Surgeons Ireland, 123 St Stephen's Green, Dublin 2, D02 YN77, Ireland; rcostello@rcsi.ie

Rajiv Dhand, MD; Division of Pulmonary and Critical Care Medicine, University of Tennessee Graduate School of Medicine, Knoxville, TN USA; rdhand@utmck.edu

Stephen A. Schworer, MD, PhD Division of Rheumatology, Allergy, and Immunology, Department of Medicine, University of North Carolina Chapel Hill, Chapel Hill, NC USA; saschworer@unc.edu

Rajan Merchant, MD Woodland Clinic Medical Group, Dignity Health Medical Foundation, CommonSpirit Health Research Institute, CommonSpirit Health Dignity Health, Woodland Clinic, 632 W Gibson Rd, Woodland, CA USA; rajan.merchant@commonspirit.org

Stephen L. Tilley, MD Division of Pulmonary Diseases and Critical Care Medicine, University of North Carolina Chapel Hill, Chapel Hill, NC USA; stephen_tilley@med.unc.edu

[*]Corresponding author (7202 Marsico Hall, 125 Mason Farm Rd, University of North Carolina at Chapel Hill, NC USA 27599, pleas005@email.unc.edu)

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Abstract

Modernizing inhaled medications through digital technology can help address persistent problems of non-adherence and poor inhaler technique in patients with obstructive lung diseases. With a growing body of supportive clinical studies, advances in digital inhaler sensors and platforms, greater support from payers and healthcare organizations, significant growth with these technologies is expected. While all digital (smart) inhalers record adherence, these are distinguished by their compatibility with commercial inhalers, capabilities to guide inhaler technique, use of patient-reported outcomes, and user-friendliness for both the healthcare professional (HCP) and patient. Due to the complexity and novelty of employing digital inhalers, collaboration with multiple entities within health systems is necessary and a well-planned integration is needed. For HCPs and patients, cybersecurity and privacy are critical, it will require review by each healthcare organization. In the US, some payers reimburse for remote monitoring using digital inhalers, but reimbursement is currently unavailable in other countries. There are several models for remote patient care, as employing an active, ongoing digital interface between the HCP and patient or they may choose to only review data at clinical encounters. Personalization of therapies and feedback are key to success. While digital inhaler malfunction uncommonly occurs, patient attrition over a year is significant. Some patients will be challenged to use digital platforms or have the necessary technology. Additional research is needed to address cost-effectiveness, in vivo accuracy of inspiratory measurement capable devices, ability to teach inhaler technique, their application for monitoring lung function, and lastly real-world adoption and implementation in routine clinical practice.

Introduction

Digital health is rapidly growing, including intensive care telemedicine, virtual outpatient encounters, and remote monitoring using digital solutions. Digital technologies are applied widely for cardiac diseases[1,2] and diabetes mellitus[3], but used infrequently for respiratory diseases, with the exception of obstructive sleep apnea.[4] Many commercial inhalers can be converted to 'smart' or 'digital' inhalers through attachable ('snap-on') or embedded electromechanical sensors to record, store and transmit patient usage.[5] The incorporation of digital inhalers into routine clinical practice is a paradigm shift in obstructive lung diseases management, especially considering the number of potential patients.

The rationale for adopting digital inhalers are ongoing medication non-adherence[6-8] and suboptimal inhaler technique.[9,10] Among patients with asthma and chronic obstructive pulmonary disease (COPD), daily use of controllers approaches 50% of prescribed doses[6] and inhaler technique is similarly sub-optimal[9]; each is associated with poor patient outcomes as inadequate control and more acute care visits.[9-12] Patients and healthcare professionals (HCP) often over-estimate medication adherence, leading to unnecessary testing and treatments.[13-16] Similarly, improper inhaler technique is inconsistently addressed during office visits[17,18] and if taught, technique wanes[19] and patients change devices.

Current circumstances favoring smart inhalers include widespread use of technology by patients, payer support,[20,21] policy organizations recognizing their importance,[22,23] widespread use of quality metrics, and expansion of telehealth. Digital inhaler technology is projected to have a worldwide market in the billions(USD) by 2030.[24]

Herein, we discuss integrating smart inhalers into patient care. We refer readers to extensive reviews on the scientific evidence for digital inhalers in asthma and COPD.[5,25-28] To provide a proper background, we present the regulatory process to bring these to the market, and a understanding of the digital inhaler health platform, the devices and functions. For the HCP, we address device and patient selection, legal and regulatory standards, cybersecurity, logistics of implementation and use, and financial considerations. From the patient perspective, we discuss privacy, costs, HCP-patient interaction, as well as functionality, acceptability and usability of smart inhalers and platforms.

Methods

Search Strategy

We searched Ovid MEDLINE, EMBASE, CrossRef, and Google Scholar for English-language publications of randomized controlled trials, systematic reviews, and guidelines with Medical Subject Headings for medication adherence, measurement, electronics, and lung disease, and terms related to ‘‘electronic monitoring devices,’’ ‘‘digital inhalers,’’ “smart inhalers”, ‘‘electronic medication monitors,’’ and ‘‘adherence monitoring’’ from January 1, 2010, to July 1, 2022. Additional searches were done employing US Food and Drug Administration (FDA), European Medicines Authority (EMA) websites concerning regulations and policies on digital or smart inhalers. Reimbursement policies were searched on the US Committee on Medicare and Medicaid Services (CMS) website. Clinical studies were included if digital inhalers and related mobile applications were used as part of clinical monitoring intervention and had the primary aim of improving maintenance medication adherence and/or reducing reliever use and were conducted in patients with asthma and/or COPD. Clinical studies were excluded if they did not report results using Consolidated Standards of Reporting Trials (CONSORT) criteria or similar

standardized reporting methods or had follow-up periods less than 12 weeks. Studies were also identified through a manual search of the reference lists of the literature and included input from contributing authors.

Digital Inhalers and Platforms

Market Approval

In many countries, attachable digital inhaler sensors must meet regulatory standards for medical devices (510K in USA), and if the sensing platform is built directly into the inhaler (combination digital inhaler), drug and device regulations apply. However, regulations do not exist in all countries, and in some, medical device regulations are in nascent stages. In addition to device approval, associated software must go through regulatory review. In the US, the Digital Health Center of Excellence is part of the FDA Center for Devices and Radiological Health, providing regulatory advice and support to the FDA regulatory review of these technologies.[29,30] The regulatory process is different between software used for an interface with digital inhaler platforms versus stand-alone smartphone health applications (Apps).[31]

The US FDA and EMA provide guidance on attachable digital inhaler devices as well as combination digital inhalers.[32,33] In Europe, software specifically developed for disease diagnosis or treatment falls under the medical device directive.[34] The US FDA provides specific guidance for premarket submissions of software combined/contained in medical devices.[29] Attachable sensors must demonstrate device safety including not interfering with inhaler operation, medication delivery, or obstruct the dose counter or label but do not need to prove therapeutic efficacy.[34] The only human study required for attachable sensors is a rudimentary usability study.[35]

Built-in and attachable electronic monitoring devices for digital inhalers are considered low risk by the US FDA. Digihaler® [36-38] was approved as a New Drug Application and device through the Center for Devices and Radiologic Health, while other federal agencies were involved in the review process including the mobile App, cybersecurity, and patient-facing materials.[27,33]

Platform

The digital inhaler platform **(Figure 1**), also referred to as digital health solution, typically consists of one or more digital inhalers for the patient, a dedicated mobile App (usually smartphone), cloud server, and dashboards for the patient and HCP. After receiving the sensor(s), the patient downloads the dedicated App, and typically pairs the inhaler with their smartphone. Synchronizing (sync) the device with the smartphone App is best done with supervision so troubleshooting can occur, although one device (FindAirOne®)[39] automatically syncs (**Table 1).** One study reported 17% of COPD patients were unsuccessful in full activation of the device and App in the first 30 days.[40]

Once downloaded, the dedicated App prompts the patient to consent to the manufacturer's Privacy Policy and User Agreement. The sensors must be in proximity (<20 meters) of their smartphone to transmit data through the Bluetooth® sensor. To use all functions, patients typically provide demographics, telephone number, email address, and inhaled medication, dose, desired dosing alert times and how and whom to share data. Encrypted inhaler data is transmitted to a secure cloud server (eg Microsoft Azure), and then to the HCP's dashboard portal. Patients may choose to upload their data through their electronic health records (EHR) portal to submit to their HCP.

Devices

Many commercial prescription inhalers can be digitalized with attachable sensors (Propeller Health®, Hailie®, Respiro®, Enerzair®, Capmedic®, FindairOne®)[39,41-45] or built-in sensors (Digihaler®, Amiko MX001®).[36-38,46] **Table 1** provides an overview of sensor functions for most digital inhalers available in the US and Europe. All can monitor adherence by time stamping actuations. Some pressurized metered dose inhaler (pMDI) sensors have capacity to detect shaking (Hailie®, Capmedic®), pMDI upright orientation (Hailie®, Capmedic®) and/or measure inspiratory flows to guide proper inhalation (Respiro®, Digihaler®, Hailie®). Using pMDIs and dry powder inhalers (DPIs), the ability to measure inspiratory flows is termed inspiratory measurement capable (IC).

While there are commonalities among digital inhaler platform functions and capabilities, there are clear differences **(Table 1).** For some, inhaler sensors illuminate to show battery status and when an actuation occurs. Audible or text alerts can be used for scheduled dosing reminders. Depending on the manufacturer's platform, the App can assist with disease management through patient entry of patient reported outcomes (PROs), general respiratory status, receive local air quality messages, receive feedback from the App related to adherence and technique, and alert messages to contact the HCP. Overall, these devise perform well in the majority of patients and for intended uses; additional clinical use will provide further insights.

For drug-device combinations, factors as sensor user-life and medication user-life after package removal are relevant. For the current combination products in the US, Airduo Digihaler®[37], Armonair Digihaler®[38] and Proair Digihaler®[36] recommended user-life are 30 days, 45 days, and one year, respectively. Attachable sensor user-life is based upon battery life (~

1 year). Such factors need consideration by the HCP and patient in terms of obtaining inhaler replacements and costs of repeat prescriptions.

The accuracy, reliability and durability of digital inhalers are critical to use. Electromechanical sensors detect inhaler functions through sound, pressure, temperature, and/or gravitational (accelerometer) changes. Published data are sometimes available on the accuracy of measuring inspiratory flows with these devices. IC-digital inhalers (INCA® - not commercially available, Respiro®, Digihaler®) report a strong correlation (>90%) between flows – peak inspiratory flow (PIF) and inhaled volume (Vin) measured by the digital inhalers – and in vitro inspiratory flow recorders.[47-51] The Digihaler® has validated inspiratory flow accuracy in patients.[47] In terms of actuation recording reliability, studies report accurate recording,[47-50] with only minor issues related to the precise time stamping.[52] The durability of these devices is less well-studied. A study among children with asthma found about 48% of snap-on devices were damaged or lost over 1 year.[53]

Privacy, Cybersecurity, Ethical and Legal Considerations for the HCP and Patient

Sharing sensitive personal and health data on mobile platforms as smartphones and the internet are important concerns.[54-57] Transfer and management of health data poses ethical issues; for example, it is important to consider the role of the HCP in managing the patient when their data shows a drop in adherence and /or change in asthma control, while also respecting patient privacy, autonomy and fostering their ability to self-manage their asthma. The American College of Physicians published a position paper on privacy and security when telehealth is employed; stating health information should be protected from improper access or use and should support an environment of trust while improving care.[56] Factors affecting an individual's willingness to

share personal health data include perceived benefits of use, user's motive, and sensitivity of the information.[57]

Digital inhaler device manufacturers meet privacy standards set forth by regulatory agencies.[29,32,33] The FDA works with other federal government agencies including the U.S. Department of Homeland Security, private industry, medical device manufacturers, health care organizations, and patients to increase security features. An updated draft of the FDA's 2014 cybersecurity guidance[58] is under review.[59] All transfer of data is encrypted and secured according to the US National Institute of Standards and Technology and Security Operations Center. In other countries, similar privacy regulations are in place. For example, the General Data Protection Regulation in the European Union governs data protection and privacy, and the European Economic Area and New Zealand updated their privacy laws with The Privacy Act 2020 that puts responsibilities on agencies and organizations for protecting personal information.

User Agreements e-signed by patients address data aggregation and de-identification for use in public health-related and/or scientific research purposes. These must meet HIPAA regulations, whether by a covered (eg. prescriber) or non-covered entity. The Privacy Policy explains how personal and health information is collected, stored, disclosed, and transferred when any element of the digital services is used. Parenteral/guardian consent is required for minors. Employing anonymous identifiers is one option to aid privacy and security.

Patient e-consents address liability concerns for the manufacturer; less clear is the liability to the HCP or their institution. Some HCPs might be reticent to accept the potential liability of real-time, remote access, and critical alerts that could require time-sensitive interventions. One approach to address legal concerns is to provide site-generated patient information describing how smart inhaler technology will be applied.

Healthcare organizations considering digital inhalers need to address cybersecurity early because an in-depth architectural review is usually required. The regulatory review that these devices undergo pre-market help address concerns, but healthcare organizations may have additional requirements including Security Assertion Markup Language (SAML) that authenticate web functions.

Financial Considerations for HCP's and Patients

Upfront costs include the effort and resources to incorporate the devices into the practice setting, and then staffing, training and infrastructure to maintain the program. To balance these costs, there are two principal ways that digital inhalers could be cost-effective: decreasing healthcare utilization (HCU) and generating revenue through a fee-for-service model. Not reported is whether patients are willing to bear costs of digital inhalers. One paper reported the annual costs of attachable devices in 2018 to be around $150 USD per patient,[53] but today costs exceed $200 USD in the US. FindairOne® (Europe) reports a direct-to-consumer cost of €59 per device.[39] With most attachable sensors, the HCP can contract with the manufacturer or distributor to receive the sensor and access the digital health solution functions. For a digital drug combination, the cost is higher than the non-digitalized product (Proair Digihaler® ~ $180, Proair Respiclick® ~ $60).[60] Access to the Digihaler® dashboard accompanies the product purchase, whereas with attachable sensors the HCP's dashboard is included in the platform's cost.

In a modeled cost-effectiveness analysis from the UK, use of smart inhalers in children with asthma led to savings of 96£/year/patient.[61] An exploratory study using the INCA device with fluticasone propionate/salmeterol in COPD patients, projected cost-effectiveness was greatest in patients who exhibited irregular use and good inhaler technique (savings

845£ /year/patient) compared to patients with regular use and good inhaler technique.[62] Costs also increased in patients with frequent inhaler technique errors, even with regular or irregular use, pointing to technique as a factor in cost-effectiveness. Clearly, more data is needed for cost-reduction effects.

In the US, Remote Physiologic Monitoring (RPM) billing codes were approved by Medicare for digital inhalers in 2019.[63-65] (**Table 2**). These are essentially the same codes used with remote digital monitoring of blood glucose for diabetes. Reimbursements vary according to when and what services are provided (~$40 - $65 per encounter up to once every 30 days).[64] Measures can not be recorded manually, rather must be digitally collected. For RPM coverage, a physiologic measure is required, as with IC-digital inhalers. In 2021, Medicare approved additional Remote Therapeutic Monitoring (RTM),[65] which permits billing for adherence monitoring; the fees are comparable (**Table 3**). Another possible means for reimbursement is through billing for inhaler teaching using IC-digital inhalers. Notably, in the US not all insurers reimburse for RPM, RTM or inhaler teaching.

In countries outside of the US, there are currently limited reimbursement schemes available to cover the costs of medical devices and costs are being met by patients themselves. In the UK, there is an active research/implementation program ongoing at the severe asthma centers to gain approval by the National Health Service. Such approval will be based on clinical validation with a commercial value.

For payers, costs associated with digital inhalers are based on HCU, drug costs, and meeting quality benchmarks. These costs are expected to be offset by savings from reduced HCU from acute care visits. Payers may also require documentation of digital data on controller adherence and inhalation quality, and HCP counseling to address potentially modifiable barriers

before approval of costly biologic therapies. US insurer payments for patient care are partially dependent on meeting medication quality metrics. For asthma, this is a medication possession ratio (>0.8) and use of inhaled corticosteroids,[66] the former readily collected digitally. For COPD, the medication quality metrics are a prescription for a long-acting bronchodilator and use of systemic corticosteroids and inhaled rescue medications for excerbations,[66] thus would not be directly impacted by smart inhalers. For US hospitals, if the number of 30-day readmissions for COPD exacerbations exceed benchmarks, this may result in a 1-2% penalty on all Medicare payments.[67] Active and frequent remote monitoring with digital inhalers needs investigation in post-hospital COPD care. Based on the only post-hospital study in COPD using smart inhalers, we learned that giving the patient a free controller, educating them, and discharging from the hospital with no short-term follow-up (passive monitoring) results in poor adherence and inhaler technique.[68]

Digital Interface Between HCP and the Patient

Digital inhaler use impacts the patient, the HCP, and patient-HCP interactions. From the HCP perspective, the greatest value of digital inhalers will be understanding the patient's behavior and adapting treatments thereof. For the patient, they will be better informed of their inhaler use and hopefully more engaged in managing their disease .

Patient interface with the digital platform consists of the inhaler with sensors, dedicated smartphone App, and interface with the HCP. The patient can review inhaler use and self-reported PROs on their dashboard. Patients will want to know how a digital inhaler benefits them, what data will be collected, the costs, how will this information be used by their HCP, who will have access, what happens if a sensor is lost, and if personal or health data will be identifiable, deidentified, or coded.

For HCPs, the dashboard portal permits them to view lists of enrolled patients, provide feedback to patients at encounters, review and generate reports for documentation and billing. At present, there is little experience with EHR 'builds' with this technology, and reports may have to be manually scanned, similar to spirograms. With some platforms, alerts to HCPs about patient inhaler use can be pre-defined, such as excessive short-acting β-2 agonist (SABA) use or declining controller adherence. One study reported that a 100% increase in SABA use was a marker of an impending exacerbation.[69] The App settings should be chosen based on agreed upon goals, recognizing the implications of alert fatigue and medicolegal liability.

For IC-digital inhalers, it should be recognized that relevant clinical evidence is based on proper inhaler technique (eg optimal PIF 30-60 L/min for pMDIs and $\geq$ 60L/min for most DPIs).[70] Using the Capmedic® and Digihaler® devices, patients can receive immediate feedback on technique, an important feature.

Overall, patients and HCPs have favorable views of smart inhaler platforms.[69,73-78] Among 35 patients with COPD using Propeller Health sensors for their SABA, 74.1% reported being very satisfied with the inhaler sensor and 80.8% rated them very convenient to use.[69] A study in adults with asthma found 79% were very satisfied with Propeller Health sensors.[69] Interviews of 18 persons with asthma indicated that Hailie® monitors were easy to use, reminders only occurred with missed doses and reminder alerts were musical.[75] These findings have been confirmed in more recent studies; a 2019 study in children with asthma reported that parents also were satisfied, including the ability to receive care remotely,[76] and a 2020 study found that children and their caregivers preferred digital inhalers easy to use and that required minimal effort.[77]

Clinical Use of Digital Inhalers

Most randomized studies of digital inhalers report greater controller adherence,[79-88] decreased SABA use,[73,79,80,83] lowered exacerbation risk[53,79] and improved PROs.[39,80,84] Conversely, others found no significant changes in PROs.[76,81,82,85,87] Studies were primarily done in specialty outpatient practices and enrolled at-risk patients.[5] A systematic review of monitoring asthma medication adherence found that those receiving a digital inhaler intervention had significantly better adherence than control.[89] In terms of asthma control, a small but not significant positive improvement favoring the intervention[89] – a surprising result considering better controller adherence. Adherence can improve with both active and passive monitoring by HCPs, but feedback to the patient in a timely and ongoing manner is best.[73,79,84,85,87] Digital inhaler studies reveal just how poor HCPs are judging patient's non-adherence, with many overestimating.[90]

Assisting Patients with Inhaler Technique

All digital inhalers detect doses administered too close together, but with the advent of smart inhalers that are IC and detect shaking and/or proper orientation of the pMDI, common critical technique errors are addressed. This is important as studies have shown HCPs do not have knowledge of proper inhaler technique, one systematic review reporting only 15% can correctly teach technique.[18] The Digihaler® DPI defines good inhalation as a PIF >45, acceptable PIF 30-45 and suboptimal PIF <30L/min.[36-38] The Capmedic® device for pMDIs provides visual and audible patient feedback including proper inhalation duration (2-4 seconds), breath-hold time, shaking and upright orientation.[45,91] Published studies employing digital inhalers show that patient technique is poor[68,85,92] and these devices can improve technique.[68,85,92] One study found technique improved after intensive teaching without feedback, and improved further with periodic patient feedback.[92] A study in 10 asthma patients using Capmedic® sensors

showed improved inhaler technique compared to audiovisual teaching.[91] Proair Digihaler® was shown to improve and maintain good inhaler technique through App and HCP feedback.[92]

Potential Ambulatory Lung Function Test

IC-digital inhalers were developed to assist with inhaler technique, but it may turn out they could serve as an ambulatory lung function measurement. By optimizing inhaler technique through a full exhalation achieving slow vital capacity followed by a fast or slow full inhalation, Vin and PIF are measured. While expiratory flows are the standard in diagnosing and monitoring obstructive lung diseases, studies using spirometry or an inspiratory device (InCheckDial®) show PIF [93-95] and Vin[95-97] are bronchodilator responsive and change with clinical worsening in patients with asthma and COPD.[94,98] Using Proair Digihaler®, studies showed mean Vin and PIF decreased during outpatient exacerbations, the former to a greater extent (asthma 18% vs 12%, COPD 16% vs 9%, respectively).[71,72] The role of inspiratory flows in obstructive lung disease needs revisiting.

Bringing Digital Inhalers to the Patient Care Setting

A number of considerations and steps are needed to integrate digital inhalers into patient care, particularly in healthcare systems. Table 4 highlights many of the pros and cons of applying digital inhalers to patient care. Perhaps the greatest benefit is the ability to personalize inhaler treatments based on patient resources and behaviors.

Initial steps to incorporate digital inhalers into patient care include identifying existing RPM infrastructure to build upon and deciding which platform is best suited for the HCPs and the target population(s). Financial feasibility, medicolegal considerations, information technology issues, cybersecurity, required staffing and workflow should all be addressed

collaboratively. Because this technology is new, a feasibility assessment and pilot project are likely needed. Scalability, data management and sustainability need early consideration.

Infrastructure

On the patient side of infrastructure is the smartphone, dedicated App, and the inhaler with sensors. Increasingly, smartphone use is common among adults even in low-middle income countries, and in the elderly.[100] Home internet facilitates some functions of the devices.

For the HCP, infrastructure is more complex and includes the dashboard portal, the resources and processes needed to integrate a digital inhaler platform into practice. Published experience with digital inhalers is in research settings, so staff time and resources needed in a clinic setting are not fully known – likely the first question the office clinician has. Staff time to teach the patient how to attach the sensor, download the App, consent, and sync the inhaler and smartphone is usually 20-30 minutes. Typically, only licensed HCPs can perform the remote monitoring independently. When employing RPM or RTM, clinical encounters $\geq$ 20 minutes are required for payment by US Medicare and can occur as often as monthly.[64,65] One study reported that with passive monitoring, physicians were notified by alerts on average by each patient 2 times over 12 months.[78]

Prescribing and Dispensing Digital Inhalers

Choosing a smart inhaler platform depends on the patient population and goals to improve care. If the goal is to improve controller adherence, then a platform compatible with a diverse range of inhalers is needed, as no single controller product would suit all patients' needs. Most clinical studies have used both digitalized controllers and SABA in each patient.[76,79-84] A digitalized SABA inhaler alone might be desired in patients where overuse is a marker for

uncontrolled disease, in line with global asthma guidelines. This sort of data might be suitable to artificial intelligence application. It may be convenient to prescribe a device dispensed through a pharmacy, rather than by contractual basis as required for attachable sensors.

Attachable inhaler sensors are medical devices that patients typically obtain through their HCP, but may do not require a prescription. The HCP could purchase them contractually, then directly dispense or have them mailed to the patient. Combination devices must be prescribed and obtained from a pharmacy. As platforms support patient initiation of device use[39], the impacts on HCP resourcing will likely be minimized, which will lend further support to implementation into routine practice.

Patient Selection

Table 5 shows patient types that might benefit from digital inhalers. It is well-known that HCP's ability to judge patient non-adherence is poor.[6] Patients with recent exacerbations and in need of expensive or costly interventions are among possible candidates.[5]

It is unclear what proportion of patients are candidates for digital inhalers as most published data is from trials.[5] Likely, smart inhalers will be most beneficial where costs are greatest, such as the poorly adherent and uncontrolled with frequent HCU[26], however there are limited studies exploring cost-effectiveness and identifying groups likely to benefit. About 50% of patients with asthma and COPD qualify based on nonadherence, but this is affected by many factors, including the recognition that not all patients need, want, or can afford daily treatment. The consequences of the non-adherent patient (intentional versus non-intentional non-adherence) should be considered[6,26], as personalization using digital inhaler data can better address patient behaviors, drug efficacy and safety.[101-104] Digital inhalers have the potential to bring benefits for

those intentionally non-adherent as well as those with unintentional non-adherence. For example, some digital inhalers can link with a patient self management App which can send the patient notifications to address or dispel myths or misplaced treatment beliefs, which may be driving intentional non-adherence. On the other hand, digital inhalers can provide audio-visual reminders to help with unintentional non-adherence.

Poor inhaler technique is as common as non-adherence.[9] Patients may see greater value when monitoring both inhaler technique and adherence.

Patient Monitoring

The strategy employed for remote monitoring should establish who 'owns' the data and expectations of both parties to manage and respond to digital inhaler data. Data collected and transmitted to the HCPs portal dashboard can be immediate, thus expectations should be set. While close monitoring may be desired such as immediate post-hospitalization, this may not be desired or possible for routine RPM. Some platforms generate messages for patients to contact their HCP with excess reliever use or worsening PROs recorded by the patient in the App. Use of a written action plan or informing patients to seek medical care as they would normally is a reasonable recommendation for most patients. Platforms that integrate action plans do not currently exist. In the future, digital inhalers might rely on the dispensing pharmacy to help monitor adherence and technique, and to provide prescription refills based on cloud access.

Smaller practices or solo clinicians may choose to have sensor data sent only directly to the patient and opt out of or subcontract the remote monitoring functions of the HCP's dashboard. The patient is directly responsible for review of alerts and contacting the HCP to determine care options as needed. Using this approach, the HCP may instruct the patient to bring

their digital inhaler and smartphone to clinic visits for data review directly, or HCPs may ask the patient to upload the digital inhaler data prior to the clinic visit using their EHR portal. Adherence and inhalation quality data may be reviewed together by the patient and HCP, along with PROs, and other measures of impairment and risk assessment during office visits.

An important decision is the duration of monitoring necessary to achieve clinical goals. Clinical studies using digital inhalers have been done over at least 12 weeks and as long as one year.[52,73,79-81,83-85,92,105] It is known that both adherence and inhaler technique decline over time.[6,9] A minimum of three months of monitoring is likely a starting point to establish adherence and any improvements in inhaler technique, as shown in one study.[106] Longer periods may be needed, such as assessing treatments.

Barriers to Implementing Digital Inhalers for the HCP and Patient

There is resistance to changing patterns of practice in medicine, even with well-established guidance. There are additional issues with digital inhalers: 1) acceptability by patients who may feel their autonomy and privacy are compromised, 2) uncertainty around clinical responsibility for reviewing and acting on these new large-scale continuous data streams, 3) lack of clarity over who will bear the cost, and 4) simply resources. Most perceived and actual barriers can be overcome by high-quality research demonstrating the efficacy and effectiveness of digital inhalers in improving inhaler use, disease monitoring, and ultimately health outcomes. Real-world experience is also critical to judging the role and impact of these devices.

Not all patients are eligible, want to enroll or persist with a digital inhaler. Digital inhalers are not an option if an attachable sensor is incompatible with their inhaler(s) or if they routinely rely on nebulized medications. Importantly, attrition to digital device use occurs, with

rates as high as 40% of patients in the first six months[78] and 55% at one year.[73] Reasons include device malfunction, loss of interest, intrusiveness, and worsening adherence.

Conclusion

Guiding proper adherence and inhaler technique using digital inhalers has great potential to maximize the response to inhaled drug therapies. Despite availability for over a decade and increasing supportive evidence of benefits to adherence and therapeutic outcomes, digital inhalers and associated health management platforms are still perceived as new to many HCP and organizations – thus the learning curve is steep. The ability to monitor appropriate inhaler use either remotely in real-time or at in-person visits yields an opportunity to improve inhalational drug delivery to patients suffering from airway diseases, particularly in this post-pandemic world where remote care delivery is more accepted. Available evidence indicates smart inhalers enhance key aspects of drug therapy management and can guide clinical care in patients with asthma and COPD. The ability of digital inhalers to improve technique and cost-effectiveness of these interventions requires further investigations relevant to policymakers, HCPs, and patients. While many factors influence the extent to which digital inhalers will be adopted, their potential to reduce morbidity and mortality from airway disease should motivate continued investigation and implementation into practice of these novel approaches.

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Table 1 Digital Inhalers and Capabilities

Sensors	**Hailie® (Adherium)**	**Respiro® (Amiko)**	**Capmedic® (Cognita)**	**Propeller Health (ResMed)**	**Digihaler® (Teva)**	**FindairOne ® (FindAir)**
Compatible devices[a]	pMDIs (most) DPIS (Diskus®, Ellipta®)	pMDIs (most), DPIs	pMDIs (most)	pMDIs (most), DPI (Diskus(R), Ellipta), Respimat®	Proprietary DPI	pMDIs (most), DPI(Ellipta®, Easyhaler®, Turbuhaler®)
Sensors	Snap-on	Snap-on and built-in[b]	Snap-on	Snap-on	Built-in	Snap on
Time stamping of actuations	Y	Y	Y	Y	Y	Y
Shaking for pMDIs	Y	Y	Y	N	NA	N
Measure inspiratory flows	Y[b]	Y[c]	Y[d]	N	Y	N
Inhaler and/or App reminder alerts	Y	Y	Y	Y	Y	Y
Automatic syncing with downloaded App	N	N	N	N	N	Y
Device User Life	Based on battery life, ~ 1 yr	Based on battery life, ~ 1 yr	Based on battery life, ~ 1 yr	Based on battery life, ~ 1 yr	Airduo® 30 days[c] Armonair 45 days[c] Proair® 1 yr[c]	Based on battery life ~ 1 year

[a] Refer to manufacturers for complete compatible inhaler products; [b] Selected devices, Amiko Respiro®, Adherium Hailie® for Symbicort pMDI, Ellipta®, and Ventolin®; [c] After removal from package; [d] Only reports inhalation duration feedback.
Abbreviations: DPI – dry powder inhaler; N – No; pMDI – pressurized metered dose inhaler; yr – year; Y - yes

Table 2 Remote Patient Monitoring (RPM) Billing Codes and Guidance for USA Medicare Patients

Must be an established patient-physician relationship for RPM services to be furnished
Patient consent to receive RPM services may be obtained at the time that RPM services are furnished
Auxiliary personnel may provide services described by CPT® codes 99453 and 99454 incident to the billing practitioner's services and under their supervision
Medical device supplied to a patient as part of RPM services must be a medical device as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act, that the device must be reliable and valid, and that the data must be electronically (i.e., automatically) collected and transmitted rather than self-reported
Physiologic measures required and must be recorded and transmitted electronically
Sixteen days of data each 30 days must be collected and transmitted to meet the requirements to bill CPT codes 99453 and 99454
Only physicians and non-physician practitioners who are eligible to furnish E/M services may bill RPM services
RPM services may be medically necessary for patients with acute conditions as well as patients with chronic conditions
For CPT codes 99457 and 99458, an "interactive communication" is a conversation that occurs in real-time and includes synchronous, two-way interactions that can be enhanced with video or other kinds of data
20-minutes of time required to bill for the services of CPT codes 99457 and 99458 can include time for furnishing care management services as well as for the required interactive communication

Abbreviations: CPT® - Codes for Procedural Terminology; ICD – International Classification of Diseases; E/M

Table 3 Remote Therapeutic Monitoring (RTM) Billing Codes and Guidance for USA Medicare Patients

RTM codes will be designated as ‘‘sometimes therapy’’ codes, which means that the services can be billed outside a therapy plan of care by a physician and certain non-physician practitioners, but only when appropriate.
RTM codes monitor: ○ Health conditions, including musculoskeletal system status, respiratory system status ○ Therapy (for example, medication) adherence, ○ Therapy (for example, medication) response, and as such, allow non physiologic data to be collected ○ RTM data can be patient-reported, as well as digitally uploaded while RPM requires that data be physiologic and be digitally uploaded ○ Device used must meet the FDA definition of a device as described in section 201(h) of the Federal Food, Drug and Cosmetic Act (FFDCA). • Remote Therapeutic Monitoring /Treatment Management Codes 98975, 98976, 98977, 98980, and 98981.

CPT® - Codes for Procedural Terminology

Table 4 Potential Benefits and Fallbacks of Digital Inhalers and Platforms

Benefits	**Fallbacks**
Able to personalize inhaler treatments to match actual patient resources and behaviors	Requires some level of training for end users to use the digital inhaler and associated platforms[104]
24/7 remote access to data on medication taking	Not all patients have adequate technology or ability to operate digital inhalers and smartphone Apps[40,100]
Generation of automatic records from digital dashboard of medication use for documentation and billing	Differences in compatibility with different inhalers among digital inhaler manufacturers[5]
Clinical studies currently support improved adherence in poorly adherent patients[79-88], decreased exacerbation risk[80,83] and reduced reliever use[8,74,88]	At present, minimal incorporation into electronic health records, making access across a health system limited
Possibility to provide granular information about inhaler technique in individuals, not possible with traditional inhalers[92] e.g. inhalation flow and duration, pMDI shaking[91]	May require replacement for attachable sensors annually or discarding built-in digital inhalers based on manufacturer's recommendations[5]
Opportunity to determine the impact of improper inhaler technique on outcomes in individuals and in populations	Variable impact on patient reported outcomes[40,76,80-82,85,87]
Potential to generate data that allows identification of patterns of inhaler use and prediction of ensuing exacerbation events[71,72]	Lack of adequate regulation to establish safety and efficacy in patients using digital inhalers in the short-term or long-term
Provides a more objective basis of inhaler use prior and after step-up therapies and expensive or risky interventions[54]	Sustainability of patient use of devices beyond 6 months not high
May empower patients to be more involved in self-care[104]	May be seen by some users as intrusive with concerns about data privacy and security
Potential to support other forms of remote care delivery as wearable sensors, spirometers, and oscillometers	May be costly upfront
	Variable payer coverage for digital inhalers and use
	Availability and accessibility to digital inhalers varies widely depending on country context

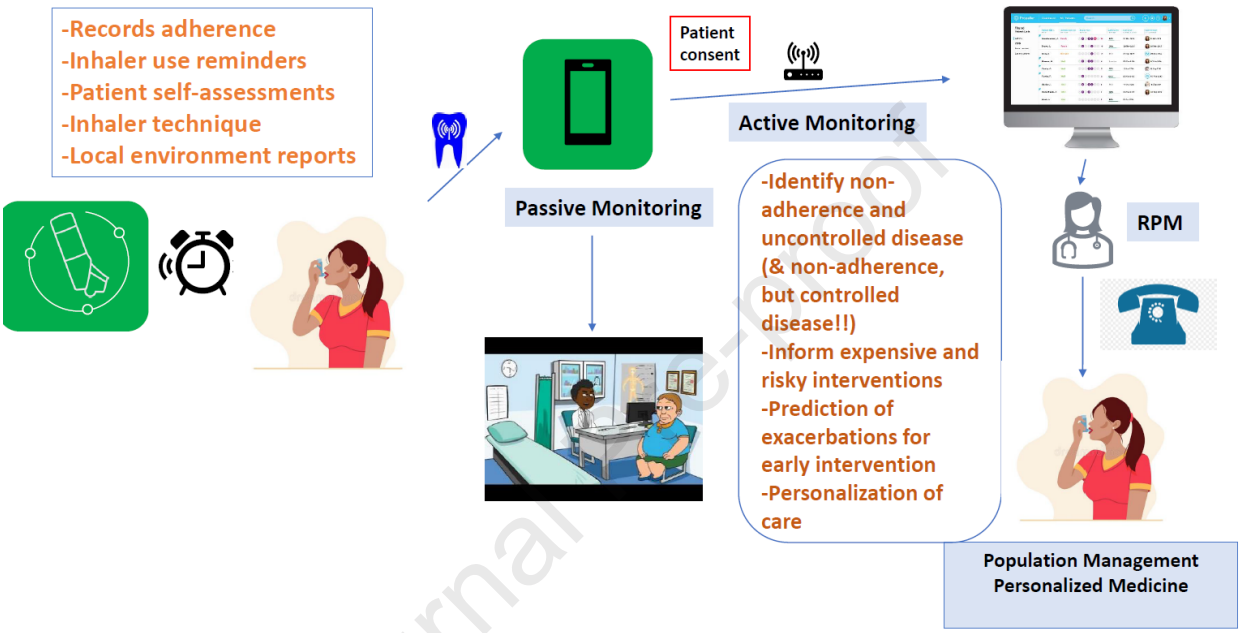
Abbreviations: pMDI – pressurized metered dose inhaler

Table 5 Potential Patient Types to Employ Digital Inhalers

Patients Using Maintenance Inhalers	**Patients Using Rescue Inhalers**
Newly prescribed inhalers	Suspected/known over-users of SABA
Evidence of medication non-adherence	Uncontrolled disease
Uncontrolled disease in patients using controllers	Being discharged from hospital for an exacerbation and not relying on nebulizers as the reliever
Establish adherence prior to initiating biologics or other costly and risky interventions	Suspected or demonstrated poor inhaler technique
Being discharged from hospital for an exacerbation	
Assess impact of biologics or other non-inhaler interventions	
Use of ICS/FOR for Maintenance and Reliever Therapy or as-needed ICS in asthma	
Suspected or demonstrated poor inhaler technique	

Abbreviations: FOR – formoterol; ICS – inhaled corticosteroid; SABA – short-acting β-2 agonist

Figure 1 Digital inhaler platform – Interfaces among patient, inhaler sensors, and healthcare provider



" **Integrating Digital Inhalers into Clinical Care of Patients with Asthma and Chronic Obstructive Pulmonary Disease"**
Pleasants RA et al.

Highlights

- Technologic advances, gaps in inhaler use, and payer reimbursement has led to greater interest in digital inhalers
- Attachable or built-in sensors, compatible with most inhalers, can record and transmit patient adherence and patient technique
- Implementing digital inhalers into patient care requires consideration of patient populations, cybersecurity, privacy, costs, and resources
- Digital inhalers facilitate healthcare provider-patient communication
- Due to the newness and complexity, a pilot clinical evaluation is advised