Improving the Transition to Biosimilars

The Influence of Communication Strategies, Companions and Patient Concerns

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Abstract

Biopharmaceuticals (biologics) have revolutionised the treatment of immune-mediated inflammatory diseases but created a significant financial burden for healthcare systems globally. Biologics are large molecule medicinal products that derive from living organisms. While patients are often transitioned from original biologics (bio-originators) to biosimilars to reduce cost and improve access, patient resistance and hesitancy have dampened their uptake. To date, it is unclear how to communicate the transition to ensure patients accept biosimilars. Patients are also frequently accompanied to consultations by companions who may influence patients' expectations and decisions. This thesis intends to understand how the transition to biosimilars can be improved. Specifically, it explores how communication strategies can increase patient acceptance of biosimilars and aims to determine and augment the involvement of companions in decisions about changing to biosimilars. Through this research, this thesis provides a rationale for using health psychology theory in future research on biosimilar acceptance.

The thesis comprises of two main sections. The first section provides insight into how communication can be improved to increase patient acceptance. A systematic review with a meta-analysis was conducted to explore 33 communication strategies used globally to inform patients about biosimilars. Patient willingness to transition was found to be the highest when receiving written and verbal information, and written information that only addressed a few key concerns. Patients were primarily notified about cost savings as a reason for the brand change. However, pharmacists and other providers were rarely upskilled prior to the transition. A cross-sectional study was conducted to identify pharmacists' readiness to educate patients before and during the early stages of the transition to biosimilar Amgevita in Aotearoa/New Zealand. The study highlighted low confidence in explaining testing and manufacturing, gaps in key knowledge, and concerns about not knowing enough to educate patients. While pharmacists require additional training and resources, they may also benefit from guidance in identifying patients who may need further reassurance or information. A correlational study was conducted to explore whether patients' characteristics are associated with concerns about taking biosimilars and safety expectations. Patients who were female, sought information online, preferred innovator drugs, and had stronger emotional responses to their condition had more negative perceptions.

The second section widens the focus to determine and augment companions' involvement in discussions about biosimilars. In a randomised controlled trial, patients with rheumatic diseases who have companions were randomly assigned to receive information about biosimilars alone or with their usual companion. Companions did not influence patients' hypothetical decisions to change to biosimilars or risk perceptions but did negatively impact understanding. Building on this, a pre-specified analysis was conducted to explore companions' concerns about biosimilars. While companions and patients had similar confidence in biosimilar use and expectations towards safety, efficacy, and side effects, companions reported some unique information needs. In the last randomised controlled trial, a community sample acting as patients or companions were randomised to receive information about biosimilars by a physician using patient-only or family-centred communication. Findings suggested that family-centred communication does not further improve patients' willingness to transition but can improve patient-provider-companion encounters. This study also showed that companions' behaviours during consultations, such as asking questions, impact patient understanding.

The research presented in this thesis is among the first to consider the application of health psychology theory and interventions to improve patient acceptance of biosimilars. In Chapter 9, it is concluded that health psychology research should be used to further understand possible mechanisms of patient resistance, and previously successful interventions should be translated to improve biosimilar acceptance. Future research in this area should further examine the interpersonal processes that occur between patients and companions during treatment deliberations and include experimental studies that explore the effects of communication in real-world transitions. The research in this thesis provides guidance on optimising communication strategies and the presence of companions, and may ultimately improve future transitions to biosimilars.

Preface

Dear reader,

It has been a privilege to pursue a PhD and a time in my life that I will always look back on fondly. Like most others, this experience came with challenges, including an unforeseeable global pandemic. However, I am grateful for the rollercoaster journey, which has helped shape me into the researcher and person I am now.

Three years ago, I naïvely thought improving patient acceptance of biosimilars would be relatively straightforward. However, as I progressed, particularly into the final year, I realised that my research had merely touched the surface of this field. Like most problems in health care, there is no definite answer or one way to solve a problem. However, we can be sure that many more unique challenges (or 'research opportunities') will arise as the development and production of biosimilars continue to evolve.

Research is truly a multidisciplinary practise. One challenge I had was becoming engrossed in other disciplines such as ethics and law and regulatory, pharmaceutical, and biomedical sciences and finding a nuanced way to draw on the multiple, relevant disciplines. Nevertheless, it also showed me that health psychology is at the heart of most problems in healthcare and that its theory is highly flexible and applicable to other disciplines. A complex problem, such as addressing patient hesitancy to transition to biosimilars, always requires a collaborative approach. The opportunity to share ideas and receive feedback from leading researchers were some of the learning opportunities I valued the most.

Research in biosimilar acceptance has grown substantially in the last three years. As I began reading in this area, there was scarce research and interest in exploring how to communicate the transition to patients, let alone involving companions in these conversations. The nocebo response was also only beginning to be highlighted as a key challenge in future biosimilar use. It has been a pleasure to see health psychology research become a frontrunner in driving solutions to improve biosimilar acceptance. However, we are only getting started.

I hope this thesis will contribute to building foundational knowledge that improves future transitions to biosimilars and ultimately helps patients and their companions.

C. Gasteiger, July 2022

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Lastly, I extend my gratitude to the reviewers for their feedback and careful reading of each manuscript, the journal editors for giving my research a 'home,' and the research community for their dedication to improving the acceptance of biosimilars. My sincere thanks to you all.

Table of Contents

List of Figures

List of Tables

Glossary

Bio-originator	An original biologic that has gained regulatory approval. Also known as an innovator, originator, or reference drug.
Biopharmaceutical	A complex, large molecule medicinal product that derives from living organisms. Known as a biologic.
Biosimilar	A biological product highly similar to an approved reference drug manufactured following patent expiry. Also known as a follow-on biologic.
European Medicines Agency	The European Medicines Agency (EMA) evaluates applications and monitors medical products for the European Union.
Food and Drug Administration	The Food and Drug Administration (FDA) is a federal agency in the United States of America responsible for protecting public health by regulating and monitoring medical products.
Generic	A traditional, small-molecule drug manufactured after patent expiry and is identical to the innovator drug.
Immunogenicity	The stimulation of an undesired immune response by a therapeutic protein, leading to the development of anti-drug antibodies (ADAs).
Indication Extrapolation	Approval of drug use to treat diseases that were not specifically evaluated during clinical trials.

Interchangeability	Drugs that are approved to be substituted for the reference product with the same expected clinical benefits and safety profile.
Medicines and Medical Devices Safety Authority	The Medicines and Medical Devices Safety Authority (Medsafe) are responsible for regulating therapeutic products in Aotearoa/New Zealand.
Microheterogeneity	The inherent variation in the chemical structure of biologics evident between batches of the same product.
Nocebo response	An adverse effect induced by negative expectations and not related to the active component of a pharmacological or non-pharmacological treatment.
Pharmaceutical Management Agency	The Pharmaceutical Management Agency (Pharmac) are responsible for deciding which pharmaceutical products will be subsidised for use in Aotearoa/New Zealand.
Substitution	Dispensing a different medicine than prescribed with the same therapeutic intent, such as a generic drug or biosimilar (e.g., pharmacist-led substitution).
Transition	The process of changing patients from one drug to another with the same therapeutic intent (e.g., from a bio-originator to a biosimilar). Often called switching.

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Chapter One: Topic Introduction and Thesis Overview

Introduction of Thesis Topic

Biopharmaceuticals (complex drugs that derive from living organisms) have revolutionised health care for patients with a broad spectrum of immune-mediated inflammatory diseases. However, access to biotherapeutics is severely restricted due to the significant associated costs (Putrik, Ramiro, Kvien, Sokka, Uhlig, et al., 2014). Biosimilars are readily being integrated into pharmaceutical markets to reduce the financial burden and improve access, but patient resistance and hesitancy are significant barriers to their uptake (Jacobs et al., 2016; Kovitwanichkanont et al., 2020; Mulcahy et al., 2018; Peyrin-Biroulet et al., 2017; Sullivan et al., 2017; van Overbeeke et al., 2017). Improving patient acceptance is crucial to avoid adverse outcomes such as the nocebo effect, discontinuation, and non-adherence, which off-set the cost saving potential of biosimilars (Müskens et al., 2020; Odinet et al., 2018; Straka et al., 2017; Tweehuysen, Huiskes, et al., 2018).

Researchers globally have recognised that effective communication is a key factor in improving patient acceptance of biosimilars (Cohen & McCabe, 2020; Kim, Alten, et al., 2020; Oskouei & Kusmierczyk, 2021; Smolen et al., 2021). For example, effectively communicating the transition to biosimilars during clinical encounters can help transfer confidence to patients and mitigate the development of negative perceptions (Colloca et al., 2019; Rezk & Pieper, 2017; Smolen et al., 2019). Yet, there are deficits in understanding how to communicate the transition to ensure patients accept biosimilars. Specifically, there is a lack of knowledge on which information should be included, how it should be delivered, pharmacists' readiness to educate patients and which patients may require additional intervention.

The changing nature of healthcare encounters has also led to providers being faced with the challenge of triadic engagement, whereby patients, companions and providers are involved in treatment decisions. While numbers vary according to the type of health care being delivered, approximately 37 to 56% of patients attending routine medical visits in the United States and 40% of outpatient rheumatology appointments in the United Kingdom are accompanied by a companion, who is usually a spouse or romantic partner, adult child, family member, or friend (Douglas et al., 2005; Wolff & Roter, 2011). Despite their presence and involvement in the patient's medical journey, research investigating the influence of companions on

treatment decisions and strategies to involve them remains scarce. Indeed, there are substantial opportunities to improve the decision-making process about changing to biosimilars for both patients and their companions.

This thesis seeks to address the aforementioned research deficits and contributes to the growing literature on improving patient acceptance of biosimilars. It investigates three key questions: How can communication about biosimilars be improved? How do companions impact patient acceptance of biosimilars? How can consultations about transitioning to biosimilars be improved when companions are present?

Research Aims

This thesis intends to understand how the transition to biosimilars can be improved. There are two primary aims: 1) to examine how communication can be improved to increase patient acceptance of biosimilars and 2) to determine and augment the involvement of companions in decisions about transitioning to biosimilars. This thesis also intends to provide a rationale for the importance of using health psychology theory in future research on biosimilar acceptance and when developing communication strategies. Aims will be addressed through knowledge gained from a systematic review with a meta-analysis, a correlational study, two experimental studies, a cross-sectional study, and a commentary.

Thesis Outline

The following chapters present research that is conducted in Aotearoa/New Zealand and addresses the thesis aims. Chapter 2 begins by establishing a theoretical overview of the literature on the acceptance and uptake of biosimilar therapies and highlights the importance of appropriate communication and patient education. The chapter also briefly reviews the limited existing research in biosimilar communication and identifies gaps in the literature which informed the research included in this thesis. A focus on including companions in discussions about transitioning to biosimilars was deemed important, as companions are often involved in the patient's medical journey and are present during treatment decisions. Understanding the role of companions in these discussions provides an exciting opportunity to optimise decision-making processes, while also improving communication about biosimilars.

The research presented in this thesis constitutes two key sections. The first section, Chapters 3, 4, and 5, focuses on understanding how communication about biosimilars can be improved to increase patient acceptance of biosimilars. Chapter 3 consists of a systematic review with a meta-analysis investigating 33 communication strategies used globally to educate patients on transitioning to biosimilars. It also explores whether willingness to transition and treatment persistence differs for the delivery (verbal or written) and the amount of information provided. The review demonstrates the central role pharmacists have in delivering communication strategies, however their preparedness to educate patients in Aotearoa/New Zealand is unclear. Chapter 4 presents the findings from a cross-sectional study with 142 pharmacists to explore their confidence in explaining key concepts about biosimilars to patients. The study also explores how pharmacists would respond to common patient queries, as negative and contradictory information can adversely impact biosimilar acceptance. Chapter 5 investigates whether patient characteristics can be used to identify those with more concerns about safety and transitioning and require more information about biosimilars.

The second section, Chapters 6, 7, and 8, focuses on determining and augmenting companions' involvement in discussions about transitioning to biosimilars. Chapter 6 consists of a randomised control trial that examines the influence of companions on a patient's hypothetical decision to transition from their bio-originator therapy to a biosimilar. In this study, 79 patients taking bio-originators for rheumatic diseases were randomised to receive information about biosimilars individually or with their usual companion. Dyads also received some time to discuss the decision to transition. The study presented in Chapter 7 explores the congruence between 39 patient and companion dyads' perceptions towards biosimilars and their information needs. This is a pre-specified analysis conducted as part of the randomised controlled trial presented in Chapter 6. The final experimental study in Chapter 8 explores a communication intervention to improve companion involvement in decisions about transitioning. In this study, 108 healthy volunteers and their companions were randomised to attend a mock consultation where information was delivered by a physician using a family-centred or patient-only approach.

The final chapters of the thesis provide an overview for future research and a general discussion of the findings from previous chapters. Chapter 9 consists of a commentary paper that discusses the importance of keeping health psychology at the forefront of future research that aims to improve biosimilar acceptance. This thesis, to the author's knowledge, is the first

piece of work to apply health psychology theory and learnings to the area of biosimilar communication. The commentary paper summarises key findings from the thesis, along with some novel ideas for using health psychology to educate patients in the future. Finally, Chapter 10 considers the key findings from the thesis, integrates these with the broader literature and reflects on clinical implications and study limitations before considering the next steps for research in this area.

Chapter Two: Biologics, Biosimilars and Patient Education

Rheumatic diseases and long-term musculoskeletal conditions are major public health challenges. In Aotearoa/New Zealand, one in six people aged 15 years or older live with diagnosed arthritis, and musculoskeletal diseases are among the highest contributors to healthcare system costs (Blakely et al., 2019; Ministry of Health, 2019). Due to the rise of chronic diseases, medicine has seen a shift towards managing chronic diseases to enable patients to lead normal lives. In tandem, there have been exciting advancements in technology and genetic engineering. These have led to the development of biopharmaceuticals ('biologics'); complex drugs that derive from living organisms (European Medicines Agency, n.d.; U.S. Food and Drug Administration, 2018b). While biologics have revolutionised health care, their use comes with a substantial financial burden to the healthcare system. Biosimilar medications can help to reduce costs due to being manufactured after the original patent has expired (European Medicines Agency, 2019; U.S. Food and Drug Administration, 2017). It is crucial to successfully integrate biosimilars into the pharmaceutical market, to meet the increasing needs for accessible and cost-effective treatments. Effective patient-practitioner communication is essential to ensuring a successful adoption.

This chapter provides an overview of the research conducted to improve patient acceptance of biosimilars and identifies gaps in the literature, which inform the studies that comprise this thesis. The chapter provides a brief introduction to biopharmaceuticals in rheumatology care and the rise of biosimilars. Key challenges to the uptake of biosimilars are highlighted, along with a discussion on the importance of using effective communication to address patient hesitancy to transition to biosimilars. Given the changing nature of healthcare encounters to triadic engagement (patient-provider-companion), a focus is provided on the importance of involving companions in discussions about biosimilars.

Biopharmaceuticals

Biopharmaceuticals (biologics) are, without a doubt, one of the most important biotechnology advancements of this century. Original biologics (bio-originators) have transformed the pharmaceutical industry and revolutionised traditional health care since their introduction in the 1980s and are the fastest-growing sector in the global pharmaceutical industry. Unlike traditional small molecule drugs (e.g., aspirin), biologics are generally large, unstable,

complex molecule drugs. Biologics work by adapting maladaptive physiological functions through targeting specific protein receptors or genotypes (European Medicines Agency, n.d.; U.S. Food and Drug Administration, 2018b). These adaptations lead to more effective, longer-lasting care.

Most biologics are developed using recombinant deoxyribonucleic acid (rDNA) technology, which enables genetically engineered living cells to produce a desired protein (Sekhon, 2010). The manufacturing process is highly variable and leads to inherent microheterogeneity (variation) between batches of the same product (Mellstedt et al., 2008; Wish, 2019). As such, it is essentially impossible to create a 'bio-identical' drug. Initially, researchers identify a protein of interest and isolate the corresponding gene that codes for the protein from human or animal cells. The gene is subsequently joined to a plasmid vector to create an expression vector used to produce the desired protein (Sekhon, 2010). The expression vector is inserted into a living host organism (e.g., a mammalian cell such as the Chinese Hamster Ovary cell line, yeast, or bacteria) to allow the living organism to produce the target protein. A cell bank is developed from the engineered cell lines through cell expansion. Genetically modified cells are then cultured in bioreactors, and the protein is filtered from the cells, purified, stabilised, formulated into a medicinal product, and stored (Sekhon & Saluja, 2011).

Biologics in Rheumatology

Biologic use in health care is widespread, including growth hormones in endocrinology, vaccines in public health, immunotherapy in oncology, and insulin for diabetes. Rheumatology has particularly benefitted from their introduction, as rheumatic diseases often stem from maladaptive immune responses. Rheumatoid arthritis, for example, remains one of the most common diseases, impacting up to 1% of the population globally (Almutairi et al., 2021; Safiri et al., 2019). This disease is a chronic systemic inflammatory autoimmune condition that impacts the synovium with hallmark symptoms of joint swelling, pain, stiffness, and deformity. Less prevalent rheumatic diseases such as psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis also negatively impact all aspects of daily living. Adverse consequences, such as indirect costs due to high work absenteeism and disability, along with less social participation, intolerable pain, fatigue, sleeping problems, and reduced emotional well-being and mental health are commonalities across rheumatic diseases (Gudu & Gossec, 2018; Hsieh et al., 2020; Lwin et al., 2020; Rosenbaum et al.,

2019; Tollisen et al., 2018). It is unsurprising that patients with rheumatic diseases report a lower quality of life.

Biologics are an alternative treatment for patients with rheumatic diseases who have not responded to conventional therapies. Patients generally commence treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), like methotrexate, or glucocorticoids. While these are favoured as first-line treatments due to their mode of administration, low cost and high safety and efficacy, some patients require biological disease-modifying antirheumatic drugs (Akram et al., 2021). Biologics work by modulating the immune system to interfere with and modify maladaptive responses. Monoclonal antibodies infliximab, etanercept, and adalimumab target the cytokine tumour necrosis factor alpha (TNF-α). By binding to TNF-α and blocking it from interacting with surface TNF receptors, pro-inflammatory effects are minimised through reduced TNF-α production. Other biological therapies have different mechanisms of action, including inhibiting the production of interleukin-6 (tocilizumab) and CD20 (rituximab). Patients generally begin with TNF-α inhibitors, however, may be switched to a drug with a different biological target if the disease remains uncontrolled (Akram et al., 2021).

Over time, biologic therapy slows the progression of the disease, reduces irreversible joint damage, and improves daily functioning. Following adalimumab initiation in Aotearoa/New Zealand, adult patients showed significant decreases in disability in as quickly as two months (Gearry et al., 2019). Studies also demonstrate that biologic use either alone or in combination with conventional synthetic disease-modifying antirheumatic drugs is more effective in improving symptoms than only conventional synthetic disease-modifying antirheumatic drugs (Emery et al., 2010; Jones et al., 2012; Jones et al., 2010; Lopez-Olivo et al., 2015). Aside from clinical benefits, biologics improve patient-reported outcomes, such as attendance at work and psychological well-being (Gearry et al., 2019; Verstappen, 2015).

It should be noted that immunomodulatory biologics increase the risk for malignancies, cytokine release syndrome, and serious infections due to immune suppression or activation (Sathish et al., 2013). A common concern is immunogenicity, where the biologic induces an unwanted immune response leading to the development of anti-drug antibodies (Sanchez-Piedra et al., 2019; Sathish et al., 2013). These may cause anaphylaxis, infusion reactions, and reduced efficacy (Strand et al., 2017). Extensive pre-clinical, clinical pharmacology (to demonstrate the pharmacokinetics of the drug) and clinical studies are required to

demonstrate safety and establish superiority to a comparator drug or placebo in regards to efficacy (Isaacs et al., 2017).

Cost and Access of Bio-Originators

Bio-originators are a revolutionary treatment in rheumatology, but the high cost is a significant barrier to their use. In the United States of America, it has been estimated that etanercept, adalimumab, and infliximab cost between US$24,859 to US$26,537 per patient annually (Gu et al., 2016). Compared to treatment with methotrexate, the average monthly cost is up to 30 times more with adalimumab (Baldo, 2016). Bio-originators also dominate the global pharmaceutical market, with adalimumab (brand name Humira, manufactured by AbbVie) remaining the top-selling global product, surpassing US$20 billion in 2020 (Urquhart, 2021). Therefore, a significant portion of the pharmaceutical budget is used on acquiring biological medicines. For example, in Europe, biologics account for approximately 40% of the total pharmaceutical expenditure (IQVIA, 2020). In Aotearoa/New Zealand, monoclonal antibodies alone account for around $150 million annually (approximately 10% of all the spending on medicines) but are used for less than one percent of prescriptions (Pharmaceutical Management Agency, 2017). Although biologics have accounted for 94% of the growth in net drug spending since 2014, the market is expected to continue growing (IQVIA, 2018b). Given the high costs associated with research and the development process, bio-originators, albeit effective, are a major financial burden to both patients and healthcare systems.

Early initiation and access to biologics is crucial to prevent irreversible damage to joints, slow disease progression and reach remission. However, access to bio-originators is restricted in an effort to reduce costs. Most European countries employ criteria that only enable qualification for bio-originator treatment after failure of two csDMARDs or with a minimum level of disease activity score (Putrik, Ramiro, Kvien, Sokka, Uhlig, et al., 2014). In Aotearoa/New Zealand, criteria are used when considering applications for Special Authority (Pharmaceutical Management Agency, 2021c). The high cost also leads to inequities in accessing bio-originators, particularly for patients who cannot afford insurance premiums and low and middle-income countries with lower pharmaceutical budgets (Makurvet, 2021; Scheinberg et al., 2018). Inequities in accessing bio-originators are evident in Europe, with low-income countries providing less reimbursement or having more strict eligibility criteria than high-income countries (Putrik, Ramiro, Kvien, Sokka, Pavlova, et al., 2014; Putrik,

Ramiro, Kvien, Sokka, Uhlig, et al., 2014). Competition is needed to drive down costs and increase access.

The Era of Biosimilars

Biosimilars are biological products that are highly similar to a biologic that has gained regulatory approval (European Medicines Agency, 2019; U.S. Food and Drug Administration, 2017). Unlike small molecule drugs, bio-originators cannot be replicated due to their inherent variation and the complexity of the manufacturing process, which naturally results in microheterogeneity. However, biosimilars have the same amino acid sequence and biological activity (European Medicines Agency & European Commission, 2017). As such, biosimilars are not regarded as a 'generic' of the reference medicine. Biosimilars must therefore, undergo robust bio-similarity exercises to demonstrate no clinically meaningful differences to the reference drug in terms of structure, safety, purity, and potency (Ebbers, 2020; Escasany & Cumplido, 2015). Some minor differences are acceptable, such as differences in the stabiliser or buffer, but these must not adversely impact clinical outcomes (U.S. Food and Drug Administration, 2017). Evidence of pharmacokinetic and pharmacodynamic studies must also be provided, along with other assessments such as immunogenicity to explore potential immune reactions (Medicines and Medical Devices Safety Authority, 2014).

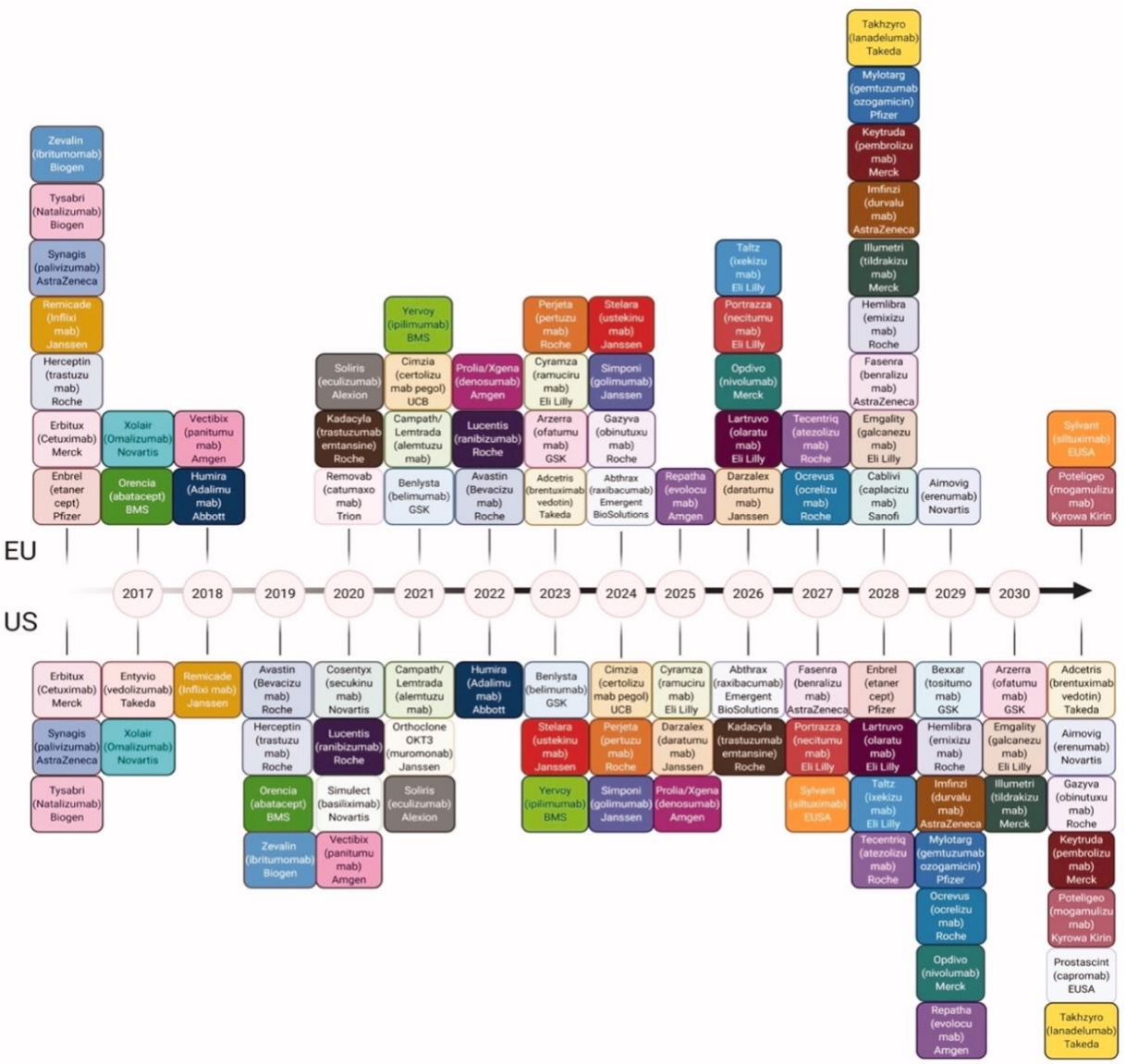
There are some concerns regarding the safety and efficacy of biosimilars. These often relate to the risk of immunogenicity due to differences in the manufacturing process and antidrug antibodies developed against the originator cross-reacting to biosimilars (Kalden & Schulze-Koops, 2017). For example, in the DANBIO study, 37 of 802 patients who changed to infliximab biosimilar (CT-P13) reported subjective complaints (e.g., headache or myalgia) and drug-specific complaints that may indicate immune-related adverse events such as fever or flu-like symptoms, infusion reactions, and skin rashes (Glintborg et al., 2017). These concerns have largely been dampened by extensive research demonstrating no significant association between immunogenicity and changing between biologics and the assurance of pharmacovigilance measures (Ebbers & Schellekens, 2019). Various large-scale studies (e.g., NOR-SWITCH and PLANETRA) conducted with patients across Europe, Asia, Latin America, and the Middle East also support biosimilar efficacy and safety (Goll et al., 2019; Jørgensen et al., 2017; Park et al., 2013; Yoo et al., 2013).

Biosimilar Cost and Access

Although they are often treated as relatively novel, biosimilars have been around for well over a decade. The European Medicines Agency (EMA) granted market authorization for its first biosimilar, Omnitrope (somatropin), in 2006. Comparatively, the Food and Drug Administration (FDA) released its final approval pathway in 2015 and approved its first biosimilar, Zarxio (filgrastim), that year (Kvien et al., 2022). In Aotearoa/New Zealand, the Medicines and Medical Devices Safety Authority (Medsafe) approved Nivestim (filgrastim) in 2012 (Medicines and Medical Devices Safety Authority, 2014). Reports indicate that by 2021, the FDA had approved approximately 31 biosimilars, compared to 77 biosimilars recommended for approval by the EMA (Generics and Biosimilar Initiative, 2021; U.S. Food and Drug Administration, 2021). The uptake of biosimilars in the United States has been slow due to multiple factors, including complex litigation processes, misinformation and a large number of patents being enforced by manufacturers of bio-originators (Cross et al., 2022; Vulto & Barbier, 2022). Variation in the uptake of biosimilars also significantly differs across European countries, as decisions on the reimbursement of medicines, including interchangeability and substitution, are made at a national level (Ebbers, 2020). Various blockbuster bio-originators are expected to lose their patents in the coming years, which provides an opportunity for cost saving and exciting new developments in biosimilar treatments. As demonstrated in Figure 1, the exclusivity period differs for the same molecules in Europe and the United States.

Figure 1

The Expected Expiry of Patents and Market Exclusivity Periods for Major Bio-Originators in Europe and the United States



Note. Reproduced from Akram et al. (2021) with permission from Taylor & Francis Group

As biosimilars are manufactured following patent expiry, they provide significant opportunities for cost reduction. Biosimilars for etanercept, infliximab, and adalimumab are sold for as little as 30% of the cost of the reference drug (Dey et al., 2021). Cost savings can be gained by biosimilar entry leading to competition with bio-originators to either 1) drive bio-originator drug prices down or 2) by entirely replacing the bio-originator for a cheaper cost. It has been estimated that biosimilars will reduce drug spending by $54 billion between

2017 and 2026 in the United States (Mulcahy et al., 2018). Savings can be deployed to other areas of care, such as funding additional nurse specialists, or enable increased and faster access to treatment (Dutta et al., 2020; Smolen et al., 2019). The introduction of Amgevita (adalimumab biosimilar) in Aotearoa/New Zealand was expected to benefit 700 patients in the first year, with 380 new patients receiving access, and led to the loosening of criteria, such as removing the need for C-reactive protein to be greater than 15 mg/L (Pharmaceutical Management Agency, 2021b). It also reduced administrative burdens by extending renewal durations and allowing renewal applications to be submitted by any prescriber.

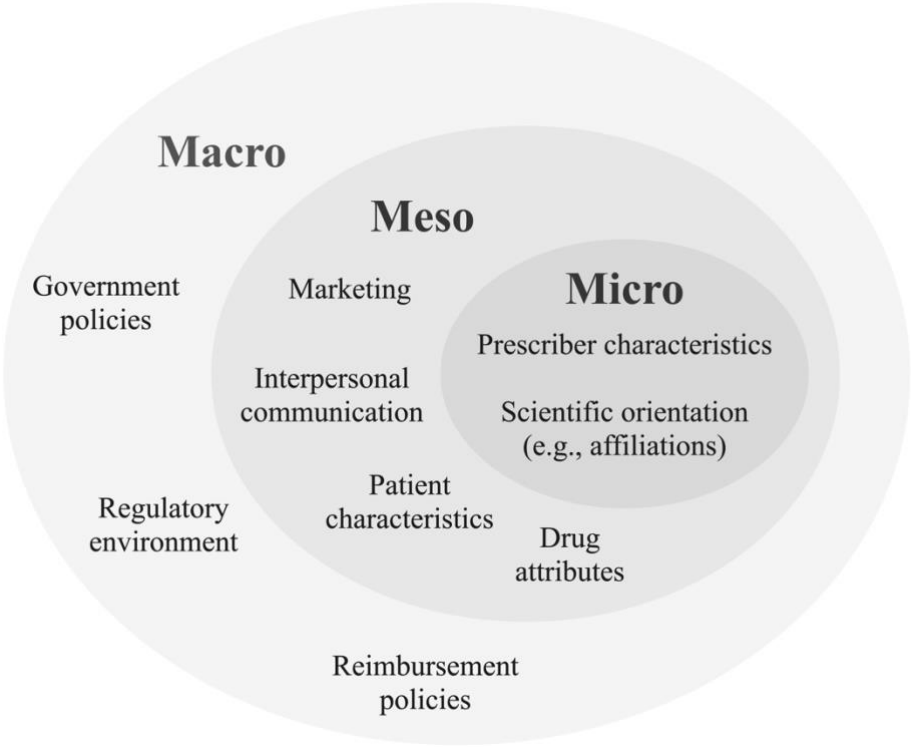
Implementing Biosimilars

Transitioning clinically stable patients to a biosimilar has become a common practice to reach their cost saving potential. As transitions are driven by economic rather than medical reasons (e.g., loss of efficacy), this process is denoted as a 'non-medical transition' (Fleischmann et al., 2020). Non-medical transitions can be mandatory (forced) or non-mandatory, whereby a shared decision-making approach is employed (Provenzano & Arcuri, 2021). The term 'switching' is commonly used in the literature. However, this term should be used with caution as it conveys the process of changing to a new drug with a different mechanism of action (Agboton & Salameh, 2022). The term 'transitioning' is recommended instead, as biosimilars have the same biological target, but the drug provider is simply being changed.

While the future seems brighter with biosimilars in the picture, the hype around biosimilars has been contested (Dey et al., 2021; Greene, 2018; Sarpatwari et al., 2019). While implementing biosimilars and transitioning patients seems simple in theory, various barriers slow their uptake. These include the professional characteristics of medical doctors (e.g., prescribing volume or experience), interpersonal communication, characteristics of patients (e.g., age, gender or co-morbidities), drug attributes, and marketing from pharmaceutical companies and government policies and regulations (Figure 2) (Lublóy, 2014). For example, physicians who are unfamiliar with biosimilars or have concerns about safety or efficacy may be less likely to prescribe biosimilars (Hemmington et al., 2017; Sarnola et al., 2020; Sullivan et al., 2017; Waller et al., 2017). Messaging that includes scare tactics from originator manufacturers may further reinforce concerns (Rowland, 2019). By no account will improving uptake be simple, and it will require an international, collaborative, and multi-level approach (Kvien et al., 2022). Given the complexity of addressing this issue, this thesis focuses on barriers relating to interpersonal communication and patient characteristics.

Figure 2

The Multiple Levels Involved in Improving Biosimilar Acceptance



Note. Figure development informed by Lublóy (2014)

Negative Perceptions

Despite abundant evidence supporting biosimilar safety and efficacy, patient concerns persist. These concerns are generally about fears of reduced efficacy, loss of disease control, the potential for experiencing additional side effects and long-term problems and being unable to transition back (Attara et al., 2016; Gasteiger et al., 2019; Ighani et al., 2018; Jacobs et al., 2016; Kovitwanichkanont et al., 2020; Peyrin-Biroulet et al., 2017; Sullivan et al., 2017; van Overbeeke et al., 2017). Other common concerns are related to the manufacturing process, such as a lack of quality control or the dissimilarity between the drugs, although there are differences between bio-originator batches too (Gasteiger et al., 2019).

While patients are the primary focus of this thesis, it should be noted that physicians, nurses, and pharmacists have also reported concerns about safety, efficacy, interchangeability, and substitution (Aladul et al., 2019; Beck et al., 2017; O'Callaghan et al., 2017; Sarnola et al., 2020; van Overbeeke et al., 2017; Waller et al., 2017). In a study with 110 medical specialists working in rheumatology, dermatology, gastroenterology, oncology, and haematology in

Aotearoa/New Zealand, 71% agreed they would prescribe biosimilars (Hemmington et al., 2017). However, participants also reported a lack of confidence in indication extrapolation and transitioning patients, and 30% expressed uncertainty about the quality of biosimilars and the manufacturing process.

Nocebo Response and Discontinuation

Negative perceptions result in biosimilar hesitancy and a lack of confidence in their use. Unsurprisingly, the nocebo effect has become a recent focus of biosimilar literature (Colloca et al., 2019; Fleischmann et al., 2020; Odinet et al., 2018; Rezk & Pieper, 2017; Smolen et al., 2019). The nocebo effect is an adverse effect of a treatment induced by negative expectations and is unrelated to the active component of a treatment (Colloca & Finniss, 2012). In biosimilar research, the nocebo effect is identified by the reporting of non-specific, subjective side effects such as arthralgia (joint pain), myalgia (muscle aches and pain), and headaches and the attribution of these to the biosimilar. A reverse transition to the bio-originator can be used to remedy non-specific side effects for some patients, which further supports the presence of a nocebo response (Boone et al., 2018).

Studies in biosimilar literature have focussed on proving comparable biosimilar safety and efficacy rather than being specifically designed to assess nocebo responses. However, open-label transitions are useful tools as they enable patients to develop expectations about the new treatment, and therefore provide an opportunity to assess the misattribution of side effects (Pouillon et al., 2018). A popular example involved transitioning 192 patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis to an infliximab biosimilar (CT-P13) (Tweehuysen, van den Bemt, et al., 2018). At six months, 24% of patients had discontinued the biosimilar, primarily due to subjective complaints (e.g., tender joints). While it is difficult to pinpoint the exact prevalence of a nocebo response, studies have observed a 12.8% nocebo response at a minimum of six months and 15% at a median of 11 months following the transition (Boone et al., 2018; Nikiphorou et al., 2015). Nocebo responses have also been identified in transitions involving etanercept and adalimumab (Müskens et al., 2020; Tweehuysen, Huiskes, et al., 2018; van Adrichem et al., 2022).

Nocebo responses can diminish a patient's quality of life and reduce treatment efficacy (Bingel, 2014). For the healthcare system, nocebo responses may also offset the potential cost savings of biosimilars due to increasing the use of resources (e.g., visits and hospitalisations)

and, importantly, lead to early discontinuation (Bakalos & Zintzaras, 2019; Straka et al., 2017). A recent systematic review of 31 trials (3,271 patients) explored whether patient knowledge of a transition (i.e., open-label) to biosimilars was associated with discontinuation and adverse effect reporting (Odinet et al., 2018). The median discontinuation rate for open-label studies (14.3%) was higher than for double-blinded studies (6.95%). Discontinuation due to adverse drug events was also higher for open-label studies (5.6% versus 3.1%). Physicians have been warned to be careful when changing patients to biosimilars and to expect approximately one in seven patients to retransition to the originator, with a perceived loss of effect being the most common reason (Liu et al., 2022; Meijboom et al., 2021). Building patient confidence in biosimilars, such as through effective patient-provider communication, is essential to mitigating these adverse outcomes, particularly as the nocebo effect commonly occurs in the initial stages of the transition (Dutt et al., 2022).

The Importance of Communication

During the 20th century, a cultural shift in medicine has led to the facilitation of patient involvement in all aspects of the medical journey and the provision of care that is respectful of and responsive to the patient's preferences, values, and needs (Bauman et al., 2003; Institute of Medicine, 2001; McMillan et al., 2013). High-quality patient-practitioner communication is crucial to meet these goals. According to the Transactional Model of Communication, communication is a dynamic, cooperative, simultaneous, and continuous process of receiving and giving messages to create a shared meaning (Barnlund, 1970). Importantly, messages encompass both verbal and non-verbal behaviours, including paralanguage (e.g., tone of voice), which conveys meaning (Makoul, 2003). The wider context also plays a crucial role in interpersonal communication. Those involved in the communication process (i.e., 'communicators') send, receive, construct, and interpret messages based on their experiences, culture, age, mood, attitudes, and knowledge. Communication also facilitates the development of relationships, such as between patients and healthcare providers (Barnlund, 1970; English et al., 2022). More recent theories have also concluded that interpersonal communication is a goal-directed and action driven process (Berger, 1997; Dillard, 1990; Greene, 1997). According to the Goal-Plan-Action theory, the production of verbal and non-verbal behaviours are purposefully planned and executed in order to reach a specific goal (Dillard, 1990). In healthcare, this is often seen by the use of strategic messaging. For example, risk information or probabilities may be framed in a

positive way to promote health-enhancing behaviours, encourage certain treatment decisions or to provide reassurance on treatment risks (Gallagher & Updegraff, 2012; Tversky & Kahneman, 1981).

Effective patient-provider communication is associated with numerous affective and behavioural outcomes in health care. These include positive emotions, self-efficacy, satisfaction with information and treatments, and improved adherence and health literacy (Hironaka & Paasche-Orlow, 2008; Peimani et al., 2020; Schoenthaler et al., 2017; Schofield et al., 2003; White et al., 2015). An appropriate provision of information also guides informed decision-making by providing an accurate perception of relevant risks and benefits. However, various factors can adversely impact patient-provider communication. These include language, health literacy and cultural barriers, provider burnout and bias, a lack of communication skills training, non-priority interruptions and perceived time constraints (Albahri et al., 2018; Back et al., 2019; Blocker et al., 2017; English et al., 2022; Guttman, 2021; Maina et al., 2018; Makoul, 2003; Robbins et al., 2019; Schinkel et al., 2019). Additional complexities to the information-giving process also arise when patients are accompanied to consultations.

Companions and Triadic Communication

There is little dispute that actively engaging patients in medical consultations and decisions provides optimal health outcomes, including greater adherence to biologics and treatment satisfaction (Doyle et al., 2013; Lofland et al., 2017; Mohammed et al., 2016). However, research suggests that approximately 37 to 56% of patients are accompanied to routine medical visits and 40% to outpatient rheumatology appointments (Douglas et al., 2005; Wolff & Roter, 2011). In reality, this number may be higher when taking into account the ethnic diversity of Aotearoa/New Zealand and preferences for family presence, and the shift towards involving the family in health care (Dijkman et al., 2021; Laidsaar-Powell, Butow, Charles, et al., 2017; Stats NZ, 2020). Companions can be a spouse or romantic partner, adult child, other family members, or a close friend (Sud, 2021). While the literature uses varying terminology to define the role of a support person (e.g., a family caregiver or decision-partner), the term ‘companion’ will be used for the purpose of this thesis (Gray et al., 2019; Laidsaar-Powell, Butow, Charles, et al., 2017). Companions have a close personal relationship to the patient and play a role in their health care, such as accompanying patients

to consultations, but may have varying preferences towards the degree of involvement in treatment decisions (Troy et al., 2019).

Companions have a meaningful role during medical encounters. It is common for patients who self-manage their disease to prefer to have a shared role with both their physician and family/close friends when making health decisions (Wolff & Boyd, 2015). The preference for companion involvement is not surprising as companions provide additional medical information, care, structural and functional support and help patients recall information (DiMatteo, 2004; Isenberg et al., 2018; Rees & Bath, 2000; Sharp & Hobson, 2016; Wolff et al., 2017; Wolff & Roter, 2011). For example, being diagnosed with a chronic condition can be shocking and act as a barrier to understanding information (i.e., cognitive overload) (Sinfield et al., 2008). In these cases, companions can remember information and advocate for care that is consistent with the patient's preferences and values. In decision-making, companions validate treatment choices (Revenson & Pranikoff, 2005). This is useful as according to the social support theory, patients seek support from important people in their lives when making difficult decisions (Rini et al., 2011). In some cultures, family involvement shields the patient from unnecessary stress (Bousquet et al., 2015; Dijkman et al., 2021; Hobbs et al., 2015). Likewise, indigenous groups who view health as holistic and have a family-orientated approach to well-being may also feel more at ease with companions present (Cunningham, 2000; Kidd, 2010). However, it should be noted that there is often substantive social and cultural diversity within groups, so healthcare providers should not make assumptions about preferences for companion involvement based on culture alone (Cunningham, 2000; Scherr et al., 2022).

Triadic (patient-provider-companion) consultations can also be challenging. Disagreement about treatment decisions can occur, leading to a patient experiencing psychological distress or resentment (Lewis & Rook, 1999; Zhang & Siminoff, 2003). Some companions feel ignored or isolated during consultations, particularly if their information needs are not met or they do not understand the information provided (McCarthy, 2011; Sinfield et al., 2008). Companions often prefer to be informed about treatment options, whereas patients prefer to understand the extent of their condition (Lee et al., 2018). Physicians also have concerns about needing additional time and companions influencing decisions, being protective of the patient, or interrupting consultations (Sharp & Hobson, 2016). There are also reservations about how to involve companions without marginalising patients in their own care (Wolff &

Roter, 2011). Providers are already challenged with soliciting a patient's desire to be involved in treatment decisions, as this may change during the encounter and is contextual to patient characteristics and the severity of the disease (Buljac-Samardzic et al., 2022; Chewning et al., 2012; Levinson et al., 2005). Thus, companion involvement can add further complexities.

Involving companions in treatment decision-making acknowledges their integral role in the patients' medical journey (Adams et al., 2009; Ervik et al., 2013; Foster et al., 2010). The concept of dyadic coping, which emerged in the mid-1990's, recognises that couples respond to a shared stressor as an interpersonal unit rather than in isolation (Bodenmann, 1997, 2005). Some chronic diseases have been coined "we-diseases," due to appraising the disease as a shared problem and using shared efforts to cope (Kayser, 2007). In rheumatology, companions may provide transport to appointments, help administer biologics or provide social support, which promotes adherence to biologics (Betegnie et al., 2016; Morgan et al., 2015). Treatment decisions may consequently have collateral effects for companions (Laidsaar-Powell, Butow, Charles, et al., 2017). The shift to providing 'patient-family centred care' further highlights the need to consider companions by developing a mutual partnership between providers, patients, and families in care planning, delivery, and evaluation (Institute for Patient- and Family-Centered Care, n.d.).

Educating Patients on Biosimilars

The idea that effective education is crucial for the successful uptake of biosimilars has been accepted by organisations globally. In 2018, the Food and Drug Administration issued the 'Biosimilars Action Plan,' which included a strategy to develop effective communication to improve understanding of biosimilars for patients, clinicians, and payors (U.S. Food and Drug Administration, 2018a). Patient advocacy organisations such as the European Crohn's and Colitis Organisation have also advocated that patients should be fully informed to enable evidence-based choice in decisions to transition (Danese et al., 2017).

Effective communication is crucial to building knowledge and familiarity with biosimilars. Patients have reported varying degrees of familiarity with biosimilars, which is a likely reflection of the differing uptake across Europe and the United States (Jacobs et al., 2016). However, a low proportion of patients globally report being familiar with biosimilars or sufficiently informed (Frantzen et al., 2019; Jacobs et al., 2016; Kovitwanichkanont et al.,

2020; van Overbeeke et al., 2017; Vandenplas et al., 2022). This limits the degree to which patients are involved in the decision-making process and shapes treatment outcomes, as patients tend to prefer familiar treatments (e.g., due to experience or media exposure) and develop negative expectations to new treatments (Faasse & Martin, 2018). The information-giving process also gives providers the opportunity to reduce nocebo responses by signalling confidence in biosimilars and reassuring patients about safety and efficacy (Smolen et al., 2021; Webster et al., 2016, 2018). Carefully considered communication strategies further ensure patients feel supported and trusting of their healthcare provider, while improving satisfaction with the transition (Attipoe et al., 2018; Kim, Alten, et al., 2020).

Previous Strategies to Educate Patients

Appropriate patient education is important to improve acceptance; however, few studies have specifically aimed to develop or test communication strategies. A promising randomised controlled trial with 96 rheumatology patients from Aotearoa/New Zealand explored the use of positive framing and an analogy on patient acceptance (Gasteiger et al., 2019). Positive framing (i.e., highlighting positive attributes of biosimilars) improved willingness to transition compared to negative framing (67% versus 46%) and perceptions of efficacy. The analogy did not further improve acceptance. Other hypothetical studies have investigated the effects of framing biosimilars as the "gold" alternative to bio-originators and the use of reassurance techniques, such as illustrations demonstrating comparability (Hrin et al., 2022; Hrin & Feldman, 2021). However, these interventions did not significantly improve patient confidence.

Other notable attempts to educate patients have occurred in real-world transitions. In a German study, adult rheumatology patients were randomised to receive education on an adalimumab biosimilar by a nurse specialist or a rheumatologist (Gall et al., 2021). While the delivery (nurse or physician) did not impact satisfaction with the information process or other outcomes, less than one-third of patients correctly answered questions about efficacy, safety, approval, manufacturing, or costs. This is concerning, as 49% of patients had already experienced one transition and 51% had undergone multiple 'switches.' It would be expected that patients have previously received education on biosimilars.

Other studies have reported the effects of 'managed switching programs' on biosimilar persistence and acceptance, which often involve a structured communication strategy (Chan

et al., 2019; Dutt et al., 2022; Haifer et al., 2021; Tweehuysen, Huiskes, et al., 2018; Tweehuysen, van den Bemt, et al., 2018). One study demonstrated high (89%) initial acceptance of biosimilars when allowing patients to opt-in to transitioning and providing ample opportunity to discuss the transition with healthcare providers (Müskens et al., 2020). However, the crude treatment persistence was lower at one year follow-up compared to the historical cohort (73% versus 89%). In the BIO-SPAN study, patients were informed of the transition to etanercept biosimilar SB4 at the same time, followed by a national media item highlighting benefits such as cost savings and less injection site reactions (Tweehuysen, Huiskes, et al., 2018). Rheumatology and pharmacy staff were educated to use 'soft skills' to mitigate patient concerns and taught to educate patients on the nocebo response and misattribution if patients reported subjective complaints (Tweehuysen et al., 2017). While initial acceptance was high (99%), the communication process did not significantly improve crude persistence rates over the six months.

Gaps in the Literature

Patient-provider communication has been accepted globally as a key factor for improving acceptance of biosimilars (Cohen & McCabe, 2020; Kim, Alten, et al., 2020; Oskouei & Kusmierczyk, 2021; Smolen et al., 2021). Previous strategies to improve biosimilar uptake focus on providing high-quality communication to build familiarity and confidence in biosimilar use (Chan et al., 2019; Peyrin-Biroulet et al., 2019; Tweehuysen, Huiskes, et al., 2018; Tweehuysen, van den Bemt, et al., 2018). More recently, research has shifted to focus on mitigating the development of nocebo responses and improving treatment persistence (Colloca et al., 2019; D'Amico et al., 2021; Kristensen et al., 2018; Odinet et al., 2018). While some recent studies have started to translate and implement strategies (i.e., positive framing) from health psychology research, there are critical gaps remaining in understanding how to communicate the transition to biosimilars to improve acceptance (Gasteiger et al., 2019).

Firstly, understanding the impact of communication strategies on biosimilar acceptance, persistence, and subjective complaints is in its infancy. Randomised controlled trials are needed to truly understand the impact of communication strategies on patient acceptance in real-world transitions. However, none have been conducted, possibly for logistical and ethical reasons. These trials would require giving one group of patients information about biosimilars and the other no (or sham) information, opposing the principle of informed

decision-making. Similarly, it would be challenging to eliminate contamination bias between groups, given that patients are often in close proximity (e.g., when receiving infusions or in waiting rooms). When this thesis was planned, biosimilars had yet to be introduced for rheumatology patients in Aotearoa/New Zealand, which eliminated the possibility of exploring communication in a real-world transition. While it is difficult to explore the impact of communication on acceptance, it is important to understand whether patient acceptance differs for varying aspects of communication (e.g., content and mode of delivery). A key starting point is to determine the communication strategies that have been employed globally and the information about biosimilars that has been provided.

Research is also needed to better understand other key aspects that play a role in biosimilar acceptance. For one, more research is needed to better understand how healthcare providers would explain biosimilars to patients and their confidence in delivering key information. Previous research conducted by Hemmington et al. (2017) demonstrated that specialists in Aotearoa/New Zealand report variation in explaining biosimilars to patients and would benefit from guidance and written patient materials. Since this study, research has predominantly focussed on guiding physicians on educating patients, with research now slowly starting to shift to including hospital nurses in the communication process (Armuzzi et al., 2019; European Medicines Agency & European Commission, 2017; Gall et al., 2021; Petit et al., 2021; Samsung Bioepis, 2020; Waller & Friganović, 2020). Pharmacy staff also play a key role in educating patients in real-world transitions (e.g., as seen in the BIO-SPAN and BIO-SWITCH studies) (Tweehuysen et al., 2017; Tweehuysen, Huiskes, et al., 2018). However, it remains unclear whether pharmacists in Aotearoa/New Zealand need upskilling and guidance before a large biosimilar transition occurs.

Research should identify patients who are more likely to be hesitant about transitioning and require additional information. It is evident that some patients have negative perceptions towards biosimilars, with concerns about safety, efficacy, and quality rife in the literature (Ighani et al., 2018; Jacobs et al., 2016; Kovitwanichkanont et al., 2020; Peyrin-Biroulet et al., 2017; Sullivan et al., 2017; van Overbeeke et al., 2017). However, it is unclear whether patient characteristics are associated with negative concerns and expectations towards biosimilars. Research in switches from an innovator drug to a generic suggests that patients who are female, older, have lower levels of educational attainment, and perceive themselves to be sensitive to medicines are more likely to have negative expectations or favour the

branded drug (Alrasheedy et al., 2014; Babar et al., 2014; Kleinstäuber et al., 2018; MacKrill & Petrie, 2018). Determining whether (and which) factors are associated with biosimilar hesitancy provides an opportunity to intervene and provide additional information and support to reduce future nocebo responses (Colloca, 2017).

A focus is also needed on communicating with companions as prior research is restricted to a dyadic (patient and provider) approach to decision-making (Gasteiger et al., 2019; Haghnejad et al., 2020; Müskens et al., 2020; Petit et al., 2021; Tweehuysen, Huiskes, et al., 2018; Tweehuysen, van den Bemt, et al., 2018). The provision of modern health care (i.e., patient-family centred care) advocates for the consideration of the wider social context, as patients are frequently accompanied by a companion who may be involved in the decision-making process (Douglas et al., 2005; McMillan et al., 2013; Troy et al., 2019; Wolff & Roter, 2011). To date, only two studies have explored companions' perceptions towards biosimilars, with one study involving parents of a paediatric sample and the second caregivers (Jacobs et al., 2016; Renton et al., 2019). Research is needed to assess companions' perceptions of biosimilars and, subsequently, determine their information needs to inform future communication strategies.

Lastly, little attention has been directed at exploring what direct effect a medical companion has on patient behaviour, such as treatment decision-making. Prior research has been qualitative and observational (Bracher et al., 2020; Isenberg et al., 2018; Sharp & Hobson, 2016; Stewart et al., 2021; Wolff et al., 2015; Wolff et al., 2017). Randomised controlled trials are necessary to infer causality. Likewise, it is unclear how to efficiently involve companions in decision-making, as interventions often rely on resources such as pre-consultation checklists or decision aids (Laidsaar-Powell et al., 2018; Laidsaar-Powell, Butow, Charles, et al., 2017; Song et al., 2017; Wolff et al., 2014). Research in triadic communication also largely focuses on advanced stages of cancer, geriatrics, and end-of-life care rather than general or routine care (Adams et al., 2009; Dijkman et al., 2021; Ervik et al., 2013; Karnieli-Miller et al., 2012; Stewart et al., 2021; Warner et al., 2013). A transition to biosimilars is an optimal opportunity to explore the influence of companions and develop a communication intervention to effectively involve companions in these decisions. This thesis aims to address these research deficits.

Summary

Patient acceptance of biosimilars plays a crucial role in the successful uptake of these revolutionary treatments. Acceptance relies largely on how healthcare providers communicate the transition, with a lack of confidence or ineffective communication strategies risking an increase in biosimilar hesitancy. Few studies have been conducted to examine how to optimise discussions about biosimilars, and these have been largely focused on dyadic communication with one patient and a physician. As companions are often present and involved in treatment decisions, a consideration of a triadic approach to biosimilar communication is crucial. Companions' perceptions of biosimilars are also unknown, and it is unclear whether they may influence decisions to transition. Various other important factors have been overlooked in the biosimilar literature. These include identifying patients who are more likely to hold concerns about biosimilars and require intervention and whether other healthcare providers, such as pharmacists, are confident in educating patients and their companions.

The following chapters address these gaps in the literature. Research in the first section of the thesis aims to understand how communication strategies can be improved to increase patient acceptance of biosimilars. The second section aims to determine and augment the involvement of companions in discussions about transitioning to biosimilars. This thesis also intends to provide a rationale for using health psychology theory and applications when developing future communication strategies about transitioning to biosimilars. Overall, this thesis endeavours to produce knowledge that can help to improve future transitions to biosimilars.

Chapter Three: Global Communication Strategies

Preface

The research presented in this section of the thesis contributes to understanding how patient-provider communication can be improved to help increase biosimilar acceptance. Communication plays an essential role in all medical encounters but particularly when transitioning patients to cheaper and seemingly 'novel' therapies. As discussed in Chapters 1 and 2, patient-provider communication is key to improving biosimilar uptake by building trust, familiarity, and confidence in efficacy, safety, and quality (Chew et al., 2021; Kristensen et al., 2018; Smolen et al., 2021; Vandenplas et al., 2021). Conversely, negative, inconsistent, and incoherent information can induce doubt and fear, ultimately deterring patients from accepting non-mandatory transitions and developing nocebo responses (Colloca et al., 2019; Kristensen et al., 2018). Effective communication is particularly essential before and in the early stages of a transition to ensure long-term persistence (Germain et al., 2020).

More guidance on informing and educating patients about transitioning to biosimilars is needed. A study conducted in France demonstrated that 67% of 44 patients felt insufficiently informed about biosimilars, and 24% of patients who were informed about the transition were not asked to provide informed consent (Frantzen et al., 2019). This is problematic as being adequately informed is essential to decision-making and is associated with improved adherence (Frantzen et al., 2019). Healthcare providers in Aotearoa/ New Zealand have also reported a need for further instruction on explaining biosimilars to patients along with written patient materials and resources (Hemmington et al., 2017).

There is scarce research demonstrating the most effective way to communicate the transition to biosimilars to ensure that patients accept and persist with treatment and to mitigate any nocebo responses. Until recently, there have been few studies that have specifically explored the use of communication strategies for biosimilars. Instead, most real-world transitions have focused on proving economic benefits or examining patient acceptance, discontinuation, or nocebo responses following a transition (Park et al., 2013; Scherlinger et al., 2018; Scherlinger et al., 2019; Tweehuysen, Huiskes, et al., 2018; Tweehuysen, van den Bemt, et al., 2018; Yoo et al., 2013). While testing the impact of communication strategies was not the focus, positive patient outcomes (e.g., persistence and acceptance) have been attributed to the use of structured communication (Tweehuysen, Huiskes, et al., 2018; Tweehuysen, van den

Bemt, et al., 2018). More recent research has also started to examine the use of managed 'switching' programs, shared decision-making, and medical interviews to improve willingness to transition and retention (Chan et al., 2019; Haghnejad et al., 2020; Müskens et al., 2020; Razanskaite et al., 2017). However, findings to date remain largely inconclusive regarding whether, to what extent, and which communication strategies play a role in patient outcomes.

The initial stage of transitioning patients usually involves informing a large group of patients about the upcoming transition and subsequently providing additional education and reassurance as needed. However, there is variability in terms of how this information has been delivered, such as through written documents, verbal discussions, or both (Bhat et al., 2020; Boone et al., 2018; Chan et al., 2019; Haghnejad et al., 2020; Tweehuysen, Huiskes, et al., 2018; Tweehuysen, van den Bemt, et al., 2018). Furthermore, it is unclear whether differences in the mode of delivery have any association with patient outcomes. There is also a lack of clear, consistent guidance in what information and how much should be provided. For example, patient advocacy groups encourage transparent information, yet providing information about cost or dissimilarity can heighten concerns about biosimilar quality (Cohen & McCabe, 2020; Danese et al., 2017; Wilkins et al., 2014). A recent article on the ethics of biosimilars also concludes that physicians are obliged to inform patients about social controversies, including that the safety and efficacy of transitioning are still considered controversial (Murdoch & Caulfield, 2020). However, Cohen and McCabe (2020) argue that this is a false narrative, given that the literature reviews included in the ethical paper did not identify any specific safety or efficacy concerns.

A systematic literature review with a meta-analysis was conducted to address these research deficits, as no best evidence synthesis was available. The review systematically examined communication strategies used globally to educate patients on transitioning to biosimilars, including their content. It also investigated whether patients' willingness to transition and persistence differed for the modes of delivery and the amount of content provided in communication strategies. Further, we collected available data on subjective adverse events to examine whether nocebo reporting differed between communication strategies. The review included a range of study designs, as randomised controlled trials are lacking due to being difficult to conduct in this area of research (see Chapter 2 'Gaps in the Literature'). Consequently, the findings cannot be used to infer causality or make conclusions about the

importance of communication. However, the review provided a comprehensive foundation for understanding how biosimilars have been communicated, which informs subsequent research in this thesis and is essential for developing future communication strategies.

Citation

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Introduction

Patient-provider communication in health care is an integral part of developing and maintaining a successful therapeutic relationship. Creating a strong communication channel enables the provider to understand the patient better, improve patient understanding, and create a foundation for transparency, patient satisfaction, rapport, and trust (Voshaar et al., 2015). This has flow-on effects by promoting a more sustainable model of care whereby the patient plays an active role in their health care, such as through self-management, treatment decision-making, and adherence (Street et al., 2009; Young et al., 2017). Most importantly, this process leads to better quality care and health outcomes (Chandra et al., 2018; Street et al., 2009). Communication is crucial when changing treatments for non-medical reasons, such as the transition from a bio-originator to a biosimilar drug. Patients are particularly vulnerable to developing negative expectations about new, cost-effective therapies, which provides the optimal opportunity for adverse outcomes such as intentional non-adherence and nocebo responses. It is therefore essential to understand the process of appropriate communication before changing treatments to mitigate negative consequences.

The benefits of biologic therapies are now widely appreciated for numerous patient populations including in rheumatology, dermatology, gastroenterology, and oncology. Biologics are complex, large molecule medical products that derive from living organisms and are administered through subcutaneous injection or intravenous infusion (European Medicines Agency, 2019). A bio-originator, also known as the reference product or an innovator, is an original biologic that has gained regulatory approval. As patents for bio-originators gradually expire, products with more competitive prices can emerge. Biosimilars are comparable, but not identical, versions of a bio-originator (Agbogbo et al., 2019; European Medicines Agency, 2019). Biosimilars must demonstrate no clinically meaningful differences to bio-originators in terms of efficacy, safety, and immunogenicity to gain entry into the pharmaceutical market (Daller, 2016). Although biosimilars offer the same

therapeutic benefits with increased potential for competition and uptake, they are only slowly gaining momentum worldwide, with substantial differences between countries (Agbogbo et al., 2019). The challenge of patient acceptance of biosimilars also persists.

The use of biosimilars in patients who are starting a biologic is not perceived as controversial or complex, and this is indeed recommended and becoming common practice (Gisondi et al., 2020; Scherlinger & Schaeverbeke, 2020). However, when patients are already using an originator, transitioning (the term 'switching' is not used because it suggests transitioning to a different drug) is seen as more challenging. Early clinical trials and observational studies support the biosimilar's safety and efficacy with regard to pharmacokinetics and dynamics when transitioning patients for non-medical reasons (Glintborg et al., 2017; Jørgensen et al., 2017; Jung et al., 2015; Park et al., 2013; Yoo et al., 2013). Landmark studies such as the NOR-SWITCH trial (a 52-week, randomised, double-blind, non-inferiority study) demonstrate that biosimilars, such as the infliximab biosimilar CT-P13, are indeed non-inferior to their reference counterparts (Jørgensen et al., 2017).

Transitioning in clinical practice can practically and ethically only be done in an un-blinded open-label fashion, and this adds a layer of complexity by introducing nocebo responses and the possibility of patients misattributing common symptoms to the new therapy (Colloca et al., 2019; Tan et al., 2014). The nocebo effect is the occurrence of adverse symptoms that cannot be explained by biological effects of the drug and usually arise from negative expectations about a treatment (Faasse & Petrie, 2013; Petrie & Rief, 2019). The nocebo effect is common in switches to new formulations of existing drugs or transitions from branded to generic medicines (Faasse et al., 2013; Faasse et al., 2010).

Nocebo effects have also been found when transitioning patients from a bio-originator to a biosimilar whereby common symptoms are falsely attributed to the change in treatment. For example, in an open-label study transitioning 192 rheumatology patients from the infliximab bio-originator to biosimilar CT-P13, 24% discontinued during the six-month study period, predominantly due to subjective health complaints or perceived loss of efficacy, but not due to objective adverse events or loss of response (Tweehuysen, van den Bemt, et al., 2018). A recent systematic review of 31 trials further supports the presence of nocebo responses, by demonstrating higher discontinuation rates in open-label transitioning (whereby patients are aware of the change to the biosimilar) compared to double-blinded studies (14.3% versus 6.95% respectively) (Odinet et al., 2018). Given the rigorous testing biosimilars undergo to

prove their comparability to the bio-originator, these differences are not likely to be due to the biosimilar itself (Rezk & Pieper, 2018).

Nocebo responses are easily amplified, such as by social modelling or by media reports of patients mentioning side effects from their new treatment (Faasse et al., 2012; Faasse & Petrie, 2016; MacKrill et al., 2020). The content and delivery of drug information can also enhance nocebo responses. Providing patients with information that focuses on negative attributes, such as side effects or the minority of patients who do not respond to the treatment, increases the risk for developing negative expectations (Colloca et al., 2019; Petrie & Rief, 2019; Wells & Kaptchuk, 2012). Negative expectations can also be induced through non-verbal and verbal communication by healthcare providers, such as by unintentionally signalling a low confidence in the treatment (Kim, Alten, et al., 2020; Rezk & Pieper, 2017). Of concern, a recent systematic review demonstrated that around two-thirds of physicians have apprehensions about biosimilars, remain doubtful about safety, efficacy, and immunogenicity, and prefer to prescribe biosimilars for biologic-naïve patients rather than transitioning existing patients (Sarnola et al., 2020). These perceptions are problematic, as patients predominantly rely on their physician to obtain information and are more willing to consider biosimilar treatment if recommended by their physician (Kovitwanichkanont et al., 2020).

Patient concerns about biosimilars, particularly about their efficacy, safety, different molecular structure, interchangeability, and automatic substitution, have frequently been noted in the literature (Jacobs et al., 2016; Sullivan et al., 2017; van Overbeeke et al., 2017; Waller et al., 2017). Holding these concerns, alongside perceiving their current bio-originator to be an effective treatment, largely translates to an unwillingness to transition to biosimilars (Gasteiger, Lobo, et al., 2021). However, patient acceptance is particularly crucial in non-mandatory transitions, and where patients do not directly pay for medicines, to ensure that biosimilars can enter the pharmaceutical market and compete with bio-originators (Ferrario et al., 2020). Although patient approval is not always needed to transition patients (i.e., in mandatory transitions), negative perceptions towards biosimilars may still result in intentional non-adherence or discontinuation (Rezk & Pieper, 2017). Thus, poor patient acceptance may lead to a lower uptake of biosimilar treatments and worse health outcomes.

Patient education and the provision of appropriate information about biosimilar transitions may assist in improving the acceptance and uptake of biosimilars (Kim, Alten, et al., 2020).

Research demonstrates that the nocebo effect generally occurs in the first weeks following a change, leading to initial low persistence rates (Germain et al., 2020). Communication, particularly that provided in the initial period of a transition, is crucial for long-term acceptance (Germain et al., 2020). Appropriate communication helps address negative perceptions, increases compliance, and reduces the risk of patients seeking additional information that lacks credibility (DeMarco et al., 2011). Previous research provides some advice on delivering patient education and content that should be included in communication strategies to improve patient acceptance. For example, using positive framing to emphasise biosimilar safety and efficacy, being cautious when presenting contextual information such as cost and providing patients time to ask questions (Colloca, 2017; Colloca et al., 2019; Gasteiger et al., 2019; Vandenplas et al., 2021). Researchers also advise that it is important to find a balance between providing enough information to ensure informed consent without inducing nocebo responses (Pouillon et al., 2018). While Vandenplas et al. (2021) suggest tailoring the amount of information provided to patients to align with preferences, it remains unclear how much information should be given in the initial stages of a communication strategy. A more comprehensive understanding of already implemented communication strategies is needed to help guide future biosimilar transitions, as no best evidence synthesis is available yet.

This study aimed to systematically review global communication strategies used to educate patients on transitioning from a bio-originator to a biosimilar. It also investigated whether patients' acceptance of biosimilars regarding 1) being willing to transition and 2) their persistence on the treatment differs for types of delivery and the amount of content provided in communication strategies. Additionally, available data on subjective adverse events was collected to explore whether nocebo reporting differs between communication strategies. For the purpose of this review, a communication strategy was conceptualised as strategic health communication, which aims to inform, educate and improve patient understanding about transitioning to biosimilars (Bernhardt, 2004).

Methods

Inclusion Criteria

Studies that reported a communication strategy conducted by healthcare professionals (nurse, pharmacist, or doctor) to notify or educate patients about transitioning to a biosimilar were

considered eligible. Studies were selected if they fulfilled the following inclusion criteria: communicated a transition from a bio-originator to a biosimilar to adult patients, were written in the English language, were published in or after 2012, and reported data on biosimilar acceptance (willingness to transition and/or persistence) (Appendix A). The year 2012 was chosen as biosimilars were becoming readily approved by the European Medicines Agency around this time and to ensure early biosimilar transitions were captured (Gherghescu & Delgado-Charro, 2020). In addition, all original papers (experimental designs and real-life observational transitions) and conference abstracts were considered eligible. Observational studies were included in the review, as randomised controlled trials that explore different communication methods may be difficult to conduct in a real-life transition (Mueller et al., 2018). Therefore, it was expected that most studies in this area would be observational. Observational studies were also chosen for inclusion in the review to capture the breadth of experience of using different communication strategies. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed (Liberati et al., 2009), and the study was registered in the International Prospective Register of Systematic Reviews (CRD42020187377).

Data Sources and Searches

MEDLINE® (via Ovid), Scopus® and Embase® were systematically searched to identify relevant published studies from January 1, 2012, to August 17, 2020. Given the relatively new interest in nocebo responses and communication strategies in biosimilar transitions, databases for relevant conferences (held in 2018 and 2019) were also searched to identify recent studies. The search strategy employed various common phrases and terms about biosimilar transitions and was developed with input from a specialist librarian. The search strategy was kept as similar as possible across each database, however minor changes were made to account for the differences in indexed search terms and keywords (Appendix A).

Data Collection

After removing duplicates in Endnote X8, one author (CG) reviewed the titles, abstracts and full texts to determine their eligibility for inclusion in Rayyan (Ouzzani et al., 2016). Two authors (CG and NG) independently reviewed the initial selection and decided on the final included studies. Data from each selected article was extracted into a structured Excel spreadsheet. Extracted data included study characteristics (aim, design, country of origin,

data collection time period), information about participants (e.g., sample size, age, gender, diagnosis, prior bio-originator treatment and biosimilar) and the transition (year, treatment involved, mandatory or non-mandatory). Non-mandatory transitions were defined as a transition whereby patients were given the choice to continue bio-originator treatment, or transition to the biosimilar at their current clinic, and that in case of perceived lack of efficacy or adverse events reinstating the originator was possible (Scherlinger & Schaeverbeke, 2020). A mandatory transition did not include any choice for the patient. We also regarded instances in which patients were notified that if they did not want to transition to the biosimilar, they had to seek care at a nearby hospital, as a mandatory transition.

Information about communication strategies (delivery, content, provider of information) and proportions for each outcome variable were also extracted. The outcome variables were patient willingness to transition, treatment persistence and subjective adverse events. Willingness to transition was defined as the true number of those eligible (e.g., absence of unstable disease activity which would prohibit a transition or when physicians do not recommend the transition) who agreed to change to a biosimilar in a non-mandatory (choice) transition. Treatment persistence was defined to be the number of patients who continued the treatment at six months follow-up. For subjective adverse events, data regarding how many patients in total experienced subjective health complaints was extracted. Subjective adverse events were conceptualised as adverse effects only perceptible to the patient (e.g., nausea, arthralgia, and fatigue) (Tweehuysen, Huiskes, et al., 2018; Ursin, 1997).

Risk of Bias

A quality analysis was performed by a single author (CG) and independently verified by a second author (NG). The quality of each study was assessed using a quality assessment tool by Sarnola et al. (2020). This tool was developed to concisely assess quality for varying study designs and was adapted from the protocols of Åkesson et al. (2007); Joanna Briggs Institute (2014); Swedish Agency for Health Technology Assessment and Assessment of Social Services (2016); and Tong et al. (2007). This tool has previously been reported and used by Sarnola et al. (2020) in a systematic review exploring physicians' perceptions towards biosimilars. The risk of bias assessment was not conducted for conference abstracts due to abstracts having to adhere to strict word limits, which restricts study detail. When disagreement occurred, the reviewers discussed the assessment to reach consensus.

Analyses

Content from each communication strategy was categorised into themes, based on information provided in relation to the definition and explanation provided about biosimilars, reason for the transition, and information that addresses patient concerns about changing identified in existing literature. After categorising information, frequencies were calculated. Frequencies exceed 100% as communication strategies often provided more than one piece of information (such as two reasons for transitioning). Only studies that provided access to reports or documents detailing the content of the information given to patients about biosimilars were included in the content analysis.

Meta-analyses were performed to calculate the pooled proportions of patients willing to transition, the pooled proportion of patients persisting to biosimilar treatment, and the pooled proportion of patients reporting subjective adverse events. Only studies which reported the numerator and denominator to calculate proportions were included. Pre-specified subgroup analyses were performed to test for differences in pooled proportions between different methods of communication using Chi^2 statistics. The delivery of communication strategies were categorised into verbal information only (such as consultations, interviews, or telephone calls), or a combination of written and verbal information (e.g., letters or information sheets and consultation). In addition, to explore whether willingness to transition and reporting of subjective adverse events differs for the amount of written information provided to patients, a subgroup analysis was undertaken based on the following three groups: basic information that addressed 3-5 concerns, moderate information addressing 6-7 concerns, and extensive information (8-11 concerns). The groups were split using the median and tertile number of concerns as guidance. These groups were developed in regard to how many concerns they addressed, based on concerns identified in previous literature (e.g., safety, efficacy, quality, manufacturing, being able to change back, testing and previous use).

All meta-analyses were performed using an inverse-variance method with an arcsine transformation. Clopper-Pearson confidence intervals were generated for individual studies. I^2 values were used as an indicator of potential heterogeneity and random effects models were used for all values greater than 0% (Higgins & Green, 2011). All meta-analyses were performed in R (version 4.0.2) using the metaprop command and a significance level of < 5% (Schwarzer, 2017). Forest plots were computed for each analysis.

Compliance with Ethics Guidelines

This review uses studies that have previously collected data. It includes three studies conducted by some of the authors, which were conducted in accordance with the Helsinki Declaration and later guidelines.

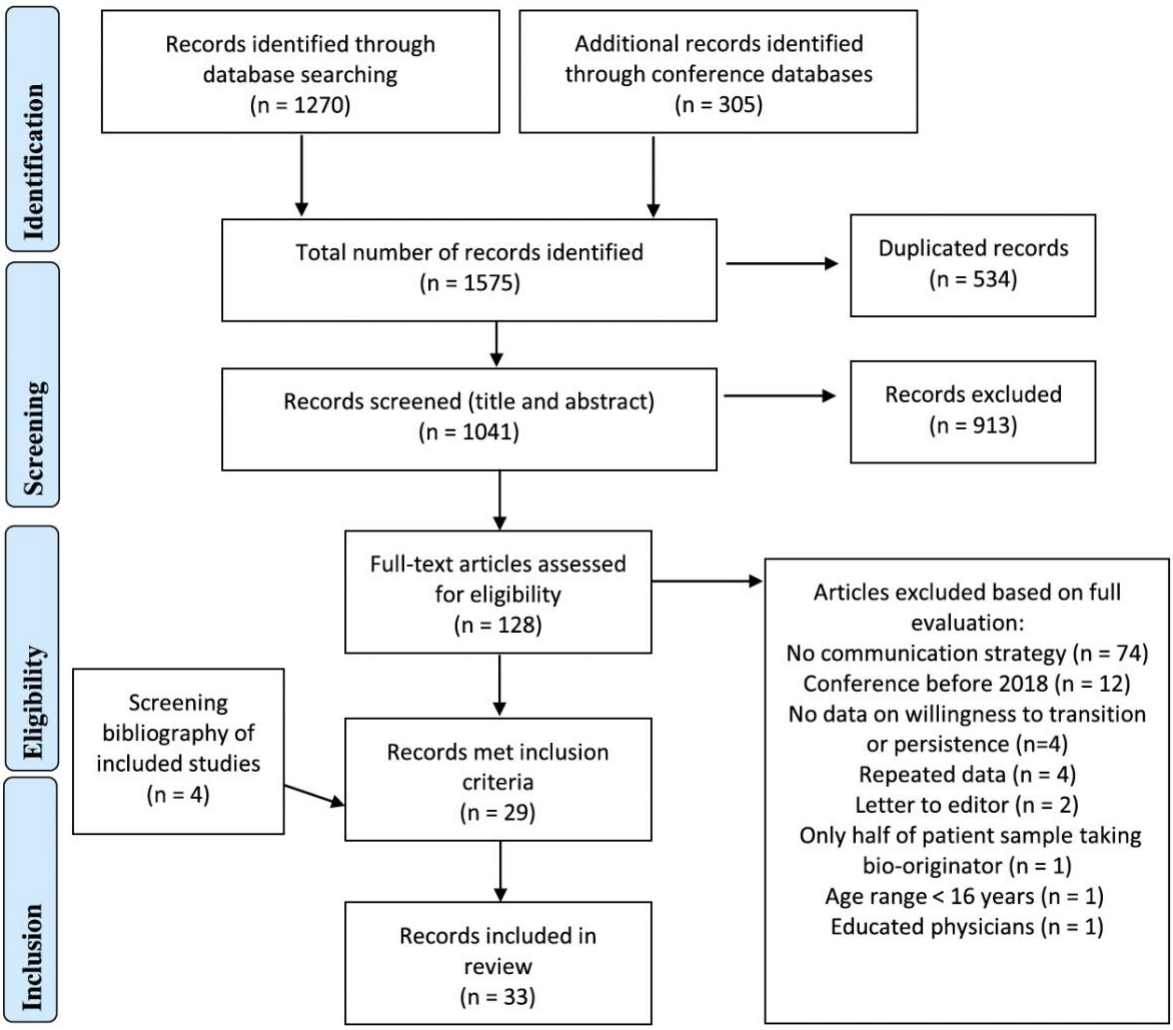
Results

Search Results

The systematic search process identified 1575 records, of which 1270 came from MEDLINE® (via Ovid), Scopus® and Embase® and 305 from conference databases. Through the screening process, 1447 were eliminated, leaving 128 for full-text review (Figure 3). Of these, 29 studies were included, with an additional four studies being identified through screening reference lists from the included studies. A total of 33 studies were included in the review (21 journal articles and 12 conference abstracts).

Figure 3

Flowchart for Results of the Search Strategy



Risk of Bias

The two raters independently made identical assessments in 17 of the 21 journal articles, leading to a Cohen's k inter-rater reliability of 0.75, (95% CI, 0.55, 0.95), 81% (substantial agreement). The remaining four cases were re-evaluated and discussed to reach consensus. Of the 21 studies, 16 were classified as high quality (> 15 points) and five were moderate quality (12-14.5 points). No studies were classified as low quality (< 12 points). Publications with high quality assessments generally presented an explicit aim, included detailed methods

and results sections, and critically discussed study findings and methods. Moderate quality studies frequently lacked some of these factors (Appendix B).

Study and Participant Characteristics

Studies were published between 2016 and 2020 and examined biosimilar transitions that occurred from 2015 to 2018 (see Appendix C for study details). Transitions mostly occurred in Europe (Netherlands *n* = 8, France *n* = 7, other *n* = 3) and the United Kingdom (England *n* = 10, other *n* = 2). Two studies occurred in the United States of America and one study occurred in Aotearoa/New Zealand.

Twenty-nine studies were real-world transitions (either retrospective or prospective observational cohort studies). Two studies were cross-sectional surveys (Chau et al., 2019; Robinson et al., 2019) and two were randomised controlled trials (Gasteiger et al., 2019; Röder et al., 2018), with one of these studying a hypothetical transitioning scenario (Gasteiger et al., 2019).

Most transitions involved only rheumatology patients (*n* = 19) or gastroenterology patients (*n* = 12). One study included a combination of rheumatology and gastroenterology patients, and a further single study involved rheumatology, gastroenterology, and dermatology patients. Mean ages of participants ranged from 37 to 60 years, with most being female (33% to 80%). Data from a total of 4822 participants was included in the review, with 2911 out of 3398 (85.7%) accepting the transition when given the choice. The most common transition was from Infliximab (Remicade®) to CT-P13 (Inflectra® or Remsima®) (*n* = 20), and Etanercept (Enbrel®) to a biosimilar (bETN) (e.g., SB4, Benepali®) (*n* = 10). Two single studies transitioned patients from adalimumab (Humira®) to a biosimilar buffered with citrate (ADA1) or a citrate-free buffer (ADA2) Amgevita®) and from Rituximab (Mabthera®) to Truxima®. One study included patients who were on a variety of biologics: adalimumab (Humira®), Etanercept (Enbrel®), Infliximab (Remicade®), Tocilizumab (Actemra®) and Rituximab (Mabthera®) (Gasteiger et al., 2019).

Communication Strategy

Seven studies used multi-disciplinary teams to develop the communication strategy or transitioning program (see Appendix D). Only two studies reported a strategy that also involved educating health professionals administrating and prescribing biosimilars (Bhat et

al., 2020; Tweehuysen, Huiskes, et al., 2018). The communication strategy was delivered by a team of clinical staff in ten studies, such as physicians, nurses, and pharmacists. In ten other studies, the information was provided by a physician only. Further, a nurse delivered the communication strategy in seven studies and in two studies pharmacists provided the information. The four remaining studies did not explicitly report who delivered the information (Petitdidier et al., 2019; Plevris et al., 2019; Röder et al., 2018; Uke et al., 2019).

Delivery. Eighteen studies reported informing patients on the transition using written information, such as letters. Seventeen of these studies provided written information, such as a letter or information sheet, alongside allowing patients to discuss the transition at an upcoming appointment (outpatient or infusion) or over the telephone. The remaining study reported only providing a letter, however, patients in the study also reported receiving verbal information (Ahmad et al., 2019).

Thirteen studies primarily delivered the information verbally using interviews, consultations, and telephone calls. Nine of these studies only used interviews and consultations to educate patients. In three other studies, patients were informed on biosimilars during the consultation and were provided information sheets during the appointment (Haghnejad et al., 2020; Petitdidier et al., 2019; Scherlinger et al., 2019). Lastly, in one study, the information was delivered over the telephone, with letters only being posted if patients could not be contacted (Bhat et al., 2020).

Two other studies only provided verbal information. In an experimental study, patients were educated using a short video of a physician providing a verbal explanation on biosimilars (Gasteiger et al., 2019). Another study reported delivering individualised information about transitioning, although it was unclear whether this was delivered in-person or over the telephone (Röder et al., 2018).

Content. Eight studies provided detailed information about the content of the communication strategy, including the provision of a telephone script, information sheet or letter (Bhat et al., 2020; Boone et al., 2018; Chan et al., 2019; Gasteiger et al., 2019; Haghnejad et al., 2020; Layegh et al., 2019; Razanskaite et al., 2017; Scherlinger et al., 2019). The remaining 25 corresponding authors were contacted for access to this information. Of those who were contacted, nine provided letters, scripts and/or information sheets.

Content analyses were conducted to explore themes pertaining to how information about biosimilars was presented. The content analyses were conducted separately for written documents (*n* = 14 studies) and information that was delivered verbally (*n* = 6 studies). As some studies provided both written and verbal information, the number of studies included in each analysis do not correspond with the number of studies who provided content to analyse. Only studies that provided detailed information were able to be included in these analyses.

Written Information. Although 18 studies reported informing patients with written information, three studies provided information sheets during consultations and one study sent letters if patients could not to be contacted, only 14 of these 22 studies provided access to this material. Therefore, only 14 studies (*n* = 15 letters or information sheets) were included in this analysis (Table 1).

Five studies defined biosimilars to be either a copy, similar to the bio-originator (*n* = 6) or used a combination of both terms (*n* = 4). Four studies did not mention the term 'biosimilar' or explained the difference between biosimilars and bio-originators in their written communication. In terms of explaining biosimilars, studies provided information about manufacturing (*n* = 11) and their difference to generic medicines (*n* = 5). The most common reason patients were provided for transitioning were cost savings (*n* = 14), the patent expiring (*n* = 11) and innovation (*n* = 3). All studies (*n* = 14) provided information about the safety and efficacy of biosimilars. Patients were also reassured about the new device (*n* = 7) and were referred to credible external resources for further information (*n* = 6). One study mentioned the possibility of transitioning back to the originator (Madenidou et al., 2019).

Verbal Information. All studies reported the use of some verbal information, including in combination with letters or information sheets, on its own during consultations, over the telephone or using a video. However, only six studies provided access to the content of the verbal information, such as interview scripts. Therefore, the content analysis only includes documents (*n* = 7 PowerPoint presentations, telephone scripts or scripts for addressing patients' questions) from six studies (Table 2).

Half of the studies (*n* = 3) defined the biosimilar as similar and five studies gave further information about the manufacturing of biosimilars. All six studies highlighted cost savings as the main reason for the transition. All studies (*n* = 6) reassured patients about the safety

and side effects of biosimilars, five studies mentioned similar efficacy and four studies reassured patients about the potential for transitioning back to the bio-originator.

Table 1

Content Analysis and Frequencies from the Available Written Information (n = 14 Studies)

Theme	N (%)	Example
Definition of Biosimilar		
Similar	6 (43)	"Different brands of Etanercept are known as 'biosimilars' because they are biological medicines which are similar to the original product." (Chan et al., 2019)
Copy	5 (36)	"A biosimilar is a copy of an originator biologic drug." (Scherlinger et al., 2019)
No specific mention of biosimilar	4 (29)	"As of June 13, 2016, we switched from the brand Enbrel to the brand Benepali as a hospital." (Tweehuysen, Huiskes, et al., 2018)
Explanation of Biosimilar		
Manufacturing	11 (79)	"Biological medicines are derived from living cells or organisms and consist of large, highly complex molecular entities which may be difficult to characterise." (Chan et al., 2019)
Generics	5 (36)	"That's why this copy is called biosimilar and not generic." (Haghnejad et al., 2020) (translated)
Variation	3 (21)	"A biologic drug is produced from cultured living cells. As all biologic products, biologic drugs have a small variability." (Scherlinger et al., 2019)
Reason for Transition		
Cost saving	14 (100)	"The big price difference between Inflectra® and Remicade® makes us choose for Inflectra®. By opting for Inflectra®, we help to ensure that care remains affordable in the future." (Boone et al., 2018)
Patent	11 (79)	"Remicade's market protection expired in February 2015…" (Tweehuysen, van den Bemt, et al., 2018)
Altruism	8 (57)	"By switching from Remicade to Remsima, the XX Clinic, together with you, contributes to keeping the care affordable in the future." (Tweehuysen, van den Bemt, et al., 2018)
Innovation	3 (21)	"Moreover, biosimilar sometimes come with technological innovations such as a needle system or an injector-pen inducing lower pain that the one from the originator drug." (Scherlinger et al., 2019)
Access	2 (14)	"The primary objective with biosimilars is therefore to guarantee optimal access for all patients to quality biological medicinal products…" (Haghnejad et al., 2020) (translated)

Choice	1 (7)	"Competition between different biological medicines, including biosimilar medicines, creates increased choice for patients and clinicians, and enhanced value propositions for individual medicines." (Chan et al., 2019)
Addressing Concerns		
Safety and side effects	14 (100)	"... demonstrating that efficacy and safety are strictly identical." (Scherlinger et al., 2019)
Efficacy	14 (100)	"This product is as good, safe and effective as the infliximab with the brand name Remicade® you are receiving now." (Boone et al., 2018)
Regulated	9 (64)	"The regulator of new drugs, the European Medicines Agency, has declared biosimilar drugs safe and interchangeable with the original drugs." (Chan et al., 2019)
Used previously	9 (64)	"Many patients have changed from Benepali® to Enbrel® without issues and we would like to consider this for you." (Chan et al., 2019)
Testing and research	9 (64)	"One Danish study, one Norwegian, and one study conducted in Bordeaux university hospital have shown excellent safety and efficacy of the switch from originator to biosimilar infliximab." (Scherlinger et al., 2019)
Quality	8 (57)	"The quality, effectiveness and safety are well researched and comparable to Remicade®." (Boone et al., 2018)
Administration	7 (50)	"The device is similar to the Enbrel device." (Chan et al., 2019)
Referral to credible resources (e.g., online)	6 (43)	"All the information on biosimilars and other treatments for IBD are available on the afa Crohn's CHR website: www.afa.asso.fr" (Haghnejad et al., 2020) (translated)
Variation	5 (36)	"Biosimilars, whom production follows the same principles than originator biologics, also have a small variability. This is the reason the term of biosimilarity exists because a strict copy is not possible." (Scherlinger et al., 2019)
Monitoring	5 (36)	"Nevertheless, we think it is important that you are being supported in the transition. Therefore, prior to the 1st infusion and during subsequent administrations, we check the inflammation values in your blood and the concentration of the drug and any antibodies against the drug." (Boone et al., 2018)

Table 2

Content Analysis and Frequencies from the Available Verbal Information (n = 6 Studies)

Theme	N (%)	Example
Definition of Biosimilar		
Similar	3 (50)	"Inflectra (IFX-dyyb) is a biosimilar, designed to be highly similar to the existing originator drug Remicade (IFX)" (Bhat et al., 2020) [Telephone call script]
As a different brand	1 (17)	"As other brand: Inflectra® and Remsima® are the brand names of infliximab biosimilar. They are identical products by the way, but are marketed under a different name by two different manufacturers." (Tweehuysen, van den Bemt, et al., 2018) [Translated F&Q for clinicians]
Explanation of Biosimilar		
Manufacturing	5 (83)	"A biological is a medicine that consists entirely or partially of animal or human protein…" (Tweehuysen, Huiskes, et al., 2018) [Translated F&Q for clinicians]
Variation	3 (50)	"The active ingredient is the same, but there may be small differences in the production process." (Tweehuysen, van den Bemt, et al., 2018) [Translated F&Q for clinicians]
How it works	2 (33)	"…inhibits the action of inflammatory proteins and immune cells in the body." (Tweehuysen, Huiskes, et al., 2018) [Translated F&Q for clinicians]
Reason for Transition		
Cost saving	6 (100)	"Switching to a biosimilar helps by saving health care costs. PHARMAC in New Zealand has a limited budget for buying medicines." (Gasteiger et al., 2019) [Script]
Access	4 (67)	"One of the benefits to using biosimilars is that they lower costs, which over time can improve insurance premiums, medication out-of-pocket costs, and medication access" (Bhat et al., 2020) [Telephone call script]
Altruism	3 (50)	"The Sint Maartens Clinic can invest this money in other care for patients with rheumatic diseases." (Tweehuysen, van den Bemt, et al., 2018) [Translated F&Q for clinicians]
Innovation	1 (17)	"It is a more modern syringe that gives less redness and irritation of the injection site"

		(Tweehuysen, Huiskes, et al., 2018) [Translated pharmacist script]
Patent	1 (17)	"Once the patent of a biological has expired, biosimilars may be marketed" (Tweehuysen, van den Bemt, et al., 2018) [Translated F&Q for clinicians]
Addressing Concerns		
Safety and side effects	6 (100)	"Most patients have been treated with Remicade for a long time without experiencing any side effects. Since both Remicade and Remsima are infliximab, the chance of side effects in Remsima is small. However, it is important to realise that some patients are a little anxious about switching to Remsima. This fear can lead to complaints (nocebo) or can lead to the assignment of symptoms to the Remsima (incorrect causal attribution)." (Tweehuysen, van den Bemt, et al., 2018) [Translated F&Q for clinicians]
Efficacy	5 (83)	"..as with any new drug, it is not possible to be absolutely certain that you will get the same beneficial effects." (Gasteiger et al., 2019) [Script]
Changing back	4 (67)	"However, if there is any thought of a side effect of Remsima that the patient previously did not have on the Remicade, it may be considered to return the Remicade." (Tweehuysen, van den Bemt, et al., 2018) [Translated F&Q for clinicians]
Testing and research	4 (67)	"Scientific research on rheumatoid arthritis patients has shown that Benepali is as good, effective and safe as Enbrel. (Tweehuysen, Huiskes, et al., 2018) [Translated F&Q for clinicians]
Administration	3 (50)	"Although these medications are not identical, they work in the same way and have the same dose, administration (intravenous infusion), and side effects. Inform patient that infusion time and frequency will be unchanged from when they received IFX." (Bhat et al., 2020) [Telephone call script]
Used previously	3 (50)	"Biosimilar medications are increasingly used in rheumatology and dermatology clinics worldwide." (Gasteiger et al., 2019) [Script]
Variation	3 (50)	"No, the excipients are not the same. Benepali's solution is less acidic, which makes it less irritating when administered. This is an advantage, because Benepali has less chance of side effects." (Tweehuysen, Huiskes, et al., 2018) [Translated F&Q for clinicians]
Regulation	2 (33)	"..and is FDA-approved to treat [insert patient condition]"

		(Bhat et al., 2020) [Telephone call script]
Referral to credible resources	2 (33)	"The instruction card also includes a website. At home you can watch the video in which the pharmacist's assistant of the Sint Maartenskliniek does the spraying." (Tweehuysen, Huiskes, et al., 2018) [Translated pharmacist script]
Quality	1 (17)	"The quality of Enbrel and Benepali is similar, they both contain the active ingredient etanercept. Benepali is a product with the same quality, maybe even better, but for a lower price." (Tweehuysen, Huiskes, et al., 2018) [Translated F&Q for clinicians]
Monitoring	1 (17)	"We will keep monitoring you in the same way as you have been while you have been taking the biologic." (Gasteiger et al., 2019) [Script]

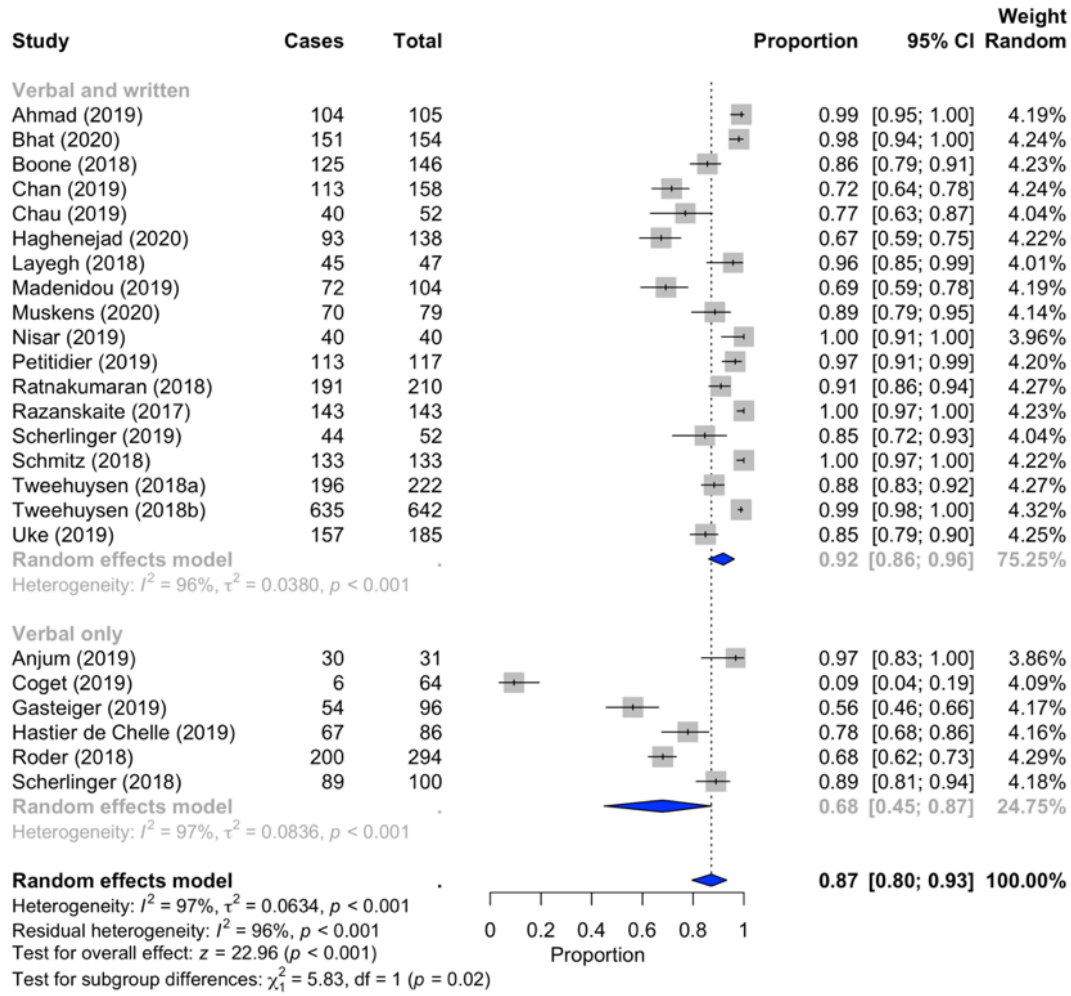
Meta-Analyses of Pooled Proportions

Delivery of Communication Strategy. Meta-analyses were conducted to explore whether there was a difference in patient willingness to transition when receiving information verbally or in a combined format (written and verbal). A total of 24 studies provided data on patient willingness to transition to the biosimilar and were able to be included in this analysis. There was a significant difference, with the highest willingness to transition (92% (95% CI, 86 – 96%)) being seen in patients who received both written and verbal information, compared to 68% (95% CI, 45 – 87%) of patients who only received verbal information, $\chi^2(1, 3398) = 5.83$, $p = .02$ (95% CI, 80 – 93%) (Figure 4). There was considerable heterogeneity between studies $I^2 = 97\%$.

Meta-analyses were also conducted to explore whether was a difference in persistence and reporting of subjective adverse events when receiving information verbally or in a combined format. Eleven studies provided data on patient persistence to the biosimilar at 3-6 months follow-up and 17 studies reported data on subjective adverse events, which were included in the analyses. There was no significant difference between communication delivery for persistence at 3-6 months follow-up, with 87% of those in the combination group and 91% in the verbal information group persisting to the biosimilar treatment, $\chi^2(1, 2244) = 1.09$, $p = .30$, $I^2 = 85\%$, 95% CI, 85 – 92%. There was also no significant difference for subjective adverse event reporting at 3-12 months follow-up, with 7% of the pooled proportion reporting subjective adverse events in the combination group and 5% in the verbal group, $\chi^2(1, 2215) = 0.78$, $p = .38$, $I^2 = 81\%$, 95% CI, 4 – 9% (see Appendix E).

Figure 4

Pooled Proportion of Patients Willing to Transition Based on Different Methods of Communication

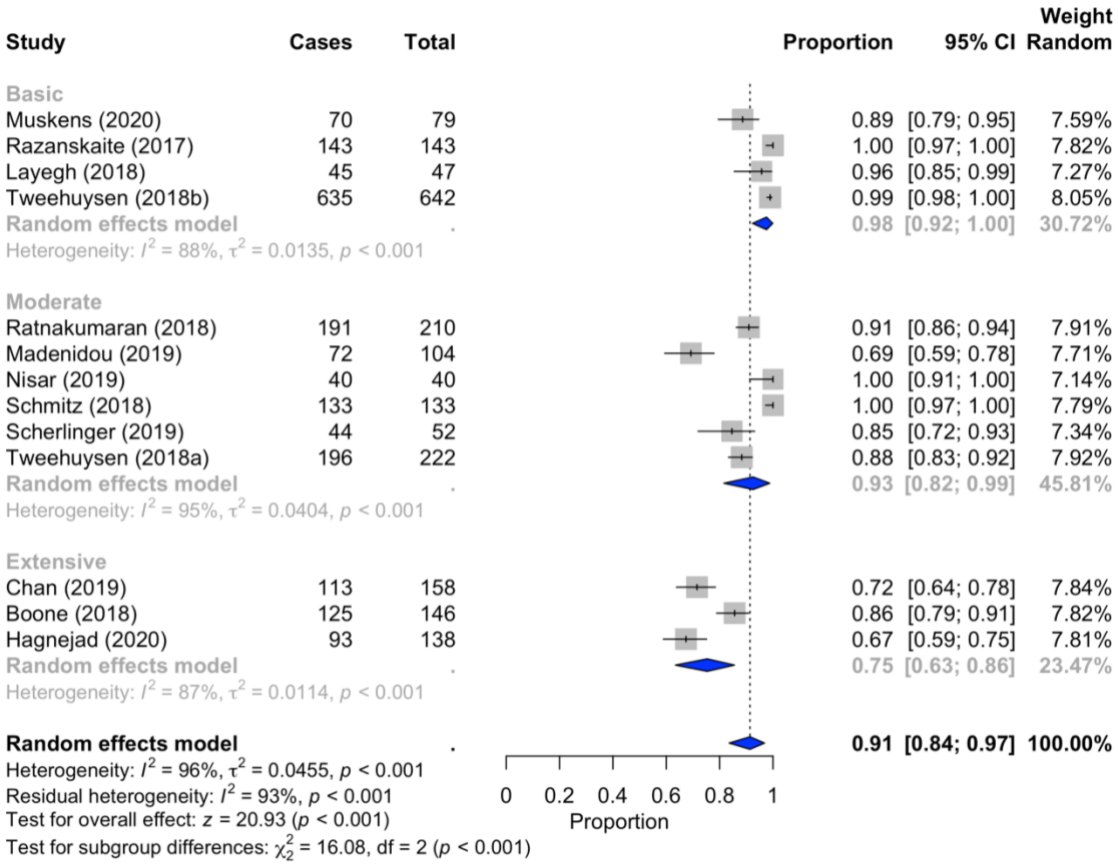


Content of Communication Strategy. Meta-analyses were conducted to explore whether there was a difference in willingness to transition when receiving different amounts of information about biosimilars. Thirteen studies reported both data on patient willingness to transition and provided access to patient information documents, so were included in the analysis. There was a significant difference between groups for the proportion of patients who were willing to transition, $\chi^2(2, 2114) = 16.08$, $p < 0.001$, 95% CI, 84 – 97%, with those receiving the least amount of information having the highest proportion of patients being willing to transition (basic 98% (95% CI, 92 – 100%), moderate 93% (95% CI, 82 – 99%) and extensive 75% (95% CI, 63 – 86%)) (Figure 5). There was considerable heterogeneity I^2 = 96%.

Meta-analyses were also conducted to explore whether there was a difference in patient reporting of subjective adverse events when receiving different amounts of information about biosimilars. Ten studies reported data on subjective adverse events and provided access to the patient information documents and were included in this analysis. There was no significant between-group difference for reporting subjective adverse events at 3-12 months follow-up (13% basic, 7% moderate and 9% extensive), $\chi^2(2, 1724) = 1.94$, $p = .38$, I2 = 87%, 95% CI, 5 – 13% (Appendix E).

Figure 5

Pooled Proportion of Patients Willing to Transition After Receiving Information



Discussion

This is the first study to systematically review and meta-analyse communication strategies used in global mandatory and non-mandatory transitions to biosimilars. Studies that provided written information that only addressed a few concerns and those which used a combined verbal and written communication strategy had a higher proportion of patients willing to take

the biosimilar in non-mandatory transitions. However, there was no significant difference for the reporting of subjective adverse events and treatment persistence.

Key information provided in previous patient communication includes highlighting similarities between the originator and biosimilar in terms of safety, side effects, and efficacy, noting that biosimilars are regulated, tested, and previously used, transparency about cost saving potential, and basic information on manufacturing. Based on these findings, future transitions should provide patients with written documents (e.g., a letter notifying patients of the transition) containing basic information that only addresses a few major concerns (e.g., comparable safety, efficacy, quality, and previous use). Clinical staff, such as physicians, specialist nurses, or pharmacists, should answer questions at an upcoming outpatient consultation, infusion appointment, or over the telephone. This strategy would enable patients time to internalise the information, discuss the transition with a support person or family, and have concerns alleviated by healthcare providers (Colloca, 2017; Colloca et al., 2019). It may also minimise the possibility of information overload, which could deter patients from being involved in decision-making for non-mandatory transitions (Khaleel et al., 2020). In line with the cognitive load theory, ensuring that patients are not overloaded with complex information about biosimilars can ensure patients have the cognitive capacity to adequately process key information about the transition (Sweller, 1988).

As consistent with previous research, the content and delivery of information provided to patients may play a role in the uptake of biosimilars (Edwards et al., 2019; Fleischmann et al., 2020; Kay, 2020; Rezk & Pieper, 2018). In addition, the information identified in the content analyses is in line with previous recommendations on communicating biosimilar transitions, such as the guidelines by the European Crohn's and Colitis Organisation (ECCO). ECCO advocates for providing appropriate and transparent information, such as the tangible benefits of biosimilars and reasons for non-medical transitioning to ensure patients are fully informed and to promote evidence-based patient choice (Danese et al., 2017).

As also consistent with previous research, the reviewed non-mandatory transitions demonstrated a relatively high willingness to take the biosimilar (average of 86%, range 9% to 100%) (Ebbers et al., 2019). Of note, the lowest willingness to transition was reported by Coget (2019) in a sample of patients taking infliximab for irritable bowel disease in France. In this study, a standardised pharmaceutical interview was conducted to assess patient acceptance of biosimilars and evaluate their knowledge. Although 38% of patients were

favourable to changing to biosimilars following the pharmaceutical interview, only six patients (9%) in the sample changed to biosimilars, which was explained to be partly related to a lack of information. While our findings show that patient willingness to transition differs by communication strategy content and delivery, high acceptance rates in previous studies indicate that other factors may also play a part. For example, non-mandatory transitions can be viewed as altruistic because changing to the biosimilar does not really benefit those transitioning. Rather, collectively changing to biosimilars generates cost savings for the healthcare system, particularly where patients do not directly pay for drugs, and can enable increased access to biosimilars for more patients (Murdoch & Caulfield, 2020). Altruism may be a noteworthy part of biosimilar acceptance, but this is yet to be extensively researched.

Biosimilar transitions studied in this review are primarily driven by economics rather than patient preference. This may heighten the risk for nocebo responses, particularly where the transition is mandated and patient choice has been restricted or removed entirely (Fleischmann et al., 2020). Patients who are not given their preferred treatment are likely to be wary and misattribute side effects to the new medication (Bartley et al., 2016). However, it can also cause distrust in the physician and health system and intentional non-adherence, which can ultimately reverse the benefits of biosimilars (Betegnie et al., 2016; Fleischmann et al., 2020; Rezk & Pieper, 2017). Effectively communicating transitions can help patients transition and aid physicians in developing trust and realising shared decision-making, which is central to providing patient-centred care. This is crucial as alongside the appropriate provision of information, clinician confidence and a good therapeutic relationship play major roles in accepting biosimilars for some patients (Kovitwanichkanont et al., 2020; Scherlinger et al., 2019; Tweehuysen, van den Bemt, et al., 2018). It is probable that the hospitals that gave patients the decision to transition and allocated resources to provide both written and verbal information had a stronger strategy to promote patient-centred care. This, along with the ability to review written information and prepare questions for the verbal discussion, may partly explain our findings that combined strategies showed higher patient willingness to transition.

An important finding was the purpose of the transition communicated to patients. Most strategies acknowledged cost savings; however, some mentioned the opportunity for more treatment options and innovation. The improved, innovative technology biosimilars can offer may be particularly appealing for patients who self-administer the drug by subcutaneous

injection, but where dexterity is an issue (Edwards et al., 2019). As most studies were conducted in Europe where biosimilars are funded through the public health system, some patients may not be concerned about cost savings. Of note, for a small group of patients the lower cost was a factor of biosimilar acceptance (Scherlinger et al., 2019). However, for others focusing on the reduced cost could lead to misconceptions that biosimilars are inferior in quality (Wilkins et al., 2014). Educating patients on the benefits of transitioning for both society (e.g., saving healthcare costs and improved access) and the individual (e.g., innovation and increased choice), may therefore help improve understanding of the wider benefits of biosimilars.

Four studies that were included in the content analysis did not mention the term 'biosimilar' in their communication strategy. Given that patients have historically reported concerns about biosimilars not being exact copies, framing a biosimilar to be a new brand instead could help address this concern (Gasteiger et al., 2019). Yet, a lack of this information could also lead to confusion and distrust for patients who independently seek information (e.g., on the Internet). The use of positive framing (such as highlighting similarities), directing patients to credible information on the Internet, and employing managed transitioning programs to ensure information is standardised may help overcome this problem (Armuzzi et al., 2019; Kristensen et al., 2018).

It is also interesting to note that the method of the transition and communicating the option to transition back to the bio-originator can play a role in acceptance. Tweehuysen, Huiskes, et al. (2018) found an acceptance rate of 99% using an 'opt-out' approach, whereby patients were transitioned to the biosimilar unless they actively objected. In contrast, Müskens et al. (2020) used an 'opt-in' approach and reported an acceptance rate of 89%. Müskens et al. (2020) also reported a high nocebo response (13%) and a significant portion of patients who discontinued returned to the originator (63%). Tweehuysen, Huiskes, et al. (2018) instead used a "wait and see" approach if patients experienced subjective health complaints and reported a high persistence at 6 months (90%). Evidence suggests that a small proportion of patients may regain treatment control by transitioning back to the originator (Fleischmann et al., 2020). Therefore, it is suggested that patients have the ability to return to the originator if experiencing adverse events or reduced response, and patients have previously been reassured by this option (Fleischmann et al., 2020; Gasteiger et al., 2019). But, communicating the option might trigger nocebo responses by unintentionally signifying that

the biosimilar is not expected to be effective. This suggests that the method of transitioning and provider-patient communication influence the acceptance rate of transitioning.

This systematic review and meta-analysis is the first to systematically explore communication strategies used in global biosimilar transitions and investigate differences in patient acceptance of biosimilars. However, several limitations should be considered. Most importantly, findings are largely based on observational data (88% were observational cohort studies). Therefore, causal claims cannot be made (Metelli & Chaimani, 2020). More randomised controlled trials are needed to confirm whether a causal relationship exists. The review also includes research from various countries with unique healthcare settings. These may impact how biosimilars are integrated into the pharmaceutical market, the extent to which prescribers adopt biosimilars, and how transitions are communicated to patients. It is also difficult to understand the true value of communication strategies without comparing communication strategies to not informing patients about the change to biosimilars. However, it should be noted that this is not possible to investigate for ethical reasons. Various studies also reported allowing patients to further discuss the transition over the telephone or at an upcoming appointment. However, it is often unclear whether patients accepted this offer or whether the written information was sufficient.

It was also not possible to gather detailed information or access materials from all of the communication strategies used in the 33 eligible studies. This was partially due to outdated correspondence details, limited responses by corresponding authors, and some clinical organisations restricting access to documents. Our findings are therefore limited to the data that we were able to gather. It should also be noted that including conference articles is a limitation, as abstracts do not contain enough information to conduct bias assessments and are not privy to rigorous peer-reviewing. However, consistent with guidelines on including abstracts, this was justified due to the limited availability of evidence in this area, and authors were contacted for supplementary information (Scherer & Saldanha, 2019).

There was also considerable heterogeneity between studies that were included, such as the content of communication strategies and varying follow-up time-periods following a transition. This is likely to be a partial explanation of why subjective adverse event reporting and treatment persistence did not significantly differ in the analyses exploring the delivery and content of communication strategies. Similarly, there was not enough data to conduct all

the pre-determined analyses for persistence and subjective adverse event reporting at more than one time point or to stratify analyses by mandatory and non-mandatory transitions.

Another limitation that needs to be considered is the conceptualisation of 'mandatory' and 'non-mandatory' transitions. In a recent article, the authors defined mandatory as the case whereby patients are informed and automatically transitioned unless actively objecting (Müskens et al., 2019). Müskens et al. (2019) therefore classified the study by Tweehuysen, Huiskes, et al. (2018) as a mandatory transition, although the authors described it as a non-mandatory transition using an 'opt-out' approach. In our review, a mandatory transition is viewed as that being one that removes all patient decision and involvement, where rather non-mandatory transitions involve patient decision via opt-in or opt-out approaches. As Tweehuysen, Huiskes, et al. (2018) enabled patients to actively refuse the transition we classed the study as non-mandatory. The definition of these terms needs to be taken into account when considering the findings of the review.

More research in this area is warranted. It seems that only six studies specifically aimed to explore communication strategies in biosimilar transitions and only one did this using a randomised controlled design (Gasteiger et al., 2019; Haghnejad et al., 2020; Hastier-De Chelle et al., 2019; Kiltz et al., 2019; Petit et al., 2019; Razanskaite et al., 2017). Very few studies also explored patients' evaluation of the transition. Further, only two studies described educating clinical staff administrating or prescribing biosimilars as part of the communication strategy. Given that health providers can transfer negative perceptions to patients, and some have demonstrated a lack of knowledge and uncertainty in how to explain the transition, more research is needed (Hemmington et al., 2017; Shakeel et al., 2020). It has also been argued that resources should be developed in parallel for caregivers who have similar negative perceptions towards biosimilars (Jacobs et al., 2016). However, no studies in the review specifically developed educational documents for people other than the patient. It should, however, be noted that this review did not specifically set out to explore education for clinical staff or caregivers.

Future research should examine whether the administration type (injection or infusion) and the environment where biosimilars are administered (home or hospital) influences subjective adverse event reporting. Most studies included in the review focused on biosimilars administered via infusion and, importantly, in close proximity to other patients (e.g., infliximab biosimilar, CT-P13). Tweehuysen, Huiskes, et al. (2018) argue that patients could

develop beliefs about inferiority after observing a fellow patient have a negative experience after transitioning to a biosimilar and may therefore be less willing to change to biosimilars. The social modelling theory supports this idea, whereby witnessing others' adverse response to a treatment can negatively influence expectations about the treatment's efficacy and ultimately increase side effect reporting (Faasse, Grey, Jordan, et al., 2015; Faasse & Petrie, 2016). Since some biosimilars, such as SB4 (etanercept biosimilar), are self-administered at home, without contact to other patients, social modelling is less likely to occur.

Conversely, the transition may be more obvious to patients who self-administer the treatment at home through subcutaneous injection. The direct exposure to differences in branding and potential changes in the administration device (i.e., autoinjector versus prefilled syringe) can heighten patients' negative expectations (Faasse et al., 2013). Following self-administration, patients are also often asked to note down their experience to help track and monitor results. Asking patients to report symptoms may lead to over-reporting side effects and misattribution to the new drug (Ferrari, 2010). Patients who receive their treatment via intravenous infusion at the hospital are not likely to be directly exposed to brand or device changes following a biosimilar transition. As nurses prepare and deliver the drug and monitor patients, there is less opportunity for patients to develop negative expectations. Nurses are also present to reassure patients should concerns arise (Waller & Friganović, 2020).

Patients who were provided written information that addressed few concerns and were able to discuss the transition with a physician, pharmacist or nurse reported higher willingness to transition to biosimilars. However, there was no significant difference for subjective adverse event reporting and drug persistence, potentially due to limited research and considerable heterogeneity between studies. A synthesis of the information provided to patients demonstrated that studies predominantly mentioned a similar safety, side effect and efficacy profile, biosimilar regulation, and approval, testing and previous use, transparency about cost saving potential, and basic information on manufacturing. Examples provided can be used to guide future patient communication. As biosimilars continue to penetrate pharmaceutical markets, much more remains to be learned about how the provision of information influences the success of biosimilar adoption.

Chapter Four: Pharmacists' Confidence in Explaining Biosimilars

Preface

In November 2021, the Pharmaceutical Management Agency (Pharmac) in Aotearoa/New Zealand announced the decision to fund a biosimilar for adalimumab, named Amgevita, as the outcome of a lengthy tendering process (Pharmaceutical Management Agency, 2021b). The transition was expected to benefit 700 patients in the first year, improve access by widening criteria and reduce injection site pain due to Amgevita containing a citrate-free buffer (Pharmaceutical Management Agency, 2021b). Patients receiving care in dermatology, gastroenterology, ophthalmology, and rheumatology began transitioning from Humira in March 2022, with adalimumab naïve patients also being initiated on Amgevita. Some patients, such as those with exceptional circumstances, Crohn's disease, or ocular inflammation at risk for vision loss or disease destabilisation, remained on Humira. Amgevita is administrated subcutaneously by patients at home and, consequently, dispensed by pharmacists, who may also educate patients, such as by demonstrating the new device (Pharmaceutical Management Agency, 2021a).

Chapter 3 highlights that global communication strategies frequently employed a multidisciplinary approach, relying on healthcare providers like pharmacists to support patients through the transition and provide education. Other research reinforces that delivering a homogenous message by a multidisciplinary team is central to a successful transition (Gasteiger, den Broeder, et al., 2021; Oskouei & Kusmierczyk, 2021). While research has yet to explore Aotearoa/New Zealand pharmacists' attitudes to biosimilars, international studies have highlighted concerns about variation, feeling uncomfortable with transitioning patients to biosimilars, and demonstrate an urgent need for more education (Aladul et al., 2019; Arnet et al., 2021; Barbier et al., 2021; Okoro et al., 2021; Pawlowska et al., 2019). A quarter of 36 Belgian pharmacists in one study also felt insufficiently trained to answer questions about biosimilars (Barbier et al., 2021).

Patients prefer physicians informing them about biosimilars, with pharmacists the second preference (Vandenplas et al., 2022). This preference may be due to their standing as 'experts of medicines,' patients' existing relationship with their pharmacist, and as pharmacists are easily accessible due to their long opening hours (Darlow et al., 2022). Ensuring that pharmacists are informed and knowledgeable about key concepts such as safety, efficacy,

quality, regulation, and testing is critical. In a transition to SB4 (etanercept biosimilar – also administered by patients), two patients refused to transition due to receiving contradicting and negative information from their regular pharmacist, although previously receiving positive information from their physician (Scherlinger et al., 2019). Pharmacists may unintentionally heighten resistance in the initial stages of a transition but also influence long-term persistence due to their ongoing communication with patients after the transition has occurred.

The upcoming adalimumab transition to Amgevita provided an opportunity to examine whether pharmacists in Aotearoa/New Zealand felt prepared to educate patients about biosimilars. The following nationwide cross-sectional study explored hospital, community, and primary care pharmacists' confidence in explaining biosimilars to patients and determined the information pharmacists would provide in response to common queries. The study also examined the characteristics associated with their confidence in explaining biosimilars. Findings highlight gaps in understanding that Pharmac and other organisations can aim to address before patients are readily transitioned to biosimilars.

Citation

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Introduction

Biosimilars have the potential to improve access to biological therapies for patients with chronic immune-mediated inflammatory diseases. These drugs are manufactured following patent expiry and are highly similar to a reference drug (bio-originator) that has previously gained regulatory approval (European Medicines Agency, 2019; U.S. Food and Drug Administration, 2017). The introduction of biosimilars can, therefore, induce price competition among biologics. This enables funders to choose the most competitive biological medicine, leading to cost savings for the healthcare system and the ability for more patients to access biological treatment. The successful uptake of biosimilars partially relies on patient acceptance. Effective patient-provider communication is important to build familiarity with biosimilars and transfer confidence to patients that the biosimilar has a comparable safety and efficacy profile (Jacobs et al., 2016; Kovitwanichkanont et al., 2020; Peyrin-Biroulet et al., 2017). Researchers have agreed that a multidisciplinary approach to educating patients is needed as patients often seek information from numerous sources (Cohen & McCabe, 2020; Peyrin-Biroulet et al., 2019; Vandenplas et al., 2021). Therefore, it is essential that all sources provide homogenous information (Scherlinger et al., 2019; Vandenplas et al., 2021). Healthcare providers such as physicians, specialist nurses, and pharmacists, should be prepared to educate patients collaboratively to improve acceptance (Oskouei & Kusmierczyk, 2021).

To date, the literature has primarily focused on exploring communication strategies in physicians, with some research now starting to explore nurse-led education (Armuzzi et al., 2019; Gall et al., 2021; Petit et al., 2021). Pharmacists also play an important role in supporting physicians and educating patients, as the trusted experts on medicines (Arnet et al., 2021). Pharmacists may provide education on a variety of topics including how biosimilars differ to the bio-originator, manufacturing and testing processes, injection techniques and possible side effects. However, some pharmacists have reported lacking

knowledge and feel uncomfortable with changing patients to biosimilars (Aladul et al., 2019; Arnet et al., 2021; Okoro et al., 2021; Pawlowska et al., 2019). A recent survey with Belgian community pharmacists demonstrated a unanimous need for information about biologics (Barbier et al., 2021). Of concern, 36% felt insufficiently trained to dispense and guide patients with biosimilars, and 25% felt insufficiently trained to answer questions. Evidently, it is important to identify pharmacists who may be less confident and require additional training. More research is also needed to assess hospital, community, and primary care pharmacists' confidence and readiness to educate patients, particularly as their experiences and knowledge differ across settings (Beck et al., 2017).

Pharmacists are well placed to support educational attempts; however, a lack of knowledge can also escalate biosimilar hesitancy. In one study, two patients who had agreed to transition (primary acceptance rate 92%) did not begin SB4 treatment (etanercept biosimilar) due to receiving negative and contradictory information from their regular pharmacist (Scherlinger et al., 2019). These patients had received positive information on biosimilars from their physician and written information previously used to improve acceptance of generic medicines. Unsatisfactory communication can also induce concerns and negative expectations about new treatments, leading to intentional non-adherence and increased side effect reporting (Kravvariti et al., 2018; Nestoriuc et al., 2016; Smith et al., 2020). However, emphasising the similarities between the brands or discussing approval processes may improve perceptions about safety and efficacy (Gasteiger et al., 2019; Kleinstäuber et al., 2021). Understanding how pharmacists specifically explain biosimilars to patients can help guide future educational attempts, as some information such as cost saving, may support negative beliefs about quality (Gasteiger, den Broeder, et al., 2021).

Biosimilars have been relatively slow to penetrate the Aotearoa/New Zealand pharmaceutical market, considering the first biosimilar Nivestim (for filgrastim) gained approval in 2012 (Medicines and Medical Devices Safety Authority, 2014). There are currently only eight biosimilars funded in New Zealand that require prescribers to seek Special Authority Approval (New Zealand Formulary, 2022). Pharmacists in Aotearoa/New Zealand currently provide education and dispense some biosimilars, including Omnitrope (somatropin), Binocrit (epoetin alfa), and Riximyo (rituximab – in hospitals only). In Aotearoa/New Zealand, a government agency known as Pharmac (Pharmaceutical Management Agency) is responsible for deciding which pharmaceuticals are publicly funded. As part of this process,

Pharmac negotiates conditions of access and the price with drug companies, while encouraging competition between suppliers (Cumming, 2010). In November 2021, Pharmac announced a funding change for adalimumab, which would require most patients to begin transitioning from bio-originator Humira to the biosimilar Amgevita in March 2022 (Pharmaceutical Management Agency, 2021b). Given the importance of patient-provider communication to improve biosimilar hesitancy and the upcoming transition to Amgevita, this study examines community, hospital, and primary care pharmacists' confidence in explaining biosimilars. It also determines their concerns about biosimilars, the information pharmacists would provide in response to common queries, and which characteristics are associated with their confidence in explaining biosimilars.

Methods

Study Design

This study was a cross-sectional survey completed over the Internet by a national sample of practising hospital, community, and primary care pharmacists in Aotearoa/New Zealand. Ethics approval was obtained from the Auckland Health Research Ethics Committee (AH23564). The study was performed in accordance with the ethical standards of the Declaration of Helsinki. All participants provided informed consent. Data collection began on 10th of February 2022 and ended on 15th of May 2022.

Participants and Procedure

Participants were practising pharmacists based in Aotearoa/New Zealand either full (≥ 30 hours per week) or part-time (≤ 29 hours per week) and working in a hospital, community, or primary care setting at the time of data collection. Pharmacists had to be fluent in the English language and able to complete the survey over the Internet to participate.

The survey was designed by two health psychology researchers who have previously conducted studies on patient acceptance of biosimilars. Consultation on the survey design was sought from two representatives from the Pharmaceutical Management Agency, one of whom was an experienced pharmacist. The survey was pilot tested by three post-graduate researchers independent of the study. Pharmacists were recruited through newsletter and email communications by Pharmac, and through social media and email notices by relevant

organisations. In 2021, there were 4,062 practicing pharmacists in New Zealand, of which most were based in Auckland (1,471), Canterbury (518) or Wellington (465) (Pharmacy Council, 2021). Based on the data received from the annual practicing certificates application period, most pharmacists (78%) worked in the community. Additionally, 14% worked in the hospital and 2% worked in either a general practice or primary health organization. Relevant organizations included the national Pharmaceutical Society of New Zealand, which represents approximately 3,700 pharmacists and pharmacy technicians through advocacy, education, and advisory services. The study was also shared by a national newspaper for pharmacists (Pharmacy Today) and educational website (He Ako Hiringa), Canterbury Community Pharmacy Group, Pharmacy Guild of New Zealand, and a national primary care network (Green Cross Health).

Interested participants followed a hyperlink to Qualtrics to access a participant information sheet, and completed two questions assessing their eligibility (e.g., if currently practising in Aotearoa/New Zealand and working full or part-time). After providing informed consent, participants completed one brief (10 to 15 minutes) anonymous questionnaire assessing their demographic characteristics, familiarity with and attitudes towards biosimilars and confidence in their ability to answer questions. Open-ended questions were used to assess concerns about biosimilars and gather the different information pharmacists would provide in response to patient questions. Upon completion of the questionnaire, participants could enter the draw to win a pharmacy staff morning tea for their workplace. Findings were disseminated to interested participants upon study completion, along with various reputable resources on biosimilars and educating patients.

Measures

Background Information. Participant characteristics included age, ethnicity, gender, educational attainment, number of years working as a pharmacist, work setting, employment status and countries worked in overseas. The background information was captured last due to the nature of the study (i.e., assessing gaps in knowledge). This ensured that pharmacists could participate without the need to provide personal information.

Familiarity. Participants rated their familiarity with bio-originators and biosimilars on a 4-point scale (“very familiar, I have complete understanding” to “I have never heard of them”) that have been previously used (Hemmington et al., 2017). Two items assessed their

experience with working with bio-originators and biosimilars on 4-point scales ranging from "a lot of experience" to "no experience." Experience with dispensing bio-originators and biosimilars were assessed with two items with three response choices (Yes, No or Not Applicable). Participants also stated how often they dispense bio-originators and biosimilars on average each week and their confidence in dispensing bio-originators and biosimilars on an 11-point Likert scale (0 = not at all to 10 = extremely).

Attitudes Towards Biosimilars. Participants completed seven items with five response options (strongly agree to strongly disagree) to assess their perceptions towards biosimilars. Items assessed perceptions in effectiveness, safety, side effects, quality of the manufacturing process, interchangeability, pharmacist-led substitution, and transitioning patients to save costs. Items are adapted from a study that measured physician perceptions towards biosimilars (Hemmington et al., 2017). Higher scores indicated more positive perceptions.

Explaining Key Concepts. Two items with three response options (Yes, No or Not Applicable) were used to assess whether pharmacists have previously answered patient questions about bio-originators and biosimilars. Participants also reported how many times on average in the past week they have provided education on bio-originators and biosimilars. Nine 11-point Likert scales ranging from 0 (not at all confident) to 10 (extremely confident) were used to assess confidence in providing education in the following domains: safety, side effects, efficacy, manufacturing process, regulatory approval processes, administration, process of immune modulation, cost savings, and testing of biosimilars. Items include, "how confident do you feel answering patients' questions about the efficacy of biosimilars?" Higher scores indicated more confidence. These domains were identified using previous research that explores patients' and companions' questions about biosimilars and information needs (Gasteiger et al., 2019; Gasteiger, Scholz, et al., 2021).

Responses to Common Questions. Four open-ended questions were used to assess how pharmacists would respond to common questions from patients and their companions about biosimilars. Participants were briefly informed about the brand change from Humira to Amjevita (biosimilar adalimumab) and asked to imagine that they were answering patients' questions about changing. Questions included explaining what a biosimilar is and if there are any differences to the reference drug, queries about efficacy and safety/side effects, and the reason for the transition (i.e., benefits of taking biosimilars). For example, one question

asked, “will the biosimilar work the same as my current drug?” The development of these questions was informed by a systematic literature review, which identified common information about biosimilars provided in communication strategies globally (Gasteiger, den Broeder, et al., 2021). Four open-ended questions were used to assess pharmacists’ concerns about biosimilars in general, information they perceive important for patients and companions to know, and which resources or information would help them better provide biosimilar education.

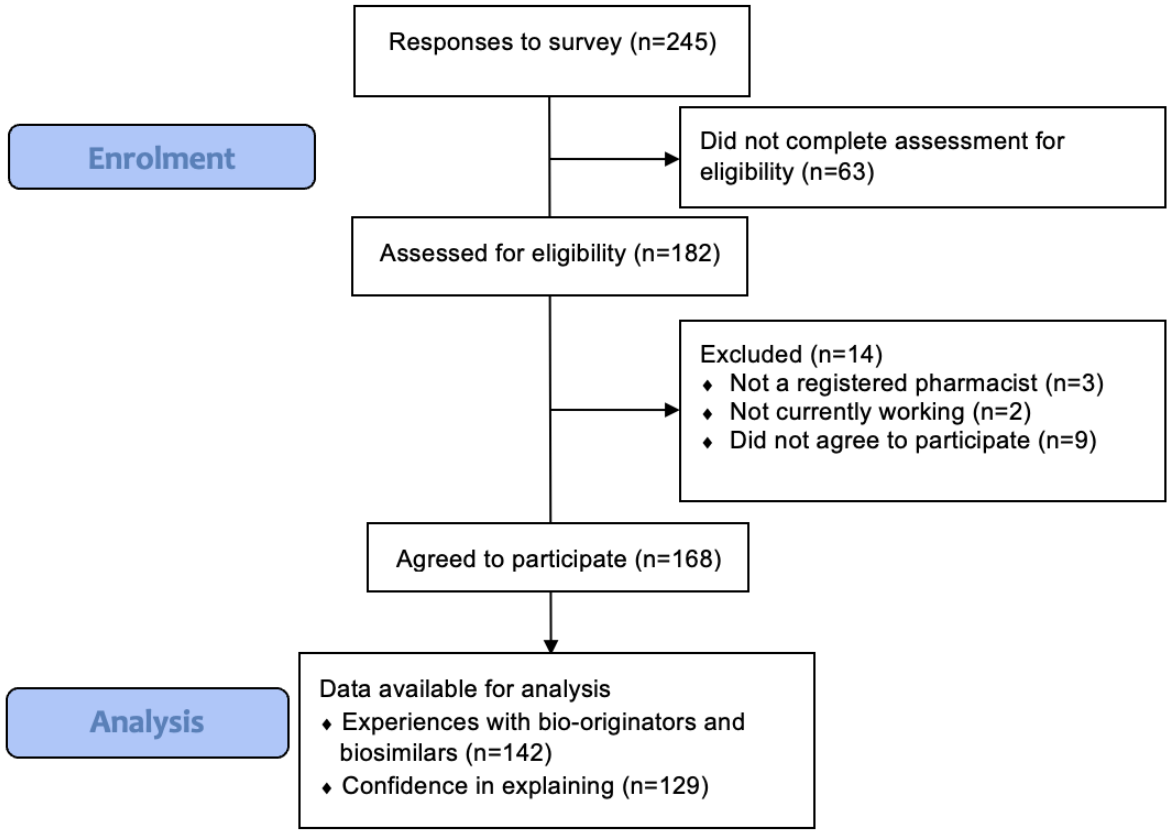
Analysis

Data was checked for parametric assumptions before being analysed in IBM SPSS Statistics (v.27). A significance level of $p < 0.05$ was maintained for all analyses. Participant characteristics, attitudes towards biosimilars and confidence in explaining biosimilars are presented using descriptive statistics. Attitudes towards biosimilars and confidence in explaining biosimilars were individually totalled to create sum scores. An analysis of variance (ANOVA) with a Bonferroni correction was conducted to examine differences in confidence in explaining key concepts between pharmacists working in the hospital, community, and primary care setting.

A two-step hierarchical linear regression was conducted to examine possible factors associated with confidence in explaining biosimilars. Demographics (gender, age (< 30 and 31-40 coded = 0 and 41+ = 1), educational attainment, and years working) were added in the first step with attitudes towards biosimilars, and familiarity with biosimilars and bio-originators (dummy coded ‘familiar’/ ‘very familiar’ = 1 and ‘had heard of them but could not define’/’had not heard of them’ = 0) added in the second. Data pertaining to the open-ended questions were downloaded from Qualtrics and exported to Excel for analysis. The data were analysed using an inductive content synthesis approach, whereby the content of the data informed the findings (rather than a pre-existing framework). Each open-ended question was analysed independently, with the researchers first applying codes that described the key concepts within the content. They then determined how many times each concept had been reported and identified supporting quotes. One researcher coded all the data, with a second researcher independently double coding a subset (27%) of the data. An inter-coder reliability was calculated to assess the agreement rate. The results are presented in the form of descriptions, supporting quotes and frequencies.

Figure 6

Diagram Demonstrating Study Flow



Note. The data available for analysis differs to the number who agreed to participate due to drop out during the survey or incomplete responses

Results

Responses were received from 142 pharmacists (Figure 6), of which 74 also provided complete demographic information (Table 3). The sample constituted 3.5% of eligible pharmacists in New Zealand when considering the practicing pharmacist workforce (Pharmacy Council, 2021). These pharmacists were primarily female (70%) and worked in the community (64%). Of the wider sample (N = 142), 25% of pharmacists were 'very familiar' with bio-originators, most (66%) had a basic understanding and only 9% could not define or had not heard of them. Most also (82%) had a lot or some experience with bio-originators, with 93% having previously dispensed bio-originators. Bio-originators were dispensed 8.7 (SD = 12.9) times a week on average. For biosimilars, only 11% were 'very familiar,' 70% had a basic understanding and 19% could not define or had not heard of them. Over half had a lot or some experience with biosimilars (66%), with 80% having previously

dispensed biosimilars. Biosimilars were dispensed 4.8 (*SD* = 11.7) times a week on average. Pharmacists were more confident dispensing bio-originators (*M* = 7.6, *SD* = 1.9) than biosimilars (*M* = 6.8, *SD* = 2.2).

Table 3

Demographic Characteristics of the Sample (N[%])

	Community (*n* = 47)	**Hospital (*n* = 16)**	**Primary Care (*n* = 11)**	**Sample (*n* = 74)**
Age category				
< 30	18[38]	6[38]	1[9]	25[34]
31-40	10[21]	4[25]	3[27]	17[23]
41-50	6[13]	2[13]	4[36]	12[16]
51-60	8[17]	4[25]	2[18]	14[19]
61-65+	5[11]	-	1[9]	6[8]
Gender				
Male	17[36]	4[25]	1[9]	22[30]
Female	30[64]	12[75]	10[91]	52[70]
Ethnicity				
NZ European	29[62]	11[69]	8[73]	48[65]
Other	9[19]	4[25]	3[27]	16[22]
Chinese	4[9]	1[6]	-	5[7]
Indian	5[11]	-	-	5[7]
Education				
Undergraduate	40[85]	4[25]	3[27]	47[64]
Postgraduate	7[15]	12[75]	8[73]	27[37]
Employment status				
Part-time (≤ 29 hours)	1[2]	4[25]	4[36]	9[12]
Full-time (≥ 30 hours)	46[98]	12[75]	7[64]	65[88]
Years Working (M(SD))	16.3(14.4)	16.3(12.2)	23.3(9.7)	17.4(13.4)
Worked overseas				
UK	6[50]	4[50]	6[75]	16[57]
Other	3[25]	-	1[13]	4[14]
Australia and UK	-	2[25]	1[13]	3[11]
Southern Africa	2[17]	1[13]	-	3[11]
Australia	1[8]	1[13]	-	2[7]

Note. NZ = Aotearoa/New Zealand; UK = United Kingdom. *n* = 28 reported working overseas and answered this question

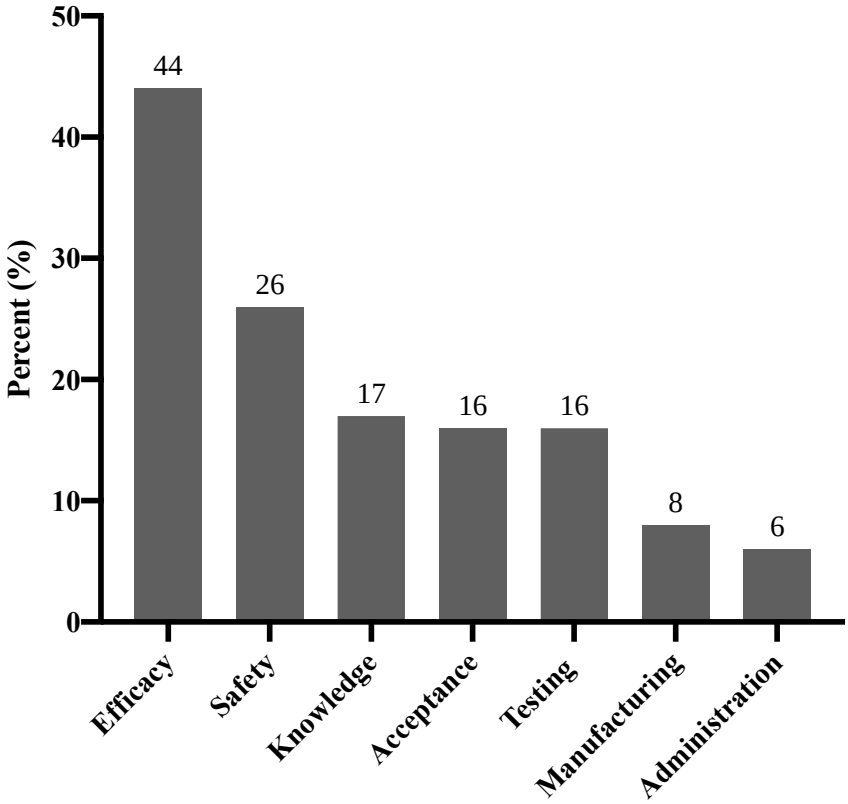
Concerns about Biosimilars

Of the pharmacists who responded (*n* = 100), most were concerned about reduced efficacy (e.g., loss of disease control) (44%) and safety, including side effects and risk for adverse reactions (immunogenicity) (26%) (Figure 7). Some (17%) had concerns about their lack of knowledge, particularly when educating patients and providing support during the transition.

Similarly, 16% had concerns about patients and providers not accepting the change. This included anticipating resistance due to cost driving the transition and the originator being life changing.

Figure 7

Common Concerns that Pharmacists Reported about Biosimilars (n = 100)



Confidence in Educating Patients

Around half (*n* = 72, 51%) of the sample (*n*= 142) reported previously answering patients' questions about bio-originators before. From those who responded (*n* = 54), pharmacists educated patients on bio-originators on average 1.8 (*SD* = 2.8, range 0.2-20) times a week. A smaller group had answered questions about biosimilars (*n* = 60, 42%). From those who responded (*n* = 46), pharmacists educated patients on biosimilars on average 1.7 (*SD* = 1.6, range 0.5-10) times a week. Pharmacists were most confident in explaining the process of administration, cost saving potential of biosimilars and efficacy (Table 4). The least confidence was reported in relation to explaining the manufacturing process and testing (e.g., non-clinical assessments and clinical trials).

Table 4

Pharmacists' Confidence in Explaining Key Concepts

Confidence	Community (*n* = 47)	Hospital (*n* = 16)	Primary Care (*n* = 11)	Full Sample (*n* = 129)
Safety	6.0 (2.6)	7.3 (2.3)	7.2 (2.2)	6.3 (2.4)
Side effects	6.1 (2.3)	6.8 (2.1)	6.9 (2.1)	6.0 (2.3)
Efficacy	5.9 (2.4)	7.2 (2.3)	7.3 (2.1)	6.4 (2.4)
Manufacturing	4.2 (2.8)	5.9 (2.7)	5.3 (2.6)	4.6 (2.7)
Regulatory and approval	6.1 (2.9)	6.6 (2.8)	6.3 (2.8)	5.7 (2.9)
Administration	6.6 (3.1)	7.3 (2.5)	7.3 (2.2)	6.6 (2.9)
Process of immune modulation	5.8 (2.8)	6.1 (2.2)	6.5 (2.4)	5.7 (2.6)
Cost saving	5.8 (2.8)*	7.8 (2.4)*	7.0 (2.5)	6.4 (2.8)
Testing	4.8 (3.0)	5.4 (2.8)	6.5 (3.7)	4.9 (2.9)
Total score	51.3 (21.6)	60.4 (16.5)	60.1 (18.4)	52.6 (19.9)

Note. Mean (SD), *Denotes significant difference ($p < .05$)

A hierarchical multiple linear regression was conducted to identify whether pharmacist characteristics are associated with more confidence in educating patients. The first model with pharmacist demographics was non-significant ($F(4, 67) = 1.40$, $p = .24$, $R^2 = 0.08$). Only educational attainment was a significant predictor, with pharmacists who had completed postgraduate study (e.g., Masters or PhD) reporting more confidence than those without a postgraduate degree ($B = 9.32$, $p = .030$). Years working, age and gender were not significant (all p's > .05). The fully adjusted model was significant ($F(7, 64) = 9.00$, $p < .001$, $R^2 = 0.50$). Having more positive attitudes towards biosimilars ($B = 1.64$, $p < .001$) and being more familiar with biosimilars ($B = 27.15$, $p = < .001$) were significantly associated with more confidence. Years working, educational attainment, gender, age, and experience with answering questions about biosimilars were not significant (all p's > .05).

Educating Patients and Companions about Biosimilars

Pharmacists responded to various open-ended questions assessing the information they would provide in response to common queries from patients and their companions and resources that they may require to support their practice. The two coders reached a raw agreement rate of 87.7% when coding the open-ended data. For those who responded ($n = 102$), most

perceived information about safety (e.g., side effects) (67%) and outcomes in relation to disease control (60%) as the most important for patients and their companions to know. Practical information, including the process of administering biosimilars, using the new device, storage, and disposal, were also important (38%), along with the biosimilar's mechanism of action (14%). Pharmacists (15%) also specifically noted that companions should be advised to monitor patients by watching for disease destabilisation or adverse drug reactions.

Defining Biosimilars. Pharmacists were asked to define a biosimilar and whether there are any differences to the bio-originator (Table 5). Of those who responded (*n* = 72), some emphasised that the biosimilar was the same (22%) or similar (31%) to the bio-originator. A small group (6%) acknowledged not having enough knowledge. Pharmacists provided reassurance that the biosimilar has the same or similar effects (47%), active ingredients (35%), safety and side effects (19%), and mechanism of action (17%). However, some (42%) noted the change in brand, discussed the manufacturing process (28%), or stated that the device may not look identical (11%). Two pharmacists (3%) provided an analogy, with one stating, "*Think the same OLED TV with same functions, but one is made by Panasonic and the other Samsung."*

Table 5

Information That Pharmacists Would Provide When Asked by Patients to Define Biosimilars (n = 72)

Content	N (%)	Example quotes
Same effects	34 (47)	It has been produced to have very similar effects.
Different brand	30 (42)	Amgevita is a biosimilar, which is essentially another brand of your Humira.
Ingredients	25 (35)	The active ingredient is the same.
Manufacturing	20 (28)	They are not exactly same, because the original medicine is naturally sourced, it is very big and complex, which makes it hard to copy exactly.
Safety (side effects)	14 (19)	Will likely have the same side effects.
Action	12 (17)	It does the same job in the same way.
Look and feel	8 (11)	Change in presentation (e.g., the device, colours).

Benefits of Biosimilars. Of the pharmacists who reported benefits of biosimilars (*n* = 75), the majority (88%) mentioned that cost savings could be enabled for Pharmac and healthcare system, with no changes to efficacy and safety (Table 6). This was expected to improve access to biosimilars and other/new medications (67%). Some (9%) mentioned improved drug administration as the new device could be easier to use and less painful as it has a citrate-free buffer. A minority (4%) also explained that administrative processes would be simplified for doctors, given that there would be no need for as frequent special authority renewals.

Table 6

Information Pharmacists Would Provide When Patients Ask Them to Describe the Benefits of Taking Biosimilars (n = 75)

Benefit	N (%)	Example quotes
Cost savings	66 (88)	It means that Pharmac has some savings and can allocate extra costs to other medicines that may be newer or more effective for other conditions and other cancers to increase access to medicines for other patients.
Access to medication	50 (67)	Changing to this medication will mean more patients can access this treatment.
Improved drug administration	7 (9)	In the case of Amgevita, unlike Humira, it is citrate-free, so we expect it to be more comfortable to inject.
Simplified administrative processes	3 (4)	It will also mean that you no longer have to harass your Dr for renewing the Special Authority as frequently and having to wait for renewal.

Efficacy. Pharmacists were asked to respond whether the biosimilar would work the same. Of the pharmacists who responded (*n* = 70), most (80%) would reassure patients that the biosimilar works in the same way as the bio-originator. A small group reported they were uncertain (11%), that the biosimilar would work in a similar way (7%) and one (1%) stated the biosimilar may work better. Some pharmacists also reported information about the biosimilar's extensive testing (24%) or warned about possible side effects (e.g., immune reactions) (6%). Some respondents asked patients to monitor for new responses and requested they contact them if concerned (11%).

Safety. Seventy pharmacists responded to the question about experiencing new side effects, and biosimilar testing and clinical trials. Over half (60%) stated that the biosimilar's side effects would be the same or similar to the bio-originator. Smaller groups also stated that

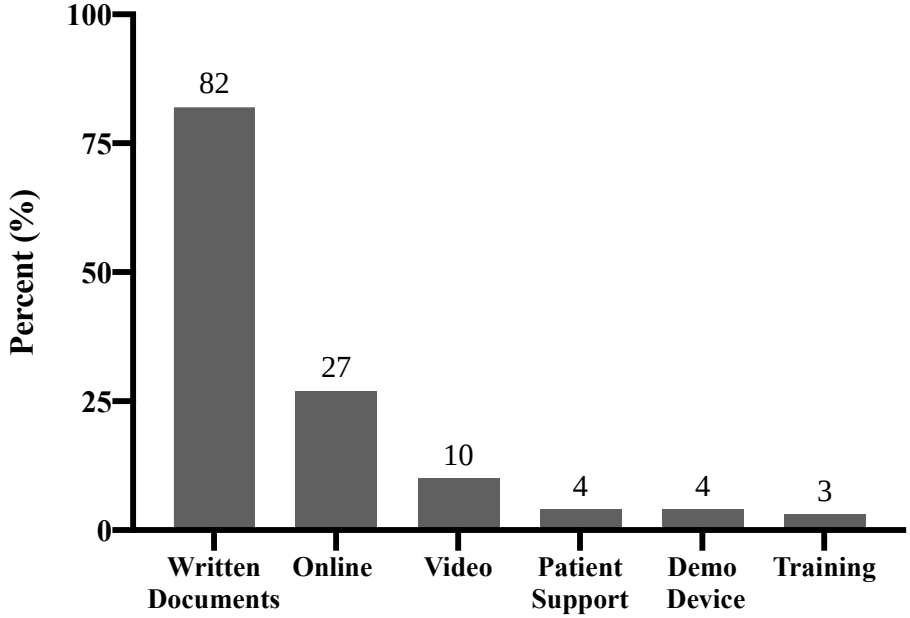
there would be new side effects (14%), all patients respond differently (13%), or they were unsure (6%). While most pharmacists provided reassurance that biosimilars had been tested before use (70%), some incorrectly stated the tests conducted were the same for bio-originators and biosimilars (19%). Other common information included that biosimilars had gained regulatory approval (21%), who to contact if side effects occurred (19%) and to monitor for side effects (10%).

Resources

Pharmacists reported which resources would help them provide education. Of those who responded (*n* = 92), most (82%) wanted written documents such as brochures, booklets, information sheets or pamphlets to help them educate patients and their companions (Figure 8). Documents were suggested to provide basic, jargon-free information about biosimilars, a comparison of both brands and responses to common questions. Other resources included websites (27%) and brief videos (10%) for pharmacists and patients (e.g., demonstrating drug administration). Pharmacists also wanted a demo device to show patients (4%) and to refer patients to other support, including Patient Support Programs from the manufacturer (4%). Lastly, some (3%) wanted pharmacist-specific training, such as webinars. Pharmacists (26%) wanted information from reputable sources including Pharmac, Medsafe, Best Practice Advocacy Centre New Zealand, New Zealand Formulary, Health Navigator or MIMS.

Figure 8

Resources Pharmacists Want to Improve Their Knowledge and Ability to Educate Patients (n = 92)



Discussion

Pharmacists play an essential role in educating patients and their companions about biosimilars. In the present study, pharmacists had less experience and knowledge with biosimilars than bio-originators. While common concerns included reduced efficacy and safety, some were worried about their lack of knowledge and patients and providers resisting the brand change. Pharmacists were most confident in explaining the process of administering biosimilars, cost savings, and efficacy. The lowest confidence was in relation to the manufacturing processes and testing. Pharmacists who were confident in explaining key concepts were more familiar and held more positive attitudes toward biosimilars. Varying confidence and levels of knowledge were also identified in how pharmacists would explain key concepts. Pharmacists reported wanting more resources from reputable sources to educate themselves and patients, including written (e.g., pamphlets, information sheets) and web-based resources.

Results from this study are consistent with previous research demonstrating that pharmacists globally require continued education on biosimilars (Arnet et al., 2021; Barbier et al., 2021; Beck et al., 2017; Okoro et al., 2021; Pasina et al., 2016). However, the findings also contribute to the existing literature by demonstrating which resources pharmacists prefer to support their practice. As evident in our sample, pharmacists were generally unfamiliar with biosimilars, lacked knowledge about development and manufacturing processes, and some did not feel sufficiently trained to counsel patients (Adé, 2017; Arnet et al., 2021; Barbier et al., 2021; Beck et al., 2017). Similar findings are evident among prescribers, including in New Zealand, where medical specialists have expressed an uncertainty about biosimilar quality and manufacturing processes (Hemmington et al., 2017; Sarnola et al., 2020). A lack of knowledge and uncertainty may unintentionally convey low confidence in the biosimilar to patients but can also negatively influence prescribing behaviours (Barbier et al., 2021). Findings also build on existing research by demonstrating that various characteristics (familiarity and positive perceptions) are associated with more confidence in communicating key concepts. It is likely that pharmacists who have more knowledge about biosimilars hold more positive perceptions and are, therefore, more confident in providing education (Poon et al., 2021). Similarly, more experiences with biosimilars, such as those who regularly educate patients, are likely to translate to more confidence. These findings should be considered when developing future biosimilar transitioning programs, as a lack of knowledge and confidence

can unintentionally promote misinformation and disparagement about biosimilars and increase patient hesitancy (Cohen & McCabe, 2020; Oskouei & Kusmierczyk, 2021).

Responses to the open-ended questions illustrated variance in how pharmacists would explain key concepts to patients. While some pharmacists focused on providing reassurance on comparable safety and efficacy, other responses confirmed gaps in knowledge or common misunderstandings. For example, some incorrectly stated that the biosimilar was the same as the bio-originator (rather than similar), may work better, and the tests conducted were the same as for the bio-originator. Incomplete and incorrect information should be countered by the provision of additional education that is easily assessable (Cohen & McCabe, 2020). Some pharmacists also noted the importance of patients monitoring for adverse effects and indicated that companions should be advised on which side effects to look for. This information may increase negative expectations and awareness of new symptoms (Kravvariti et al., 2018). Ultimately, symptom reporting may be exacerbated and non-specific symptoms misattributed to the new drug (Petrie & Rief, 2019).

The study findings have important clinical implications. It is evident that pharmacists would benefit from more resources and guidance in educating patients and their companions on biosimilars. This is particularly important as a high portion of pharmacists had already dispensed and answered questions about biosimilars, but a high proportion lacked familiarity or could not define them. Educating pharmacists is important as some patients transitioning to Amgevita in the United Kingdom reported dissatisfaction with the information, and this was associated with more side effects, difficulty in using the new device and negative perceptions about symptom control (Kaneko et al., 2022). The results also pose an important question on where the responsibility falls to ensure pharmacists are sufficiently informed. A coordinated approach to sharing information is essential before a medicine brand changes to ensure pharmacists and other healthcare providers obtain up-to-date and balanced information on newly funded pharmaceuticals. However, the responsibility of sharing information about biosimilars should not be restricted to healthcare providers (e.g., physicians, nurses, and pharmacists). Instead, regulatory and pharmaceutical funding agencies, professional medical organizations, patient advocacy associations, and formal educational institutions (including continued professional development) should also play a role in upskilling providers. Nonetheless, pharmacists also have some degree of individual responsibility to identify and seek to fill their gaps in knowledge.

This study had various strengths, including the high intercoder reliability. Open-ended questions demonstrated how pharmacists would explain key concepts about biosimilars while further highlighting gaps in knowledge and attitudes towards biosimilars beyond self-report items. The data were also collected before and during the early months of the transition to Amgevita. During these stages, pharmacists were still largely inexperienced with Amgevita, but it provided the opportunity to identify their information needs. An evaluation study is needed following the completion of the transition to Amgevita to identify areas for improvement.

A key limitation was the modest sample, which may not have been representative and limited the reliability of the hierarchical regression. The low response rate was likely due to the increased workload from the COVID-19 pandemic, as pharmacists were required to administer COVID-19 tests and vaccinations. This may also explain the high drop-out rate throughout the survey, as the questionnaire was relatively short. While an effort was made to distribute the survey to all pharmacists in New Zealand, it is also not possible to identify the exact reach of the survey, such as how many saw the social media posts or read the email. This would be useful for future research to identify effective recruitment methods and ensure a generalisable sample. A lack of general knowledge and experience with biosimilars may have impacted the response rate as those without knowledge might have elected not to participate. Similarly, pharmacists with more experience with bio-originators may have been more likely to respond. However, it was not possible to continue collecting data, as pharmacists would have gained more experience during further stages of the transition to Amgevita. Further, not all participants completed demographic information, possibly due to the nature of the topic. More research, especially with larger samples, is needed following the transition to Amgevita to identify whether pharmacists still require additional training. A focus is also needed on the development and assessment of educational initiatives.

The present study is the first to specifically explore pharmacists' confidence in educating patients and their companions on biosimilars, with previous research primarily focusing on identifying gaps in knowledge. Findings demonstrate that pharmacists have concerns about their lack of knowledge, alongside reductions in efficacy and safety. Pharmacists are least confident in explaining the testing and manufacturing of biosimilars, and the most confident in explaining how biosimilars are administered, their efficacy, and cost saving. Those who were more familiar with biosimilars and had positive attitudes were more confident in

educating patients. Pharmacists would provide varying explanations about biosimilars, but responses also demonstrated gaps in understanding. Pharmacists would benefit from additional resources to support their practice. Resources should include written and web-based information developed by reputable sources covering biosimilars' testing and manufacturing processes.

Chapter Five: Identifying Hesitant Patients

Preface

As discussed in Chapter 2, negative perceptions hinder patients' acceptance of biosimilars and consequently provide challenges for their adoption. In previous transitions to biosimilars, some patients have reported nocebo responses (e.g., in 12.8% and 15% of patients) and/or were unwilling to transition when provided with a choice (Boone et al., 2018; Chan et al., 2019; Müskens et al., 2020; Nikiphorou et al., 2015; Petitdidier et al., 2019; Tweehuysen, Huiskes, et al., 2018). These findings suggest that a group of patients, but definitely not all, are more resistant to transitioning or predisposed to experiencing and misattributing non-specific side effects. Identifying biosimilar-hesitant patients may be useful in improving drug transitions (Colloca, 2017).

Determining which patients are likely to be biosimilar hesitant is particularly useful for developing communication strategies and educational materials. Chapter 3 found that a higher proportion of patients who received combined (verbal and written) information were willing to transition to biosimilars compared to those only receiving information verbally. In addition, Chapter 4 demonstrated that pharmacists in Aotearoa/New Zealand have gaps in knowledge about biosimilars and would benefit from additional resources and training. Identifying patients who exhibit more biosimilar hesitancy provides additional guidance for pharmacists and other providers. Verbal information and written resources could be tailored to provide additional reassurance on previous use, along with standard information about safety and efficacy. Targeting 'at-risk' patients is likely to augment biosimilar acceptance further.

It is useful to look at the literature on innovator (branded) to generic medicine switches to understand how patient factors influence the acceptance of cheaper treatments and nocebo responses. The concept of transitioning to biosimilars has some similarities with a switch to generic medicines (i.e., changing to a cheaper treatment to reduce costs). It is, therefore, unsurprising that patients who are satisfied with generic medicines in general are also more likely to accept the transition to biosimilars (Haghnejad et al., 2020). As evident in transitions to generic medicines, patients frequently report side effects following a switch and demonstrate strong preferences for innovators. Patients with high levels of anxiety, negative perceptions of generics, older age, lower educational attainment, and high perceived

sensitivity to medicines tend to prefer innovators (Barton et al., 2021; Kleinstäuber et al., 2018; MacKrill & Petrie, 2018).

Patient factors also predict side effect reporting following medicine brand changes. In 2017, Pharmac funded a new generic antidepressant, forcing 45000 patients to change from the branded drug Efexor XR or the generic drug Arrow-Venlafaxine XR to Enlafax XR. A cross-sectional study with 310 patients found that different factors predicted side effect reporting for those changing from the generic (Arrow-Venlafaxine XR) or innovator (Efexor XR) (MacKrill & Petrie, 2018). Patients changing from the innovator drug were more likely to report side effects when they did not hold a tertiary education, were older, female, had taken the drug for longer, and perceived the generic to be less effective. Only low perceived efficacy predicted side effect reporting for patients changing from the generic. The authors also found that patients rated the new generic as less effective when they had experienced more side effects from the new drug and held less trust in pharmaceutical agencies. Findings demonstrate that both patient factors and previous experiences with branded medicines predict nocebo responses and perceptions of generics.

To date, no research has specifically examined patient factors associated with perceptions towards biosimilars. Although research exploring generic medicine brand changes is a useful starting point, the transition to biosimilars is likely to cause even more concerns about dissimilarity, quality, safety, and efficacy as microheterogeneity is inevitable. As such, unique factors may be involved. The following study addressed this research deficit by examining the demographic and psychological characteristics associated with patients' safety perceptions and concerns about transitioning to biosimilars. The study also investigated whether current experiences with a bio-originator are associated with negative perceptions towards biosimilars. We used a hypothetical transitioning scenario with patients taking bio-originators for rheumatic diseases and assessed their perceptions about safety and concerns about transitioning. It was not possible to explore the experience of side effects following a transition, as biosimilars had not been introduced for patients with rheumatic diseases at the time of the study.

Citation

Gasteiger, C., Lobo, M., Dalbeth, N., & Petrie, K. J. (2020). Patients' beliefs and behaviours are associated with perceptions of safety and concerns in a hypothetical biosimilar switch. *Rheumatology International, 41*(1), 163-171. https://doi.org/10.1007/s00296-020-04576-7

Introduction

Biosimilars are competitive alternatives to bio-originators due to providing a similar therapeutic effect at a substantially lower cost (Eleryan et al., 2016; Escasany & Cumplido, 2015; Patel & Park, 2017). However, the successful adoption of biosimilars relies partly on patient acceptance. Studies show that some patients hold negative perceptions of biosimilars and may be unwilling to switch from their bio-originator (Attara et al., 2016; Ighani et al., 2018; Sullivan et al., 2017; Wilkins et al., 2014). Negative perceptions include beliefs that biosimilars are substandard in quality, safety, and efficacy to bio-originators (Sullivan et al., 2017; Wilkins et al., 2014). Some patients also report concerns about being switched to a biosimilar without previous discussion with their treating physician (Attara et al., 2016; Ighani et al., 2018) and perceive the cheaper cost to be associated with inferior quality (Wilkins et al., 2014). Negative perceptions have the ability to induce nocebo responses and enhance intentional non-adherence, ultimately leading to wasted healthcare resources (Betegnie et al., 2016; Rezk & Pieper, 2017).

Although there is limited research on patient acceptance of biosimilars, studies from innovator to generic medicine switches demonstrate that patient characteristics can influence perceptions and preferences towards switching to cheaper alternatives (Figueiras et al., 2009; Kleinstäuber et al., 2018; MacKrill & Petrie, 2018). Specifically, older age may predict a stronger preference towards branded medicines (MacKrill & Petrie, 2018), but may also predict the belief that generics and branded medicines are highly similar (Figueiras et al., 2009). Those with lower levels of education are less likely to perceive generics to be effective, and females have greater mistrust in the bioequivalence of generics (Babar et al., 2014; Figueiras et al., 2009; Kleinstäuber et al., 2018; Olsson et al., 2018). Patients who perceive themselves to be sensitive to medicines or have negative illness beliefs also favour branded medicines (Alrasheedy et al., 2014; Kleinstäuber et al., 2018; MacKrill & Petrie, 2018). It is likely that these patient groups are more cautious about medicines, especially as patients who report a high perceived sensitivity to medicines also engage in more

information-seeking behaviours, visit their general practitioner more and report more symptoms (Faasse, Grey, Horne, et al., 2015).

Previous experiences with medicines can also impact decisions to switch, and perceptions towards a generic's safety and efficacy (Alrasheedy et al., 2014; Pechlivanoglou et al., 2011). Patients established on branded medicines are often less willing to switch to a generic (MacKrill & Petrie, 2018; Pechlivanoglou et al., 2011). In one study, patients switching from a generic medicine and patients switching from an innovator, perceived the generic to be more effective when they had higher levels of trust in pharmaceutical agencies and experienced fewer side effects (MacKrill & Petrie, 2018).

Research on generic medicines demonstrates that a patient's characteristics and prior experiences with medicines influence their acceptance of generics. However, to the authors knowledge no studies have specifically examined the impact of patient characteristics on biosimilar acceptance. Given that patients report negative perceptions towards biosimilars and the importance of patient acceptance in the adoption of biosimilars, research in this area is needed. The aim of this study was to therefore investigate which demographic and psychological characteristics are associated with negative perceptions towards a biosimilar's safety and concerns towards switching. We also investigated whether current experiences with a bio-originator are associated with negative perceptions towards biosimilars.

Methods

Patients taking a bio-originator treatment at a rheumatology service in Auckland, Aotearoa/New Zealand completed questionnaires in April to July 2018. This analysis is part of a study that also explored the effects of framing information about switching to a biosimilar and has been previously reported (Gasteiger et al., 2019).

Patients

Patients (N = 247) taking bio-originator treatments at a rheumatology clinic were sent letters with information about the study. Forty-one patients were directly recruited from the letters. Additionally, 52 patients responded to flyers provided by clinical staff at outpatient appointments and 3 patients were recruited through Facebook. The final analytic sample consisted of 96 patients who completed the questionnaires. To be eligible to participate patients had to be over 18 years old, taking a bio-originator therapy for a rheumatic disease

and be fluent in English. At the time of the study biosimilars were not publicly funded for patients with rheumatic diseases in Aotearoa/New Zealand.

Procedure

Participants provided demographic and clinical information and completed baseline measures assessing illness perceptions. As part of a wider study, participants were given an information-based video explanation on a computer tablet that discussed the switch from a bio-originator to a biosimilar (Gasteiger et al., 2019). The explanation included information about manufacturing biosimilars, safety and risks, and the potential for cost savings. Some patients also received an analogy that focused on the concept of using a cheaper yeast to bake bread, which still leads to the same outcome despite differences in cost and manufacturing. The video script has been previously made available (Gasteiger et al., 2019). After viewing the explanation, participants completed post-intervention measures that assessed psychological characteristics and perceptions towards biosimilars. All participants were offered a $20 voucher for their participation.

Measures

Patients provided information about their age, gender, educational attainment, and ethnicity. The name of the current bio-originator treatment and the time taking the treatment were also reported.

Illness perceptions were assessed with the nine-item Brief Illness Perceptions Questionnaire (B-IPQ) (Broadbent et al., 2006; Broadbent et al., 2015). Beliefs about medicines were assessed using the General Beliefs about Medicines Questionnaire (BMQ-G) (Bautista et al., 2011; Heller et al., 2015; Horne et al., 1999). BMQ-G has two subscales that assess medicine harm and overuse beliefs. Sensitivity to medicines was assessed with the Perceived Sensitivity to Medicines Scale (PSM) (Faasse, Grey, Horne, et al., 2015; Horne et al., 2013).

Participants also responded to two items that assessed how often they read information sheets in medication packs and seek health information on the Internet (MacKrill & Petrie, 2018). To measure medication preference, participants indicated whether they would prefer a branded or generic medicine with no difference in cost (MacKrill & Petrie, 2018).

Concerns about switching to a biosimilar and expected side effects were measured with 11-point numerical rating scales (i.e., how concerned would you be about taking the biosimilar?). The perceived safety of a biosimilar was also assessed with an 11-point numerical rating scale, which was reverse scored. Experiences with the bio-originator treatment in terms of side effects, perceived effectiveness, and safety (reverse scored), were also assessed on an 11-point Likert scale (Faasse, Grey, Horne, et al., 2015). A numerical rating scale was also used to assess preferences for a bio-originator and biosimilar.

Statistical Analyses

Analyses were performed with IBM SPSS v.22. Data was checked for normality with the Kolmogorov-Smirnov test in conjunction with assessing Q-Q plots and values of skew and kurtosis. Pearson's correlations and independent sample t-tests were computed to examine the relationship between demographic and psychological variables and perceptions towards biosimilars. Correlations were conducted to explore the association between current bio-originator use and perceptions towards biosimilars in terms of safety, expected side effects and concern about switching. Non-parametric tests (Spearman's rank) were employed when the assumptions of parametric tests were violated. Any missing data were excluded from analyses using pairwise deletion for correlations and listwise deletion for the hierarchical linear regression. As data were collected from an intervention group-design study (Gasteiger et al., 2019), only outcomes that were unaffected by the intervention were included. The significant variables ($p < .05$) were included in a hierarchical linear regression analysis for each perception.

Predictor variables included demographic characteristics such as age, gender, education level (dichotomised and dummy coded as university degree 1 or lower 0) and ethnicity (1 = NZ European or 0 = other ethnicities). Psychological characteristics were illness perceptions, perceived sensitivity to medicines, preference towards branded medicines (coded as 0 = no preference and prefer generic, or 1 = prefer branded), general beliefs about medicines and health information-seeking behaviours. Intervention group allocation was also included in each hierarchical linear regression.

Ethical Statement

This study was approved by the Health and Disability Ethics Committee (17/NTB/245) and Auckland District Health Board (A+7961). The study was performed in accordance with the ethical standards of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Results

Participant Characteristics

The analytic sample was predominantly female (69%) with an average age of 54 years (*SD* = 16). Most were New Zealand European (67%) and had completed a tertiary education (53%). The most common bio-originator therapy was rituximab (35%), and the most frequent condition was rheumatoid arthritis (65%). See Table 7 for more details on patient characteristics.

Table 7

Demographic and Clinical Characteristics of the Sample

	Sample N = 96 **Mean (SD) [%]**
Age (years)	54 (16)
Range	19-88
Gender	
Female	66 [69%]
Male	30 [31%]
Ethnicity	
NZ European	64 [67%]
Other (Asian, Pacific, Māori, Other)	32 [33%]
Education	
University higher education	61 [64%]
Non-university education	35 [37%]
Bio-originator	
Rituximab (MabThera)	34 [35%]
Adalimumab (Humira)	21 [22%]
Tocilizumab (Actemra)	17 [18%]
Infliximab (Remicade)	16 [17%]
Etanercept (Enbrel)	8 [8%]
Time on bio-originator (months)	30 (29)
Range	0.5-146
Rheumatic disease	
Rheumatoid arthritis	62 [65%]
Ankylosing spondylitis	16 [17%]
Psoriatic arthritis	13 [14%]
Granulomatosis with polyangiitis	2 [2%]
Juvenile idiopathic arthritis	2 [2%]
Adult-onset Stills disease	1 [1%]

Note. NZ = Aotearoa/New Zealand

Experiences with Bio-Originator Treatment

We investigated the association between patients' experiences with their current bio-originator and with a biosimilar. The findings suggest that experiences with bio-originators, in terms of safety and side effects, are also expected from a biosimilar treatment. There was a significant positive association between the number of side effects experienced from the current bio-originator ($M = 2.34$) and the side effects expected from the biosimilar ($M = 3.48$) ($r_s = .40$, $p < .001$). There was also a significant positive association between perceptions of bio-originator safety ($M = 2.73$) and the expectation that biosimilars are unsafe ($M = 3.82$) ($r_s = .62$, $p < .001$).

We also explored associations between experiences with the current bio-originator and a preference towards taking a bio-originator over a biosimilar. Those who perceive their current bio-originator to be effective seemed to prefer their biologic treatment over switching to a biosimilar. There was a significant negative association between the perceived effectiveness of the current bio-originator (M = 7.91) and a preference for a biosimilar medicine (M = 3.21) (r_s = -.33, p < .001).

Safety Perceptions

From the demographic variables only gender and the time spent taking the current bio-originator were significantly associated with perceptions of a biosimilar's safety (see Table 8). Those who were female and had taken the bio-originator for a short time perceived the biosimilar to be less safe. For psychological characteristics, there was a significant negative association between safety perceptions and beliefs about how much a treatment can control the condition (see Table 9). Consequence beliefs and emotional response beliefs were positively correlated. Those who had high perceptions of medicine sensitivity and looked up information on the Internet were less likely to perceive the biosimilar to be safe. Lastly, there was a significant negative association between safety perceptions and beliefs about medicines (harm and overuse).

Table 8

Associations Between Demographic Variables and Perceptions Towards Biosimilars

Characteristics	**Perceptions towards biosimilars**	
	Safety *How safe do you expect the biosimilar to be?*	***Concern about switching*** *How concerned would you be about taking the biosimilar?*
	Pearson's r	
Age	-.00 (p = .97)	.10 (p = .33)
Time on Bio-originator	**-.31* (p = .002)**	-.12 (p = .26)
	t-statistic	
Ethnicity	-1.03 (p = .30)	.08 (p = .94)
Education	.39 (p = .70)	-.50 (p = .62)
Gender	**-3.53* (p < .001)**	**-2.13* (p = .04)**
Medication Preference	-.41 (p = .69)	**-3.42* (p < .001)**
Intervention Groups	-.24 (p = .81)	1.32 (p = .19)

Note. The bold values are significant at p < .05. Safety perception was reverse coded. Spearman's rho was used for age

Table 9

Associations Between Psychological Variables and Perceptions Towards Biosimilars

Characteristics	**Perceptions towards biosimilars (Pearson's r)**	
	Safety *How safe do you expect the biosimilar to be?*	***Concern about switching*** *How concerned would you be about taking the biosimilar?*
Illness Beliefs (B-IPQ)		
Consequences	**.21* (*p* = .045)**	.10 (*p* = .38)
Timeline	-.08 (*p* = .43)	**-.25* (*p* = .02)**
Personal Control	-.19 (*p* = .07)	-.03 (*p* = .76)
Treatment Control	**-.33* (*p* < .001)**	-.13 (*p* = .22)
Emotional Response	**.24* (*p* = .02)**	**.21* (*p* = .04)**
Understanding	-.13 (*p* = .20)	.10 (*p* = .53)
Identity	.17 (*p* = .10)	-.00 (*p* = .97)
Concern	.10 (*p* = .32)	.09 (*p* = .37)
Beliefs about Medicines - Harm (BMQ-G)	**-.37* (*p* < .001)**	-.11 (*p* = .28)
Beliefs about Medicines - Overuse (BMQ-G)	**-.36* (*p* < .001)**	-.08 (*p* = .43)
Perceived Sensitivity to Medicines (PSM)	**.28* (*p* < .001)**	**.33* (*p* < .001)**
Information Seeking - Internet	**.25* (*p* = .01)**	**.35* (*p* < .001)**
Information Seeking - Reading	.02 (*p* = .86)	**.22* (*p* = .03)**

Note. The bold values are significant at $p < .05$. Safety perception was reverse coded. Spearman's rho was used for B-IPQ, BMQ-G overuse and information seeking items

In the hierarchical linear regression (see Table 10) we subsequentially adjusted for the groups used in the intervention (Model 1) and gender, time spent on the bio-originator, beliefs about medicines (overuse and harm), perceptions of medicine sensitivity, information seeking and illness beliefs (Model 2). As expected, the intervention groups did not significantly explain any variance in safety perceptions ($p = .95$). In the fully adjusted Model (Model 2) only female gender ($\beta = .28$, $p = .01$) was a significant predictor, explaining 36% of the variance in perceived biosimilar safety. Findings suggest that females are more likely to perceive biosimilars to be unsafe.

Table 10

Hierarchical Linear Regression for Factors Associated with a Biosimilar's Expected Safety

Variable	Mean	Model 1	P-value	Model Statistics	Model 2	P-value	Model Statistics
		β			β		
Intervention Groups		.01	.95	R^2 = .00	-.01	.89	R^2 = .36
Gender				F = 0.00	.24	**.02**	F = 4.64
Time on Bio-originator	29.19			*p* = .95	-.19	.05	***p* < .001**
Harm Medicine Beliefs	14.44				-.11	.42	
Overuse Medicine Beliefs	12.90				-.18	.16	
Sensitivity to Medicines	14.44				.09	.37	
Info. Seeking- Internet	6.34				.10	.30	
Illness Perceptions							
Consequence	5.81				-.01	.97	
Treatment control	7.98				-.15	.17	
Emotional response	5.05				.07	.54	

Note. The bold values are significant at $p < .05$. Safety perception was reverse coded

Concerns about Switching

From the demographic variables, gender was significantly correlated with perceptions of a biosimilar's safety (see Table 8). Female patients were more concerned about switching from a bio-originator to a biosimilar. A preference for branded medicines was also significantly associated with higher concerns towards switching. For psychological characteristics, timeline beliefs (beliefs about the duration of the condition) were negatively correlated with concerns about switching (see Table 9). Emotional responses, perceived sensitivity to medicines and information seeking (looking up information online and reading medicine information sheets) were positively associated with concerns.

In the hierarchical linear regression (Table 11) we subsequentially adjusted for the groups used in the intervention (Model 1) and gender, perceptions of medicine sensitivity, information seeking, preference for branded medicines and illness beliefs (Model 2). The intervention groups did not significantly explain variance in safety perceptions ($p = .19$). In the fully adjusted model searching for information on the Internet ($\beta = .20$, $p = .04$), a preference for branded medicines ($\beta = .29$, $p = .004$) and emotional responses ($\beta = .26$, $p = .01$) were significant predictors, explaining 34% of the variance in concerns about switching ($p < .001$). Findings suggest that patients who search for health information on the Internet, have stronger emotional responses to their condition and prefer branded medicines are more concerned about switching to a biosimilar.

Table 11

Hierarchical Linear Regression for Factors Associated with Concerns Towards Switching

Variable	Mean	Model 1	P-value	Model Statistics	Model 2	P-value	Model Statistics
		β			β		
Intervention Groups		-.13	.19	R^2 = .02	-.03	.77	R^2 = .34
Gender				F = 1.73	-.01	.96	F = 5.69
Medication Preference				*p* = .19	.29	**.004**	***p* < .001**
Sensitivity to Medicines	14.53				.13	.22	
Info. Seeking - Reading	7.10				.17	.11	
Info. Seeking - Internet	6.30				.20	**.04**	
Illness Perceptions							
Timeline	9.42				-.18	.05	
Emotional Response	4.99				.26	**.01**	

Note. The bold values are significant at $p < .05$

Discussion

To the author's knowledge, this is the first study to specifically explore whether patient characteristics are associated with negative beliefs towards biosimilars. In a sample of patients taking bio-originator therapies for rheumatic diseases, different demographics and characteristics were associated with safety perceptions and concerns about switching to biosimilars. Taking a bio-originator for a short time, seeking health-related information on the Internet, having a high perceived sensitivity to medicines and negative beliefs about medicines were associated with adverse perceptions about a biosimilar's safety. Three illness perceptions were also associated. In the linear regression only being female was independently associated with negative safety perceptions. Concerns about switching were associated with timeline beliefs, emotional responses, being female, perceiving oneself to be sensitive to medicines, engaging in information-seeking behaviours and having a preference for branded medicines. Seeking information on the Internet, having stronger emotional responses to their condition and a preference for branded medicines were independently associated with negative concerns about switching in the linear regression.

Study findings are consistent with previous literature that patient's characteristics play a role in developing negative perceptions towards unbranded medicines. Literature shows that females engage in more information seeking behaviours and report more negative perceptions towards generic bioequivalence (Faasse, Grey, Horne, et al., 2015; Nolke et al., 2015; Olsson et al., 2018). As a preference for branded medicines is frequently related to the beliefs that

generics are inferior, and less effective and safe, it is unsurprising that patients with this preference report more concerns about switching (Dunne, Shannon, Dunne, et al., 2014).

Interestingly, the study findings show that concerns about switching to a biosimilar are exacerbated in patients who have stronger emotional responses to their condition. This is an important finding as negative affective responses such as anger or fear are common in patients with arthritis, but can bias treatment decision-making and risk perceptions (Shaw et al., 2018). A recent study also demonstrated that emotional states can impact inflammatory responses (Graham-Engeland et al., 2019). Perhaps, patients who are emotionally impacted by their condition have more concerns about switching due to the uncertainty in the biosimilars ability to control inflammatory responses. This finding suggests a need to improve coping and resilience, as emotions may heighten negative attitudes towards new treatments (Dures et al., 2017).

Another important finding is that patients who seek information on the Internet are more concerned about switching. Research demonstrates that people with high levels of health anxiety and perceived sensitivity to medicines search for health information online (Faasse, Grey, Horne, et al., 2015; McMullan et al., 2019). However, this can lead to Internet users accessing non-factual information and can influence their perceptions towards unbranded medicines, particularly as information shared online often does not align with best practice guidelines (Gasteiger et al., 2018). Directing patients to credible material after a discussion about switching to biosimilars may help reduce concerns (Gasteiger et al., 2019).

In our study patients' experiences with their current bio-originator also influenced perceptions of the biosimilars side effects and safety. Furthermore, those who perceived their bio-originator to be more effective were more likely to prefer their biologic therapy over switching to a biosimilar. This finding is consistent with recent studies, which have demonstrated that rheumatology patients who have effective bio-originator treatments or are satisfied with their treatment are hesitant to change, due to fearing new side effects (Teeple et al., 2019). Although patients in our study reported expecting the biosimilar to have a similar safety and side effect profile to the bio-originator, fears of reduced efficacy and the potential for new side effects may still persist and influence treatment preferences (Edwards et al., 2019; Teeple et al., 2019). Our findings provide support that clinical experiences of a bio-originator treatment influence perceptions and preferences to switch to biosimilars (Alrasheedy et al., 2014; Rathe et al., 2013).

Healthcare professionals should refer patients to credible information to reduce the risk of patients seeking incorrect information about biosimilars. Providers should also assess and reassure patients who have had unfavourable experiences with bio-originators, in terms of safety and side effects, as these influence perceptions towards biosimilars. By assessing patients' preferences for branded medicines, healthcare professionals can provide educational interventions to address misconceptions towards medicines (Babar et al., 2014). This is important as a lack of understanding about generic medicines contributes to the development of negative perceptions, increases nocebo responses and limits uptake (Alrasheedy et al., 2014; Dunne, 2016; Dunne, Shannon, Hannigan, et al., 2014).

A key strength of the study was using a patient sample who are likely to be impacted by biosimilar adoption. Participants are therefore highly similar to other patients who may have the decision to switch. We also explored a number of psychological and demographic variables previously examined in research on generic medicines. Some limitations also need to be considered. First, we relied on single-item outcome measures. Exploring other dimensions of perceptions, such as safety concerns about manufacturing may improve content validity. The study did also not consider previous experiences with unbranded medicines, which have recently been shown to impact perceptions towards biosimilars in patients with inflammatory bowel disease (Haghnejad et al., 2020). Similarly, it was unknown whether patients were on stable treatment with the bio-originator, as this may impact perceptions towards biosimilars. Another limitation is the heterogeneity of rheumatic conditions and biologics presented in the patient sample. As the sample was not large enough to conduct analyses for each patient group, it is unclear whether group differences exist.

Differential uptake across pharmaceutical markets must be acknowledged, as biosimilars are not publicly funded for rheumatic disease indications in Aotearoa/New Zealand. Although patients in countries with a high uptake of biosimilars have demonstrated relatively low levels of familiarity with biosimilars (Jacobs et al., 2016; van Overbeeke et al., 2017), it is likely that for our patient sample this study was their first exposure to biosimilars. This is important as patients who are aware of biosimilars have reported more positive perceptions about their safety and efficacy (Jacobs et al., 2016). As we did not assess patients' prior understanding of biosimilars it is unknown how these factors may influence perceptions in our sample. The study findings might be limited in generalisability to patients in countries

with a high biosimilar uptake. Patients were also predominantly recruited from one clinic, which may further impact generalisability.

More research is needed to explore whether the predictive ability of the characteristics identified in this study are evident in other patient groups and whether additional characteristics, such as health-related anxiety, are associated with negative perceptions towards biosimilars. Research should also examine the potential impact of these characteristics on adherence following a switch. Lastly, more research is needed to develop educational interventions to educate patients and their families, who may be involved in the decision to switch to biosimilars.

These findings suggest that various demographic and psychological characteristics are associated with negative perceptions towards biosimilars. The study also revealed that previous experiences with bio-originator treatment are associated with perceptions towards a biosimilar's safety and expected side effects, as well as preferences towards switching. Educational interventions should focus on patients taking bio-originators who are female, seek health information on the Internet, have strong emotional responses to their condition and prefer branded medicines, to improve biosimilar acceptance.

Chapter Six: The Influence of Companions

Preface

The research in the first section of this thesis has contributed to understanding how patient-provider communication can be improved to help increase biosimilar acceptance. Specifically, it provides guidance on what information should be included, how it should be delivered, which patients should be targeted, and the importance of upskilling other healthcare providers involved in patient education, such as pharmacists (Gasteiger, den Broeder, et al., 2021; Gasteiger, Lobo, et al., 2021). However, in Chapter 2, it was argued that dyadic decision-making (i.e., one patient and provider) is an outdated approach, as companions often accompany patients (Douglas et al., 2005; Wolff & Roter, 2011). Treatment decisions are also made with consideration of collateral effects and the perceived approval (or disapproval) of companions (Fishbein & Ajzen, 1975; Laidsaar-Powell, Butow, Charles, et al., 2017). Given that decisions are not made in isolation, this section of the thesis focuses on the influence and involvement of companions in discussions about biosimilars.

The shift to patient and family-centred care has resulted in the involvement of companions in shared decision-making garnering considerable research attention. Therefore, it has been widely accepted that treatment decisions are interactional and are made within a broader social context (Elwyn et al., 2014; Epstein & Street, 2011a; Ho, 2008). According to the concept of shared mind, new perspectives and ideas emerge through sharing feelings, meanings, thoughts, and perceptions (Epstein & Street, 2011a). This idea of active deliberation is also referenced by the model of collaborative deliberation, which acknowledges the value of collaborating with others, such as family and friends, when making important decisions (Elwyn et al., 2014). However, not all collaboration is constructive. In some instances, enabling the family to autonomously deliberate can lead to conflict or disagreement about treatment options, causing the patient to experience decisional conflict and psychological distress (Hamano et al., 2018; O'Connor et al., 2002; Stacey et al., 2008). Patients' medical decisions are also strongly influenced by social costs (e.g., not wanting to be an inconvenience) and so deliberation with family may restrict their autonomy to make decisions they are satisfied and comfortable with (Segan et al., 2018).

Some companion influence is also expected when patients make decisions about transitioning to biosimilars. Some influences may be positive, with companions assisting the decision-

making process, such as by providing support and gathering information about biosimilars (DiMatteo, 2004; Isenberg et al., 2018; Rees & Bath, 2000; Sharp & Hobson, 2016; Wolff et al., 2017; Wolff & Roter, 2011). Importantly, discussions with companions can improve cognitive processing and help patients understand risks and benefits, a key element of informed decision-making (Beauchamp & Childress, 2001; Dijkman et al., 2021). While companions frequently validate treatment choices, they may also influence decisions by reinforcing negative perceptions or disapproval (Holt-Lunstad, 2018; Revenson & Pranikoff, 2005; Sharp & Hobson, 2016).

Chapter 5 demonstrated that patients were less likely to prefer biosimilars if their current bio-originator is effective (Gasteiger, Lobo, et al., 2021). This finding could be emulated in companions who have witnessed the benefits from the bio-originator. Companions may remind patients of their extensive treatment journey to find an effective treatment and discourage transitioning due to a perceived risk of loss of efficacy. As such, companion influence can be an added burden for already time-constrained healthcare providers, who may need to address and modify misconceptions from both patients and companions. Healthcare providers may also face the challenge of dealing with companions who disapprove entirely of the patient's decision to transition (Lamore et al., 2017; Lewis & Rook, 1999; Zhang & Siminoff, 2003).

To date, there is limited experimental research exploring the influence of companions in treatment decision-making in general. The lack of experimental research is fathomable, given the difficulty in understanding this area. Research designs need to be carefully considered as accompanied patients often have certain characteristics, such as being female or older, in worse physical health, or less educated (Laidsaar-Powell et al., 2013). Therefore, it is not possible to directly compare treatment decisions from patients with companions and those without, as comparisons are confounded (Laidsaar-Powell et al., 2013; Shields et al., 2005). A pilot study with 30 geriatric patients reduced confounding by randomising patients with companions to attend their next medical appointment alone or with a companion (Shields et al., 2005). However, the study explored patient-centred communication rather than treatment decisions, was limited in statistical power, only involved older patients, and involved various physicians, who may have changed their communication style based on the study aims.

A randomised controlled trial was conducted to address these research deficits. The study explored the influence of companions on a patient's decision to transition from their bio-

originator therapy to a biosimilar. As biosimilars were not readily funded for rheumatology patients and it is not ethically possible to transition patients simply for research purposes, a hypothetical transitioning scenario was employed. Patients with companions were randomised to receive a standardised explanation on transitioning to biosimilars either with their usual companion or alone. Patients were also provided a brief opportunity to deliberate with their companion when accompanied. This study design enabled us to objectively explore whether companion involvement influences patient decision-making while removing confounders relating to accompaniment and physician behaviour (Laidsaar-Powell et al., 2013; Shields et al., 2005).

Citation

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Introduction

Actively enabling individual patients to participate in medical decisions has become commonplace in modern health care and it is estimated that adult patients now bring a medical companion (support person) to 35-56% of consultations (Doyle et al., 2013; Mohammed et al., 2016; Wolff & Roter, 2011). Companions are predominantly a spouse or adult child but may also be relatives, friends, or service companions (Wolff & Roter, 2011). Although there are mixed findings, the literature suggests that accompanied patients are often older, female, in worse physical health, and less educated than unaccompanied patients (Laidsaar-Powell et al., 2013).

Companions provide various benefits such as advocating for patients, reducing stress, validating decisions, gathering information, and promoting self-management of chronic conditions (Cené et al., 2015; Revenson & Pranikoff, 2005). Accompanied patients also report greater satisfaction with their doctor in terms of information giving and interpersonal and technical skills (Wolff & Roter, 2008). At times patients defer decisions to companions, especially when not feeling adequately equipped (e.g., lacking understanding) (Weir et al., 2018).

There are also potential downsides to having a companion present in a medical consultation. Companions can increase distractions for patients, which can negatively impact the patient's ability to process new information (Lindsey, 2003; van Bruinessen et al., 2013). Research also shows that accompanied patients report lower levels of attention during consultations than unaccompanied patients (Jansen et al., 2010). Further, conflict between patients and companions that stems from disagreements about treatment options can lead to psychological distress (Lewis & Rook, 1999; Zhang & Siminoff, 2003). Allowing families to deliberate and make autonomous decisions can cause uncertainty about the best treatment decision (Stacey et al., 2008). This is problematic as research suggests that a lack of knowledge, unclear

perceptions of others and social pressure can heighten decisional conflict (O'Connor et al., 2002). Patients who face decisional conflict are more likely to demonstrate low understanding, regret decisions, display signs of anxiety, and blame their doctor for poor outcomes (Stacey et al., 2008). Understanding the impact of companions in the decision-making process is arguably essential, given that companions can impact understanding, heighten decisional conflict, and ultimately reduce decision satisfaction.

Existing literature on patient and medical companion decision-making is sparse and primarily limited to decisions in geriatric, end of life or oncology care rather than routine treatment changes (Adams et al., 2009; Ervik et al., 2013; Karnieli-Miller et al., 2012; Warner et al., 2013; Weir et al., 2018). Exploring the influence of companions on patient decision-making is difficult to conduct using experimental designs, as patients who have companions may have different characteristics than those without companions – so comparisons are always confounded with these differences (Laidsaar-Powell et al., 2013; Shields et al., 2005). Given the presence of companions in routine treatment decisions, more experimental research is needed to examine their influencing role on patient decision-making. Experimental research would also clarify whether companions impact other important factors involved in the decision-making process, such as patient understanding and decisional conflict.

A medical decision that warrants further investigation is the transition from a bio-originator to a biosimilar. Bio-originators are original biopharmaceuticals (biologics), which are a class of medical products that derive from living organisms. In rheumatology, biologics such as infliximab and adalimumab have revolutionised health care by significantly reducing symptoms, slowing the progression of disease, and improving quality of life and physical function (Curtis & Singh, 2011; Jones et al., 2012). However, bio-originator use comes with a high cost to the healthcare system (Baldo, 2016; Skingle, 2015).

Biosimilars are highly similar versions made after the patent for the bio-originator has expired (Edwards et al., 2019). Unlike small-molecule generic medicines, biosimilars cannot be manufactured to be identical to the reference drug (Sekhon & Saluja, 2011). Biosimilars must have no clinically meaningful differences to the bio-originator and demonstrate comparable safety, efficacy, and purity to gain approval. Biosimilars, therefore, can provide the same therapeutic benefit at a competitive cost. One way to reach the cost saving potential of biosimilars is to transition patients from their bio-originator in what is deemed a ‘non-medical transition’ (Edwards et al., 2019). However, some rheumatology patients report

negative perceptions towards the safety, efficacy, and quality of biosimilars and perceive the transition to have associated risks (Gasteiger, Lobo, et al., 2021; van Overbeeke et al., 2017). Rheumatology patients are also less willing to transition when their current bio-originator treatment is perceived to be effective (Gasteiger, Lobo, et al., 2021).

Research in this area, particularly on communicating biosimilar transitions to patients, is in its early stages (Gasteiger et al., 2019; Vandenplas et al., 2021). Although companions are likely to be present in the discussion to transition, no research has explored their involvement in the decision-making process. Companions could increase patients' hesitancy to transition by raising unique concerns about biosimilars. Companions may also discourage transitioning, especially if they have seen how effectively the bio-originator controls the patient's symptoms and improves daily function. Treatment decisions are also often made with familial roles or relationships in mind (Ho, 2008). The presence of the companion may remind patients of the wider collateral effects to family or friends if the biosimilar is not effective. The perceived risk associated with the decision to change to biosimilars provides an optimal opportunity to use this treatment decision as part of an experimental study, particularly as patients are largely unfamiliar with biosimilars (Kovitwanichkanont et al., 2020; Teeple et al., 2019; van Overbeeke et al., 2017).

This study uses the decision to transition to biosimilars to investigate the impact of companions on patient decision-making. It was hypothesised that 1) accompanied patients would be less willing to change medications and 2) be more risk averse, than unaccompanied patients. The study also investigates the effect of companions on patients' ability to understand the explanation, decision satisfaction, and decisional conflict. Lastly, the study explores the association between social support, decision satisfaction and decisional conflict.

Methods

Study Design

This study was a parallel, two-arm randomised controlled trial with two assessment points (baseline and post-explanation). Ethics approval was obtained from the Aotearoa/New Zealand Health and Disability Ethics Committee (19/CEN/163) and all patients and companions provided written informed consent. Institutional approval was obtained from Auckland District Health Board (+8700) and Waitematā District Health Board (RM14629).

The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619001435178).

Participants and Procedure

The power calculation was based on a study that tested framed explanations about transitioning to a biosimilar and used the same primary outcome variable (willingness to transition) (Gasteiger et al., 2019). Seventy-eight patients (39 per arm) were required for the trial to have 80% power, a significance level of 0.05 (2-tailed) and an effect size of f = 0.24 (OR = 2.36). Participants were recruited between December 2019 and November 2020. Due to the COVID-19 pandemic and strict hospital policies during lockdowns, breaks were taken from recruiting during March to June and August to September 2020. Patients were invited to participate if they were taking a bio-originator (Humira, Actemra, Remicade, Enbrel or Mabthera) at a rheumatology clinic in Auckland, Aotearoa/New Zealand, were fluent in English and ≥ 18 years old. Patients recruited to the study were asked to nominate a support person who could attend the study session with them if needed. The support person was someone ≥ 18 years (e.g., spouse, carer, relative or adult child) who has a close relationship with the patient. Any dyads where the patient or companion were unable to fill out the questionnaires, unwilling to participate, and/or could not understand, read, or write English were excluded.

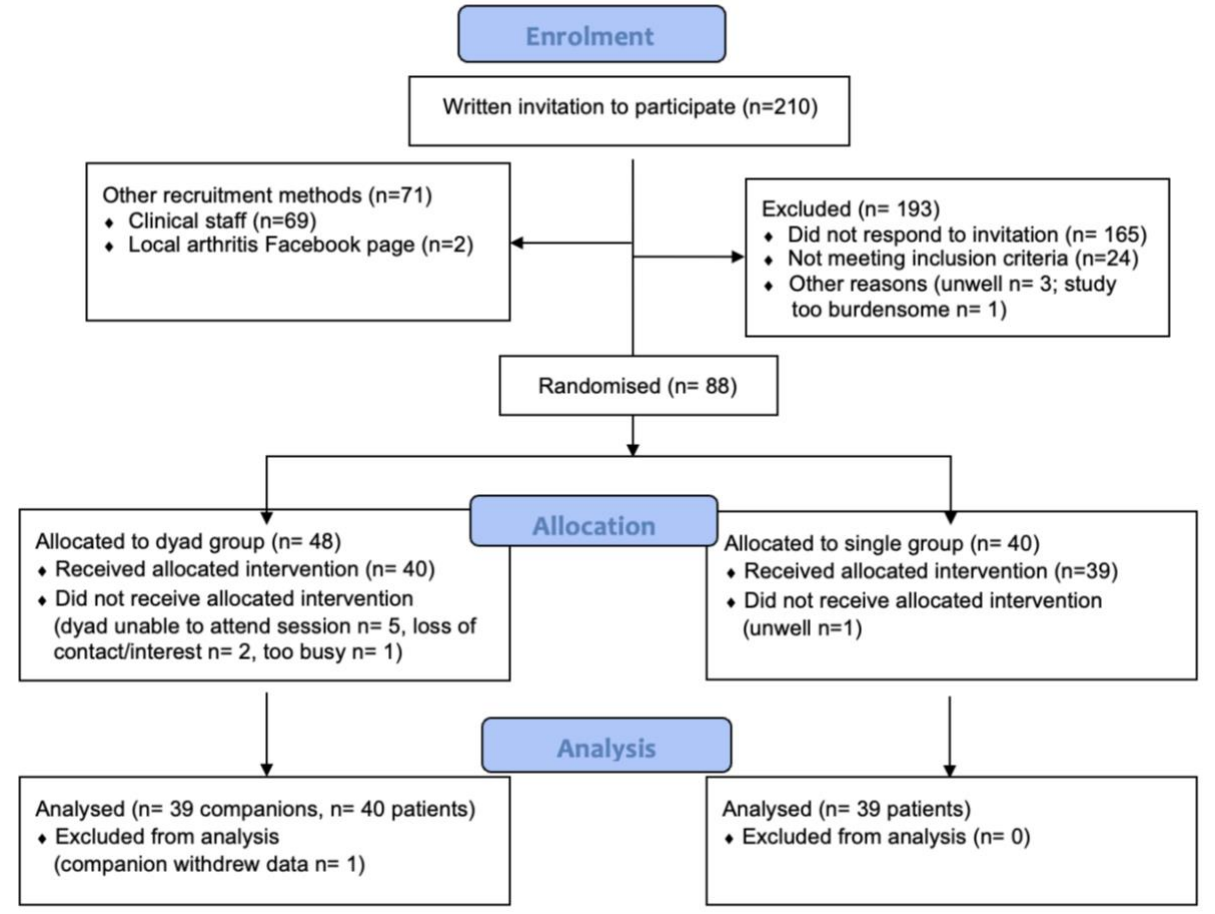
Eligible patients were sent invitation letters and information sheets before their appointment or were referred by their healthcare provider. Interested patients contacted the researcher and were randomised to the single patient group or dyad group (patients and support person) prior to the study session. In the case that patients were referred directly after their outpatient appointment or during their infusion appointment and did not have their usual support person with them, the researcher randomised the participant and organised a suitable time to conduct the study session if necessary. Participants could attend at either Greenlane Clinical Centre or North Shore Hospital (e.g., before or after their appointment) or the Clinical Research Centre of the University of Auckland Clinical Campus. Randomisation was completed by an independent researcher, using a random number generator, and contained in sequentially numbered opaque envelopes. Due to the nature of the intervention, it was not possible for the researchers to be blinded to treatment group allocation. Participants remained blinded to the study hypotheses until the results were disseminated.

During the study session participants provided informed consent and completed baseline measures assessing demographic and psychological information. Depending on group allocation, patients received an explanation about transitioning to a biosimilar by themselves or with their usual support person. The explanation was delivered using a laptop and featured the same doctor (KG) to ensure consistency and eliminate likeability or other biases. Information included the safety and efficacy of biosimilars, manufacturing processes and costs to the patient and healthcare system, as our previous study demonstrated that this was important for patients to know (see Appendix F) (Gasteiger et al., 2019). Participants in the dyad group were given a short time (no more than five minutes) to discuss the transition with their support person before coming to a decision, to ensure ecological validity relating to a normal consultation. This discussion time provided companions and patients the opportunity to discuss the explanation, concerns about transitioning, and their decision in general. Participants completed the post-intervention questionnaire immediately after the discussion (dyad group) or after watching the video explanation (single group). All participants were offered a $20 shopping voucher.

Of the 210 patients sent recruitment letters, 17 were enrolled in the study. Other participants (n = 71) were recruited from flyers distributed by clinical staff (nurses and rheumatologists) at appointments or from the local arthritis organisation Facebook page. Twelve patients in the dyad group were referred after their outpatient or during their infusion appointment and did not have their companion with them. See Figure 9 for the participant flow. To be eligible for publicly funded bio-originator treatments in Aotearoa/New Zealand, patients must meet predetermined criteria. At the time of study design no biosimilars were funded for rheumatic disease indications. Participants had not received biosimilar treatment for their rheumatic disease previously. Riximyo (rituximab biosimilar) was funded for rheumatic disease indications (excluding rheumatoid arthritis) during the recruitment period. However, the introduction of Riximyo did not impact patients in the present study. Only a small number of patients in both rheumatology departments were transitioned, and only the impacted patients were informed about biosimilar treatments. Therefore, it was not expected to impact the validity of the study.

Figure 9

Study Enrolment and Retention



Baseline Measures

Demographic. Patients reported their age, gender, ethnicity, educational attainment, and their relationship to the companion. Patients also reported their rheumatic disease, current bio-originator treatment, time on treatment, and number of previous bio-originators.

Post-Explanation Measures

Willingness to Transition. Patients indicated whether they would be willing to change to a biosimilar using binary response options (yes or no) in this hypothetical scenario. This item has been used previously (Gasteiger et al., 2019).

Preferences Towards Biosimilars. A preference towards biosimilars was assessed with one 11-point Likert scale, “which medicine would you prefer to take?” Two labels were provided: 0 (strongly prefer current biologic) and 10 (strongly prefer the biosimilar). Higher

scores indicated stronger preferences for biosimilars. This item has been used previously (Gasteiger et al., 2019).

Risk Perceptions. Participants reported their perceptions of cognitive and affective risk on two horizontal 100-millimetre visual analogue scales. To capture cognitive risk perceptions, participants completed the following item: "please place a mark on the line that best represents how much risk you think is associated to switching to the biosimilar." This item was re-worded to assess affective risk "…best represents how worried you would be about switching to a biosimilar." Two labels were provided: 0 (no risk or not at all worried) and 100 (very high risk or very worried). Higher scores indicated more perceived risk. The two items were adapted from previous research (Nieuwenhuijsen et al., 2018; Phueanpinit et al., 2016).

Decisional Conflict. The 16-item Decisional Conflict Scale (DCS) was used to assess decisional conflict (O'Connor, 1995). The scale provides five response choices and measures five dimensions: feeling informed, supported, and certain, feeling clear about values and effective decision-making. Items include "I am satisfied with my decision," with higher scores indicating more decisional conflict. The DCS has been used in rheumatology and has an appropriate reliability ($\alpha = 0.88$) (Garvelink et al., 2019). The Cronbach's alpha of the total score was appropriate ($\alpha = 0.90$).

Decision Satisfaction. The 6-item Satisfaction with Decision (SWD) scale was used to assess patient satisfaction with their decision (Holmes-Rovner et al., 1996). The scale has 5 response options with higher scores indicating more satisfaction. Items include "I am satisfied that this was my decision to make." This scale has appropriate reliability in patients and companions (McCabe et al., 2019). The Cronbach's alpha for the present study was appropriate ($\alpha = 0.89$).

Social Support. Two items were used to assess the practical and emotional support received by accompanied patients during the decision-making process. Items included, "During the appointment (study session) did you receive emotional support from your companion?" (Berli et al., 2018; Bolger et al., 2000). Although participants were provided with five response options ranging from 1 (strongly agree) to 5 (strongly disagree), items were reverse coded so that higher scores indicated receiving more social support.

Explanation. Two single items were used to assess how easy to understand, and reassuring patients found the explanation. To capture understanding, participants completed the following item: "how easy was the explanation to understand?" This was re-worded to assess reassurance: "how reassuring was the explanation?" Both items have been used previously (Gasteiger et al., 2019). One further item assessed how important participants believe it is to receive information accompanied. This item was: "how important do you think it is that the companion receives medical information with you?" All three items were rated on an 11-point numerical Likert scale with two labels: 0 (not at all) and 10 (extremely). Higher scores indicated more understanding and reassurance, and stronger preferences in receiving information accompanied.

Analyses

IBM SPSS Statistics (v. 27) was used for analyses, with statistical significance taken at $p < 0.05$. Independent sample t-tests or chi-square tests of independence were conducted to examine group differences at baseline. Bootstrapping or non-parametric tests were used when assumptions of normality were violated. To test the primary hypothesis (H1) that companions influence patient willingness to transition, a logistic regression was used with the outcome variable being binary coded (0 = unwilling to transition, 1 = willing to transition). An independent sample t-test was conducted to test the secondary hypothesis (H2) that companions increase patient risk perceptions.

Independent sample t-tests were also used to explore group differences in how reassuring patients found the explanation and their reporting of their ability to understand the explanation, and the importance of receiving information accompanied. Independent sample t-tests were used to explore group differences in decision satisfaction and decisional conflict. Linear regressions were conducted to explore whether practical and emotional social support predict decisional conflict and decision satisfaction in accompanied patients. Further, Spearman's correlations were conducted in the entire patient sample to explore whether risk perceptions were associated with a preference towards biosimilars. A hierarchical logistic regression was conducted to explore if risk perceptions predict the probability of willingness to transition, with the first step controlling for the intervention groups. Intercorrelations among constructs can be seen in Appendix G.

Results

Characteristics of the full sample are shown in Table 12. Most patients were female (60%), with a mean age of 54 years ± 17.1, identified as New Zealand European (61%), and had received a tertiary education (53%). Patients were predominantly taking rituximab (34%), and more than half (66%) were taking the bio-originator treatment for the management of rheumatoid arthritis. Most patients (65%) had taken another bio-originator previously. Patients reported their companion to be a spouse or partner (56%), adult child (19%), close friend (9%) or parent (8%) and knew their companion for an average of 30 years ± 16.1. There were no significant differences in demographic characteristics between unaccompanied and accompanied patients.

Table 12

Demographic and Clinical Characteristics of the Sample (N = 79)

	Unaccompanied Patients (*N* = 39)	Accompanied Patients (*N* = 40)	All patients (*N* = 79)
Age (years)	53.5±18.1	54.7±16.2	54.1±17.1
Gender, no. [%]			
Female	23[59%]	24[60%]	47[60%]
Male	16[41%]	16[40%]	32[41%]
Ethnicity, no. [%]			
NZ European	25[64%]	23[58%]	48[61%]
Other	9[23%]	7[18%]	16[20%]
Pacific	3[8%]	4[10%]	7[9%]
Asian	2[5%]	4[10%]	6[8%]
Māori	-	2[5%]	2[3%]
Education, no. [%]			
Secondary	12[31%]	17[43%]	29[37%]
Tertiary	21[54%]	21[53%]	42[53%]
Postgraduate	6[15%]	2[5%]	8[10%]
Bio-originator, no. [%]			
Rituximab	16[41%]	11[28%]	27[34%]
Infliximab	7[18%]	10[25%]	17[22%]
Etanercept	6[15%]	11[28%]	17[22%]
Adalimumab	5[13%]	4[10%]	9[11%]
Tocilizumab	5[13%]	4[10%]	9[11%]
Time taking bio-originator (months)	32±29	32.6±37.7	32.3±33.5
Previous bio-originator	26[67%]	25[63%]	51[65%]
Number of previous biologics			
0	13[33%]	15[38%]	28[35%]
1-2	21[54%]	24[60%]	45[57%]
3-4	5[13%]	1[3%]	6[8%]
Rheumatic disease, no. [%]			
Rheumatoid arthritis	28[72%]	24[60%]	52[66%]
Ankylosing spondylitis	6[15%]	6[15%]	12[15%]
Psoriatic arthritis	3[8%]	6[15%]	9[11%]
Granulomatosis with polyangiitis	1[3%]	1[3%]	2[3%]
Juvenile idiopathic arthritis	1[3%]	1[3%]	2[3%]
Other	-	2[5%]	3[4%]

Note. NZ = Aotearoa/New Zealand

The Influence of Companions

Willingness to Transition. A logistic regression model was conducted to explore the primary hypothesis (H1) that having a companion present decreases patient willingness to change to the biosimilar (Table 13). Unaccompanied and accompanied patients had a similar willingness to transition (56% versus 53% respectively). The model was not statistically significant ($\chi^2(1,79) = .12$, $p = .73$, Nagelkerke $R^2 = .002$). The presence of a companion did not influence patient willingness to transition (Wald $\chi^2 = .12$, $p = .73$, B = .16, Exp(B) = 1.17).

Table 13

Logistic Regression Testing the Impact of Companions on Willingness to Transition

Variable	***B***	***SE***	***Wald* χ^2**	***Odds Ratio Exp(B)***	***Sig.***	***95% CI for OR***	
						Lower	**Upper**
Companion[a]	.16	.45	.12	1.17	.73	.48	2.84
Model χ^2	= .12, p = .73						
Nagelkerke R^2	= .002						

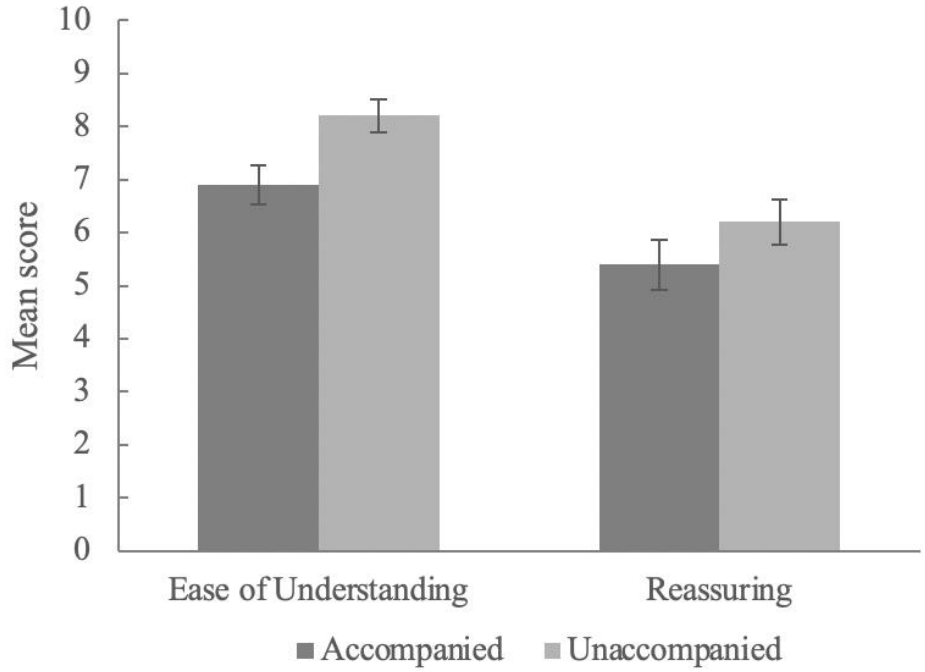
Note. The dependent variable is being willing to switch to a biosimilar, coded 0 = no, 1 = yes.
[a]0 = unaccompanied, 1 = accompanied

Risk Perceptions. Bootstrapped independent sample t-tests were conducted to explore the secondary hypothesis (H2) that companions increase patient risk perceptions. These analyses demonstrated that being accompanied did not significantly influence patients' cognitive ($t(77) = -.35$, $p = .72$, 95% CI = -12.46, 9.25, Cohen's d = -.08) or affective risk perceptions ($t(76) = -1.20$, $p = .23$, 95% CI = -21.85, 5.76, Cohen's d = -.27).

Reported Understanding and Reassurance. Analyses were conducted to explore group differences on how reassuring and easy it was to understand the explanation. Independent sample t-tests demonstrated a significant difference in ease of reported understanding, $t(75) = 2.85$, $p = .006$, 95% CI, .42, 2.35. There was a medium effect (Cohen's d = .64), with unaccompanied patients ($M = 8.2$, $SD = 1.9$) reporting that it was easier to understand the explanation compared to accompanied patients ($M = 6.9$, $SD = 2.4$) (see Figure 10). There was no significant difference between accompanied ($M = 5.4$, $SD = 2.9$) and unaccompanied patients ($M = 6.2$, $SD = 2.7$) for how reassuring the explanation was, $t(76) = 1.13$, $p = .26$, 95% CI, -.55, 1.99, Cohen's d = .25.

Figure 10

Differences Between Accompanied and Unaccompanied Patients in their Ability to Understand and Perceptions of Reassurance Towards the Explanation



Decisional Conflict and Decision Satisfaction. Being accompanied by a companion (*M* = 29.4, *SD* = 15.5) did not significantly improve patient decisional conflict (t(76) = .17, *p* = .86, 95% CI -6.17, 7.42, Cohen's d = .04), compared to being unaccompanied (*M* = 29.9, *SD* = 12.8). There was also no significant difference between accompanied (*M* = 22.4 , *SD* = 5.5) and unaccompanied patients (*M* = 24.0, *SD* = 3.1) for decision satisfaction (t(60) = 1.63, *p* = .12, 95% CI -.35, 3.66, Cohen's d = .37). Accompanied patients (*M* = 8.3, *SD* = 2.6) thought it was more important to receive medical information with their companion than unaccompanied patients (*M* = 6.8, *SD* = 3.2), *t*(77) = -2.32, *p* = .023, 95% CI, -2.84, -.22, Cohen's d = -.52).

Social Support for Accompanied Patients

Bootstrapped linear regressions were conducted to explore whether receiving emotional and practical support predicts decisional conflict or decision satisfaction. More emotional support (B = -12.28, *p* = .038) but not practical support (B = 4.17, *p* = .29) predicted less decisional conflict (F(2,36) = 4.48, *p* = .018, R^2 = 0.20). Neither emotional (B = .53, *p* = .73) or practical support (B = -.55, *p* = .65) were significantly associated with decision satisfaction

(F(2,36)= .04, p = .96, R^2 = 0.00). Findings indicate that receiving more emotional support during the discussion was associated with less decisional conflict, but not with decision satisfaction.

Risk Perceptions and Biosimilar Acceptance

Spearman's rho correlations demonstrated that cognitive risk (r_s = -.66, p < .001) and affective risk (r_s = -.66, p < .001) perceptions had a moderate, negative association with a preference towards biosimilars. Thus, as risk perceptions increased, the association with a preference towards biosimilars decreased. A hierarchical logistic regression was conducted to explore whether risk perceptions influence willingness to transition, rather than the presence of a companion. The presence of a companion (Wald χ^2 = 0.21, p = .63, B = .21, Exp(B) = 1.23) did not significantly influence willingness to transition in the first model (χ^2(1,78) = 0.21, p = .65, Nagelkerke R^2 = .004). The fully adjusted bootstrapped logistic regression demonstrated that more cognitive (Wald χ^2 = 3.07, p = .049, B = -.03, Exp(B) = .97) and affective risk perceptions (Wald χ^2 = 2.96, p = .047, B = -.03, Exp(B) = .97) uniquely, negatively related to participants' willingness to transition (Table 14). The logistic regression model was statistically significant (χ^2(3,78) = 30.59, p < .001, Nagelkerke R^2 = .43).

Table 14

Fully Adjusted Model of the Relationship Between Risk Perceptions and Willingness to Transition when Controlling for Intervention Groups

Variable	***B***	***SE***	***Wald χ^2***	***Exp(B)***	***Sig.***	***95% CI for OR***	
						Lower	**Upper**
Intervention Group[a]	-.02	.61	0.00	.98	.98	-1.29	1.18
Cognitive Risk[b]	-.03	.02	3.07	.97	.049	-.08	.00
Affective Risk[b]	-.03	.02	2.96	.97	.047	-.06	.00
Model χ^2	= 30.59, p < .001						
Nagelkerke R^2	= .43						

Note. The dependent variable is being willing to transition to a biosimilar, coded 0 = no, 1 = yes. [a]coded 0 = not accompanied, 1 = accompanied; [b]0 = no risk at all to 100 = very high risk

Discussion

Findings demonstrate that being accompanied by a companion does not change a patient's decision to transition to a biosimilar or their risk perceptions. However, companions may interfere with patients' understanding of the clinician's explanation about changing medical treatments. Further, receiving emotional support during a decision-making process was associated with reduced decisional conflict. As would be expected, greater perceived risk was associated with less willingness to transition to biosimilars. The presence of companions did not attenuate this relationship. These findings show the complexities of elucidating companions' influences during routine medical decisions, such as changing to cheaper medications.

Interestingly, companions did not alter patients' decisions to change treatments or risk perceptions. Companions may have seen their role as providing support or validation, rather than influencing decisions or playing 'devil's advocate' (Lamore et al., 2017). In previous research, companions have reported self-censoring their opinions and directly acknowledged it is the patient's right to make decisions while privately feeling upset or angry about the outcome (Laidsaar-Powell et al., 2016). Further, companions may have perceived the patient to be more knowledgeable and so expected them to be able to make an informed, autonomous decision (Lamore et al., 2017).

Accompanied patients reported more difficulty understanding medical information given during the consultation. There may be a number of reasons for this interesting finding. Firstly, companions may have distracted patients and caused their attention to be split between the doctor and the companion. Companions may negatively impact patient attention by interrupting patients or causing distractions such as increasing external noise (Clapp et al., 2010). These actions may obscure the explanation, disrupt the working memory, and interfere with the patient's ability to encode and recall detailed information (Clapp et al., 2010; Craik, 2014). Secondly, the presence of a companion may have shifted the balance of responsibility within the consultation, so the patient could feel that with the companion there the patient may not need to focus on the material as intently (Jansen et al., 2010). The self-regulatory outsourcing and the diffusion in responsibility theories also support that patients may have relied on or 'outsourced' self-regulatory effort to their companion and therefore missed key detail (Darley, 1968; Fitzsimons & Finkel, 2011). Thirdly, there is also the possibility that this difference in reported understanding may represent a reporting bias in that the presence

of companions could have made patients feel more comfortable admitting difficulties in understanding complex information. Further research is needed to understand what may be causing this difference in understanding. However, the results do suggest that physicians should still check understanding in accompanied patients.

Of interest, being accompanied did not improve patient decisional conflict or decision satisfaction. Instead, the patient's perceptions of received emotional support during the consultation were more valuable. Supported patients may have received validation and reassurance, felt informed through their opportunity to deliberate, and voice concerns, and felt they were not making a big decision alone (Lamore et al., 2017). Literature also shows that patients often value the silent, intangible emotional support of family members, such as simply being present (Laidsaar-Powell et al., 2016; Lamore et al., 2017; Stewart et al., 2021). This provides implications for companions who do not provide support and oppose decisions, causing conflict or feelings of isolation during the decision-making process.

Findings should be considered in light of limitations. The study used a proxy for a real transition and had a relatively low response rate. The low response may be explained by the initiation of recruitment before the holiday season and throughout the COVID-19 pandemic, which likely heightened anxiety and discouraged patients from visiting the hospital unnecessarily. The study was also limited to the decision-making process within the consultation and did not enable participants to ask questions. Methodologically, the companion's involvement in the decision-making process (five-minute discussion) could have been too brief. However, this time is reflective of real-life practice, where in reality, dyads may have even less time to discuss decisions due to time constraints. Sometimes patients are notified about drug transitions before the consultation or are given time to consider the decision after the consultation, which would enable the opportunity for the patient to consult with a wider range of support people (Müskens et al., 2020; Tweehuysen, Huiskes, et al., 2018). Future research should therefore replicate the study with a short follow-up time period and where possible, use a real-life transition.

The present study relied on one self-report item to assess perceived understanding. However, research demonstrates that patients and companions remember different types of information from consultations (Jansen et al., 2010). Future research should measure understanding by testing the recall of key information. This method may also help identify specific information that is commonly misunderstood or topics that patients and companions find the most

important to discuss. The eligibility criteria also did not specify previous companion involvement. It is likely that some only provide practical support (e.g., provide transport) or emotional support at home but are not usually involved in decision-making processes. Results may therefore differ when the entire companion sample always attend appointments. These companions may be more comfortable and clear of their role and thus may be more influential (Laidsaar-Powell et al., 2013). However, as the present sample consisted of patients who brought their usual support person, regardless of prior involvement, the sample were representative of the wider patient population.

Further research in this area is warranted, particularly concerning the companion-physician dyad. Some research has demonstrated that physicians communicate differently in triadic consultations, such as engaging in more medical talk, but more experimental research is needed to explore how this influences patient decision-making processes (Clayman et al., 2005; Isenberg et al., 2018; Troy et al., 2019). Future research should employ a pretest-posttest design, whereby accompanied patients' willingness to transition is tested immediately after receiving the standardised information and following a discussion with their companion. This could further clarify whether and to which extent companions influence patients' initial attitudes towards biosimilars.

Further, research predominantly focuses on the presence of one companion and oncology care. However, companion roles and involvement may differ for other specialities (Troy et al., 2019). Research should also further explore the role of social support in treatment decision-making, particularly how to optimise time-constrained consultations and create an environment to enable companions to provide support. Research is needed to disentangle the reasons for accompanied patients reporting more difficulty in understanding the explanation. Possible explanations such as the companion being distracting, sharing the responsibility of the decision, and having less time focused on one person should be explored. Lastly, more research is needed to explore the remaining variance of decisional conflict, and interventions should be developed to modify risk perceptions for patients transitioning to biosimilars.

The present study is the first to employ an experimental design to explore the influence of companions by modifying their presence in medical discussions about changing treatments. Findings highlight the complexity of companion involvement in decision-making processes. Specifically, companions did not change patient decisions or risk perceptions. However, the emotional support provided by companions appeared to be associated with a reduction in

patient decisional conflict. Accompanied patients also reported more difficulties in understanding the explanation. Healthcare providers should be aware that patient reporting of understanding may differ when accompanied. Providers should check understanding in all patients but may benefit from allocating extra time or providing additional educational resources to accompanied patients and their companions.

Chapter Seven: Companions' Perceptions Towards Biosimilars

Preface

It has been readily accepted that negative perceptions and expectations provide challenges for the uptake of biosimilars. As discussed in Chapter 2, patients' negative perceptions regarding safety, efficacy, and quality are rife within the literature and partly contribute to resisting the transition, early discontinuation, and nocebo responses (Jacobs et al., 2016; Kovitwanichkanont et al., 2020; Odinet et al., 2018; Tweehuysen, van den Bemt, et al., 2018; van Overbeeke et al., 2017). Patient perceptions and expectations may arise from various individual and contextual factors, including previous experiences and media reporting (Colloca et al., 2019; Webster et al., 2016). Chapter 5 also demonstrated that patient characteristics and behaviours, including being female and seeking health information on the Internet, are associated with negative perceptions towards biosimilars (Gasteiger, Lobo, et al., 2021).

The social environment is a key factor in developing negative perceptions and expectations about treatments. Research has primarily focused on the patient-provider encounter and how body language and communication can unintentionally induce negative expectations (Chen et al., 2019; Colloca & Finniss, 2012; Kravvariti et al., 2018; Petrie & Rief, 2019). Other studies have shown that social modelling (i.e., observing patients reporting side effects) triggers adverse expectations and influences symptom reporting (Faasse, Grey, Jordan, et al., 2015; Webster et al., 2016). Although less researched, interactions with family or friends may influence perceptions, particularly when sharing negative experiences (Dohnhammar et al., 2016; Enck et al., 2017). Cultural beliefs and social stigma about medicine usage (e.g., long-term use is seen as harmful) further influence patient attitudes (Dohnhammar et al., 2016; Horne et al., 2004; Kumar et al., 2011). Understanding companions' attitudes towards biosimilars may provide further insight into patients' perceptions and whether companions could reinforce expectations towards biosimilars.

Elucidating companions' perceptions of biosimilars could also provide a more comprehensive understanding of the findings in Chapter 6. These findings demonstrated that companions did not influence patients' decisions to transition to biosimilars or risk perceptions (Gasteiger, Groom, et al., 2022). While unsupportive of the primary hypothesis, the finding is encouraging for the involvement of companions in future discussions about

biosimilars. Prior research suggests that companion involvement can occasionally obstruct patient autonomy, especially if controlling the decision-making process (Clayman et al., 2005). While speculative, findings suggest the contrary, as companions did not influence patient acceptance. However, it is also possible that companions were more accepting of biosimilars than anticipated and consequently did not deter patients from accepting the transition.

Ascertaining companions' perceptions towards biosimilars is an essential first step to developing inclusive communication strategies and education resources. Without understanding whether companions have unique information needs, it is almost impossible to tell whether communication strategies address their concerns. This is particularly important as companions often report higher unmet information needs compared to patients, have different information needs, and are unsure how to obtain information for themselves (Laidsaar-Powell et al., 2016; Lee et al., 2018; McCarthy, 2011; Sinfield et al., 2008). Although research has extensively explored patient perceptions towards biosimilars, it has primarily overlooked companions' perceptions. Only two studies are evident in this area (Jacobs et al., 2016; Renton et al., 2019). The more recent study is limited to a paediatric sample, whereby parents play an entirely different and more paternalistic role than adults commonly do when accompanying adult patients (Renton et al., 2019). The second study involved caregivers, but their attitudes were not specifically presented due to the authors stating that these were the same as for the patients (Jacobs et al., 2016).

Research that specifically explores companions' perceptions towards biosimilars and their information needs is warranted. The following study addresses this gap in the literature by exploring the congruence between patient and companion perceptions towards biosimilars and their information needs. This study is a pre-specified analysis conducted as part of the randomised controlled trial presented in the previous chapter. As the study explores congruency between the dyads, it only utilises the data from the companions and patients who participated together.

Citation

Gasteiger, C., Scholz, U., Petrie, K. J. & Dalbeth, N. (2021). A bio-what? Medical companions' concerns and expectations towards biosimilars in rheumatology. *Rheumatology International, 42*(11) 1993-2002. https://doi.org/10.1007/s00296-021-05037-5

Introduction

Recent literature has demonstrated problems with early discontinuation following non-medical transitions to biosimilars (Odinet et al., 2018; Tweehuysen, van den Bemt, et al., 2018). Negative perceptions towards biosimilar safety, efficacy, and quality and perceiving the transition to have associated risks partly explain this problem (Jacobs et al., 2016; Kovitwanichkanont et al., 2020; van Overbeeke et al., 2017). These can increase hesitancy to accept biosimilars and heighten the risk for nocebo responses, where adverse outcomes occur due to negative expectations and not the treatment itself (Oskouei & Kusmierczyk, 2021; Rezk & Pieper, 2017). Patients are also largely unfamiliar with biosimilars (Kovitwanichkanont et al., 2020; van Overbeeke et al., 2017), and for some patients, this impacts their confidence even if physicians explain and prescribe them (Peyrin-Biroulet et al., 2017). An unfamiliarity with biosimilars also increases the risk for familiarity biases, where individuals prefer bio-originators due to prior experience and more knowledge and exposure (Oskouei & Kusmierczyk, 2021). Effective patient-provider communication is crucial to transfer confidence to patients during the initial stages of a transition (Germain et al., 2020; Rezk & Pieper, 2018).

Research is beginning to gather momentum in the area of patient communication of biosimilars, but to date, this has focused on the information needs of individual patients (Gasteiger et al., 2019; Vandenplas et al., 2021). However, medical companions (support people) attend approximately 37-56% of consultations; therefore, not all decisions to transition to biosimilars will be made alone (Wolff & Roter, 2011). In some cases, companions may share or make decisions entirely, particularly when the accompanied patient is unwell (Laidsaar-Powell et al., 2013). Research further demonstrates that medical decisions are not individual affairs but are made with familial roles in mind (Ho, 2008). Involving family is also a key component of patient-centred care; a strategy expected in the provision of modern health care (Epstein & Street, 2011b).

It is not a new concept that the social environment influences how patients carry out decisions and form perceptions towards health behaviours (Ajzen, 1985; Hale et al., 2002; Holt-Lunstad, 2018). Companions influence health behaviours by assisting with biologic administration and providing social support, which promotes self-management and adherence to biologics in patients with rheumatic diseases (Betegnie et al., 2016; Cené et al., 2015). However, interpersonal communication, such as solicitous responses from partners, can increase health-care seeking behaviours, as evident in patients with fibromyalgia (Vriezekolk et al., 2019). As the social environment plays an influential role in a patient's medical journey, it is essential to understand companion concerns about biosimilars, as these may shape patient attitudes and behaviours.

Given the presence of support people in consultations and the importance of the social environment, surprisingly few studies have explored companion perceptions towards biosimilars. In a qualitative study involving a paediatric sample, parents expressed concerns about the administration of biosimilars and the logistics of the transition, alongside fears about uncertainty (Renton et al., 2019). In another study, caregivers were described as having the same attitudes and awareness towards biosimilars as patients, and therefore their responses were not presented (Jacobs et al., 2016).

More research that explores companion perceptions towards biosimilars and their specific information needs is necessary. This is crucial as companions may be involved in these important decisions and often report higher unmet information needs than patients (Laidsaar-Powell et al., 2016). Research is also needed to help guide clinician communication in triadic consultations, particularly as some clinicians already report an uncertainty in explaining biosimilars to patients (Hemmington et al., 2017). This study explores the congruence between patient and companion perceptions towards biosimilars and their specific information needs.

Methods

The present study is a pre-specified analysis of a parallel, two-arm randomised controlled trial that explored the influence of companions on patients' decisions to transition to biosimilars (Gasteiger, Groom, et al., 2022). Ethical approval was obtained from the Aotearoa/New Zealand Health and Disability Ethics Committee (19/CEN/163) and institutional approval was obtained from Auckland District Health Board (A+8700) and

Waitematā District Health Board (RM14629). All patients and companions provided written informed consent. A detailed description of the methods, including trial registration, has been published previously (Gasteiger, Groom, et al., 2022).

Participants

Patients taking bio-originators (Humira, Actemra, Remicade, Enbrel or Mabthera) at a rheumatology clinic in Auckland, Aotearoa/New Zealand were sent letters (n = 210) with study information. A second clinic in Auckland was used as an additional recruiting site. Seventeen patients directly enrolled in the study. A further 69 were recruited via flyers provided at routine outpatient or infusion appointments by rheumatologists or specialist nurses, or a local arthritis Facebook page (n = 2). Patients were randomised to attend the study session by themselves or with their usual companion (support person). Treatment allocations were computer generated by a researcher independent of the study and were placed in sealed opaque, sequentially numbered envelopes. Participants remained blinded to the study aims and hypotheses until the results were disseminated.

Companions were conceptualised as someone who has a close relationship with the patient such as romantic partners or spouses, close friends, or other relatives, as these groups often accompany patients (Bracher et al., 2020; Lamore et al., 2017). Patients and companions had to be fluent in English and at least 18 years old to participate. Only patients taking bio-originators at the time of the study session were eligible to participate. During the data collection phase of the study, Riximyo (rituximab biosimilar supplied by Novartis), was funded for some rheumatic disease indications aside from rheumatoid arthritis. However, patients in the present study were not impacted by the introduction of Riximyo. During the study, no other biosimilars were approved or funded in Aotearoa/New Zealand for rheumatic diseases. The sample of the wider study consisted of 118 participants (79 patients and 39 companions). This study presents data from 78 participants (39 pairs of accompanied patients and companions).

Procedure

All participants provided informed consent and completed the baseline measure assessing demographic characteristics and familiarity with biosimilars. After completing the questionnaire, participants viewed a brief standardised video delivered on a laptop featuring a

physician explaining the benefits and potential risks of transitioning to a biosimilar. The information included the safety and efficacy of biosimilars, manufacturing processes, and benefits such as reduced cost for the healthcare system and increased access. The script has been published previously (Gasteiger, Groom, et al., 2022). The explanation was informed by our previous study, which demonstrated the information patients would like to know about biosimilars before transitioning (Gasteiger et al., 2019). Participants were reassured that their current bio-originator treatment would not change due to the study, as it was based on a hypothetical situation.

Immediately following the explanation, dyads were given no more than five minutes to discuss the transition. Participants subsequently completed the post-intervention questionnaire, which included questions on risk and general perceptions towards biosimilars. The questionnaires were developed with input from all authors. Questionnaires were pilot tested and assessed for face and content validity by a researcher independent of the study and an individual with limited knowledge on biosimilars. Participants were offered a $20 NZD shopping voucher at study completion.

Measures

All participants reported their age, gender, ethnicity, educational attainment, and relationship to the companion or patient. Patients reported their biologic treatment, rheumatic condition, time on current bio-originator, and the number of previous bio-originator treatments. Companions indicated how often they accompany patients to consultations and provide information during the consultation with five response options (ranging from ‘always’ to ‘never’).

Participant familiarity with biosimilars was assessed at baseline with binary response choices (Yes or No). Participants also reported confidence in their knowledge about biosimilars on an 11-point numerical scale (0 = not at all, 10 = extremely).

Four items were used to assess perceptions towards biosimilar efficacy, side effects, safety, and participant confidence in the biosimilar following the explanation. Items include, “How confident are you that the biosimilar will be as safe as the current drug?” Participants responded on an 11-point numerical scale (0 = not at all, 10 = extremely), with higher scores

indicating more favourable perceptions. These items have been used previously (Gasteiger et al., 2019).

Cognitive and affective risk were assessed with two 100-mm visual analogue scales. For example, the following item assessed cognitive risk: “Place a mark on the line that best represents how much risk you think is associated with switching to the biosimilar.” Higher scores indicated more perceived risk.

Participants completed three open-ended questions to assess concerns about biosimilars, information that was reassuring, and the benefits of being accompanied. Open-ended questions were used to capture the breadth of participants’ concerns and elicit a more detailed understanding of their information needs. Items include “What would be your main concerns about taking the biosimilar?” Most items have been used previously (Gasteiger et al., 2019).

Statistical Analyses

Analyses were performed with IBM SPSS Statistics (v. 27). Bootstrapping or non-parametric tests were used when the assumptions of normality were violated. Statistical significance was taken at $p < 0.05$. A chi-square test of independence was conducted to explore differences in familiarity between patients and companions. Further, a paired sample t-test was used to explore differences in confidence in prior knowledge about biosimilars. A series of individual paired sample t-tests were conducted to test the differences between companion and patient perceptions and expectations towards biosimilars in relation to risk, confidence in biosimilar use and safety, efficacy, and side effect expectations. To test for the consistency between companion and patient perceptions and expectations towards biosimilars, two-way mixed intra-class correlation coefficient models were employed. Responses to each open-ended question were categorised and frequencies reported. Total percentages exceeded 100% as participants could provide more than one response.

Results

Participant Characteristics

Most patients were female (59%), had a mean age of 54.8 ± 16.4 years and identified as New Zealand European (59%) (Table 15). Over half had received a tertiary education (diploma or undergraduate degree) (54%). Patients were predominantly taking rituximab or etanercept

(28% each) and most (59%) were taking the bio-originator treatment for management of rheumatoid arthritis. Most patients (62%) had taken another bio-originator previously, with over half (59%) having taken one or two.

Companions were predominantly female (59%) and 54.5 ± 17 years old. Companions were mostly spouses or partners (56%), adult children (18%), siblings, close friends, or parents (all 8%), and knew the patient for an average of 31 ± 16.8 years. In relation to consultations, 42% of companions always or mostly attended consultations with the patient and 41% attended only half of the time or occasionally. Some companions (23%) always or mostly provided information during the consultation and a portion (31%) never provided information.

Table 15

Demographic and Clinical Characteristics of the Analytic Sample (N = 78)

	Accompanied Patients (*N* = 39)	Companions (*N* = 39)
Age (years)	54.8±16.4	54.5 ± 17.0
Gender, no. [%]		
Female	23[59%]	23[59%]
Male	16[41%]	16[41%]
Ethnicity, no. [%]		
Asian	3[8%]	2[5%]
Māori	2[5%]	-
NZ European	23[59%]	26[67%]
Other	7[18%]	6[15%]
Pacific	4[10%]	5[13%}
Education, no. [%]		
Secondary	16[41%]	15[39%]
Tertiary	21[54%]	20[51%]
Postgraduate	2[5%]	4[10%]
Bio-originator, no. [%]		
Rituximab	11[28%]	-
Etanercept	11[28%]	-
Infliximab	9[23%]	-
Adalimumab	4[10%]	-
Tocilizumab	4[10%]	-
Time taking bio-originator (months)	33.3±38.0	-
Previous bio-originator	24[62%]	
Number of biologics		
0	15 [39%]	
1-2	23[59%]	
3-4	1[3%]	
Rheumatic disease, no. [%]		
Rheumatoid arthritis	23[59%]	-
Ankylosing spondylitis	6[15%]	-
Psoriatic arthritis	6[15%]	-
Granulomatosis with polyangiitis	1[3%]	-
Juvenile idiopathic arthritis	1[3%]	-
Other	2[5%]	

Note. NZ = Aotearoa/New Zealand

Familiarity with Biosimilars

There was a general low familiarity with biosimilars at baseline, with companions reporting significantly less familiarity than patients ($p = 0.014$, Cramer's V = .28) (Table 16). Companions also reported significantly less confidence in their knowledge about biosimilars ($p = 0.006$, Cohen's d = .47).

Perceptions Towards Biosimilars

Companions and patients were congruent in terms of confidence in biosimilars and expectations regarding efficacy, safety, and side effects (Table 16). There was a moderate to good agreement between the two groups (average measure ICC's ranging from 0.75- 0.81). There was a poor agreement between companions and patients in terms of cognitive and affective risk perceptions.

Table 16

Patient and Companion Familiarity and Perceptions Towards Biosimilars

	Patients	**Companions**	**Mean group difference**	**Effect size**	**Agreement**
	***M* (SD)**	***M* (SD)**	***P*-value**	**Cohen's d**	**ICC [95% CI]**
Familiarity (Yes, [N(%]))	13 (33%)	4 (10%)	**0.014**	Cramer's V = .28	-
Confidence in knowledge	3.2 (2.7)	1.6 (2.4)	**0.006**	.47	0.19 [-.55, .57]
Perceptions					
Confidence in biosimilar	5.0 (2.7)	5.4 (2.6)	0.21	-.21	0.81 [.64, .90]
Efficacy expectations	5.1 (2.6)	5.3 (2.7)	0.54	-.10	0.76 [.54, .87]
Safety expectations	5.0 (3.1)	5.5 (2.7)	0.21	-.20	0.75 [.52, .87]
Side effect expectations	4.1 (2.7)	4.6 (2.7)	0.29	-.17	0.76 [.54, .87]
Risk					
Affective risk	45.6 (23.9)	45.1 (23.2)	0.93	.01	0.31 [-.32, .64]
Cognitive risk	54.1 (29.4)	47.3 (26.4)	0.22	.20	0.43 [-.09, .71]

Note. Bold variables are significant at $p < .05$. ICC = intra-class correlation coefficient

Concerns

A similar proportion of companions and patients reported the possibility of reduced safety (increased side effects) as their main concern for transitioning to the biosimilar (Table 17).

Following this, companions and patients reported concerns about loss of efficacy. Companions also found cost as the reason for the transition and the differences in manufacturing to be concerning. Patients, however, were more concerned about the uncertainty of the transition and testing of biosimilars.

Reassuring Information

Patients and companions were primarily reassured by the same information (Table 18). Several participants in each group found the reduced cost and the potential for increased access to be reassuring. In both groups, some participants were reassured by the similarity between biosimilars and bio-originators. A group of participants also reported information on the biosimilar's testing to be reassuring.

Benefits of Being Accompanied

Patients primarily found it helpful to discuss the transition with their companion and reported that the companion improved their understanding (Table 19). Further, companions validated their hypothetical decision to transition and feelings towards the biosimilar. Companions also liked being able to discuss and agree with the decision. Being present improved their understanding about biosimilars but also enabled them to help improve the patient's understanding. A proportion of companions found it helpful being able to access the information first-hand rather than relying on the patient's explanation.

Table 17

Companion and Patient Concerns about the Biosimilar Transition

Companions			**Accompanied Patients**		
Category	***N (%)***	***Examples***	***Category***	***N (%)***	***Examples***
Reduced safety	17 (44%)	"Any unknown side effects." "The potential risks."	**Reduced safety**	18(46%)	"Side effects - as I do experience side effects with taking rituximab, I don't want these to escalate." "Possible side effects."
Reduced efficacy	14 (36%)	"That the benefits are not the same as medication being taken now." "That the benefits will not be the same in terms of symptom control."	**Reduced efficacy**	12 (31%)	"Length of effectiveness, does it work as well as what I am on now?? "Doesn't work the same as the one I take."
Cost	5 (13%)	"Only money/cost reduction was the main benefit, and it wasn't even for the patient." "Cost based decision to switch."	**Uncertainty**	4 (10%)	"Change means uncertainty." "Uncertainty of the outcome."
Manufacturing	5 (13%)	"Not knowing ingredients compared to current biologic." "Inconsistency between batches."	**Testing**	4 (10%)	"Biosimilars are not tested as much as biologics." "…are not tested as much as biologics."
Uncertainty	3 (8%)	"Venturing into the personal unknown." "Not knowing the unknown."	**Other (e.g., changing back, quality)**	7 (18%)	"… that I could return to my original medication and not have changes made to stop its due to lowering cost of biosimilar." "Quality of manufacturing."
Other (e.g., regulation, transitioning back)	6 (15%)	"If it wasn't working how easy would it be to switch back to a biologic?" "Medsafe approved."	-	-	-

Table 18

Information that was Reassuring to Companions and Patients

Companions			**Accompanied Patients**		
Category	***N (%)***	***Examples***	***Category***	***N (%)***	***Examples***
Cost	9 (23%)	" …but more cost effective." "Cheaper."	**Cost**	9 (23%)	"The cost of biosimilar." "That its cheaper."
Access	3 (8%)	"… would free up money to treat more people." "The lower cost means more patients can receive."	**Access**	4 (10%)	"It can help somebody else with the price (e.g., two for the price of one)." "It would enable more patients access to the meds."
Similarity	5 (13%)	"Doctor saying it will be similar in procedure and result/benefits should be same." "It works in the same way."	**Similarity**	5 (13%)	"That it does the same thing." "Works in the same way."
Testing	5 (13%)	"That it has been extensively tested." "The length of time and amount of studies required for it to be approved."	**Testing**	4 (10%)	"The test/trial results." "Amount of times tested."
Transitioning back	4 (10%)	"That if symptoms changed you could resume prior medication." "…and that can switch back."	**Previous use**	3 (8%)	"Drug has been used on other patients." "That it's been used overseas with good results."
Previous use	4 (10%)	"Successfully used world-wide." "That it is being used overseas and helping other patients"	**Transitioning back**	2 (5%)	"That you could switch back to the original medication." "Could always switch back if needed."
Choice	3 (8%)	"Patient given choice." "No pressure to change medication."	**Other (e.g., regulation)**	4 (10%)	"That Medsafe has high quality standards…"
Other (e.g., monitoring)	3 (8%)	"That symptoms will be monitored closely if the switch occurs."	-	-	-

Table 19

Benefits of Being Accompanied During the Consultation

Companions			**Accompanied Patients**		
Category	***N (%)***	***Examples***	***Category***	***N (%)***	***Examples***
Ability to discuss	12 (31%)	"Be a sounding board and help to play devil's advocate." "Can discuss options afterwards."	**Ability to discuss**	10 (26%)	"We both have similar conditions that could be treated the same way, and hearing the explanation together helps us discuss it more in depth."
Agree with decision	3 (8%)	"Agreeing on outcome." "Same page with info."			"That I was not alone - had someone to talk this over."
Improve own understanding	9 (23%)	"That I could understand this new medicine she would be taking." "Having an idea about it and try understand more."	**Improve understanding**	8 (21%)	"Helped me unpack it. She picks up things I don't and has more medical knowledge." "Him understanding."
Improve patient understanding	5 (13%)	"Could try and explain practical bits that weren't understood." "Able to check her understanding of the explanation, explain medical jargon."	**Validation**	6 (15%)	"It reinforces how we feel about treatment." "I can ask support in my decision."
Access to information	4 (10%)	"I was able to find out information first-hand about the alternative." "Both being given direct first-hand information."	**Access to information**	3 (8%)	"Always good to have companion with me, another set of ears is always good." "So I can check if I get the same information."
Other	2 (5%)	"Reassuring."	**Second opinion**	3 (8%)	"Having a second opinion from someone who has my best interests at heart." "To get a different perspective on the topic."

Discussion

This study aimed to explore companions' perceptions of biosimilars and identify their information needs. Participants were largely unfamiliar with biosimilars, with companions reporting significantly less familiarity and confidence in their knowledge than patients. Companions reported some unique concerns about transitioning to biosimilars, including cost savings driving the transition. Patients reported concerns about the testing of biosimilars and uncertainty about the clinical outcomes of biosimilars. Both patients and companions valued the ability to discuss biosimilars and felt that being accompanied improved their understanding. Findings contribute to the scarce literature on companion perceptions towards biosimilars and highlight the need to build both companion and patient confidence in biosimilar use.

Participants, and in particular companions, reported low familiarity with biosimilars. Although this is unsurprising as biosimilars have yet to be readily integrated into the Aotearoa/New Zealand pharmaceutical market for rheumatic disease indications, it causes potential implications for future use. In previous research, a lack of familiarity has translated to less confidence in new treatments and ultimately less acceptance (Jacobs et al., 2016). As such, a lack of awareness may increase hesitancy and partially explain participants' concerns and negative expectations towards biosimilars. Low confidence in existing knowledge among all participants further highlights the general unfamiliarity with biosimilars. However, it may also demonstrate a lack of understanding in those who are familiar with biosimilars. Building knowledge is crucial, especially to ensure positive outcomes such as long-term persistence and mitigating nocebo responses in patients (Vandenplas et al., 2021).

As consistent with the literature, companions' and patients' perceptions towards biosimilars did not significantly differ (Jacobs et al., 2016). It is likely that providing the opportunity to discuss biosimilars aligned their perceptions. This may become problematic as negative patient perceptions have been a challenge in the uptake and persistence of biosimilars (Jacobs et al., 2016; Kovitwanichkanont et al., 2020; van Overbeeke et al., 2017). Companions who also hold negative perceptions may further reinforce a lack of acceptance and low persistence, such as through exhibiting negative social control (e.g., disapproval) (Holt-Lunstad, 2018). Companions are likely to benefit from being involved in biosimilar

discussions. In particular, to build confidence about biosimilar use and encourage positive behaviours such as motivation and support.

Education for companions should be developed in parallel to those of patients, as companions report some distinct information needs (Jacobs et al., 2016). As consistent with prior research with patients, participant concerns predominantly involved reduced efficacy and safety (Gasteiger et al., 2019; Jacobs et al., 2016; Peyrin-Biroulet et al., 2017). However, companions were also concerned about the transition being cost-driven and the differences in the manufacturing process. Providing information related to cost saving has been contentious in the literature (Danese et al., 2017; Frantzen et al., 2019; Vandenplas et al., 2021). Although the transition's purpose should be transparent, focusing on cost savings alone may reinforce negative perceptions about poor quality (Danese et al., 2017; Wilkins et al., 2014). Conversely, the potential for cost saving and improved access reassures some groups (Scherlinger et al., 2019). Other factors that could impact patients' decisions should therefore be mentioned, including product use, increased choice for the patient and access (Jacobs et al., 2016; Vandenplas et al., 2021). Companions may benefit from information regarding practical use or finances, particularly when actively involved in the care (e.g., helping with drug administration or providing transport) (Lamore et al., 2017). As companions were reported to enhance patient understanding, building their knowledge may encourage patients to develop positive expectations and enable continued support.

Various limitations should be considered. The present study was based on a hypothetical medical decision. This may have masked actual risk perceptions, as participants were reassured that their treatment would not change due to the study. Participants were also not given the opportunity to ask questions, which may have altered their perceptions towards biosimilars and is part of the standard information-giving process. However, the standardised explanation was necessary to ensure that biases were not introduced. Further, the explanation was not tailored, particularly to health literacy needs (Petit et al., 2021; Vandenplas et al., 2021). Other factors, however, mimicked an authentic transition, such as discussing the decision with a support person and the sample consisting of patients likely to be impacted by a future biosimilar transition.

The study sample was also relatively small and underpowered to explore the influence of companion characteristics and their association with biosimilar perceptions. A previous study highlighted that specific patient characteristics, such as gender, information-seeking

behaviours, and a preference for innovator medicines, are associated with negative expectations about biosimilars (Gasteiger, Lobo, et al., 2021). Given the small number of companions in the present study, it was not possible to test whether companions have unique characteristics that play a role in developing negative perceptions. Previous research also suggests that accompanied patients are often in worse physical health than unaccompanied patients (Laidsaar-Powell, Butow, Charles, et al., 2017; Laidsaar-Powell et al., 2013). The present sample was limited to adult rheumatology patients, who were well enough to participate in the study. As companions accompanying unwell patients are more actively involved in decisions, their treatment perceptions may differ (Clayman et al., 2005; Weir et al., 2018). Study findings may therefore be limited in generalisability.

Further research is warranted in this area. Extensive research has focused on patient acceptance of biosimilars, but research has primarily overlooked companions' perceptions. Larger samples of companions and within other medical specialities in future studies would clarify the generalisability of our findings. Research should focus on understanding the possible underlying mechanisms of biosimilar hesitancy. For example, how the social environment, including social modelling, might shape attitudes towards biosimilars (Tweehuysen, Huiskes, et al., 2018). Other psychological factors of biosimilar acceptance have yet to be understood. Research (including the present study) has highlighted altruistic tendencies (i.e., transitioning to improve access for others and save costs for the healthcare system), but no research has specifically set out to explore the role of altruism (Frantzen et al., 2019; Scherlinger et al., 2019). Patient and companion familiarity and confidence in biosimilars need to be improved. Future communication strategies and educational resources should be developed to meet both patient and companion information needs (Jacobs et al., 2016). Clinicians may benefit from guidance to effectively involve companions in these discussions without increasing time constraints.

This study extends existing research on biosimilar acceptance and, to our knowledge, is the first study to specifically explore companions' perceptions of biosimilars and their information needs. Findings suggest that companions and patients have similar levels of perceptions towards biosimilars; however, companions report some distinct information needs. Patients value being able to discuss the transition with companions and feel that companions improve their understanding of biosimilars. Healthcare providers should consider the presence of companions during discussions about biosimilars and aim to address

their concerns. Future communication strategies and educational resources should be developed with both patients and companions in mind. Communication strategies should also attempt to meet companions' unique information needs to improve acceptance of biosimilars.

Chapter Eight: Involving Companions in Treatment Decisions

Preface

The previous chapters illustrate the significant challenge of ensuring patients, and their companions, accept the transition to biosimilars. While previous communication strategies have focused on optimising the communication process for individual patients (see Chapter 3), it is currently unclear how to actively involve companions in decisions about transitioning to biosimilars. Chapters 6 and 7 both highlighted a need for healthcare providers to be aware of companions' presence and address their information needs. Research shows that companions can benefit the decision-making process (Clayman et al., 2017; Troy et al., 2019). Nonetheless, some companions are unclear of their role, feel excluded, and their presence is often associated with jargon and less psychosocial communication (Isenberg et al., 2018; Laidsaar-Powell et al., 2013; Wolff & Roter, 2011). Healthcare providers are also apprehensive about involving companions due to time constraints (Sharp & Hobson, 2016). It is evident that interventions are needed to optimise patient-provider-companion communication during decision-making processes.

Providing the opportunity for involvement in medical encounters is important, as most companions rely on support and inclusion from healthcare providers to be involved in the decision-making process (Dijkman et al., 2021; Gray et al., 2019). In modern health care, it is expected that providers include companions; a key aspect of patient and family-centred care (Clay & Parsh, 2016). Previous attempts to involve companions include pre-visit prompt lists and agenda setting-checklists to align perspectives regarding health concerns, stimulate discussions around the companion's role during the visit and prepare questions (Clayton et al., 2007; Jenkins et al., 2021; Wolff et al., 2014; Wolff et al., 2021). While effective, pre-visit checklists are resource-heavy and further contribute to existing time constraints.

Research also suggests that a healthcare provider's communication and body language facilitate companion involvement. Verbal prompts, such as encouraging questions from companions and positive body language, may encourage participation (Laidsaar-Powell et al., 2018; Laidsaar-Powell, Butow, Bu, et al., 2017). However, there is a lack of experimental research in this area, so causality cannot be inferred. A focus is also needed on improving triadic engagement, as companions often only communicate individually with the patient or the physician (Mitchell et al., 2020). More research on healthcare provider communication

styles is also required to better understand how the social environment (e.g., healthcare interactions) influences decision-making processes.

Chapters in this thesis have primarily focused on the content and mode of delivery of communication strategies rather than considering the impact of communication styles on treatment decisions. However, research suggests that a provider's style of communication is important and may influence decision-making, not just the information provided (Hargraves et al., 2016; Nicolai et al., 2016). Currently, there is scarce experimental research that has manipulated providers' communication styles and even less in a triadic encounter or involving a transition to biosimilars. A recent experimental study explored the differences between a patient-centred or doctor-centred consultation or no consultation (control) on behavioural outcomes (Haas et al., 2021). While there were no differences in behavioural outcomes, the patient-centred consultation led to a higher self-rated intention to take the concentration-enhancing medication than the control group. The study did not involve companions and was limited to a researcher playing the role of a physician, which creates problems with authenticity. Augmenting healthcare providers' styles of communication could be a useful avenue to improve triadic decision-making.

The findings from previous chapters have raised other important gaps in knowledge that should be explored. In Chapter 6, accompanied patients reported more difficulties in understanding the explanation about biosimilars than unaccompanied patients. While there are various plausible explanations, such as causing distractions, sharing the responsibility of the decision, and having less time focused on one person, the cause for this finding remains unclear. It is also possible that this finding reflects a reporting bias, as a single self-reported measure was relied on. Chapters 5, 6 and 7 were also limited to communication strategies that were not delivered in person and did not provide the ability to ask questions, which is a crucial component of decision-making. An intervention that closely mimics communication delivered in real-life transitions (such as those presented in Chapter 3) is needed. Chapter 3 also shows that only one previous communication strategy has specifically modified (upskilled) providers' communication styles about transitioning to biosimilars.

A randomised controlled trial was conducted to address these research deficits. The study explored whether a brief family-centred communication intervention improves companion involvement during consultations and treatment decision-making. The study also examines

whether the intervention impacts participant understanding of the information provided and satisfaction with the consultation, the provider's communication, and the treatment decision. A community sample was randomised to attend a mock consultation about transitioning to biosimilars with a companion. A physician delivered the information in either a family-centred communication style or only focused on the patient. A community sample was chosen as hospital-based research was severely restricted during the COVID-19 pandemic. The study draws on findings from previous chapters, such as by using a combined communication approach (Chapter 3) and testing various plausible explanations for why companions impacted patient understanding in Chapter 6.

Citation

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Introduction

Companions (support people) often accompany patients to medical encounters and play an important role during decision-making, such as by gathering information, facilitating communication, and asking questions (Cené et al., 2017; Mitchell et al., 2019; Wolff et al., 2015). Companions are generally a spouse or romantic partner, adult child, other family member, or a close friend, who has a close personal relationship to the patient and provides support throughout the medical journey (Troy et al., 2019). In medicine, a social shift has led to healthcare providers delivering patient-family centred care, in which a mutual partnership is developed and all partners are involved in care planning, delivery, and evaluation (Institute for Patient- and Family-Centered Care, n.d.). A key aspect of this is effective communication and the participation of companions in decision-making. However, some companions still report feeling ignored by healthcare providers, and their presence is often associated with less patient-centred care and patient attention (Isenberg et al., 2018; Jansen et al., 2010; Laidsaar-Powell et al., 2013). Some companions have reported feeling they are perceived as trouble, with providers not welcoming questions or taking their concerns seriously (Sinfield et al., 2008). Consequently, companions may be discouraged from supporting patients during treatment decision-making and may feel unclear of their role (Clayman et al., 2005).

Research that aims to optimise companion involvement is important as companions often rely on physicians to be a part of healthcare conversations (Gray et al., 2019). Understanding how clinicians can optimise time-constrained consultations and effectively involve companions is an emerging area of research. Literature is limited to dementia or oncology care, rather than primary or routine specialist care, where companions are also frequently present but may be less familiar with their role (Adams et al., 2009; Ervik et al., 2013; Laidsaar-Powell et al., 2018; Laidsaar-Powell et al., 2016; Laidsaar-Powell et al., 2013; Stewart et al., 2021; Weir et al., 2018). Resources such as pre-visit question prompt lists facilitate companion engagement but increase the workload for administrative staff and rely on clinicians to promote the

resource (Cené et al., 2017; Clayton et al., 2007; van der Meulen et al., 2008; Wolff et al., 2014). However, healthcare providers can also employ simple family-centred communication strategies to actively involve companions. Simple companion behaviours, such as asking questions, can be encouraged and may improve psychosocial health outcomes (Venetis et al., 2015). Other recommended family-centred communication strategies include directing information to companions, identifying the relationship, establishing preferences for companion involvement, and using positive body language (Laidsaar-Powell et al., 2018; Laidsaar-Powell, Butow, Bu, et al., 2017; Omole et al., 2011). Although suggested in the literature, a simple verbal communication intervention has yet to be developed and experimentally tested (Isenberg et al., 2018).

The decision to transition from a bio-originator drug to a biosimilar provides an optimal opportunity to test a communication strategy, particularly as biosimilars are yet to be readily adopted in Aotearoa/New Zealand. Bio-originators (original biologics) are complex immune-modulatory drugs that derive from living organisms (U.S. Food and Drug Administration, 2018b). Patients globally are being transitioned to similar counterparts ('biosimilars') that are produced when the original patent has expired in order to reduce healthcare costs (U.S. Food and Drug Administration, 2021). While many patients generally accept the transition when given a choice (86% in one systematic review), some are reluctant to change brands due to negative perceptions about safety and efficacy (Gasteiger, den Broeder, et al., 2021; van Overbeeke et al., 2017). Companions have also reported similar negative concerns (Gasteiger, Scholz, et al., 2021). Adequate communication is necessary to support patients changing to biosimilars and to promote long-term biosimilar use (Kaneko et al., 2022; Müskens et al., 2020; Oskouei & Kusmierczyk, 2021). Some research has focused on changing physician communication styles to improve patient acceptance of biosimilars and treatment decision-making in other areas (Haas et al., 2021; Nicolai et al., 2016; Tweehuysen, Huiskes, et al., 2018). However, it is unclear whether family-centred communication strategies influence decision-making. It should be noted that companions have also reported similar negative concerns about biosimilars (Gasteiger, Scholz, et al., 2021). So, it is possible that engaging with companions may further improve acceptance of new drugs due to meeting their information needs, addressing concerns, and creating a more trusting and supportive environment.

Facilitating companion involvement during decision-making may also influence patient understanding. Non-experimental research demonstrates that companions improve understanding by seeking clarification and repeating explanations (Laidsaar-Powell et al., 2013; Sheehan et al., 2019; Wolff et al., 2015). However, in an experimental study, accompanied patients with rheumatic diseases found it more difficult to understand an explanation about biosimilars compared to unaccompanied patients (Gasteiger, Groom, et al., 2022). While this finding may be due to the presence of companions distracting patients, a reporting bias (e.g., feeling comfortable admitting difficulties), or patients outsourcing self-regulatory effort to companions, further research is needed (Clapp et al., 2010; Darley, 1968; Fitzsimons & Finkel, 2011). Identifying whether companions' behaviours impact patient understanding may enable either intervention or the promotion of positive behaviours.

This study uses the decision to change to biosimilars to investigate whether a brief family-centred communication strategy improves decision-making when companions are present. The primary hypothesis (H1) was that family-centred communication will further increase willingness to transition. Secondary hypotheses were that family-centred communication will improve (H2) perceptions about risk and side effects and (H3) patient satisfaction and (H4) understanding. Manipulation checks will be conducted to demonstrate whether family-centred communication worked as intended by improving companion involvement and the provision of social support.

Methods

Study Design

This study was a randomised controlled trial with a two-arm, between-subject design and two assessment points (baseline and post-intervention). Ethical approval was obtained from Auckland Health Research Ethics Committee (AH22772) and the trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621001103853). All participants provided written informed consent. Consolidated Standards of Reporting Trials were followed (Schulz et al., 2011).

Participants and Procedure

The power calculation was conducted with G*Power and was based on a randomised controlled trial that tested the impact of communication framing on patients' willingness to transition to biosimilars (Faul et al., 2009; Gasteiger et al., 2019). Fifty-two pairs (26 in each group) were required for the trial to have a power of 95%, a significance level of 0.05 (2-tailed) and a large effect (Cohen's $w = 0.5$). The data were collected during February and March 2022.

Participants were recruited as self-selected pairs from the community, including romantic partners/spouses, family (e.g., siblings) or close friends. Pairs had to be ≥18 years old, able to complete the questionnaires, and be fluent in English to participate. Pairs had to have known each other for at least six months to ensure they were comfortable being in a health-related scenario together. Participants were recruited through poster advertisements, university-associated social media, and social media community websites. The study was advertised as an assessment of a healthcare provider's communication and to understand how to explain biosimilars. Interested participants read the Participant Information Sheet and completed a screening survey on Qualtrics. If eligible, participants booked a study session at the University Clinical Research Centre.

Participants provided informed consent and were randomised. Randomisation was completed by an independent researcher, using a random number generator, and contained in sequentially numbered opaque envelopes. Throughout the study, the researchers (CG and RY) remained blinded to group allocation and the physician (AP) was blinded to the hypotheses. Participants selected who would take on the role of the patient or companion and completed the baseline questionnaire. Participants received standardised information on the treatment scenario, which was based on the transition from an original biologic (Humira) to the biosimilar (Amgevita). The information sheet included a description of inflammatory arthritis, the current treatment, and the role of the companion in their medical journey. Subsequently, participants read a letter from the rheumatology clinic introducing the brand change. This was based on information from a real-world transition (Boone et al., 2018; Dutch Association of Hospital Pharmacists (NVZA)). Both documents are available in Appendix H.

Participants then attended a mock consultation, whereby a physician (AP) presented standardised information about changing to a biosimilar using patient-only or a family-centred approach (Appendix I). Participants were asked to act as if they were attending a real consultation. A community sample and mock consultation were utilised as the study is a proof-of-principle trial. This shows whether family-centred communication influences decision-making before being employed in standard care and is both feasible and functions as envisioned. While not identical, mock consultations create a highly similar scenario to what patients may experience. Mock consultations have been used to test communication interventions in controlled environments and similar designs are frequently used in nocebo research (Haas et al., 2021; Helfer et al., 2022). A physician who had experience with educating patients delivered the explanations to promote ecological validity.

In the patient-only consultation, the physician focused on the patient and used neutral cues towards the companion (Table 20) (Laidsaar-Powell et al., 2018; Little et al., 2015). If companions asked questions, these were briefly answered, and subsequently the focus was redirected to the patient. The control group was designed to reflect companions' experiences of care that only focuses on the patient, such as the companion being largely ignored and not having the opportunity to ask questions (Laidsaar-Powell et al., 2016; Sinfield et al., 2008). The intervention was a consultation delivered in a family-centred approach. In family-centred care, the family is considered a part of the medical journey (e.g., in planning, delivery, and evaluation) (Institute for Patient- and Family-Centered Care, n.d.). Therefore, the intervention aimed to provide an environment to facilitate companion involvement. This included acknowledging the companion, enquiring about the relationship, clarifying the companion's role, and encouraging discussion. The concept of family-centred care was extended to include all companions, not just family. Consultations were limited to ten minutes. The physician closely followed the script and, when needed, repeated information from the script to answer questions. Participants completed the post-intervention questionnaire and received a $40 voucher.

Participants were also invited to share their perceptions towards the consultation in a semi-structured interview. Interviews were conducted by two researchers (CG and RY) in pairs and in-person (or over the telephone/with virtual tools if needed) within 24 hours of the consultation. Participants were informed of the aims at the conclusion of data collection. The interview script was developed with input from an independent qualitative researcher. A

patient with four years of experience with the bio-originator was involved in the study design by consulting on the priority of the research question, measures, and material. The intervention was pilot tested with four post-graduate students, who were unfamiliar with the study aims and design, to ensure the information was easy to understand and delivered correctly.

Table 20

Description of the Family-Centred and Patient-Only Consultations

Behaviour	Family-centred		Patient-only (control)	
Introduction	Acknowledge companion.	"Hello" "What is your name?"	Briefly greet companion.	"Hello."
	Briefly enquire about the relationship.	"How do you know each other?" "How long have you known each other?"	Only focus on the participant.	"How are you doing today?"
Role clarification	Clarify role of companion.	"As long as you (patient) are comfortable, I am happy for your companion to be involved in this discussion and help you make a decision. Is this okay with you or would you rather make the decision alone?"	No role clarification.	
Information	Direct some practical information to companion.	"I know some family and friends help with transport and administration, so you'll be pleased to know that the biosimilar is administered in the same way…."	Direct all information to the participant.	
Questions	Ask companion.	"And.. do you (companion) have any questions?"	Only ask patient.	"Do you have any questions?"
Non-verbal	Lean forward; face both participants; look between both when communicating.		Lean toward patient only; look at patient primarily; only look at companion if they speak.	
Environment	Companion seated next to participant (similar distance to the healthcare professional).		Companion seated on the side of the participant (1 to 2 meters away).	

Baseline Measures

All participants reported their age, gender, ethnicity, educational attainment, nature of the relationship with the companion/patient and how long they have known one another.

Participants also reported if they had previous experiences of being accompanied or accompanying an adult to medical appointments. Familiarity with biosimilars and bio-originators were assessed using two items with binary response choices (yes or no).

Post-Intervention Measures

All participants indicated whether they would be willing to change to the biosimilar (yes or no). A horizontal 100 millimeter visual analogue scale, adapted from a previous study, was used to assess intentions to take the biosimilar (Haas et al., 2021). The item, "How likely would you be to take the biosimilar regularly?" had two anchors 'not at all likely' and 'extremely likely.'

Participants reported their cognitive and affective (emotional) risk on two-100 millimetre visual analogue scales. These have been used previously (Gasteiger, Groom, et al., 2022). Cognitive risk is how much risk is perceived to be associated with changing to the biosimilar and emotional risk refers to how worried participants would be about changing. Scales had two labels, 0 (no risk/not at all worried) and 100 (very high risk/very worried), with higher scores indicating more risk. One 11-point (0 = not at all, 10 = extremely) Likert scale was used to assess expectations towards the biosimilar's side effects (Gasteiger et al., 2019; Gasteiger, Scholz, et al., 2021).

One 11-point Likert scale assessed how easy the explanation was to understand, with higher scores indicating more understanding. This item has been used previously (Gasteiger, Groom, et al., 2022). Participants also completed six open-ended questions, which required them to recall key information from the consultation (see Appendix J) (Kreps, 2018). For example, "why do biosimilars cost less?" The questions derived from information patients wanted to know in previous research and enabled a more objective assessment of understanding (Gasteiger et al., 2019). Higher summed scores indicated better understanding.

The 6-item Satisfaction with Decision Scale and the two-item General Satisfaction subscale from the Short Patient Satisfaction Questionnaire were used to assess satisfaction (Holmes-Rovner et al., 1996; Marshall & Hays, 1994). Both scales had 5 response options ranging from strongly disagree to strongly agree. Higher scores indicated more satisfaction. The Cronbach's alpha for the Satisfaction with Decision Scale was appropriate ($\alpha = 0.86$).

Participants also completed the 9-item Patient Perception Scale, which measures the degree to which the communication is patient-centred (Reinders et al., 2009; Stewart et al., 2000). Responses range from 1 (completely) to 4 (not at all). This scale has been previously used to assess patient satisfaction and is reliable ($\alpha = 0.88$) (Hack et al., 2012). Higher scores indicate more satisfaction. The Cronbach's alpha for the present study was appropriate ($\alpha = 0.81$). One 11-point Likert scale (from 0, not at all to 10, extremely) also assessed how reassuring participants found the explanation.

Two items assessed the emotional and informational social support provided by companions. Participants responded with five response options ranging from 1 (strongly agree) to 5 (strongly disagree). Higher scores indicated more support. Items have been used previously (Berli et al., 2018; Gasteiger, Groom, et al., 2022).

Participants reported the number of questions they asked during the consultation as a more objective measure of involvement. Participants also reported if their decision changed after a discussion with their companion (yes, no or did not discuss). Participants also rated their own and the companion's involvement in the decision and during the consultation using two 11-point Likert scales with two labels ranging from 0 (not at all) to 10 (extremely).

Participants completed one open-ended question to capture their reason for choosing to change to the biosimilar. Semi-structured, audio-recorded interviews with both participants were used to capture their experiences of the consultation. See Appendix J for the interview script.

Analysis

Data were analysed in IBM SPSS Statistics v.27. A significance level of $p < 0.05$ was maintained for all analyses. Bootstrapping or nonparametric tests were used when assumptions of normality were violated. For the manipulation check, independent sample t-tests or chi-square tests were used to assess differences between groups for companion involvement, number of questions asked, discussion and provision of social support. Companion involvement in the decision and consultation were summed to create a total score. To test the primary hypothesis (H1) a logistic regression was used with the outcome variable, willingness to change, being binary coded (1 = willing to change, 0 = unwilling).

Independent sample t-tests were used to assess differences between groups for perceptions towards biosimilars (H2), satisfaction with the communication, decision, and consultation (H3) and perceived understanding and recall of key information (H4). Two hierarchical multiple linear regressions were conducted to identify whether various companion and physician behaviours reduced patient worries and whether companion behaviours are associated with recall of key information.

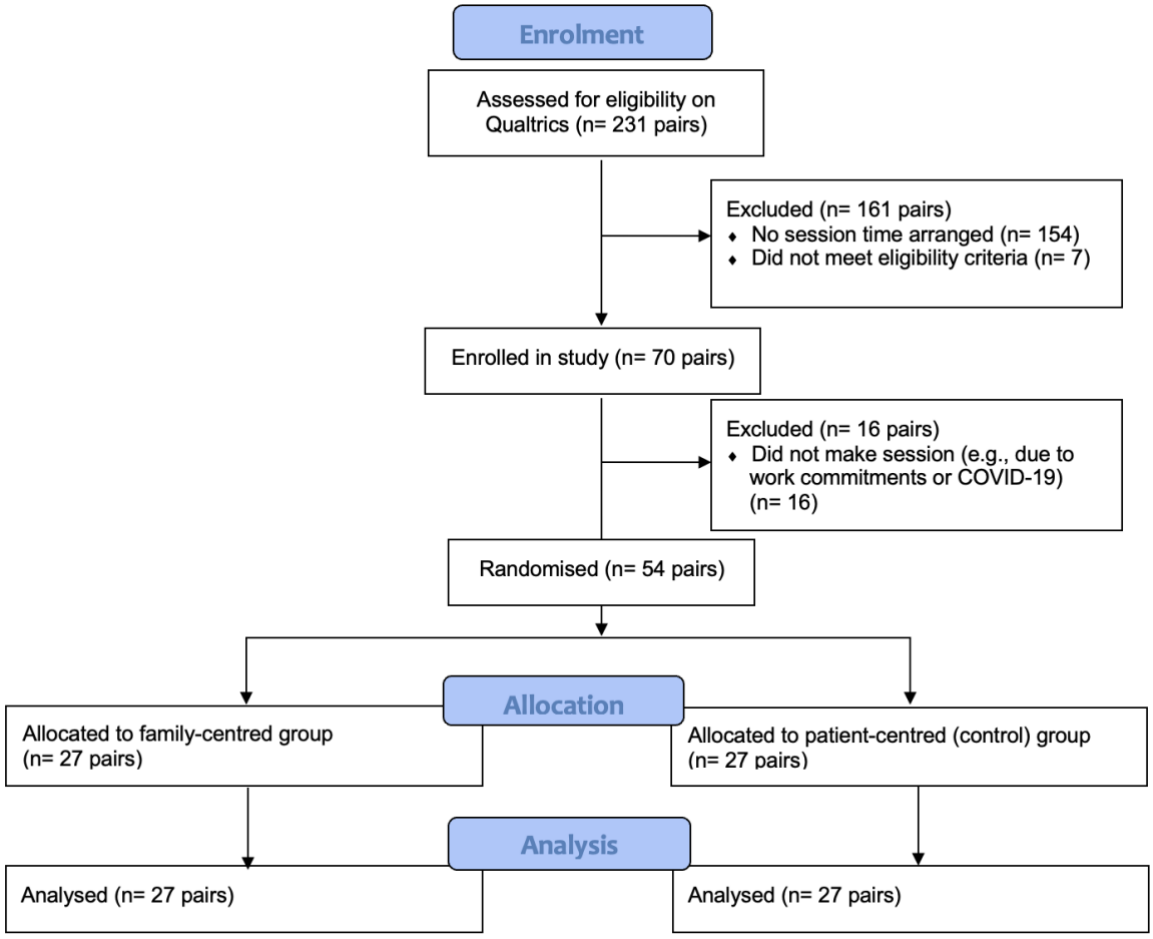
The data from the interviews and open-ended responses were analysed using an inductive content synthesis approach, whereby the content of the data informed the findings (rather than a pre-existing framework) (Elo & Kyngas, 2008). Each question was analysed independently, by first applying codes that described the key concepts within the content. The number of times each concept had been reported was determined and supporting quotes were identified. The results from the most common responses are presented in the form of descriptions, supporting quotes and frequencies. One researcher coded all of the data, with a second researcher independently double coding a subset (26%) of the data. The two coders reached a raw agreement rate of 80% when coding the data from the open-ended responses and interviews. Data from the open-ended question and interviews were used to further understand participants' experiences with the consultations and reasons for being willing to change to biosimilars.

Results

Of the 231 pairs who completed the eligibility screening questionnaire on Qualtrics, 161 did not arrange a session time or did not meet eligibility criteria. Seventy pairs were enrolled in the study, with 16 pairs being excluded due to not being able to attend the session (e.g., due to exposure to COVID-19). A total of 54 pairs (108 participants) were randomised. Thirty-one pairs participated in the interview, which ranged from 7 to 21 minutes. See Figure 11 for study flow.

Figure 11

Study Enrolment and Retention



Most participants were female (69%) and had a mean age of 30 years ± 14.1 (range 18-75 years) (Table 21). Participants mostly identified as New Zealand European (31%) and had completed secondary education (40%). Twenty-three percent of participants had heard of bio-originators and 28% of biosimilars previously. Companions were close friends (48%), romantic partners or spouses (37%), parents (7%), siblings (6%), or other relatives (2%). Pairs had known each other for an average of 10 years ± 10.7, with a range of 7 months to 52 years. Most 'patients' (76%) had experiences of being accompanied by another adult to a medical consultation. Similarly, most companions (69%) reported having experiences in accompanying an adult to a consultation. There were no significant differences in demographic characteristics between patients and companions in each group or patients between both groups.

Table 21

Characteristics of the Sample (N = 108)

	Family-centred		Patient-only		All
	Patients	Companions	Patients	Companions	Participants
Age (years) (M ± SD)	30.9±14.7	32.7±16.0	25.9±10.2	28.9±14.4	29.6±14.1
Gender, no. [%]					
Female	16[59%]	18[67%]	20[74%]	20[74%]	74[69%]
Male	11[41%]	9[33%]	7[26%]	7[26%]	34[32%]
Ethnicity, no. [%]					
NZ European	8[30%]	10[37%]	9[33%]	6[22%]	33[31%]
Other (e.g., two ethnicities)	6[22%]	5[19%]	6[22%]	12[44%]	29[27%]
Asian	9[33%]	7[26%]	7[26%]	3[11%]	26[24%]
Indian	4[15%]	4[15%]	4[15%]	5[19%]	17[16%]
Māori	-	1[4%]	-	1[4%]	2[2%]
Pacific	-	-	1[4%]	-	1[1%]
Education, no. [%]					
Secondary	10[37%]	10[37%]	12[44%]	11[41%]	43[40%]
Tertiary	9[33%]	11[41%]	10[37%]	7[26%]	37[34%]
Postgraduate	8[30%]	6[22%]	5[19%]	9[33%]	28[26%]
Familiarity: bio-originator					
Yes, %	7[26%]	2[7%]	8[30%]	8[30%]	25[23%]
Familiarity: biosimilar					
Yes, %	8[30%]	8[30%]	7[26%]	7[26%]	30[28%]

Note. NZ = Aotearoa/New Zealand

Manipulation Check

Independent sample *t*-tests demonstrated that patients perceived companions in the family-centred consultation to be significantly more involved in the consultation and decision-making process than those in the patient-only communication group ($t(52) = 4.51$, $p < .001$, 95% CI = 3.62, 9.09, Cohen's d = 1.23). Companions in the family-centred consultation did not significantly ask more questions ($p = .18$) but were more likely to discuss the decision ($X^2(1,54) = 6.31$, $p = .012$, Cramer's V = .34) (Table 22). Patients in the family-centred consultation also received more emotional and informational support ($t(52) = 3.17$, $p = .002$, 95% CI = .62, 2.58, Cohen's d = .86) from companions.

Patient Decision-Making

A logistic regression model was conducted to explore the primary hypothesis (H1) that the family-centred consultation improves patient willingness to change to the biosimilar. All patients in the family-centred (100%) and most patient-only consultation (96.3%) were willing to transition to the biosimilar. The model was not statistically significant ($\chi^2(1,54) = 1.41$, $p = .24$, Nagelkerke $R^2 = .153$). The family-centred consultation did not influence patient willingness to transition (Wald $\chi^2 = 002$, $p = .99$, $B = -17.95$, Exp(B) = .00). There was no significant difference for patients' intention to take biosimilars ($p = .64$) (Table 22).

Perceptions Towards Biosimilars

For the second hypothesis (H2), independent sample t-tests showed that the intervention significantly reduced patients' perceptions of emotional risk ($t(52) = 2.02$, $p = .047$, 95% CI = .43, 25.51, Cohen's d = .55). There was no significant group difference for perceptions of cognitive risk ($p = .07$) or side effect expectations ($p = .25$) (Table 22). A hierarchical multiple linear regression was conducted to identify whether companion and doctor behaviours during the consultation reduced patients' perceptions of emotional risk. The two groups (B = -13.11, $p = .049$) were controlled for in the first step, $F(1, 52) = 4.08$, $p = .049$, $R^2 = 0.07$. The fully adjusted model also included receiving reassurance, emotional and informational support, satisfaction with communication and companion involvement. The model was significant, $F(6, 47) = 6.66$, $p < .001$, $R^2 = 0.46$. Receiving more reassurance (B = -7.09, $p = .004$) significantly predicted fewer perceptions of emotional risk. Receiving more emotional support (B = 5.95, $p = .06$) and satisfaction with communication (B = 14.69, $p = .06$) approached but did not reach significance. Companion involvement (B = -1.29, $p = .09$), receiving informational support (B = 1.69, $p = .59$) and the two groups (B = -1.60, $p = .85$) were also not significant predictors.

Satisfaction

For hypothesis three (H3), independent sample *t*-tests showed that patients were significantly more satisfied with the communication in the family-centred consultation ($t(52) = 2.60$, $p = .015$, 95% CI = .07, .54, Cohen's d = .71). There was no significant difference for decision satisfaction ($p = .18$) or patients' general satisfaction with the consultation ($p = .29$) (Table 22).

Table 22

Mean Differences for Patients Between Groups

	Family-centred *M* (SD)	Patient-only *M* (SD)	*P*-value	Effect Size Cohen's d
Intention to Take Biosimilar Changing Medicines	81.4 (13.5)	79.0 (23.8)	.64	.13
Cognitive Risk (thoughts about risk)	26.4 (19.6)	38.0 (25.5)	.07	.51
Emotional Risk (worries)	30.0 (20.4)	43.1 (26.9)	**.047***	.55
Side effect expectations	6.9 (1.9)	6.2 (2.1)	.25	.32
Companion Involvement				
Consultation and Decision	12.0 (4.6)	5.4 (6.0)	**< .001***	1.23
Number of Questions	1.7 (1.4)	1.1 (1.8)	.18	.37
Social Support Satisfaction	7.8 (1.7)	6.2 (2.0)	**.002***	.86
Communication	1.6 (0.4)	1.9 (0.5)	**.015***	.71
Decision	25.8 (3.0)	24.4 (4.3)	.18	.37
Consultation	4.2 (0.7)	4.0 (0.7)	.29	.29

Understanding

Independent sample *t*-tests were conducted to examine whether family-centred consultation improved patient understanding (H4). There was no significant difference for patients' perceived understanding ($t(52) = -.96$, $p = .34$, 95% CI = -1.19, .39, Cohen's d = -.26) and recall of key information between groups ($t(52) = 1.22$, $p = .23$, 95% CI = -.25, 1.04, Cohen's d = .33). A hierarchical multiple linear regression was conducted to understand whether companions' behaviours during the consultation were associated with patient recall of key information. Prior familiarity with bio-originators ($p = .047$) and biosimilars ($p = .299$) were controlled for in the first step, $F(2, 51) = 2.64$, $p = .08$, $R^2 = 0.09$. The fully adjusted model was significant, $F(7, 46) = 2.72$, $p = .019$, $R^2 = 0.29$. Receiving more emotional support (B = .40, $p = .014$) and companions asking fewer questions (B = -.22, $p = .046$) were significantly associated with higher information recall. Perceived companion involvement in the decision and consultation, and receiving informational support were not significant.

Reasons for Transitioning

The responses to the open-ended question demonstrated that the reasons for agreeing to the hypothetical medicine change were similar between groups (Table 23). This suggests that the delivery of the information did not change participants' understanding of the benefits of biosimilars. Participants in the patient-only consultation mentioned biosimilars being more

cost effective for the healthcare system (35%), having a similar effect to the bio-originator (20%) and increasing access for more patients (20%) as the main reasons. Those in the family-centred group also reported these, with more participants reporting similar efficacy (51%), cost-effectiveness (45%) and improved access (25%). Some participants in the patient-only consultation also agreed to transition due to feeling like there was no real choice (14%), as the bio-originator would not be funded eventually, and all patients would be forced to change.

Table 23

Patients' and Companions' Reasons for Agreeing to Transition Between Groups

Family-centred (*n* = 53)			**Patient-only (*n* = 49)**		
Category	***N* (%)**	***Examples***	***Category***	***N* (%)**	***Examples***
Similar effect	27 (51)	"Similar effect on body - as in similar side effects etc.."	Less cost	17 (35)	"..costs less so more efficient for our health system."
Less cost	24 (45)	"..reduce the cost/impact on the health system."	Similar effect	9 (18)	"Theoretically it should be the same.."
Improved access	13 (25)	"..more sufferers of arthritis will benefit from lower cost."	Improved access	9 (18)	"..it allows Pharmac to get more helpful drugs for the community."
More treatment options	4 (8)	"..more options if it stops working."	Lack of choice	7 (14)	"..the government will change the funding anyways, so eventually my husband will have to change the medication.."
Testing	2 (4)	"..it is always tested and approved by Pharmac and Medsafe."	Testing	2 (4)	"…has undergone tests to prove efficacy."
Humira not available in future	2 (4)	"Good to have a plan B in case the bio-originator is no longer available, more time to find out if alternatives work."	More treatment options	2 (4)	"Recommend as more money to fund other drugs."
Development	2 (4)	"..further research for arthritis can occur."	Development	2 (4)	"To further the development of drugs for my condition.."

Mechanisms of Companion Involvement

Interviews were used to demonstrate which mechanisms of the intervention facilitated or obstructed companion involvement (Table 24). Participants (patients and companions) who

attended the family-centred consultation primarily reported the opportunity for companions to ask questions (85%), the physician's non-verbal cues and positive body language (46%) and acknowledgement of both participants (31%) as facilitators. In the patient-only consultation, most participants reported a lack of companion acknowledgement (95%) and the physical environment (67%), such as the companion being distanced from the patient, as primary barriers. In some pairs, companions reported feeling awkward and disengaged (33%) due to being excluded. Other barriers included the inability to discuss the decision (44%) and for companions to ask questions (39%).

Table 24

Facilitators and Barriers of Companion Involvement Reported by Companions and Patients

Family-centred (n = 13 pairs)			**Patient-only (n = 18 pairs)**		
Category	***N (%)***	***Examples***	***Category***	***N (%)***	***Examples***
Questions	11 (85)	"Targeted questions.. like, what do you think?"	Lack of being acknowledged	17 (94)	"..just like a bystander.. I guess… not a part of the consultation."
Non-verbal cues	6 (46)	".. the doctor was really looking at both of us and checking and we were nodding… we were telling her that we were understanding."	Feeling awkward/ disengaged	6 (33)	"I just felt like awkward at the time." "I think I was like disengaged from the beginning because I wasn't acknowledged."
Address both	4 (31)	"She spoke to both of us not just me."	Environment	12 (67)	"I don't know if this was a COVID thing but I was sort of pushed to the other side of the room.."
Direct practical info. to companion	2 (15)	"..and like when asking about like how it was administered and was asking if I helped to administer and stuff so that was kind of good just to have kind of an inclusive position."	Lack of discussion	8 (44)	"I felt like that as a patient like it was like it would have always been my decision, but I felt like I couldn't even like consult with my companion."
Encourage discussion	1 (8)	"..the doctor asked us to talk about it so she gave us time to you know decide on that medication."	Inability to ask questions	7 (39)	"..it felt like an unsafe environment for the companion to ask a question…"
Introduction	1 (8)	"..she specifically wanted to really introduce the companion and we talked a little bit about us, which was good."	Non-verbal cues	7 (39)	"..even just like the eye contact.. it was like straight to the patient, just the patient, all about the patient."
Clarify role	1 (8)	"..like actually she said obviously like we want you involved in this discussion because you will be dealing with a lot of the same things right so that was really good.. just kind of front loaded so it wasn't awkward like why are you talking to him."	Unclear role	4 (22)	"..felt like I was kind of not meant to say anything possibly.." "I could have been an Uber driver."

Discussion

This study investigated the effects of a family-centred communication intervention on decision-making processes in patient-provider-companion encounters about changing to biosimilars. As expected, family-centred communication improved companion involvement, social support, and satisfaction with communication. However, it did not impact decisions to change to biosimilars or cognitive risk perceptions, or perceptions about side effects. Interestingly, family-centred communication seemed to reduce perceptions of emotional risk (i.e., worries about changing), with receiving a reassuring explanation being the strongest contributor. Family-centred communication did not improve patient understanding, but various companion behaviours impacted understanding, including asking questions and providing emotional support. Patients primarily wanted to change brands due to the biosimilar having a similar effect, lower cost, and improving access. Key facilitators of companion involvement included the ability to ask questions, the physician's positive body language, and being acknowledged. Barriers included a lack of acknowledgement and the environment.

Previous research demonstrates that physician communication influences decision-making (Haas et al., 2021; Nicolai et al., 2016; Veilleux et al., 2018). For example, a randomised controlled trial showed that highlighting positive attributes of biosimilars increases patients' willingness to change, but without the presence of companions (Gasteiger et al., 2019). However, family-centred communication did not further improve decisions, with patient willingness to change to biosimilars being high in both groups. This finding may be due to a ceiling effect but also reflects real-world transitions, whereby a significant proportion of patients generally tend to accept biosimilars, especially after receiving satisfactory information from a trusted source (Gasteiger, den Broeder, et al., 2021). The consultation used various strategies, including the provision of both written and verbal information, delivered by a confident physician, with an emphasis on personal and societal benefits and reassurance on safety and efficacy, known to improve acceptance (Gasteiger, den Broeder, et al., 2021; Gasteiger & Petrie, 2022; Rezk & Pieper, 2017; Vandenplas et al., 2021). This may have made the consultation too convincing. Patients in both groups also received attention and the same information from the physician, with companions being the most impacted by the communication strategy. It is plausible that companions only played a minor role in the decision-making process so their involvement in the family-centred consultation did not

further influence treatment decisions. While the intervention reduced perceptions of emotional risk (i.e., worries about changing medicines) more than the control group, receiving a reassuring explanation was the most important contributor. This is an important finding as those who are worried are more likely to search for symptoms that demonstrate the drug is not working, and may then misattribute these to the brand change and discontinue treatment (Petrie & Rief, 2019).

The study contributes to the inconsistent findings on companions influencing understanding by showing that companion behaviours impact the ability to recall key information (Gasteiger, Groom, et al., 2022; Laidsaar-Powell et al., 2013; Sheehan et al., 2019; Wolff et al., 2015). Patients who received emotional support may have felt more comfortable due to the companion's presence and reassurance (Stewart et al., 2021). Emotional support may also have increased positive emotions leading to more motivation to engage and self-efficacy to understand the information, which leads to deeper processing and better retention (Tyng et al., 2017). However, companions who asked more questions may have caused an information overload, especially if the questions were not perceived to be important to the patient. Research shows companions often ask unique questions, and their presence is associated with more biomedical information-giving (Isenberg et al., 2018; Labrecque et al., 1991). Asking more questions may also signal distrust and worries about the new medicine and this could undermine the patient's confidence in the decision. It is also possible that this draws the physician's attention from the patient causing them to disengage, or lead to less time to ask their questions (Buizza et al., 2021).

There are various strengths to this study, including the use of an actual physician rather than a study confederate (Haas et al., 2021). Another key strength was the use of objective measures (e.g., recall of key information) to complement self-report questionnaires and reduce self-reporting biases. The use of semi-structured interviews also enabled further insight to participants' experiences with the consultations. Our community sample had various similarities to patient samples in previous research on changing to biosimilars, including being primarily female, New Zealand European and having a comparable familiarity with biosimilars (Gasteiger, Groom, et al., 2022; Gasteiger, Scholz, et al., 2021). While the present sample had a wide age range (18 to 75 years), the mean age was younger than previous studies (approximately 31 versus 54 years) (Gasteiger, Groom, et al., 2022; Gasteiger et al., 2019). However, this still captured ages of which patients are diagnosed with inflammatory

arthritis, with rheumatoid arthritis often occurring at ages 30 to 50 and increasing in prevalence with age (Innala et al., 2014). Companions in previous research were also primarily romantic partners or spouses rather than close friends, which may impact generalisability.

An important limitation is that the sample did not have rheumatic diseases or experiences with the bio-originator, so may not have entirely understood or embodied the risk of changing brands (e.g., loss of disease control). Prior positive experiences with bio-originators translate to more hesitancy to change (Gasteiger, Lobo, et al., 2021). Similarly, participants did not have an established trusting relationship with the physician, which promotes biosimilar acceptance (Kovitwanichkanont et al., 2020). The study is also prone to self-selection bias, whereby participants who had higher health literacy may have chosen to participate. The treatment decision was also hypothetical, whereby a proxy (willingness to change) was assessed rather than actual behavior change. However, this is a first proof-of-principle trial that explores the benefits of family-centred communication in decisions about biosimilars.

There are many opportunities for more research in this area. Ideally, family-centred communication strategies should be tested with a patient sample. The degree of family-centredness should initially be assessed in decisions about biosimilars, and then family-centred communication strategies employed during usual care to see if the effects are replicated. The study should also be replicated using other treatment decisions. The present study provided information about changing to biosimilars consistent with the regulations from the upcoming change to Amgevita in Aotearoa/New Zealand (Pharmaceutical Management Agency, 2021a, 2021b). However, some participants still reported feeling like there was a restricted choice due to funding regulations. Other treatment decisions may yield different results, particularly where funding does not play a role.

The current study is the first proof-of-principle trial that examines the use of family-centred communication in treatment decision-making when companions are present. While the intervention did not impact decision-making due to ceiling effects, findings demonstrate that healthcare providers can use simple communication strategies to improve companion involvement, provision of support, and satisfaction with communication. The study also highlights that companions' behaviours (asking fewer questions and providing emotional support) are associated with improved recall of key information. Providers should focus on

providing reassurance to reduce patient worries about changing to biosimilars, encourage the provision of emotional support and summarise key points to improve understanding.

The findings from this study have important clinical implications. Companions should be considered as a resource, and findings provide guidance on how family-centred communication strategies can improve companion involvement in routine consultations. These include using inclusive body language and addressing both the patient and their companion. These behaviours may also help create an environment that promotes the provision of emotional support during decision-making to improve patient understanding. Findings highlight a need for providers to check understanding or to address specific worries/concerns when companions enquire for additional information. Summarising key points may help to reduce information overload when making treatment decisions.

Chapter Nine: Using Health Psychology to Improve Hesitancy

Preface

In 1990, Professor Shelley Taylor predicted that increasing healthcare costs and mounting pressure for cost containment would be the most pressing issue for health psychology in the coming years (Taylor, 1990). These predictions were primarily based on developing cost-effective interventions and reducing healthcare utilisation by promoting preventative health behaviours. Over 30 years later, the need for cost containment remains, including for largely inaccessible pharmaceuticals, such as biologics. The research that constitutes this thesis demonstrates the applicability and practicality of using a health psychology approach when tackling biosimilar acceptance. Put briefly, the discipline of health psychology focuses on the intersection of health and behaviour and is guided by the idea that psychosocial factors contribute to health-related behaviours (Miller et al., 2009; Rodin & Salovey, 1989).

As discussed in Chapter 2, researchers have readily accepted that psychological factors (e.g., negative expectations) partially underpin patient acceptance of biosimilars (Mazzoni, 2021; Rezk & Pieper, 2018). Similarly, it is known that psychological factors contribute to some of the most significant challenges following a transition, namely nocebo responses and early discontinuation (Colloca et al., 2019; D'Amico et al., 2021; Odinet et al., 2018; Rezk & Pieper, 2018; Tweehuysen, van den Bemt, et al., 2018). The application of health psychology theory and practice could further help to improve acceptance, given the psychological aspects of biosimilar hesitancy.

The success of behaviour change interventions in health psychology relies on collaboration and infrastructure that fosters a multidisciplinary approach (Kaplan, 2009). Chapters 3 and 4 illustrate how multiple healthcare professions have been involved in educating patients and identify whether pharmacists' communication skills can be enhanced. The interplay of the social environment (e.g., companions and provider communication) and psychological factors (e.g., illness beliefs) is also integral to health psychology theory and practice (Miller et al., 2009; Rodin & Salovey, 1989). The influence of psychosocial factors on biosimilar acceptance is evident throughout the thesis, specifically in Chapters 5, 6, 7, and 8.

The following commentary proposes that health psychology theory should be kept at the forefront of future research into biosimilar acceptance and when transitioning patients to

biosimilars. We argue that researchers need a better understanding of the factors that contribute to patient hesitancy, engage with patients throughout the transitioning process and undertake research that will lead to more effective biosimilar transitions. It is also argued that health psychology theory can be used to understand patient resistance better. Similarly, successful strategies from health psychology, such as active visualisation, mindset framing, and motivational interviewing, should be translated and implemented to improve acceptance.

Citation

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Introduction

It goes without saying that biopharmaceuticals (biologics) have revolutionised rheumatology care. However, in the United States (US), biologics accounted for only 2% of all prescriptions in 2017 but 37% of net drug spending (IQVIA, 2018b). The financial burden associated with biologics results in an unsustainable model of care, particularly for healthcare systems where patients do not entirely finance their treatment. While it has been readily accepted that biosimilars can help reduce the financial strain of bio-originators (original biologics), biosimilar uptake remains slow with significant global variance (Agbogbo et al., 2019; Chen et al., 2020; Kim, Kwon, et al., 2020). In the US, biosimilars only account for 0.9% of the market share and, while the European Medicines Agency has approved 55 biosimilars that were available on the European market in 2020 (versus 11 on the US market), biosimilar cost reductions drastically differ across countries (Gherghescu & Delgado-Charro, 2020; Kim, Sarpatwari, et al., 2020; Vogler et al., 2021).

Aside from macro-level characteristics (e.g., reimbursement policies and regulatory requirements), the literature unfailingly points to patient factors as key contributory barriers to uptake (D'Amico et al., 2021; Lublóy, 2014; Sullivan et al., 2017; Waller et al., 2017). Low levels of familiarity and confidence in the new biosimilar treatment translate to non-adherence, early discontinuation, and an unwillingness to transition to biosimilars when given a choice. Patients may also experience poor clinical outcomes, such as adverse effects, due to having negative pre-treatment expectancies.

The nocebo effect is an important factor in many biosimilar transitions. Boone et al. (2018) were among the first to demonstrate a nocebo response following a transition to biosimilar infliximab in their one-year pragmatic trial with 125 rheumatology and gastroenterology patients. While there was no significant change in disease activity or biomarkers (including infliximab trough levels and C-reactive protein), a nocebo rate of 12.8% was identified as supported by the successful re-initiation of infliximab originator. Various literature reviews

support the presence of nocebo responses following a transition to biosimilars (D'Amico et al., 2021; Odinet et al., 2018; Rezk & Pieper, 2018).

Healthcare providers, such as pharmacists, physicians, and nurses, have played a significant role in transitioning patients to biosimilars (Gasteiger, den Broeder, et al., 2021). While clinical pharmacists generally work alongside physicians and nurses, some pharmacists have delivered communication strategies entirely and led education efforts to improve acceptance and support patients through the transitioning process (Gasteiger, den Broeder, et al., 2021). Due to their training, pharmacists are well-placed to address concerns and misconceptions, and provide reassurance. Despite these noteworthy efforts, biosimilar hesitancy persists. Moving forward, key healthcare professionals and researchers need a better understanding of the factors that cultivate patient hesitancy, engage with patients throughout the transitioning process and undertake research that will lead to successful transitions. Applying findings from health psychology research may help understand patient resistance and develop more effective transitioning programs. This will help ensure cost saving potential is reached and improve access to these expensive treatments.

Patient Acceptance as a Key Barrier

Biosimilar uptake cannot be improved without patient acceptance, yet concerns of incomparable safety, low efficacy, and poor quality are rife within the literature (Jacobs et al., 2016; Kovitwanichkanont et al., 2020; Peyrin-Biroulet et al., 2017). Other concerns, albeit less frequent, include the inability to transition back if the biosimilar is ineffective, differences in manufacturing processes, and a lack of testing (Gasteiger et al., 2019). These concerns provide challenges for all biosimilar transitions but particularly non-mandatory transitions, as patients can simply refuse or ‘opt out’ of receiving biosimilar treatment. Negative perceptions also heighten the risk for nocebo responses, which partly account for poor adherence and early discontinuation following a transition (Colloca et al., 2019; Müskens et al., 2020; Tweehuysen, van den Bemt, et al., 2018). Not only does this encourage healthcare providers to unnecessarily prescribe other costly biologics in an effort to control the disease, but it may undermine patient trust in the prescriber and health system.

The importance of employing a multidisciplinary approach and involving pharmacists, nurses, physicians, and patient advocacy organisations to improve patient acceptance has already been recognised (Cohen & McCabe, 2020; Vandenplas et al., 2021). However, skills

from health behaviour change researchers have been overlooked. The health psychology discipline focuses on the intersection of health and behaviour and is guided by the understanding that psychological and social factors contribute to behaviours, which influence the development and progression of illness (Miller et al., 2009; Rodin & Salovey, 1989). Given the psychological factors that underpin patient acceptance of biosimilars, this area has, without a doubt, moved into the domain of health psychology. Key challenges of biosimilar adoption, including non-adherence, the nocebo effect, patient education and the influence of emotion (e.g., fear) in decision-making have been extensively researched in health psychology, with significant advances in nocebo research occurring over the past 10 years (Faasse, 2020; Ferrer & Mendes, 2018; Holmes et al., 2014; Marcus, 2014; Martin et al., 2018; Petrie & Rief, 2019; Simonsmeier et al., 2021). Biosimilar acceptance will remain a significant challenge and gain importance as biosimilars readily enter the pharmaceutical market. It is logical for pharmacists, other healthcare providers and researchers to implement and translate strategies that have been successful in areas of health psychology with similar challenges, rather than to inefficiently reproduce existing, foundational knowledge.

Understanding Resistance

Understanding the underlying mechanisms of patient resistance is an important first step to improving biosimilar acceptance. Negative expectations are one of the most influential mechanisms of biosimilar hesitancy (Pouillon et al., 2018; Rezk & Pieper, 2017). These may stem from personal experiences with medications and the social environment (e.g., media, peers and family) (Kleine-Borgmann & Bingel, 2018). A patient's experience with previous biologic transitions and generic medicines or hearing narratives of others' negative experiences can heighten expectations of treatment failure. Pharmacists and other healthcare providers may also unintentionally amplify negative expectations by providing inconsistent information or focusing on treatment risks and side effects (Colloca et al., 2019). Equally, reluctance may be demonstrated by patients who have had positive experiences with their bio-originator treatment, who may think along the line of 'if it's not broken, don't fix it' (Gasteiger, Lobo, et al., 2021). A recent study also highlights that patient characteristics, such as gender, seeking health information online, preferring innovator drugs, and having strong emotional responses are associated with negative expectations (Gasteiger, Lobo, et al., 2021). These patients are likely to require additional reassurance and educational resources to overcome resistance.

Health psychology research also points to various other mechanisms that have yet to be seen in biosimilar research. Believing that one is particularly sensitive to medicines is associated with an elevated reporting of adverse effects and medical care utilisation (Faasse, Grey, Horne, et al., 2015; Petrie et al., 2004). Patients may also have negative beliefs about medications in general, such as concerns about the likelihood of experiencing possible adverse effects (Horne et al., 2013). Other psychological factors, such as negative affect and anxiety, further exacerbate symptom reporting (Petrie et al., 2004). Patients with these beliefs and characteristics are likely to misattribute non-specific symptoms to new treatments and search for information that confirms their beliefs. Negative beliefs may then be intensified if the biosimilar's 'look and feel' is significantly different, as pharmaceutical branding reassures patients on authenticity, safety, and efficacy. As such, mechanisms that underlie decisions to accept biosimilars (or not to) should be kept at the forefront when developing interventions and transitioning programs.

Engaging with Patients

Patient advocacy organisations promote patient engagement by encouraging thorough discussions on biosimilars and patient involvement in decision-making (Danese et al., 2017; European League Against Rheumatism, 2018). Health psychology literature postulates that shared decisions are essential to maintaining a successful therapeutic relationship and encouraging treatment adherence (DiMatteo, 2012). A feeling of involvement or having a choice in decision-making can also reduce the nocebo response, as people look for information that supports their decision (Bartley et al., 2016). However, a patient's choice to transition to a biosimilar may be removed entirely in some circumstances, such as when the bio-originator is no longer funded. Indeed, there are many opportunities for patients to be engaged regardless of whether the transition is mandatory or non-mandatory. For example, patients may be consulted during Patient and Public Involvement and Engagement (PPIE) activities, both during the development process of transitioning programs and pilot testing of interventions. There is also scope for PPIE following a transition through evaluations of the transitioning program.

Patient engagement, however, relies on the appropriate provision of information. Education ensures that patients are positioned to contribute to discussions about biosimilars and builds familiarity and confidence in their use. However, disclosing certain information, such as cost savings for the healthcare system, can induce nocebo responses by reinforcing negative

perceptions about quality and suggests a lack of regard for the individual patient (Gasteiger, den Broeder, et al., 2021). As such, patient feedback on educational strategies and resources through PPIE is crucial before dissemination. Pharmacists and other healthcare providers should also involve patients during the information-giving process by inquiring about preferences for information (e.g., visual, numerical, verbal or amount) and tailoring education strategies to health literacy (Jones et al., 2019). Companions, such as family, should be included if desired (Gasteiger, Scholz, et al., 2021).

Making Better Transitions

Health psychology interventions employ various behavioural change strategies that can be translated to improve biosimilar transitions. Balancing risk-benefit information, presenting information with confidence and tailoring information to reduce expectancy-induced side effects are highly effective in reducing nocebo responses, but are relatively simple strategies to adopt in all types of clinical care (Akroyd et al., 2020; Petrie & Rief, 2019; Wells & Kaptchuk, 2012). A recent experimental study also showed that simply highlighting similarities between bio-originators and biosimilars improves initial acceptance and perceptions of efficacy (Gasteiger et al., 2019). Active visualisation interventions where the patient is shown models of how the drug is working in the body could further augment the effects of positive framing and provide a novel way to educate patients (Jones & Petrie, 2017). Enabling patients to see the similarities in how bio-originators and biosimilars modulate the immune system may improve understanding and reservations about efficacy. This information could be presented to patients and their family/companions, along with additional benefits of biosimilars (e.g., cost reduction and access) and narratives of patients who have successfully transitioned.

Changing mindsets about treatment side effects is a recent but promising approach to mitigating the development of negative expectations. Informing patients that symptoms are a sign of a treatment working decreases anxiety and concerns about side effects (Leibowitz et al., 2021). While the presence of specific side effects may indicate a drug reaction, reframing mindsets could help patients who report subjective complaints (e.g., arthralgia or fatigue) whereby symptoms allude to a nocebo response. Reassuring patients that there is an absence of unstable disease activity, and their side effects are a sign of a helpful immune response rather than a safety concern may encourage biosimilar persistence. Physicians and nurses could initially introduce this idea, while clinical pharmacists could reinforce the message and

provide ongoing reassurance for patients with subjective complaints. All healthcare providers can also implement strategies from motivational interviewing to guide patients to explore and resolve their ambivalence towards biosimilars. Training should be provided to guide healthcare professionals to use open-ended questions to elicit concerns, take time to actively listen, and express empathy rather than attempt to persuade patients, which is likely to be met with resistance (Morton et al., 2015). Providers can help patients identify motivations to change to biosimilars and develop a plan to support patients through the transition.

Future Directions

The field of health psychology will continue to grow rapidly as the importance of psychological factors in health care become more recognised. Future research in health psychology is crucial to better understand the role of psychosocial factors involved in patient acceptance of biosimilars. Various psychological factors are yet to be examined, including negative affect and anxiety (previously mentioned) (Faasse, Grey, Horne, et al., 2015; Petrie et al., 2004). Researchers should also continue to investigate the impact of the broader social environment of patients. Research has explored the presence of companions during discussions about biosimilars, but more focus is needed on other social interactions and sources of information (Gasteiger, Groom, et al., 2022). It is unclear to what extent informal interactions outside the medical setting (e.g., in the community or support groups) impact adherence to biosimilars and the development of nocebo responses.

A focus on the influence of online social interactions is needed, as health-related misinformation is easily disseminated on the Internet (Suarez-Lledo & Alvarez-Galvez, 2021). Social media and support groups provide an optimum platform for sharing negative experiences, scaremongering, and inducing unhelpful perceptions about biosimilars. However, the advances in technology and mHealth interventions also bring exciting opportunities. Researchers should leverage technology to build patient acceptance of biosimilars by sharing patient narratives of successful transitions (Drewniak et al., 2020). Highlighting that other patients have transitioned without difficulties may reduce negative expectations about side effects and reporting of non-specific side effects (O'Connor et al., 1996). Digital health interventions could support adherence and build on educational attempts by sending reminders and reinforcing positive messages about biosimilars.

Research in biosimilar acceptance should also explore interventions to support and manage patients who report non-specific side effects following a transition. Prevention is challenging, given the multitude of complex factors that contribute to nocebo responses (Manaï et al., 2019). Therefore, future interventions should also aim to reverse or minimise existing responses, particularly where re-initiation of the bio-originator is not possible. Additional challenges will include training pharmacists and other healthcare providers on implementing health psychology strategies and interventions. Education for the public is also crucial to build familiarity with the nocebo response and confidence in biosimilars (Oskouei & Kusmierczyk, 2021). Mass education may help lessen patients' perceptions of symptoms being misunderstood or undermined when nocebo responses are discussed.

Conclusions

It is encouraging to see researchers and healthcare professionals begin to strategise how to address the challenge of patient acceptance collaboratively. However, a better understanding of the specific underlying mechanisms of patient resistance is needed to improve biosimilar transitions as they allow the targeting of these specific beliefs. Patient engagement throughout the transitioning process is also important. Extensive research demonstrates that psychological factors, such as negative perceptions towards safety and efficacy, contribute to biosimilar hesitancy. It, therefore, seems both logical and efficient for pharmacists, other healthcare providers and researchers to build on existing knowledge and implement successful strategies from health psychology research. Possible mechanisms of resistance should be kept at the forefront, and novel, clinically useful strategies such as active visualisation, mindset framing, and motivational interviewing used to modify negative expectations and improve acceptance.

Chapter Ten: Discussion

Overview

Healthcare systems globally are confronted with challenges relating to cost containment. Transitioning patients from bio-originator therapies to biosimilars is becoming more common to reduce costs, particularly for patients with immune-mediated inflammatory disorders. Medicine brand changes can be especially daunting for patients and their companions but also for healthcare providers who must provide support throughout the transitioning process. Although biosimilars have been readily integrated into pharmaceutical markets for almost the past ten years, patient acceptance of biosimilars remains a key barrier to their uptake.

Researchers acknowledge that patient-provider communication is important during the initial stages of the transition to biosimilars. Effective communication builds trust and provides reassurance on the biosimilar's comparable safety and efficacy profile, which mitigates the development of concerns and negative expectations. This ultimately prevents adverse clinical outcomes that arise from non-adherence and early treatment discontinuation. Despite this, there were large gaps in knowledge about how to best communicate the transition to patients to ensure that the brand change is accepted. Specifically, gaps in the research included not knowing which mode of delivery to use, how much information should be provided and how these could impact patient acceptance. Additionally, research had yet to examine the readiness of other healthcare providers to educate patients and whether patients with more negative perceptions could be identified and targeted in future education attempts. More knowledge on improving communication about biosimilars provides an opportunity to inform, guide, and develop effective strategies while ensuring that information is delivered appropriately and to the patients who need it most.

The changing nature of medical encounters has also led to the need to consider companion engagement in decisions about biosimilars. Previous literature has focused on helping patients through the transition, with little regard for others who may be present during the consultation. Companions are important to many patients as they assist in the decision-making process and can experience collateral effects from the brand change. However, considering external influences, such as companions, adds another layer of complexity when transitioning patients. Research on companion involvement in decision-making has been largely restricted to caregivers and patients receiving end-of-life or oncology care, where

companions primarily act as surrogate decision-makers. However, other patients have been overlooked. These include patients who largely self-manage their condition and receive routine care but may also have companions and prefer their involvement. Understanding whether and to which extent companions influence decisions and perceptions of biosimilars can assist in intervention. Exploring their concerns and how to engage with companions during discussions about biosimilars effectively provides opportunities to optimise future communication attempts.

This thesis aimed to address the limitations within the current literature. The overarching aims were to understand how to increase biosimilar acceptance through communication and to determine and augment the involvement of companions in decisions about transitioning to biosimilars. In doing so, this thesis provides a rationale for considering how health psychology can contribute to future research on biosimilar acceptance and its value when developing communication strategies for brand changes. This final chapter synthesises the conclusions drawn from the research presented in previous chapters. Key findings will be integrated into the existing literature on biosimilar acceptance and involving companions in decision-making. Clinical implications will be discussed, along with strengths, limitations, and directions for future research.

Summary of Key Findings

The study aims were addressed through five studies and a commentary. The first section of the thesis aimed to understand how different aspects of communication can be improved to increase patient acceptance of biosimilars. Chapter 3 consists of a systematic review with a meta-analysis that examined 33 global communication strategies used to inform patients with inflammatory disorders about biosimilars (Gasteiger, den Broeder, et al., 2021). It explored the content and whether patients' willingness to transition, treatment persistence, and reporting of adverse events differed for the mode of delivery (written or verbal) and the amount of information provided. The analysis showed that patient willingness to transition was significantly higher when receiving both written and verbal information and when the written information only addressed a few key concerns. There were no significant differences for persistence or subjective adverse events. The content was also synthesised and demonstrated commonalities among information, including reassurance on comparable safety and efficacy, but also that cost saving was the main reason for the transition. These results

suggest that the mode of delivery and amount of information provided play a role in patient acceptance of biosimilars, but more randomised controlled trials are needed in this area.

Chapter 4 builds on findings from the systematic review. The review had also illustrated that pharmacists play a noteworthy role in educating patients as part of multidisciplinary teams, but only two studies had reported educating health professionals to ensure readiness in this role (Gasteiger, den Broeder, et al., 2021). Therefore, the cross-sectional study presented in Chapter 4 explored Aotearoa/New Zealand pharmacists' confidence in educating patients about biosimilars and the information they would provide in response to common queries (Gasteiger, Gasteiger, et al., 2022). Pharmacists were the least confident in explaining the manufacturing and testing processes of biosimilars and most confident in how biosimilars are administered, their efficacy, and cost savings. Those who were more confident in educating patients were more familiar with and had more positive perceptions towards biosimilars. Responses to common queries demonstrated gaps in knowledge, including not being able to define biosimilars or provide information on side effects. It was concluded that pharmacists in Aotearoa/New Zealand would benefit from additional training and resources (e.g., written and Internet-based) to support their role in educating patients about biosimilars.

Chapters 3 and 4 demonstrated that modes of delivery and upskilling healthcare professionals involved in educating patients might improve communication attempts. These efforts are particularly important to mitigate the development of negative expectations and patient concerns. Chapter 5 builds on these findings by exploring patient characteristics associated with negative expectations toward biosimilars (Gasteiger, Lobo, et al., 2021). Patients who were female, sought information online, preferred innovator drugs, and had stronger emotional responses to their condition had more concerns about safety and transitioning to biosimilars. Additional efforts should be made to inform and provide reassurance for these patients. Taken together, findings in Chapters 3, 4, and 5 provide guidance on what information should be included in future communication attempts, how it should be delivered, the importance of upskilling pharmacists involved in educating patients, and which patients should be targeted.

The transition to biosimilars also impacts companions, yet the first section of the thesis largely focused on improving transitions for individual patients. The second section of the thesis widened the focus and aimed to determine and augment companions' involvement in

discussions about transitioning to biosimilars. In Chapter 6, a parallel two-arm randomised controlled trial was conducted to examine companion influence in decisions to change to biosimilars (Gasteiger, Groom, et al., 2022). Patients taking bio-originators who are often accompanied were randomised to receive information about biosimilars alone or with their usual companion. Companionship did not influence decisions, cognitive or affective risk perceptions, decision satisfaction, or decisional conflict. However, those who were accompanied found it more difficult to understand the explanation than those who were unaccompanied. It was also identified that receiving emotional support from the companion was associated with less decisional conflict. These findings demonstrate the complexity of companion involvement in decision-making and suggest that providers should take more care to ensure understanding in patients who are accompanied.

As research had only focussed on educating patients and addressing their concerns, we examined whether companions have unique information needs that should be taken into consideration. Chapter 7 explored the congruence between patients' and companions' perceptions of biosimilars and their information needs (Gasteiger, Scholz, et al., 2021). Companions and patients had similar confidence in biosimilar use and expectations regarding safety, efficacy, and side effects. The main concerns for participants were reduced safety and efficacy. However, companions were also concerned about cost savings as the main reason for the transition, while patients had concerns about uncertainty and testing. Patients also valued the presence of companions when discussing biosimilars, especially to deliberate the decision, receive validation and improve their understanding. Findings suggest that future educational attempts should consider the presence of companions and adapt communication strategies to include information that also meets their needs.

Findings from Chapters 6 and 7 demonstrated that patients value the presence of companions in discussions about biosimilars and that companions have unique information needs that should be considered. However, as evident in Chapter 3, previous attempts to involve companions in these discussions were scarce. The final randomised controlled trial presented in Chapter 8 builds on this research by examining whether family-centred communication impacts decisions and optimises patient-companion-provider consultations (Gasteiger et al., 2023). A community sample was used due to ongoing hospital restrictions relating to COVID-19. Participants who acted as a patient or companion were randomised to receive information about biosimilars from a physician using a family-centred or patient-only

communication style. Family-centred communication did not influence decisions, likely due to a ceiling effect. It did also not influence cognitive risk perceptions. However, family-centred communication reduced emotional risk perceptions and improved companion involvement, the provision of social support, and satisfaction with communication. Perceiving the explanation to be reassuring was associated with less emotional risk perceptions. Importantly, various physician behaviours facilitated companion involvement, including using positive body language and actively acknowledging the companion. In Chapter 6, companions negatively influenced patient understanding, but the reasons for this were unclear. In the current study, patients recalled more information when their companion asked fewer questions but provided more emotional support. Family-centred communication may help improve patient-companion-provider encounters about biosimilars.

The previous chapters of this thesis presented research that is among the first to apply health psychology theory and interventions to improve patient acceptance of biosimilars. Chapters 3 and 4 acknowledged that multidisciplinary teams are important to ensure successful transitions. However, these had not yet been extended to consider involving experts in psychological science. In Chapter 9, we drew on our previous research to argue that the challenge of biosimilar acceptance is relevant for the study of health psychology due to the underlying psychological causes of patient hesitancy. It was also noted that health psychology research can help to explain possible mechanisms of resistance and enable intervention. It was suggested that previously successful interventions from health psychology should be translated to improve biosimilar acceptance, including motivational interviewing, mindset framing, and active visualisation. Collectively, the studies in this thesis advance knowledge on improving future transitions to biosimilars.

Integration into Broader Literature

The research presented in this thesis offers three key contributions to the literature. First, it provides further evidence on communicating the transition to patients to improve acceptance of biosimilars, including the provision and delivery of information. Secondly, it contributes to understanding concerns about biosimilars, particularly companions' attitudes towards biosimilars and psychological factors that contribute to the development of patients' concerns. Lastly, it provides further understanding of the influence and role of companions in

treatment decision-making, such as the interpersonal processes that impact outcomes, including patient understanding.

Contribution One: Communication and Provider Knowledge

The thesis provides important contributions to the existing literature on educating patients about biosimilars. Findings highlight a need to consider the delivery of communication strategies along with the content. Prior research has already begun to explore how information about biosimilars can be adapted (e.g., using message framing to highlight similarities) to improve perceptions and willingness to transition (Gasteiger et al., 2019). Recommendations also have significant variance in relation to providing information to patients, with patient organisation groups advocating for full transparency and others deeming it unnecessary to mention all information, including possible side effects (Danese et al., 2017; Vandenplas et al., 2021). This discrepancy raises an interesting ethical conflict. Giving too much information can cause harm by inducing nocebo responses, but physicians are legally obliged to disclose all the information that a reasonable person would need to make an informed decision (Colloca et al., 2019; Murdoch & Caulfield, 2020). Our research assists with this problem. Findings show that patients should receive standardised written information initially but should have the opportunity to discuss concerns and receive additional information from a credible and trusted source, such as during consultations (Gasteiger, den Broeder, et al., 2021). This aligns with recommendations to use a tailored approach to meet information needs (Vandenplas et al., 2021).

Our findings also contribute to the literature on how the provision of information shapes risk perceptions and influences health behaviours (i.e., acceptance of new treatments) (Waters et al., 2010). Providers have been advised to balance information about risks (e.g., side effects) carefully with benefits when discussing new treatments (Colloca, 2017; Rief, 2021; Siegel, 2012). However, it is less clear what kind of benefits should be highlighted. People are generally intrinsically motivated by personal benefits (e.g., protection from COVID-19), but research suggests their motivation can be enhanced by prosocial appeals, such as contributing to public health efforts (Guttman et al., 2016). Our findings showed that patients are often informed that the transition to biosimilars is occurring to save costs for the healthcare system, which induced concerns about inferior quality (Babar et al., 2010; Gasteiger, den Broeder, et al., 2021; Gasteiger, Scholz, et al., 2021). Yet, cost savings were a motivator to accept the change for others (Gasteiger et al., 2023; Gasteiger, Scholz, et al., 2021). Evidently, there are

significant individual differences in how risk is perceived and the effects of prosocial appeals (Waters et al., 2010). While it was beyond the scope of this thesis to examine possible mediators, patients' prior experiences with biologics likely play a role. Understandably, patients are less willing to take risks when their current treatment is effective (Gasteiger, Lobo, et al., 2021). Future transitions should balance information by highlighting the benefits for the individual patient, such as less injection-site pain or improved ease of device use, along with increased access for patients.

Research shows that some healthcare providers lack knowledge about biosimilars and want guidance on educating patients (Arnet et al., 2021; Barbier et al., 2021; Hemmington et al., 2017; Ismailov et al., 2021). Our findings support this with some pharmacists in Aotearoa/New Zealand lacking a foundational understanding of biosimilars (Gasteiger, Gasteiger, et al., 2022). Interestingly, pharmacists in this study were the first to explicitly report being worried about their lack of knowledge and ability to answer patients' questions, in addition to concerns about safety and efficacy. This is troubling as the research also highlighted that upskilling pharmacists is rarely part of the communication strategy, and there is even less focus on teaching providers to assuage concerns (Gasteiger, den Broeder, et al., 2021). It seems that pharmacists, and other providers, are simply expected to be ready to assume the role of providing patient education without first considering their gaps in knowledge. In Aotearoa/New Zealand, there was also no standardised process of communicating the transition to Amgevita or mandatory education for pharmacists. This may cause problems with patient acceptance, particularly as receiving unsatisfactory information increases problems with using biosimilar devices and negative perceptions about symptom control (Kaneko et al., 2022; van Adrichem et al., 2022). Findings support a need for balanced educational outreach across regulatory and pharmaceutical funding agencies, professional medical organisations, and patient advocacy associations as well as building knowledge earlier during formal education (Cohen et al., 2017; Oskouei & Kusmierczyk, 2021).

Contribution Two: Companions' Concerns and Predicting Patient Hesitancy

Findings also contribute to understanding patients' and companions' concerns about biosimilars. Patients globally have reported concerns about biosimilar safety, efficacy, and testing processes (Attara et al., 2016; Ighani et al., 2018; Kovitwanichkanont et al., 2020;

Sullivan et al., 2017; van Overbeeke et al., 2017). Our research also demonstrates that patients in Aotearoa/New Zealand hold similar concerns, although biosimilars have yet to be readily introduced for patients receiving rheumatology and gastroenterology care (Gasteiger, Scholz, et al., 2021). Research from this thesis also demonstrates a low familiarity with biosimilars among patients, companions, and within the general public, which is consistent with research from Europe and the United States (Frantzen et al., 2019; Gasteiger et al., 2023; Gasteiger, Scholz, et al., 2021; Jacobs et al., 2016; Kovitwanichkanont et al., 2020; van Overbeeke et al., 2017; Vandenplas et al., 2022). These findings support the recommendation to educate patients and the public (before they become patients or companions), as more familiarity is associated with positive perceptions (Oskouei & Kusmierczyk, 2021). Additionally, this thesis highlights that companions have congruent expectations towards biosimilar safety, efficacy and side effects, and similar confidence in biosimilar use. Companions' perceptions were less known, with prior research being restricted to paediatric samples or not reporting their specific concerns (Jacobs et al., 2016; Renton et al., 2019). The research, therefore, extends existing knowledge on concerns about biosimilars.

In 2019, Colloca et al. (2019) argued that it was important for researchers to be able to identify patients who are particularly susceptible to the nocebo effect when transitioning to biosimilars. While this may be difficult due to the various learning processes and psychological and genetic factors involved, our research helps to contribute to this understanding (Colloca, 2017). Patient factors such as female gender, seeking information online, preferring innovator drugs, and having a strong emotional response were associated with negative expectations towards biosimilar safety and concerns about transitioning (Gasteiger, Lobo, et al., 2021). Given that negative expectations lead to nocebo responses, these patients are more likely to be impacted by nocebo effects and may require additional intervention in future transitions (Petrie & Rief, 2019). Findings also build on prior research in generic medicine changes demonstrating that patient characteristics such as education, age, and perceived sensitivity to medicines influence acceptance of generics and side effect reporting (Kleinstäuber et al., 2018; MacKrill & Petrie, 2018). This research was the first to apply health psychology theory, namely illness perceptions in Leventhal's self-regulatory model, to patient acceptance of biosimilars (Leventhal et al., 2016; Moss-Morris et al., 2002). Negative emotions (e.g., fear, anxiety, or anger) generated towards one's illness heighten adverse perceptions about transitioning. This indicates a need to help patients manage negative emotions surrounding their condition, as these may also induce nocebo responses,

dysfunctional coping strategies, and ultimately adverse health outcomes (Klinger et al., 2017; Ziarko et al., 2014).

Contribution Three: The Influence of Companions in Decision-Making

The final contribution to the literature is further understanding the role of companions in treatment decision-making. First, it should be noted that recent research on the influence of companions in routine treatment decisions (e.g., treatment brand changes) is scarce (Bracher et al., 2020; Laidsaar-Powell et al., 2016; Laidsaar-Powell et al., 2013). Presumably, the focus has been on oncology and geriatrics as these patients are more likely to require extensive support and have carers (Laidsaar-Powell et al., 2013). However, treatment decisions are not made in isolation and, to some extent, are influenced by social factors, such as perceived social norms (e.g., seen in Social Cognitive Theory and Theory of Reasoned Action), regardless of the degree of support required from companions (Bandura, 1986; Fishbein & Ajzen, 1975; Ho, 2008). Research with adult dyads is also often restricted to romantic partners, which excludes other important relationships such as those with family and close friends (Gasteiger, Groom, et al., 2022; Gasteiger, Scholz, et al., 2021; Scholz et al., 2020; Stewart et al., 2021). However, patients often rely on other relationships for emotional support, navigating challenges, and advice on health-related matters, with sources of support fluctuating over time (Epstein & Street, 2011a; Gray et al., 2019; Lewis et al., 2009). This thesis builds on the literature on triadic decision-making by extending the concept of dyads to encompass any companions involved in the patient's medical journey.

The findings from this thesis also contribute to the growing body of literature on understanding the interpersonal processes involved in triadic decision-making. Companion influences vary significantly across contexts, with some adopting a dominating approach and acting as the decision-maker and others preferring a more passive role (Bracher et al., 2020; Stewart et al., 2021). In our research, companions did not influence treatment decisions but rather seemed to validate patients' feelings and decisions (Gasteiger, Groom, et al., 2022; Gasteiger, Scholz, et al., 2021). This is promising, as unhelpful interpersonal processes, such as negative social control, were not evident. According to the contextual model, the use of social control is influenced by the wider context (Craddock et al., 2015). Social control is often received more by men (our samples were primarily female) and is dependent on the quality of the relationship (Craddock et al., 2015; Knoll et al., 2012; Lewis & Butterfield, 2007). It is also possible that companions did not interfere as they felt less impacted by the

outcome and perceived patients to be able to make their own decisions. However, problems may arise when patients exhibit negative perceptions, which are then supported and intensified by the companion. In these cases, it is crucial to involve companions in the discussion to elicit and address their concerns. Our research supports existing recommendations on facilitating companion involvement by using positive and inclusive body language and acknowledging the companion throughout the conversation (Laidsaar-Powell et al., 2018; Omole et al., 2011).

There are also contributions to understanding how companions impact other important factors involved in shared decision-making. Observational research suggests that companions support patient understanding by gathering information and seeking clarification, with negative effects on understanding less frequently reported (Laidsaar-Powell et al., 2013; Schilling et al., 2002; Sheehan et al., 2019; Wolff et al., 2015). Some of our findings support this as some patients (21%) reported that companions helped them unpack and understand the information as a benefit of being accompanied (Gasteiger, Scholz, et al., 2021). However, our randomised controlled trial showed the contrary; accompanied patients found it more difficult to understand a standardised explanation than unaccompanied patients (Gasteiger, Groom, et al., 2022). It should be noted that understanding was self-reported, so it is plausible that there was a reporting bias where accompanied patients received validation that the explanation was complex and felt more comfortable reporting this difficulty. Our subsequent study helps to elucidate these findings by showing that companions' behaviours are associated with patient understanding (Gasteiger et al., 2023). Receiving less emotional support and companions asking more questions was associated with decreased recall. This is likely due to patients feeling less comfortable seeking clarity and companions drawing attention from the patient or causing cognitive overload by requesting additional information (Buizza et al., 2021; Stewart et al., 2021; Tyng et al., 2017). Taken together, the findings provide further evidence on the specific interpersonal processes that negatively affect patients' understanding in triadic consultations.

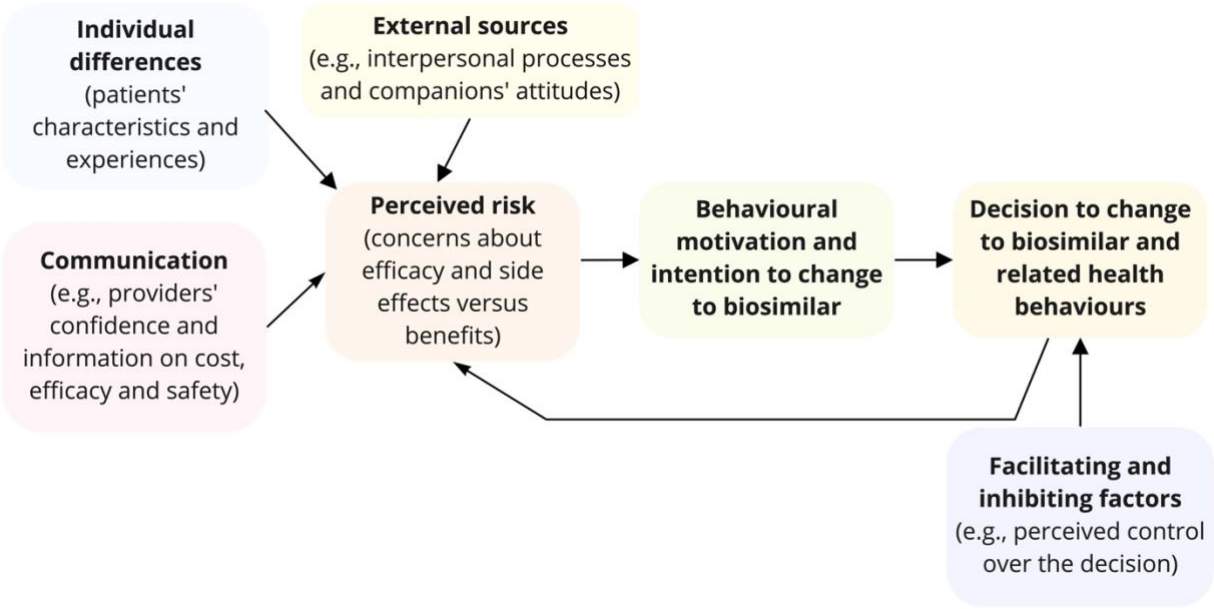
Consistent with prior research, companions should be encouraged to be present for treatment decisions, especially to receive information on future treatments and provide social support (Gasteiger, Groom, et al., 2022; Gasteiger, Scholz, et al., 2021; Laidsaar-Powell et al., 2013). In our research, receiving emotional support (rather than informational or practical support) was associated with positive outcomes like reduced decisional conflict and improved

information recall (Gasteiger, Groom, et al., 2022; Gasteiger et al., 2023). This is unsurprising, as emotional support is associated with a plethora of benefits, including stress reduction, empowerment, self-efficacy, and a reduction in inflammatory responses, but it also outweighs other functions of support (Carluzzo et al., 2022; Gottlieb, 1978; Khan et al., 2009; Reblin & Uchino, 2008). Emotional support is also communicated through an array of verbal and non-verbal behaviours, such as active listening, reassurance, and empathy, which could help patients feel encouraged and at ease when discussing biosimilars (Cobb, 1976; Dale et al., 2012; Langford et al., 1997). Evidently, healthcare providers should create an environment where companions are encouraged to provide emotional support. However, existing resources (e.g., decision aids or pre-consultation checklists) employed to facilitate companion involvement in consultations seem to focus on boosting practical or informational functions instead (Clayton et al., 2007; Wolff et al., 2014). It is important to note that when companions provide instrumental support, they are not always emotionally engaged (Morelli et al., 2015). Therefore, future interventions should focus on cultivating emotional support.

Taken together, the contributions from this thesis help to further understand the complex, intertwined pathway through which concerns, provider communication, and companions may influence patient acceptance of biosimilars. The key factors are demonstrated in Figure 12, which is an adaptation from common theories of health behaviour (e.g., Theory of Planned Behaviour and Health Belief Model) (Ajzen, 1985; Fishbein & Ajzen, 1975; Hochbaum et al., 1952; Waters et al., 2010). Communication (including the content and delivery), individual differences (i.e., patients' psychological and demographic characteristics), and validation of negative perceptions by companions contribute to patients' risk perceptions and expectations. These subsequently increase or dampen patients' intentions to change to biosimilars and, ultimately, their acceptance of biosimilars. The decision to change to the biosimilar (or not to) may then also influence perceptions of risk. Facilitating and inhibiting factors, such as perceived control over the decision to transition to biosimilars, were less studied in this thesis but were also identified to influence patients' decisions (Gasteiger et al., 2023). It should also be noted that the framework does not include macro-level factors such as reimbursement policies (e.g., prescribing incentives) and regulatory requirements. While these are likely to influence the uptake and acceptance of biosimilars, their impact was not specifically explored in this thesis (Vogler et al., 2021).

Figure 12

Conceptual Framework of the Factors Explored That Contribute to Biosimilar Acceptance Adapted From Waters et al. (2010)



Clinical Implications

The research presented in this thesis has various clinical implications for healthcare providers, patients, companions, and the wider healthcare system. The thesis focused on providers' communication strategies, as communication lies at the heart of almost every medical encounter. While effective health communication is often taken for granted, it can foster positive health outcomes, including adherence, trust, lower disease activity, and greater treatment satisfaction with fewer medication side effects (Georgopoulou et al., 2018; Zolnierek & Dimatteo, 2009). Communication interventions, such as those developed for this thesis, are highly applicable to other settings or contexts (e.g., other treatment decisions). They are also relatively easy to adopt and do not add to existing time or resource constraints. It was specifically ensured that all communication attempts in this thesis were restricted to ten minutes or less to reflect the existing challenges with time constraints in medical appointments (Gasteiger, Groom, et al., 2022; Gasteiger et al., 2023).

The findings from the studies presented in this thesis are intended to provide guidance and help inform the development of future communication strategies. There is a need to not only educate patients and their companions about biosimilars but to upskill healthcare providers involved in supporting patients through the transition. Physicians and pharmacists should collaborate with other providers and healthcare organisations to prioritise and develop a

communication strategy that employs written and verbal information. Written content (e.g., letters) should initially be kept simple to avoid information overload, with patients and companions having the opportunity to discuss any additional concerns. Companions' information needs should be considered, as these are often unique. Providers should also offer more support to patients who have stronger emotional responses to their condition, are female, seek health information online and prefer innovator drugs, as these are associated with more concerns and negative expectations towards safety. Receiving guidance in communicating biosimilars is likely to boost confidence in delivery, which is important for mitigating the development of negative expectations (Petrie & Rief, 2019).

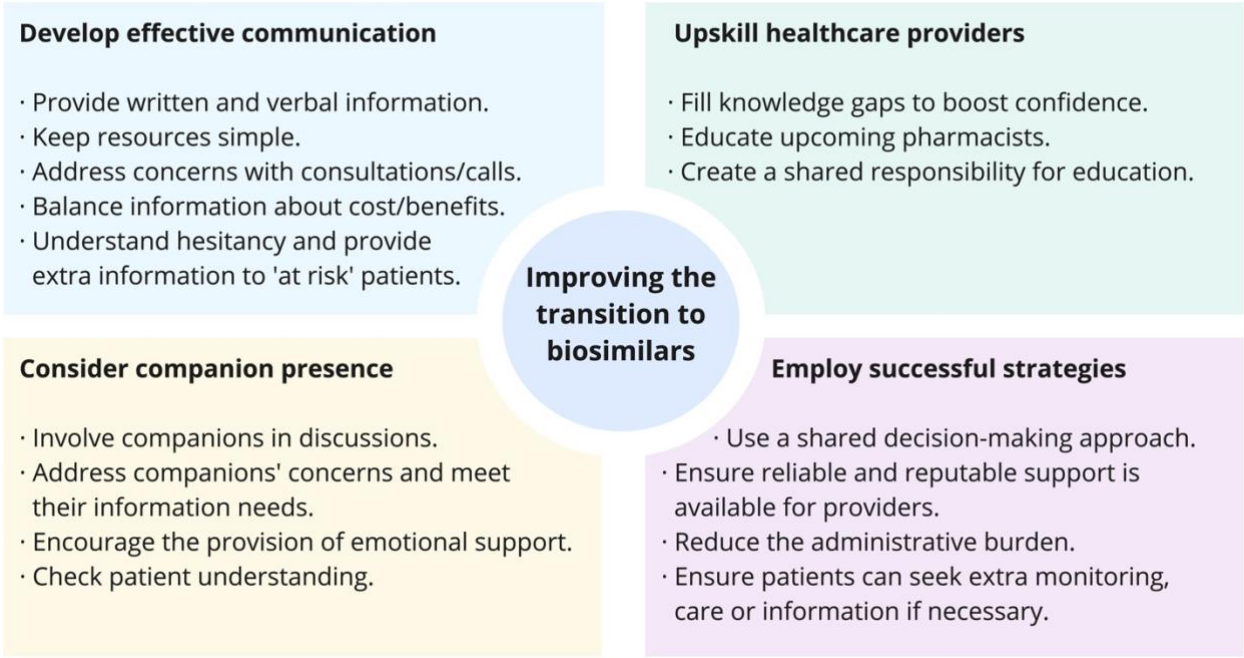
The consideration of external factors in treatment decision-making is an important strength and clinical implication in this thesis. Companions are often present during discussions about treatments in routine care but shared decision-making research has largely focussed on patients and providers. The research also considered companions' information needs rather than restricting the focus on patients. As such, our research takes a more holistic view of decision-making, as decisions are rarely made in isolation (Ho, 2008). Findings are also clinically relevant and support that healthcare providers should engage with companions in future discussions about biosimilars. Companions do not negatively influence patients' acceptance of biosimilars but can be seen as a useful resource and 'safe space' during treatment decision-making. Healthcare providers should employ various simple strategies that facilitate companion involvement, including using inclusive body language and acknowledging the companion throughout the conversation.

There are also clinical implications for the wider healthcare system. Cost containment remains a challenge for healthcare systems globally, particularly as more bio-pharmaceutical treatments for chronic diseases emerge. Effective communication helps improve the acceptance of biosimilars, which is evident in increased uptake and access for more patients. Benefits from biosimilar uptake also extend to market attractiveness and innovation, such as developing novel therapeutics or more convenient and longer-acting drug formulations (IQVIA, 2018a; Kim, Alten, et al., 2020). This is evident in the development of Amgevita, where the device is considered easier to use and less painful to inject (Pharmaceutical Management Agency, 2022). Additionally, ensuring patients are confident in the new brand may boost adherence and persistence with biosimilars. Ultimately, this can reduce wasted resources such as unnecessary healthcare appointments or changing treatments.

Findings are also relevant for regulators and funders, and may inform future initiatives. The research supports that patients largely accept non-medical transitions, especially when appropriate provisions, such as adequate communication, are in place. Similarly, findings support recommendations for using shared decision-making, as participants in the research valued having the choice to transition (Gasteiger, Scholz, et al., 2021; Müskens et al., 2020; Provenzano & Arcuri, 2021). Future initiatives should ensure that adequate support is available for all providers and patients impacted by the brand change. Pharmacists, and other providers, should be upskilled before the transition but should also have reputable and reliable sources of support available, including manufacturer patient support programs (Gasteiger, Gasteiger, et al., 2022). The reduced administrative burden was also a key benefit of biosimilars, which may help incentivise prescribers in future brand changes. Lastly, plans should be in place to enable patients to receive extra information, monitoring or care if needed, as some are vulnerable to developing nocebo responses during the initial stages (Dutt et al., 2022; Gasteiger, Lobo, et al., 2021). Collectively, findings can be drawn upon to improve future transitions. The recommendations synthesised in Figure 13 stem from contributions to the wider literature and the clinical implications discussed in this chapter.

Figure 13

Recommendations to Improve Future Transitions



Strengths, Limitations and Future Directions

The research in this thesis has various strengths. Diverse research designs and methods were employed, which produce different insights into the phenomena and are ultimately more compelling and robust than single methods (Davis et al., 2010). For example, a systematic review with a meta-analysis and a cross-sectional study were conducted to capture different aspects of communication (e.g., patient characteristics and modes of delivery and confidence) that can be targeted to improve patient acceptance. Randomised controlled trials also enabled inferences of causality and built on existing research methods (Kendall, 2003). Prior research on companion engagement is primarily limited to observational methods, such as using the Roter Interaction Analysis System to study interpersonal influences in videotapes of consultations (Bracher et al., 2020). We conducted a randomised controlled trial and simply altered an aspect of the normal environment (companion presence) to assess companion influence directly. This provides greater confidence in knowing that companions do not negatively influence decisions to change to biosimilars.

Previous research in communicating the transition to biosimilars has also rarely employed randomised controlled trials (Gasteiger, den Broeder, et al., 2021). Conducting randomised controlled trials with patients in hospital settings is often difficult as the procedure needs to be standardised (Kendall, 2003). Patients receiving care with biologics are also in close proximity in the infusion centre or in waiting rooms, which could lead to cross-contamination if the intervention is discussed. We used a standardised explanation (delivered via video) and ensured participants were unaware of the true study aims to create a controlled environment and avoid cross-contamination. Similarly, it may not be ethically appropriate to purposefully exclude companions during treatment decision-making, even if needed as part of the control group. The involvement of companions is a crucial part of care for patients who have high relational interdependence and strong beliefs in social hierarchy (Scherr et al., 2022). A lack of social conversation with companions also reduces the ability to build rapport and trust (Mitchell et al., 2020). These possible harms were mitigated by using a community sample and a hypothetical treatment decision.

Findings from this thesis should be considered in light of various limitations. The current section outlines the overall limitations of the body of research, as those pertaining to individual studies have already been discussed in each chapter. The most prominent limitation is the use of hypothetical transitioning scenarios and using patients' willingness to

transition as a proxy for decision-making due to a lack of biosimilar transitions occurring in Aotearoa/New Zealand at the time of the research. Patients also had to be reassured that partaking in the research would not influence future treatment decisions. Therefore, findings may not entirely capture risk or emotional responses to changing medicines. Given this limitation, the research presented in Chapters 3 and 4 involved real-world transitions. As these were observational studies, future experimental research with real-world transitions would be an optimal starting point. However, there are likely to be additional ethical implications when testing different communication strategies. These include ensuring that all patients are adequately informed of the medicine change and mitigating any possible harm, including potential nocebo responses (Beauchamp & Childress, 2001).

The generalisability of the findings should be considered. Firstly, the experimental studies were conducted in a controlled hospital and laboratory environment and, therefore, may not entirely reflect usual care. However, this was necessary to conduct robust randomised controlled trials to ensure inferences of causality (Kendall, 2003). Secondly, Chapter 8 used a community sample rather than patients due to the COVID-19 pandemic. However, it should be acknowledged that the remaining research involved patients, pharmacists, or rheumatology patients taking bio-originators and their companions who are likely to be impacted by future transitions. Thirdly, the research in the thesis focussed on rheumatology patients. It is unclear whether other patient groups impacted by biosimilar transitions (e.g., in oncology) would respond differently as their companions may be more actively involved (Stewart et al., 2021).

The research was primarily conducted with the Aotearoa/New Zealand healthcare system in mind and in relation to non-mandatory transitions to biosimilars. As such, findings (particularly concerning the methods of transitioning patients) may not generalise to other healthcare systems with unique processes and funding models. For example, there are various unique external barriers to biosimilar adoption in the United States, including Medicare policies and payers' incentives (Cross et al., 2022). Findings may also not generalise to scenarios where patients are transitioned between multiple biosimilars, which is expected to become a challenge as more cost-effective biosimilars are developed (Dey et al., 2021). Future research should employ more naturalistic settings, involve patients transitioning between biosimilars, and consider how communication strategies should be adapted in line with different funding models.

Research in this thesis also relied heavily on self-report questionnaires, which can be susceptible to reporting biases. The primary outcome, willingness to transition, may have been influenced by social-desirability biases, whereby participants respond in a manner they believe the researcher expects rather than their feelings (Grimm, 2010). Additional objective measures, such as physiological responses (heart rate or blood pressure), may have provided further insight into participants' emotional responses to changing brands, including anxiety or fear. Currently, there are no validated measures to assess attitudes or expectations towards biosimilars or methods to measure patients' understanding of key information. Research is needed to develop clinically usable measures to identify patients susceptible to nocebo responses and where more reassurance or information may be required.

The communication strategies explored in this thesis also have various limitations. In Chapters 5, 6, and 7, rheumatology patients and their companions were provided an explanation about transitioning to biosimilars through a video of a physician displayed on a computer. Clearly, this does not replicate or reflect actual practice, which would ideally involve an in-person discussion with a healthcare provider. Chapter 8, however, increased ecological validity by testing an in-person consultation with a physician and allowed participants to ask questions and, in some cases, discuss the decision with their companion. Research in Chapters 5, 6, 7, and 8 was also unable to use the patients' usual physician to deliver the communication strategy. However, rapport and trust play a role in patient acceptance of biosimilars (Kovitwanichkanont et al., 2020). Additionally, patients frequently rely on other sources of information, including social and print media and patients' narratives, to inform decisions (Clarke et al., 2016; Dohan et al., 2016). Communication strategies that employ these methods likely optimise decisions about biosimilars, but research is needed in this area.

The research in this thesis is primarily restricted to the decision-making process occurring within the consultation (e.g., the deliberation phase), as external influences are difficult to adapt or mitigate. In reality, decisions may be made after seeking additional information online or through conversations with other family members (Bracher et al., 2020). Enabling patients and companions to read the letter in advance, as previously done in real-world biosimilar transitions, and reflect on the decision before the consultation may create different outcomes (Chan et al., 2019; Layegh et al., 2019). Decision-making processes are also limited to one companion, as dyads are the most common and important social group

(Peperkoorn et al., 2020). However, some patients may have more than one source of support, and this may change depending on the context of the decision and the health of the patient (Bracher et al., 2020; Laidsaar-Powell, Butow, Charles, et al., 2017). Patients were also recruited throughout the COVID-19 pandemic, so it is possible that the study participants had relatively low health anxiety and stress and had better health due to choosing to visit the hospital outside of usual appointments. Future research should consider the presence of multiple companions in treatment decisions, especially for patients who require additional support.

Conclusion

Biosimilars have been integrated into healthcare systems globally to assist with cost containment and to improve access to biopharmaceuticals. However, patient acceptance remains a key barrier to the adoption of biosimilars and restricts their cost saving potential. Concerns about safety and efficacy also translate to a reluctance to transition, early discontinuation, seeking unnecessary health care, and developing nocebo responses. Additionally, companions frequently accompany patients to medical encounters, which adds an additional layer of complexity for healthcare providers when discussing the brand change. Prior to this thesis, there were questions on how to improve the transition to biosimilars for patients to enhance uptake and ensure positive clinical outcomes. This thesis contributes to understanding how communication about biosimilars can be improved to increase patient acceptance and determines and augments companion involvement in discussions about biosimilars.

The key findings from this body of work provide important contributions to the literature on educating patients about biosimilars and involving companions in treatment decision-making. Findings from a systematic review and cross-sectional and correlational studies demonstrated that communication plays a role in patient acceptance of biosimilars. Specifically, patient willingness to transition differed for the mode of delivery and amount of content provided in communication strategies. Pharmacists also reported knowledge gaps and low confidence in explaining key concepts, indicating a need to upskill providers to further improve delivery. Findings also highlighted that patients with certain characteristics would benefit from additional information, as patient factors are associated with negative expectations. Findings from two randomised controlled trials contribute to understanding the involvement of

companions in discussions about biosimilars. While companions did not influence decisions, they reported unique information needs and concerns and engaged in interpersonal processes that impacted patient understanding. Family-centred communication augmented patient-provider-companion encounters. Future research should further examine the interpersonal processes that occur between patients and companions during treatment deliberations outside and during consultations and include experimental studies that explore the effects of communication in real-world transitions.

Overall, the studies in this thesis have significant clinical implications and highlight novel factors, such as information delivery and the social environment, that should be carefully considered when transitioning patients to biosimilars in the future. With these studies, this thesis provides strong support for implementing health psychology research and theory to further improve future transitions. Various blockbuster bio-originators will lose their patents in the upcoming years, providing a significant opportunity to introduce more biosimilars into the pharmaceutical market and ultimately reduce cost, improve access, and drive innovation. It is crucial to continue understanding how non-medical transitions can be improved to ensure patients and their companions are adequately supported and to mitigate fear, disparagement, and misinformation. Nonetheless, this thesis presents preliminary findings that provide guidance to help improve the transition to biosimilars.

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Appendices

Appendix A. Inclusion Criteria and Search Results for the Systematic Literature Review

	Inclusion Criteria	Exclusion Criteria
Population	Adult (18 years old and over) rheumatology, dermatology, or gastroenterology patients, transitioning from any bio-originator to any biosimilar.	• Patients not involved in a transitioning scenario. • Patients 17 years and under.
Intervention	Studies reporting patient communication about a transition from a bio-originator to a biosimilar	• Biologic to biologic transition • Biosimilar to biologic transition • Biosimilar to biosimilar transition • No mention of a communication strategy
Comparators	No restrictions	No restrictions
Outcomes	Studies that mention a form of patient communication Secondary: willingness to transition, persistence	• No mention of patient communication • No reporting of willingness to transition or persistence
Study Design	All studies including real-world data, observational (prospective/retrospective) and experimental designs	• Editorial (commentary, letters to editor) • Reviews and meta-analyses • Guidelines
Language, Geographic Scope	• English • All countries	• Non-English languages
Time Period	• Publication date from January 1st, 2012 to August 17th, 2020 • Conference abstracts from Jan 1st, 2018 to August 17th, 2020	• Publications before 2012 • Conference abstracts published before 2016

MEDLINE via Ovid Search Strategy (17th August, 2020)

#	Search Statement	Results
1	Biosimilar Pharmaceuticals/	2047
2	biosimilar*.tw,kw,kf.	3573
3	((followon or follow-on or subsequent entry) adj2 biologic*).ti,ab,kw,kf.	136
4	or/1-3	3799
5	(switch* or transition*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	596534
6	4 and 5	490
7	Communication/	84107
8	Health Communication/	2376
9	(communicat* or explain* or explanation*).tw,kw,kf.	953698
10	or/7-9	993103
11	"Patient Acceptance of Health Care"/	47029
12	patient satisfaction/ or patient preference/	89715
13	Patient Education as Topic/	85252
14	decision making/ or choice behavior/ or uncertainty/	135106
15	((willingness or accept* or education or workshop* or prefer* or decision or satisf* or understand* or knowledge or perception* or perceiv*) adj10 patient*).mp.	563397
16	or/11-15	677500
17	(real-world or real-life or realworld or reallife or realife).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	60436
18	6 and 10	22
19	6 and 16	67
20	4 and 17	224
21	18 or 19 or 20	282
22	limit 21 to english language	273
23	remove duplicates from 22	272
24	limit 23 to yr="2012 - 2020"	271

EMBASE via Ovid Search Strategy (17th August, 2020)

#	Search Statement	Results
1	Biosimilar Pharmaceuticals/	3387
2	biosimilar*.tw,kw.	7297
3	((followon or follow-on or subsequent entry) adj2 biologic*).ti,ab,kw.	246
4	or/1-3	7988
5	(switch* or transition*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	731296
6	4 and 5	1307
7	Interpersonal Communication/	153330
8	Medical Information/	74006
9	(communicat* or explain* or explanation*).tw,kw.	1140133
10	or/7-9	1271747
11	Patient Attitude/	66753
12	patient satisfaction/ or patient preference/	155893
13	Patient Education as Topic/	93122
14	decision making/ or choice behaviour/ or choice behavior/	225977
15	((willingness or accept* or education or workshop* or prefer* or decision or satisf* or understand* or knowledge or perception* or perceiv*) adj10 patient*).mp.	809422
16	or/11-15	1041107
17	(real-world or real-life or realworld or reallife or realife).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	104234
18	6 and 10	65
19	6 and 16	241
20	4 and 17	574
21	18 or 19 or 20	796
22	limit 21 to english language	783
23	remove duplicates from 22	772
24	limit 23 to yr="2012 – Current”	770

Scopus Search Strategy (17th August, 2020). Total = 229

Keyword search (as title, abstract or keyword): (Generics and Biosimilar Initiative) AND (educat* OR communicat* OR inform*) AND (switch* OR real-word*) OR (prefer* OR accept*) AND PUBYEAR > 2011 AND (LIMIT-TO (LANGUAGE, "English"))

Conference database search strategy

Conference	**Database webpage**	**Search term(s)**	**Search date**	**Results**
United European Gastroenterology Week	https://www.ueg.eu/education/library/#stq=*&stp=1&sts=Default&stc=All&stcf=UEG%20Week%202018&stf=All&stms=All&sty=All	"biosimilar AND switch"	17th August, 2020	14
European Crohn's and Colitis Organisation (ECCO)	https://www.ecco-ibd.eu/publications/congress-abstracts/abstracts-2019/	"biosimilar switch"	17th August, 2020	125
European League Against Rheumatism (EULAR)	http://scientific.sparx-ip.net/archiveeular/	"Biosimilar"	17th August, 2020	128
American College of Rheumatology (ACR) Annual Meeting	https://acrabstracts.org/	"Biosimilar AND switch"	17th August, 2020	38

Appendix B. Quality Evaluation of the 21 Included Journal Articles

Study	Aim and Context	Methodology	Results	Discussion and Conclusions	Ethics	Overall
Anjum et al. (2019)	No concerns	No concerns	No concerns	Some concerns: critical discussion on the method	No concerns	High
Bhat et al. (2020)	No concerns	Some concerns: analysis described accurately and is repeatable	No concerns	No concerns	Some concerns: ethical discussion, authors free from conflicts of interests	High
Binkhorst et al. (2018)	No concerns	Some concerns: analysis described accurately and is repeatable	No concerns	No concerns	No concerns	High
Boone et al. (2018)	No concerns	Some concerns: description of dropout	No concerns	Some concerns: critical discussion on the method	Some concerns: authors free from conflicts of interests	High
Chan et al. (2019)	No concerns	Some concerns: data collection described accurately and is repeatable, statistical methods are adequate and applicable in relation to the aims of the study	No concerns	Some concerns: reliability of instruments	Some concerns: ethical discussion	Moderate
Chau et al. (2019)	No concerns	No concerns	No concerns	Some concerns: reliability of instruments	No concerns	High
Gasteiger et al. (2019)	No concerns	No concerns	No concerns	Some concerns: reliability of instruments	Some concerns: authors free from conflicts of interests	High
Haghnejad et al. (2020)	No concerns	No concerns	No concerns	Some concerns: reliability of instruments	Some concerns: ethical discussion, authors free from conflicts of interests	High
Layegh et al. (2019)	Some concerns: explicit aim	Some concerns: analysis described accurately and is repeatable	No concerns	Some concerns: critical discussion on the method	Some concerns: ethical discussion, authors free from conflicts of interests	Moderate
Madenidou et al. (2019)	No concerns	Some concerns: analysis described accurately and is repeatable	No concerns	Some concerns: critical discussion on method	Some concerns: authors free from conflicts of interests	High
Müskens et al. (2020)	No concerns	No concerns	No concerns	No concerns	Some concerns: authors free from conflicts of interests	High

Petitdidier et al. (2019)	No concerns	No concerns	No concerns	No concerns	Some concerns: authors free from conflicts of interests	High
Plevris et al. (2019)	No concerns	No concerns	No concerns	No concerns	Some concerns: authors free from conflicts of interests	High
Ratnakumaran et al. (2018)	No concerns	No concerns	No concerns	No concerns	Some concerns: authors free from conflicts of interests	High
Razanskaite et al. (2017)	No concerns	Some concerns: description of dropout	No concerns	No concerns	Some concerns: ethical discussion, authors free from conflicts of interests	Moderate
Scherlinger et al. (2019)	No concerns	Some concerns: analysis described accurately and is repeatable	No concerns	Some concerns: critical discussion on method	Some concerns: authors free from conflicts of interests	Moderate
Scherlinger et al. (2018)	No concerns	Some concerns: description of dropout, analysis described accurately and is repeatable	No concerns	Some concerns: critical discussion on method	Some concerns: ethical discussion, authors free from conflicts of interests	Moderate
Schmitz et al. (2018)	No concerns	No concerns	No concerns	Some concerns: critical discussion on method	Some concerns: ethical discussion	High
Smits et al. (2016)	No concerns	Some concerns: data collection described accurately and is repeatable, analysis described accurately and is repeatable	No concerns	No concerns	Some concerns: authors free from conflicts of interests	High
Tweehuysen, Huiskes, et al. (2018)	No concerns	No concerns	No concerns	No concerns	Some concerns: authors free from conflicts of interests	High
Tweehuysen, van den Bemt, et al. (2018)	No concerns	No concerns	No concerns	No concerns	Some concerns: authors free from conflicts of interests	High

Appendix C. Summary of Study Design and Participant Characteristics of the Included Studies for the Systematic Literature Review

Reference and location	Study type	Aims	Study design	Patient population and sample size	M (SD or range) age, years	Gender, females, %	Transition drugs	Year transition began
Ahmad et al. (2019) (England)	Conference	To review patient experiences of the transitioning process, and to assess how many are transitioned back to the originator or alternative biologics due to side effects/worsening disease.	Observational cohort study	Rheumatology	55 (29-82)	NR	Enbrel to Benepali	2016
Anjum et al. (2019) (Ireland)	Published paper	To explore efficacy, safety, and retention rate of biosimilar Inflectra when transitioning from Remicade, in patients with rheumatic diseases.	Observational cohort study (prospective)	Rheumatology; ANK n = 9 (30%), RA n = 6 (20%), Behcets disease n = 6 (20%), PSA n = 2 (6.7%), Enteropathic arthritis n = 3 (10%), other: n = 4 (13.2%)	50 (12.2)	66.7%	Remicade to Inflectra (CT-P13)	2017
Bhat et al. (2020) (United States of America)	Published paper	To describe a biosimilar adoption process of IFX-dyyb in patients on IFX for ≥ 6 months; characterize cost savings of transitioning patients; and evaluate real-world clinical outcomes of adult patients with inflammatory bowel disease who transitioned to IFX-dyyb.	Observational cohort study (retrospective)	Gastroenterology; CD n = 41 (65%), UC n = 22 (35%)	38 (13)	33%	Remicade to Inflectra	2018
Binkhorst et al. (2018) (Netherlands)	Published paper	To investigate the feasibility and safety of switching patients with IBD from Remicade to a biosimilar infliximab.	Observational cohort study (retrospective)	Gastroenterology; CD n = 135 (69%), UC n = 62 (31%)	Median of 43 (18-85)	51%	Remicade to Inflectra or Remsima	NR
Boone et al. (2018) (Netherlands)	Published paper	To describe the 1-year results of a pragmatic study on infliximab biosimilar implementation in immune-mediated inflammatory	Observational cohort study (prospective)	Gastroenterology, rheumatology; CD n = 73 (58.4%), ulcerative	NR for total sample	NR for total sample	Remicade to Inflectra	2016

		disease patients on the basis of shared decision-making under effectiveness and safety monitoring.		disease n = 28 (22.4%), RA n = 9 (7.2%), PsA n = 5 (4%), ANK n = 10 (8%).				
Chan et al. (2019) (England)	Published paper	To support the transition of patients from originator etanercept (Enbrel) to biosimilar Benepali and to realise savings potential.	Observational cohort study (prospective)	Rheumatology; RA n = 43 (38%), axSpA n = 43 (38%), PsA n = 27 (24%)	NR	NR	Etanercept to Benepali	2016
Chau et al. (2019) (United States of America)	Published paper	To describe patients' perspectives of transitioning from infliximab to infliximab-dyyb.	Cross-sectional study	Rheumatology; ANK n = 3 (5.8%), PsA n = 9 (17.3%), RA n = 40 (76.9%)	60 (13.5)	76.9%	Remicade to Inflectra	2017
Coget et al. (2019) (France)	Conference	To evaluate the knowledge about biosimilars of patients treated with the reference product, assess the number of patients who would accept transitioning and to produce an economic analysis.	Observational cohort study (prospective)	Gastroenterology; Crohn's disease n = 46 (71.9%), ulcerative disease n = 18 (28.1%)	44 (NR)	NR	Remicade to infliximab biosimilar	2018
Dayer et al. (2019) (Spain)	Conference	To describe the transition experience from original etanercept to BE, and to evaluate the economic impact of this strategy.	Observational cohort study (retrospective)	Rheumatology; RA n = 25 (45%), psoriatic arthropathy n = 26 (46%), ANK n = 5 (9%)	NR	73%	Etanercept to etanercept biosimilar	NR
Dubash et al. (2018) (England)	Conference	To measure serum drug trough levels and anti-drug antibodies in a cohort of SpA patients receiving infliximab (remicade), with the aims of informing decision making before a possible transition to biosimilar and assessing the possible impact of this approach to clinical practice.	Observational cohort study	Rheumatology; axSpA n = 22 (61%), PSA n = 13 (39%)	NR	34%	Infliximab to Inflectra (CT-P13)	NR
Gasteiger et al. (2019)	Published paper	To measure the effect of differently framed explanations on patients' perceptions of and willingness to	Randomised controlled trial	Rheumatology; RA n = 62 (65%), ANK n = 16	54 (15.9)	69%	Enbrel, Humira, Remicade,	NR

(Aotearoa/New Zealand)		change to a biosimilar in a hypothetical drug transition.		(17%), PsA n = 13 (14%), GPA n = 2 (2%), JIA = 2 (2%), AOSD n = 1 (1%)			Mabthera and Actemra to biosimilar	
Haghnejad et al. (2020) (France)	Published paper	To explore the impact of a gastroenterologist's interview on IBD patients' acceptance for transitioning from infliximab bio-originator Remicade to CT-P13 Inflectra.	Observational cohort study (prospective)	Gastroenterology; CD n = 95 (79.8%), UC n = 24 (20.2%)	42.4 (14.5)	43.7%	Remicade to Inflectra	NR
Hastier-De Chelle et al. (2019) (France)	Conference	The aim of this study was to evaluate the impact of patient education on the acceptance of a transition from IFX originator to biosimilar in IBD patients treated with IFX originator.	Observational cohort study (prospective)	Gastroenterology; CD n = 55 (64%); UC n = 31 (36%)	Median of 44 (19-79)	NR	Remicade to Inflectra	NR
Kiltz et al. (2019) (Germany)	Conference	To evaluate the effectiveness and safety of systematic nonmedical switching from innovator etanercept to biosimilar etanercept SB4 in adult patients with rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis in a real-life setting based on different information strategies before transitioning.	Observational cohort study (retrospective)	Rheumatology; RA n = 44 (52%), axSpA n = 25 (30%), PsA n = 15 (18%)	NR	NR	Etanercept to etanercept biosimilar	2017
Layegh et al. (2019) (Netherlands)	Published paper	To evaluate the transition from reference infliximab Remicade to biosimilar Remsima in patients with rheumatoid arthritis or psoriatic arthritis.	Observational cohort study (retrospective)	Rheumatology; RA n = 41 (91%), PsA n = 4 (9%)	65 (14)	71%	Remicade to Remsima	2015
Madenidou et al. (2019) (England)	Published paper	To investigate the reasons of SB4 withdrawal and compare results with current evidence.	Observational cohort study (retrospective)	Rheumatology; RA n = 36 (50%), axSpA n = 23 (32%), PsA n = 13 (18%)	NR for total sample	NR for total sample	Enbrel to SB4	2016

Müskens et al. (2020) (Netherlands)	Published paper	Study the effect of non-mandatory transitioning from etanercept originator to etanercept biosimilar on retention rates in a shared decision making-promoting setting.	Observational cohort study	Rheumatology; RA n = 48 (69%), PsA n = 11 (16%), AS n = 11 (16%)	58 (14)	51%	Etanercept to etanercept biosimilar	2016
Nisar (2019) (England)	Conference	To report an early experience of introducing rituximab biosimilar in people with RA.	Observational cohort study	Rheumatology; RA n = 40 (100%)	58.6 (26-80)	80%	Mabthera to Truxima	2017
Petit et al. (2019) (France)	Conference	To assess the efficacy of a multidisciplinary team intervention to reduce the nocebo effect among inflammatory arthritis patients concerned by systematic switch from originator Infliximab to the biosimilar infliximab SB2.	Observational cohort study	Rheumatology; RA n = 17 (38%), SpA n = 23 (51%), PsA n = 5 (11%)	NR	NR	Infliximab to SB2	NR
Petitdidier et al. (2019) (France)	Published paper	To assess patients' perspectives concerning infliximab biosimilars after switching from infliximab to CT-P13 during a 1-year period on a prospective basis, and to assess the effectiveness, safety, and trough concentrations of CT-P13 on a prospective basis.	Observational cohort study (prospective)	Gastroenterology; CD n = 85 (75%), UC or UBDU n = 28 (25%)	NR for total sample	NR for total sample	Infliximab to CT-P13	NR
Plevris et al. (2019) (Scotland)	Published paper	To evaluate the efficacy (clinical disease activity, CRP, and faecal calprotectin), pharmacokinetics and safety of switching CD patients from Remicade to CT-P13 over 12 months.	Observational cohort study (prospective)	Gastroenterology; CD n = 110 (100%)	Median of 33 (IQR 26-47)	36.4%	Remicade to CT-P13	2015
Ratnakumaran et al. (2018) (England)	Published paper	To assess the efficacy and safety of switching from originator infliximab to CT-P13 for new and existing patients.	Prospective clinical audit	Gastroenterology; luminal CD n = 129 (67.5%), fistulising CD n = 44 (23%), UC n = 14 (7.3%), IBD-U n = 4 (2.1%)	42.7 (15.3)	45.5%	Remicade to CT-P13	2016

Razanskaite et al. (2017) (England)	Published paper	To present the outcomes of switching IBD patients established on originator infliximab to biosimilar infliximab, using a managed switching programme funded via a gain share agreement in a UK teaching hospital.	Observational cohort study (prospective)	Gastroenterology; CD n = 118 (82.5%), UC n = 23 (16.1%), IBD-U n = 2 (1.4%)	Median of 39 (17-87)	56.6%	Remicade to Inflectra	2015
Robinson et al. (2019) (England)	Conference	To survey patients experience of the process of switching.	Cross-sectional study	Rheumatology; RA (67%), PsA (25%) and AS (8%)	NR	NR	Enbrel to Benepali	NR
Röder et al. (2018) (Germany)	Conference	To perform an independent, prospective and randomised, double-blinded trial in patients of the IBD centre Munich with CD and UC who had responded to originator infliximab for at least 3 months.	Prospective and randomised, double blinded trial	Gastroenterology; CD n = 69 (62.2%), UC n = 42 (37.8%)	37	46.8%	Infliximab to CT-P13	2015
Rosembert et al. (2020) (England)	Conference	NR.	Observational cohort study	Rheumatology; gastroenterology; dermatology	NR	NR	Adalimumab to Amgevita	NR
Scherlinger et al. (2019) (France)	Published paper	To conduct a real-life study by systematically offering a switch from originator etanercept (Enbrel) to biosimilar SB4 (Benepali). The main outcome was the primary switch acceptance rate. The secondary outcomes were to evaluate real switch adherence, socio-cultural factors and fears or beliefs influencing the acceptance rate.	Observational cohort study (prospective)	Rheumatology; RA n = 20 (38%), SpA n = 32 (62%), n = 24 axSpA, PsA n = 4, SAPHO syndromes n = 4, reactive arthritis n = 2	51.7 (14.4)	56%	Etanercept to SB4	NR
Scherlinger et al. (2018) (France)	Published paper	To assess the retention rate of CT-P13 in real-life setting after switching from OI; to compare this retention rate with the ones observed in a cohort of infliximab-	Observational cohort study (prospective and retrospective)	Rheumatology; SpA n = 75 (84%) (with n = 63 having axial involvement),	50.5 (13.3)	43%	Infliximab to Inflectra (CT-P13)	NR

		naïve patients starting with CT-P13, and in a retrospective cohort of OI-treated patients.		PsA n = 12 (16%), RA n = 14 (16%)				
Schmitz et al. (2018) (Netherlands)	Published paper	To study prospectively the switch from infliximab innovator to biosimilar in an IBD cohort with 12 months follow-up to evaluate safety and effectiveness.	Observational cohort study (prospective)	Gastroenterology; CD n = 86 (64.7%), UC n = 47 (35.3%)	NR for total sample	NR for total sample	Remicade to Inflectra	2016
Smits et al. (2016) (Netherlands)	Published paper	To prospectively investigate efficacy, safety, pharmacokinetic profile, and immunogenicity following a switch from Remicade to CT-P13 in IBD patients.	Observational cohort study (prospective)	Gastroenterology; CD n = 57 (69%), UC n = 24 (29%), UBD-U n = 2 (2%)	Median of 36 (18-79)	66%	Remicade to CT-P13	2015
Tweehuysen, Huiskes, et al. (2018) (Netherlands)	Published paper	To evaluate the effects of non-mandatory transitioning from the originator biologic drug etanercept to its biosimilar, SB4, on drug survival and effectiveness in a controlled cohort study of patients with an inflammatory rheumatic disease.	Observational controlled cohort study (prospective)	Rheumatology; RA n = 433 (69%), PsA n = 128 (21%), ANK n = 64 (10%)	57 (14)	55%	Etanercept to Benepali (SB4)	2016
Tweehuysen, van den Bemt, et al. (2018) (Netherlands)	Published paper	To prospectively evaluate drug survival, effectiveness, pharmacokinetics, immunogenicity, and safety after open-label transitioning treatment from REM to CT-P13 in patients with RA, PsA or AS.	Observational cohort study (prospective)	Rheumatology; RA n = 75 (39%), PsA n = 50 (26%), AS n = 67 (35%)	55 (14)	52%	Remicade to CT-P13	2015
Uke et al. (2019) (England)	Conference	To review the efficacy, safety, and retention rate of SB4 switches already done in Wrightington Hospital.	Observational cohort study	Rheumatology; RA n = 89 (57%), PsA n = 44 (28%), axSpA n = 24 (15%)	NR	NR	Etanercept to SB4	2017

Note. NR = not reported, CD = Crohn's disease, UC = ulcerative colitis, IBD and IBD-U= Inflammatory bowel disease (unclassified), RA = rheumatoid arthritis, ANK = ankylosing spondylitis, PsA = psoriatic arthritis, axSpA = axial spondyloarthritis, SAPHO = synovitis–acne–pustulosis–hyperostosis–osteitis syndrome, GPA = Granulomatosis with polyangiitis, JIA = Juvenile idiopathic arthritis, AOSD = Adult onset Stills disease

Appendix D. Communication Strategies Used in Biosimilar Transitions

Author	Strategy	Provider of Information	Approach	Willingness to Transition (Acceptance)	Persistence	Subjective Adverse Events	Other Info. About Strategy	Perceptions of Transition and Biosimilar
Ahmad et al. (2019)	Letter (patients also reported receiving verbal information)	Pharmacy department	Non-mandatory	104/105 (99%)	93/104 (90%) - follow-up time unclear	7 patients (7%). Injection site reaction (*n* = 5), dry mouth (*n* = 1), sore throat (*n* = 1).	NR	Patients wanted more notice before transitioning, a better delivery process and more staffing to be seen quicker.
Anjum et al. (2019)	Consultation – 'physical interview'	Rheumatology registrar	Non-mandatory	30/31 (97%)	26/30 (87%) at 6 months	3 patients (10%). Nausea, dizziness, and abdominal pain (*n* = 1), subjective worsening of pain without objective/serological worsening of disease activity (*n* = 2)	NR	NR
Bhat et al. (2020)	Individual education provided, then given a telephone call, letters sent if no response	Healthcare providers, clinical pharmacists	Non-mandatory	151/154 (98%)	38/46 (83%) - patients with data at 12-15 months	NR	Strategy informed by multidisciplinary stakeholders. Infusion nurses given presentation and educational materials for patients.	NR
Binkhorst et al. (2018)	Consultation 'Counselling'	Physician or IBD nurse	Non-mandatory	NR. 197/256 (77%) but unclear how many due to patient preference only.	177/197 (90%) at 16 weeks	NR Unclear how many patients reported SAE's. 11 AEs were reported in total (arthralgia (n= 2), fatigue (n=1), headache (n=1), exclude- rash (n=1), skin problems (n= 3), adverse effects not specified (n =3), severe acute	NR	NR

						infusion reaction (n = 1).		
Boone et al. (2018)	Letter accompanied by oral clarification (if requested)	Physician or nurse practitioner	Non-mandatory	125/146 (86%)	102/125 (82%) at 9 months	8 patients (6%). Discontinued due to chills during infusion (*n* = 4); numbness of facial skin with tingling limbs (*n* = 1); fatigue (*n* = 2); new onset headache (*n* = 1).	Transition protocol developed by multidisciplinary team in accordance with Dutch Society of Gastroenterologists, Dutch Association of Rheumatology, the Dutch Society for Consultants, and the Dutch Medicine Evaluation Board guidelines.	NR
Chan et al. (2019)	Letters and information sheets sent to patients, clinic or phone discussions, or group educational sessions	Physicians and nurses	Non-mandatory	113/158 (72%)	102/113 (90%) at 3 months	26 patients (23%). Worsening pain or stiffness (*n* =12), increased fatigue (*n* =4), painful injections (*n* = 5) and other (one each of breathlessness, itchy eyes, thumb nodule, abdominal pain, and headache).	A working group consisting of clinicians and stakeholders across Berkshire West (Medicines Optimisation Network, Regional Procurement Pharmacists, Chief Pharmacists Group) was formed.	Most patients recalled receiving written information (86%) and discussing biosimilars in clinic (83%). 63% had no concerns about changing. Concerns were about efficacy (29%), safety (5%) and side effects (3%). Mean visual analogue score for confidence in the biosimilar was 7.86 (median 8, 1–10). Most (58/94) reported no problems with the change.
Chau et al. (2019)	Letter, given chance to discuss transition at appointment or over telephone	Rheumatologist	Non-mandatory	40/52 (77%)	NR	NR	NR	Most patients were satisfied or very satisfied with the biosimilar's disease control (80%). Concerns included not knowing enough (38%), potential side effects (35%), and loss of disease activity control (35%).
Coget et al. (2019)	Consultation - 'standardised pharmaceutical interview'	Pharmacist	Non-mandatory	6/64 (9%)	NR	NR	NR	Patients unwilling to change had concerns about tolerance (15%) or efficiency loss (18%) or both (35%). Some (30%) wanted to discuss the change with their physician. Few

								patients knew about biosimilars, but after the interview 38% were in favour of changing. Few patients actually transitioned, mostly due to lack of information.
Dayer et al. (2019)	Consultation - 'specific biosimilar consultation'	Rheumatologist and nurse	Non-mandatory	NR 31/56 (55%) but unclear how many patients specifically refused.	NR	NR	NR	NR
Dubash et al. (2018)	Consultation – 'counselling'	Specialist nurse	Mandatory	20 patients were transitioned.	NR	NR	NR	NR
Gasteiger et al. (2019)	Video of doctor's explanation	Researcher – video of physician	Non-mandatory	54/96 (56%) Based on a hypothetical situation.	NR	NR	Four explanations were used – positive and negative framing, with and without an analogy. Positive framing increased willingness to transition (67%), compared to negative framing (46%).	Positive framing improved perceptions of the biosimilars efficacy. Patients were concerned about reduced efficacy (50%) and safety (46%). From the explanation, patients were most worried about reduced efficacy (34%), cost and quality (28%), and safety (25%). Patients want to know about safety (38%), efficacy (37%), evidence from clinical trials (19%), manufacturing information (10%), and the possibility of changing back (7%).
Haghnejad et al. (2020)	Consultation – structured interview and information sheet after interview	Gastroenterologist	Non-mandatory	93/138 (67%)	NR	NR	Interview structure was agreed upon by two other gastroenterologists and one pharmacist. Patients were given time to ask questions. The information sheet was	Most (80%) had never heard about biosimilars. Having heard about biosimilars was associated with a lower chance of changing. Satisfaction with generics increased acceptance of the

							provided by the French National IBD patients association (Association Franc¸ ois Aupetit (AFA)) as a support measure.	transition. There were 1.47 (Relative Risk RR [95% CI] = 1.47 [1.07–2.01]) times more chance to agree to the transition if the interview modified the patient's opinion on biosimilars.
Hastier-De Chelle et al. (2019)	Consultation – 'educational interview'	Patient education nurse	Non-mandatory	67/86 (78%) Initial acceptance 46/86 (53%), and an extra 21 patients agreed after interview.	53/59 (91%) at 4 months	NR	NR	At baseline patients (77%) had never heard about biosimilars, 85% were favourable towards transitioning and 61% expressed fears about biosimilars. At 4 months, 84% of patients knew about biosimilars, 93% were in favour of the transition and 39% were still concerned.
Kiltz et al. (2019)	Consultation	Physician	Mandatory	84 patients were transitioned	81/84 (96%) at 3 months; 71/84 (88%) at 6 months	2 patients (2%). Generalised itching (1), and nausea (1). Author also reported that one patient had partial loss of hair via correspondence (not SAE with our definition).	Whether or not patients were informed about the change was left to the discretion of the treating physician. Twenty-four patients received information about transitioning (29%).	NR
Layegh et al. (2019)	Informed by letter and subsequently contacted to provide time to ask question	Nurse and pharmacist, could contact rheumatologist if had doubts	Non-mandatory	45/47 (96%)	39/45 (87%) at 24 months	NR	The communication strategy was in accordance with the Dutch Association of Hospital Pharmacists by using the NVZA toolbox Biosimilars	33% of patients scored the information provision as excellent, 54% as good, 9% as reasonable and 4% found the information sufficient. Most patients were informed by nurses and rheumatologists prior to the letter. 26% of patients were initially informed by a rheumatology nurse and 26% by the rheumatologist. 9% were informed via the letter and 7% gained information elsewhere.

Madenidou et al. (2019)	Letter, patient information meetings (routine appointment if unable to attend)	Rheumatologist	Non-mandatory	72/104 (69%)	52/72 (74%) at 6 months	6 patients (8%). Headache, dyspnoea, weight gain, hair loss, rash, and fatigue.	NR	NR
Müskens et al. (2020)	Letter and outpatient consultation (if needed consultation with nurse about transition or administration)	Rheumatologist, (specialist nurse if needed)	Non-mandatory	70/79 (89%)	55/70 (79%) at 12 months	9 patients (13%). Discontinued due to general discomfort/overall malaise (*n* =2), increased tiredness (*n* =1), arthralgia without clinical sign of arthritis (*n* =3), muscle aches in arms (*n* =1), tingling in hands and feet (*n* =1), arthralgia without clinical sign of arthritis & general discomfort/overall malaise (*n* =1).	NR	NR
Nisar (2019)	Letter, information sheet, nurse helpline for concerns	Nurse	Non-mandatory	40/40 (100%)	34/40 (85%) no follow-up time reported	7 patients (18%). Experienced 18 AE's (*n* = 1 gen unwell, achy, flu like symptoms; *n* = 1 itchy scalp, brain fog; *n* = 1 vomiting; *n* = 1 palpitations, dizziness; *n* = 1 headache, flushing; *n* = 1 nausea, flushing headache; *n* = 1 body pains, headache, distaste, lethargy (hospitalised).	NR	NR

Petit et al. (2019)	Written information (informative leaflet), oral information	Nurses, nurse-led patient education	Mandatory	45 patients were transitioned	41/45 (91%) at median follow-up of 34 weeks	1 patient (2.2%). Increased fatigue and pain.	Intervention was part of a multidisciplinary patient education program. Step 1: semi-directive qualitative interviews with 5 patients treated by other intravenous biologics – showing fears about efficacy and tolerability, need for information, importance of sharing experiences of adverse effects with practitioners, and having the opportunity to transition back. Also wanted nurses to discuss their experience of biosimilars. Step 2: meeting with the multidisciplinary team (3 rheumatologists, 1 resident, 1 pharmacist, 3 nurses, 1 peer-patient from a patient's association) to design the intervention based on the interviews, non-systematic literature review about transitions and on patients' perspective regarding nocebo effect. Step 3: Agreement on the intervention and the chosen pieces of language to be used by all providers. Step 4: Implementation.	NR
Petitdidier et al. (2019)	Personalised information,	NR	Non-mandatory	113/117 (97%)	103/113 (91%) at 12 months	1 patient (1%). Infusion reaction.	Personalised information was provided using documentation from the	Most patients (65%) were initially concerned about the use of biosimilars and the risks

	written information						Groupe d'Etudes Thérapeutiques Affections Inflammatoires Digestives and the Société Nationale Franc¸aise de GastroEntérologie.	of transitioning. After transitioning only 42% had these concerns.
Plevris et al. (2019)	Letter, given opportunity to discuss transition via telephone consultation or at final originator infusion	NR	Mandatory	110 patients were transitioned	93/110 85% at 12 months	NR	NR	NR
Ratnakumaran et al. (2018)	Letter, chance to discuss transition at next infusion	IBD nurse	Non-mandatory	191/210 (91%)	146/191 (76%) at 12 months	4 patients (2%). Infusion reaction (*n* = 3) and neurological syndrome of headache and loss of consciousness *n* = 1).	NR	NR
Razanskaite et al. (2017)	Managed switching program: information sheet, time to discuss at originator infusion, chance to ask questions at following infusion	IBD nurse	Non-mandatory	143/143 (100%)	104/143 (73%) at 12 months	NR Unclear how many patients reported SAE's. 67 AEs were reported in total (joint pains n = 13, headaches n = 16, pins and needles/tingling = 10, infusion reaction n = 2, breathlessness = 8, chest pain = 7, other n = 11 (e.g., abdominal bloating, general malaise, tinnitus, fatigue,	A managed switching programme was designed with input from all key stakeholders. Biosimilars were discussed at the department meeting. There was unanimous agreement to the switching programme; key to this agreement was the reassurance provided by the risk management plan (robust pharmacovigilance procedures and the prevention of interchangeability by brand prescribing only).	The patient panel had concerns about gaps in evidence and the concept of transitioning patients. They were reassured by monitoring and risk management and were keen to see some savings invested in developing the service.

						indigestion, depression).		
Robinson et al. (2019)	Letter, consultation if needed	Specialist nurse	Non-mandatory	NR 26 patients were surveyed.	NR	3 patients (12%). Headaches, injection site pain and runny nose.	2 patients who already changed were interviewed. The results of this informed a questionnaire which was designed to seek patient opinions on how the transition affected efficacy and side effects; their opinions on the information they were given, how willing they were to change, their satisfaction with the process and whether they would like to change back to the bio-originator.	72% felt that they had been given the right amount of information, 27% would have liked more. 1 patient had no understanding of the change. Willingness to change was evenly split between satisfied and not. 44% would elect to return to the originator drug with 28% unwilling and 28% unsure. 82% were very or somewhat happy with the process, but 17% were not satisfied. Qualitative comments included disappointment and wishing to change back, 1 complaint of 3 months absence from work and 1 patient thought that Benapali was a miracle.
Röder et al. (2018)	Individualised information	NR	Non-mandatory	200/294 (68%)	69/111 (62%) at 12 months	NR	NR	NR
Rosembert et al. (2020)	Letter, clinic visits	IBD physicians and nurses	Mandatory	744 patients were transitioned	696/744 (94%) at 1 week- 7 months (median = 3 months)	21 patients (3%). Injection site pain or reaction.	NR	NR
Scherlinger et al. (2019)	Consultation, information sheet, dedicated time to address questions	Physician	Non-mandatory	44/52 (85%)	41/44 (93%) median of 4 months	2 patients (5%). Axial pain with a morning stiffness lasting two hours after the change (*n*= 1) and 1 misattribution asymptomatic increased INR above 4 (*n*= 1).	The information was provided by two rheumatology residents who reached agreement to communicate homogenous information.	All patients wanted to receive information about biosimilars and reported questions about efficacy, safety, and previous transition experiences. Many were reassured by data from the NOR-SWITCH and DANBIO studies. In patients refusing the change, suspicious and defensive behaviour was noted. These patients had lower interest in biosimilars

								and asked less questions. Two patients refused as contradictory and negative information had been given by their regular pharmacist. The major concerns reported were efficacy, biosimilarity, adverse events, and wanting to keep control of their treatment. None reported a lack of confidence in the physician as a reason for refusal. These patients were more likely to report bad opinions on generics. Patients who accepted the transition agreed due to confidence in their physician (and the physician's good opinion of biosimilars) (70%), or because of the lower price (30%). Most had a good experience of the transition (86%), but 15% felt pressured. The transition positively affected pain for 3 patients, but 4 had a negative effect.
Scherlinger et al. (2018)	Consultation 'oral information'	Attending physician	Non-mandatory	89/100 (89%)	64/89 (72%) at median of 33 weeks	5 patients (6%). Infusion reactions (fever and chills) (*n* = 2), headaches (*n* = 2) and mild serum-sickness-like disease after the third infusion of CT-P13 (*n* = 1).	The different practitioners reached agreement before the beginning of the study to communicate homogenous information to patients about biosimilars.	Almost half (44%) of the patients that requested to transition back to the originator reported a negative perception towards the biosimilar without any worsening of their disease activity score.
Schmitz et al. (2018)	Letter, explanation if severe doubts	Gastroenterologist	Non-mandatory Classified as non-mandatory as patients were described to	100% (133/133)	98/133 (74%) at 12 months	13 patients (9.8%) Discontinued due to AE's: (general malaise and/or fatigue (n = 7), arthralgia (n = 2), skin problems (n = 2), infusion reaction	NR	NR

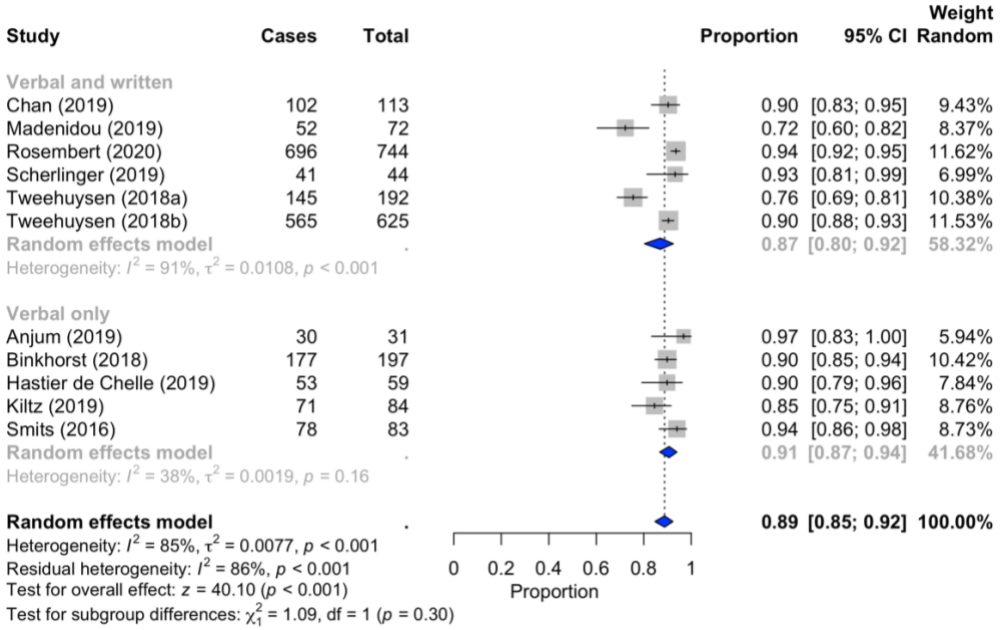
			agree with the transition.			to the first biosimilar infusion (n = 1), and suspected delayed allergic reaction (n = 1).		
Smits et al. (2016)	Consultation: 'counselling'	Gastroenterologist	Mandatory All patients were transitioned. If refusal, corresponding author clarified that patients had to change hospitals.	83 patients were transitioned	78/83 (94%) at 16 weeks	NR Unclear how many patients reported SAE's. 20 AEs reported in total.	NR	NR
Tweehuysen, Huiskes, et al. (2018)	Letter, telephone call, physician if no consent	Pharmacy technician, rheumatologist	Non-mandatory	635/642 (99%) 635 patients agreed to transition. 625 participated in study.	565/625 (90%) at 6 months	NR Unclear how many patients reported SAE's. 46 AEs were reported in total.	A multi-stakeholder group was formed to develop an implementation plan and involved patient input. Providers participated in a two-hour soft skills training to learn how to act if a patient has doubts or concerns or reports subjective complaints. Uniform information was provided. Trained pharmacists had a dedicated phone number and answered questions in accordance with a script. Positive framing and tailored information were provided in the patient information letter. The letter was sent simultaneously to all patients followed by a	Patients had stronger necessity beliefs compared to concern beliefs about the medication, and had stronger positive expectations about transitioning to the biosimilar. Lower self-efficacy in relation to coping with pain and other symptoms was associated with biosimilar discontinuation.

							national news item on television the following day.	
Tweehuysen, van den Bemt, et al. (2018)	Letter, telephone call	Pharmacy technician, rheumatologist	Non-mandatory	196/222 (88%) 196 patients agreed to transition. 192 gave consent to participate in BIO-SWITCH study.	145/192 (76%) at 6 months	13 patients (7%). Discontinued due to 25 SAE's (3 = mood disturbances; 3= dyspnoea; 1 = nausea; 2 = dizziness; 1 = angina pectoris; 5 = malaise; 2 = headache; 1 = paraesthesia; 2 = pruritus; 2 = myalgia; 1 = palpitations)	NR	NR
Uke et al. (2019)	Letter, telephone consultation, face to face if needed	NR	Non-mandatory	157/185 (85%)	140/157 (89%) at 3-12 months	NR	NR	NR

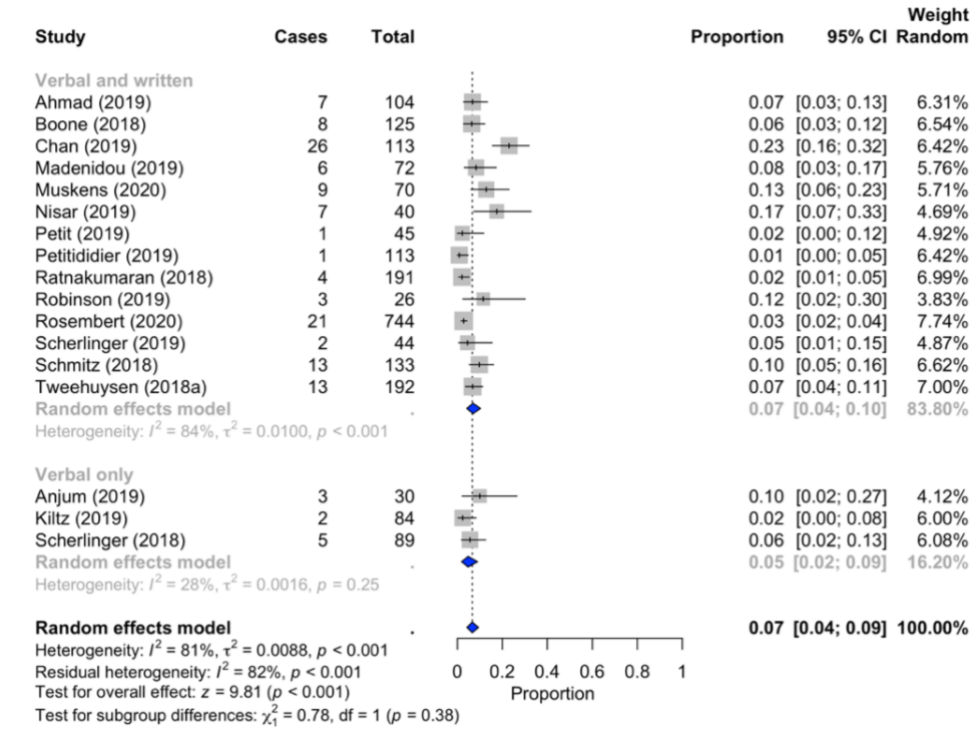
*NR = not reported

Appendix E. Forrest Plots Showing Pooled Proportions of Patients Persisting to Biosimilar Treatment and Reporting Subjective Adverse Events for Different Modes of Delivery and Amount of Content

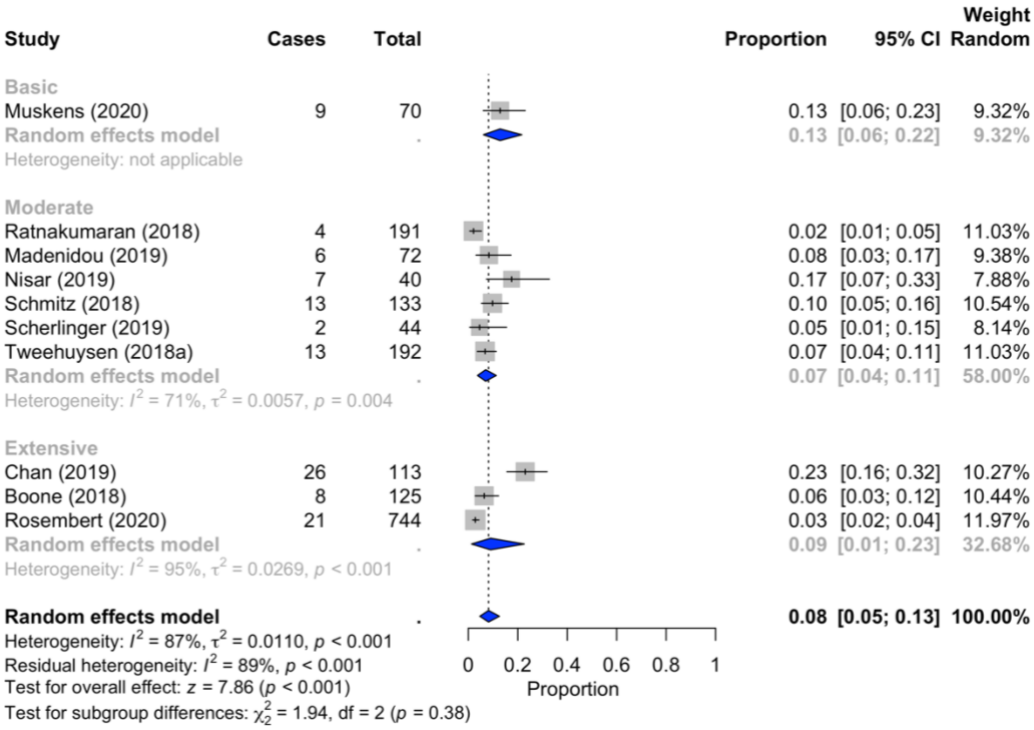
Pooled proportion of patients persisting to the biosimilar at 3-6 months follow-up based on different methods of communication (p = 0.30).



Pooled proportion of patients reporting subjective adverse events to the biosimilar based on different methods of communication (p = 0.38).



Pooled proportion of patients reporting subjective adverse events to the biosimilar based on different amounts of information ($p = 0.38$).



Appendix F. Script From the Standardised Explanation About Transitioning to Biosimilars

Preamble

Biosimilar medications are used in rheumatology and dermatology clinics worldwide. At present these medicines are not used in Aotearoa/New Zealand, but it is possible that they will be used in the future. You have been invited to participate in this study because you are taking a biologic medicine and we want to get the thoughts of patients currently on this type of medicine. It is important to say that the situation we describe is hypothetical and not related to you or your current medicine. There are no plans at the moment to switch Aotearoa/New Zealand patients to biosimilars. As biosimilars are likely to be prescribed for some patients in the future, this is an important study where we are interested in getting patients, and sometimes their family members, reactions to an explanation.

In this study, we want you to imagine that a doctor is explaining the switch from your current biologic to a biosimilar, and we want to gather your reactions to this explanation. Before taking part, it is important to tell you that you were randomised (or assigned by chance) to hear an explanation by yourself or with a support person. After you hear the explanation, we will ask you to complete some questions, including whether you would be willing to switch in this imaginary situation. I want you to imagine that you are in a clinic with your rheumatologist. After your doctor has completed a clinical assessment, she wants to discuss a change in your medication. This is a video of Dr X explaining the change. Please be as honest as you can about your reaction to the explanation.

Explanation

So now that we have talked about your clinical progress and assessed how you are doing, I would like to talk to you about changing your medication. I want to talk to you about switching to another biologic drug called a biosimilar. As you might know, you currently take a type of biologic medicine. And these biologics are drugs that are made of or from living things like yeast, bacteria, or an animal cell, and they usually have a more complex structure than other medicines. They can work extremely well, and in some cases with less side effects than other medicines. So, we've now got a choice whether you would like to switch from the biologic you are taking, to something that's called a biosimilar medicine.

A biosimilar is based on an existing biologic, but it is not an identical copy. Biosimilars are often made by different companies, who then obviously use a different manufacturing process. But, because these biologics are so complex and made from living cells, each batch has some unique differences. This means that batches are not identical to each other. And therefore of course, the biosimilars can't be absolutely identical to the biologic, does that make sense? So, the biosimilars work in the same way, on the same biologic target as your current drug, they also have the same strength and dose, and more importantly there is no additional cost to you.

So, I'm just going to give you a little bit more information about the biosimilar. They've been used in patients overseas and have been proven to be safe and effective by Medsafe. Making a biosimilar takes around 7 to 8 years and really extensive tests - about 250 tests to prove their quality and their strength. Medsafe in Aotearoa/New Zealand have some pretty strict rules about how all drugs are made and all companies selling these drugs must follow the same rules to ensure the quality of the ingredients. It is also important for you to know that as with any new drug, it is possible that you may get some side effects, and we can't be absolutely certain that you will get the same beneficial effect. But if we have some concerns about that, particularly if you get any side effects, we can discuss the options for switching back to the biologic or to a different biosimilar.

Thinking about why we're talking about biosimilars, well, one of the reasons that Aotearoa/New Zealand's pharmaceutical funding agency PHARMAC, have introduced biosimilars, is to help save on healthcare costs. Because PHARMAC has a fixed budget to buy new medicines. As you might know the biologic you are taking is pretty expensive that costs about $15 to $20,000 per year. Because this cost is so high, not every patient who might benefit from a biological treatment can have access to them. But these biosimilars have been made after the patent for the biologic has expired, and that means that the biosimilar can really help to reduce the cost, almost by a half. That's because the company making the biosimilar don't have the need to do the highly intensive randomised controlled clinical trials as the company that's originally made the biologic. That means that they can cost a bit less and can compete with the biologic medicine that is already being offered.

So, if we can switch to biosimilars we can save money – that won't be money you get to keep. But that does mean that more people with arthritis and dermatology problems who previously couldn't access these expensive treatments can. So that's a little bit about the

potential for moving across to the biosimilar. And just to reassure you, if you choose to switch, we will keep monitoring you in the same way as you have been while you have been taking the biologic.

Appendix G. Spearman's Rho Intercorrelations Amongst Continuous Constructs

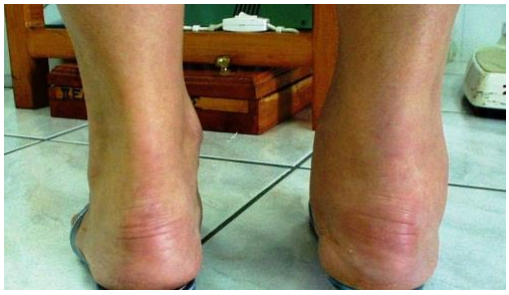
Variables	Age	Time on Originator	Cognitive Risk	Affective Risk	Preference for Biosimilars	Explanation: Reassuring	Ability to Understand Explanation	Decisional Conflict	Decision Satisfaction	Importance of Receiving Info. Together	Emotional Support	Practical Support
Age	-	.31 (.006)*	.08 (.46)	-.04 (.73)	-.06 (.60)	-.06 (.60)	-.19 (.07)	.21 (.07)	-.03 (.81)	.10 (.38)	.05 (.78)	-.03 (.86)
Time on Originator	.31(.006)*	-	.04 (.72)	.00 (.99)	-.07 (.55)	-.06 (.59)	-.07 (.53)	.04 (.73)	.01 (.96)	-.16 (.17)	-.00 (.99)	-.14 (.40)
Cognitive Risk	.08 (.46)	.04 (.72)	-	.81 (<.001)*	-.66 (<.001)*	-.57 (<.001)*	-.29 (.008)*	.38 (<.001)*	-.13 (.25)	-.06 (.63)	-.37 (.019)*	-.21 (.19)
Affective Risk	-.04 (.73)	.00 (.99)	.81 (<.001)*	-	-.66 (<.001)*	-.59 (<.001)*	-.32 (.004)*	.44 (<.001)*	-.13 (.26)	-.07 (.55)	-.33 (.043)*	-.21 (.21)
Preference for Biosimilars	-.06 (.60)	-.07 (.55)	-.66 (<.001)*	-.66 (<.001)*	-	.57 (<.001)*	.23 (.047)*	-.33 (.004)*	.17 (.13)	.17 (.13)	.32 (.046)*	.07 (.66)
Explanation: Reassuring	-.06 (.60)	-.06 (.59)	-.57 (<.001)*	-.59 (<.001)*	.57 (<.001)*	-	.53 (<.001)*	-.55 (<.001)*	.23 (.045)*	.22 (.06)	.36 (.023)*	.18 (.28)
Ability to Understand Explanation	-.19 (.09)	-.07 (.53)	-.29 (.008)*	-.32 (.004)*	.23 (.047)*	.53 (<.001)*	-	-.35 (.002)*	.29 (.009)*	-.00 (.98)	.26 (.12)	.19 (.25)
Decisional Conflict	.21 (.07)	.04 (.73)	.38 (<.001)*	.44 (<.001)*	-.33 (.004)*	-.55 (<.001)*	-.35 (.002)*	-	-.51 (<.001)*	-.36 (<.001)*	-.45 (.004)*	-.38 (.018)*
Decision Satisfaction	-.03 (.81)	.01 (.96)	-.13 (.25)	-.13 (.26)	.17 (.13)	.23 (.045)*	.29 (.009)*	-.51 (<.001)*	-	.14 (.23)	.11 (.52)	.13 (.42)
Importance of Receiving Info. Together	.10 (.38)	-.16 (.17)	-.06 (.63)	-.07 (.55)	.17 (.13)	.22 (.06)	-.00 (.98)	-.36 (<.001)*	.14 (.23)	-	.51 (<.001)*	
Emotional Support	.05 (.78)	-.00 (.99)	-.37 (.019)*	-.33 (.043)*	.32 (.046)*	.36 (.023)*	.26 (.12)	-.45 (.004)*	.11 (.52)	.51 (<.001)*	-	.86 (<.001)*
Practical Support	-.03 (.86)	-.14 (.40)	-.21 (.19)	-.21 (.21)	.07 (.66)	.18 (.28)	.19 (.25)	-.38 (.018)*	.13 (.42)	.49 (<.001)*	.86 (<.001)*	-

Note. R_s (*p*-value); *Denotes significance at $p < .05$

Appendix H. Background Information and Letter About the Transition

In this study, we want you to imagine that you have inflammatory arthritis and are attending a specialist rheumatology clinic consultation with your support person to discuss a potential change in your treatment. Please imagine that you have had inflammatory arthritis for the past three years. Inflammatory arthritis affects people of all ages and is caused by an overactive immune system, as the immune system attacks itself. This has damaged the tissue around your finger and ankle joints, causing deformed hands and swelling, pain and stiffness.

In the past, the joint inflammation was so *debilitating* that you struggled to leave the house. Your support person had to drive you to your medical appointments and saw your persistent pain. You tried *numerous* treatments, which did not completely control the inflammation. After two years of trialling medication and constantly experiencing joint pain and swelling, you were eligible to receive Humira.



Example of joint swelling.

You take Humira by injecting it at home every two weeks. Injecting this drug is often quite painful, and you sometimes get some symptoms, such as pain or swelling near the injection spot, headaches, and a small rash. Your support person occasionally helps you, by providing encouragement or distracting you from the pain. Humira is free of charge for you (funded by PHARMAC). As Humira weakens the body's immune system it can make you more likely to get minor infections, such as colds, but also severe conditions such as tuberculosis (TB). This means that you have regular blood tests and specialist appointments to monitor your inflammation.

Humira is a type of biologic medicine. Biologics are drugs that are made *of* or *from* living things like yeast, bacteria, or animal cells. Biologics work by *changing immune responses*. Biologics can work extremely well, and in some cases with fewer side effects than other medicines. However, these drugs are expensive for the healthcare system. This means that PHARMAC only funds a few biologic treatments, which can be limiting if your current treatment stops working.

Humira being administered.

Humira has worked well for you and enabled you to return to work and education. You do not get the same painful flare ups, and finally feel like you are living a 'normal' life. Your support person has seen the positive, significant impact Humira has made on your life.

Note. Images have been adapted for this thesis for copyright reasons. Images are by Harrygouvas at Greek Wikipedia., CC BY-SA 3.0,, via Wikimedia Commons and stefamerpik on Freepik

Date: 02/03/2022
ID: Id/1606x
Subject: Change of adalimumab brand; Humira® becomes Amgevita®

Dear Sir, dear Madam,

You are currently receiving the medication adalimumab (brand name Humira®). The market protection (patent) for Humira® expired in December 2016. This means that other companies can now make adalimumab. Adalimumab branded Amgevita® has been approved for the same medical conditions as Humira®.

The transfer from Humira® to the brand Amgevita® begins on 1st August 2022. In this letter, you can read why New Zealand's Pharmaceutical Management Agency (PHARMAC) has chosen to fund Amgevita® and what that means for you.

Why is your hospital changing to a different brand of adalimumab?
When making a decision, PHARMAC always looks at the effectiveness and safety of a medicine first. Extensive scientific research in patients has shown that Amgevita® is just as effective and safe as Humira®. So, you can rest assured that the treatment you receive will remain equally effective and safe.

Then PHARMAC takes into account the cost and benefits to patients. The cost is much lower for Amgevita®, but the quality of Humira® and Amgevita® is the same - they both contain the active ingredient adalimumab. The reduced cost will mean that more patients can get access to Amgevita®. With your support, changing from Humira® to Amgevita® contributes to keeping future hospital care affordable.

What does this mean for you?
Amgevita® is administered in a similar way to Humira®. You will have an appointment with a specialist nurse to ensure that you can use the new device without problems.

Practical matters
We value your informed consent. If you agree to changing from Humira® to Amgevita® using a guided transition, you can let us know by sending an email to: info@rheumatologyCNS.ac.nz

If you already have an outpatient appointment, your rheumatologist will discuss the transition to Amgevita® with you during the visit. If you would like to be further informed by telephone, you can also let us know by sending an email to: info@rheumatologyCNS.ac.nz

If you have any questions after reading this letter, please contact the rheumatology department by telephone or email.

We look forward to hearing from you.

Yours sincerely,

Dr. Annie Lawson
on behalf of the Rheumatology Medical Staff

Appendix I. Intervention Script for the Family-Centred and Patient-Only Mock Consultation

Intervention script – family-centred

"Hello" (look at both companion and patient).
"What is your name (companion)?"
"How do you know each other? How long have you known each other?"

"Great! Well, as long as you (participant name) are comfortable, I am happy for (companion name) to be involved in this appointment and help you with any decisions. Is this okay with you, or would you rather make your treatment decisions alone?"

"Okay, so (participant name), I have had a look at your recent blood test results and I'm happy with your progress. Because you seem to be stable on biologic treatment, I would like to talk to you about changing to a different brand. Did you *both* have the chance to read the letter about the possibility to change to Amgevita?"

"Perfect. I'll tell you more about Amgevita, and then you can both ask me any questions at the end."

"As you know, you are currently taking Humira, which is a type of biologic medicine. You probably remember, but biologics are drugs that are made from living things like yeasts, bacteria, or animal cells. PHARMAC has decided to fund Amgevita, which is a biosimilar medicine. Biosimilars are based on an existing biologic, but they are not identical. Because biologics are made from living cells, each batch has some slight differences. Biosimilars are also often made by different companies, who use a different manufacturing process."

"Biosimilars work the same way and on the same biologic target as your current drug. They also have the same strength and dose as the biologic. There is no additional cost to you or your family."

"I know (companion name) often helps with transport and administration, so you'll be pleased to know that the biosimilar is administered in a similar way. The device is a little bit different, but I think with the help from your companion, this will be easy for you to adapt to! We can also organise an appointment with a nurse if you need help. Depending on how smooth the change goes, there may be a couple additional appointments for monitoring straight after you change."

"So, you might be wondering why I'm asking you to consider changing."

"The main reason is that changing to a biosimilar will help to save money for the healthcare system. As you might know the biologic you are taking is an expensive drug that costs about $15-$20,000 per year. Biosimilars like Amgevita are a lot cheaper as they are made after the patent has expired. Because the original drug manufacturer has done all the expensive randomised controlled clinical trials already, biosimilar manufactures do not need to repeat these. Instead, they just need to prove that the biosimilar is as similar as possible to the bio-originator."

"The biggest benefit for you, is that PHARMAC may be able to fund more biologics, which would give you more options in case Humira stops working for you."

“Also, Humira is really expensive, so not every patient who might benefit can access the treatment. But, by saving money, PHARMAC is able to fund the medicine for more people. This might mean that more families and friends (look at companion) can experience the benefits of biologic treatments, and their loved ones might lead a less painful and restrictive life.”

“Biosimilars have been used overseas and have been proven to be safe and effective by Medsafe. Making a biosimilar takes around 7-8 years and includes about 250 tests to prove their quality and strength. Medsafe in Aotearoa/New Zealand has rules about how all drugs are made and all companies selling drugs must follow the same rules to ensure the quality of their ingredients.”

“Based on research, we do not expect you to get any more side effects than what you experience now. But, as with any new drug, it is not possible to be absolutely certain that you will get the same beneficial effects or whether there might be some new side effects.”

“If you do get side effects or Amgevita doesn’t work for you, we can discuss options for changing to a different biologic. We will also monitor you in the same way as when you started with Humira.”

“So, you now have some time to decide whether you would like to change from Humira to Amgevita.”
“Do you have any questions or concerns?” (Address both participant and companion).
“Did you (companion) have any other concerns or questions?”
“Okay, what do you think? Do you two want to have a quick discussion and then let me or the nurse know?”

Intervention script – patient only

“Hello” (look at both companion and patient).
“How are you (participant) doing today?”

“I have had a look at your recent blood test results and I’m happy with your progress. You seem to be stable since starting Humira. Because you seem to be doing well, I would like to talk to you about changing to a different brand. Did you have the chance to read the letter from the clinic about the possibility to change to Amgevita? I’ll tell you more about Amgevita, and then you can ask me any questions you might have at the end.”

“As you know, you are currently taking Humira, which is a type of biologic medicine. You probably remember, but biologics are drugs that are made from living things like yeasts, bacteria, or animal cells. PHARMAC has decided to fund Amgevita, which is a biosimilar medicine. Biosimilars are based on an existing biologic, but they are not identical. Because biologics are made from living cells, each batch has some slight differences. Biosimilars are also often made by different companies, who use a different manufacturing process.”

“Biosimilars work the same way and on the same biologic target as your current drug. They also have the same strength and dose as the biologic, and there is no additional cost to you. The biosimilar will also be given in a similar way as the biologic you are taking. The device is a little bit different, but we can organise an appointment with a nurse if you need help.”

“So, you might be wondering why I’m asking you to consider changing.”

“The main reason is that changing to a biosimilar will help to save money for the healthcare system. As you might know the biologic you are taking is an expensive drug that costs about $15-$20,000 per year. Biosimilars like Amgevita are a lot cheaper as they are made after the patent has expired. Because the original drug manufacturer has done all the expensive randomised controlled clinical trials already, biosimilar manufactures do not need to repeat these. Instead, they just need to prove that the biosimilar is as similar as possible to the bio-originator.”

“The biggest benefit for you, is that PHARMAC may be able to fund more biologics, which would give you more options in case Humira stops working for you. Also, Humira is really expensive, so not every patient who might benefit can access the treatment. But, by saving money, PHARMAC is able to fund the medicine for more people. So, other people could also benefit from your decision to change to Amgevita.”

“Biosimilars have been used overseas and have been proven to be safe and effective by Medsafe. Making a biosimilar takes around 7-8 years and includes about 250 tests to prove their quality and strength. Medsafe in Aotearoa/New Zealand has rules about how all drugs are made and all companies selling drugs must follow the same rules to ensure the quality of their ingredients.”

“Based on research, we do not expect you to get any more side effects than what you experience now. But, as with any new drug, it is not possible to be absolutely certain that you will get the same beneficial effects or whether there might be some new side effects.”

“If you do get side effects or Amgevita doesn’t work for you, we can discuss options for changing to a different biologic. We will also monitor you in the same way as when you started with Humira.”

“So, you now have some time to decide whether you would like to change from Humira to Amgevita. What do you think? Do you have any questions or concerns?” (Address participant only).

Appendix J. Questions and Grading of Information Recall and the Interview Script

1. **What condition did the 'patient' have, and what brand biologic drug were they taking? (2 points)**

Condition: Inflammatory arthritis, arthritis, or rheumatoid arthritis (1 point), similar terms e.g., rheumatic disease (0.5)

Brand name: Humira (or if spelling looks like Humira, e.g., "humera") (1 point)

2. **What is a biosimilar? (1.5 points)**

Similar to biologic (or existing biologic) (0.5 point); made by another company/manufacturer/different place (0.5 point); works same way/same dose/strength (0.5)

3. **Other than cost, what is *one* benefit of changing to the biosimilar? (1 point)**

Save money to healthcare system (1 point); OR fund more biologics/increase options or choice (1 point); OR increase access/more people benefit (1 point)

4. **Why do biosimilars cost less? (1 point)**

Made after patent expiration (0.5 point); no need to repeat RCTs/trials (0.5 point)

5. **How many tests do biosimilars undergo to prove their quality and strength? (1 point)**

250 tests OR approximately 250 tests (1 point)

6. **What happens if the biosimilar does not work as well as the biologic? (1 point)**

Change to a different biologic OR change back to Humira (1 point)

Interview script

Topic	Questions	Follow-up Questions and Prompts
Introduction	Introduce aim of interview. Clarify confidentiality. Remind participants that the interview will be audio-recorded and that there is not one correct answer.	
Previous Experience	What are your experiences of accompanying someone to a consultation?	Who was this person in relation to you? To what extent did the doctor involve you? How did you feel about this?
	Have you ever been accompanied by another adult to a medical appointment?	If yes, what was this experience like? Who was this person in relation to you? To what extent did the doctor involve the companion? If no, why not?
Consultation		
Biosimilars	What was your initial reaction or thoughts about biosimilars? Would you change them? Did the consultation change your initial reaction at all?	Why? Or why not? How? To what extent?
Actions	What did you find helpful or like about the consultation? What did you *not* find helpful or like about the consultation?	Was there anything that the doctor did or did not do to involve you? Did the doctor do anything to exclude you? Can you tell me more? How did you feel when they did/did not do that?
Information	What other information would you want to know about biosimilars? Was any of the information (letter or the explanation in the consultation) particularly helpful or not helpful?	 Can you give me an example? Why was this helpful (or not)?
Improvement	What could the doctor improve on? How could we improve the overall consultation?	What about in terms of their behaviour, body language or verbal language?
Ending	Give a short summary of the main points (feelings toward the consultation and areas for improvement). Ask participants if they want to add anything or clarify/correct the summary. Ask if participants have any other comments or questions. Inform participant that the audio-recorder is being turned off and re-affirm what will happen to the recording and their data next. Thank participants for their time.	