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Assessing the Uptake of Biosimilar Insulin Glargine Among Physicians for the Treatment of Diabetes in South Africa

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Abstract

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by

Euganthri Pillay

Doctoral Study Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Public Health

Walden University

May 2024

Abstract

In South Africa, diabetes is a serious problem where 1 in 9 adults has diabetes, making it the country with the highest diabetes prevalence on the African continent. Even though insulin is an absolute necessity for treating diabetes, it is unaffordable to millions. Biosimilar insulins, however, are innovative medicines that are similar but not exact copies of the originator insulin, making alternative treatment affordable to patients. The problem is that, in South Africa, it is still not known whether patients have access to biosimilar insulin in a country where diabetes is rampant. The diffusion of innovation theory was used to understand the uptake of biosimilar and originator insulin glargine because the theory states that it is often quite difficult to adopt an innovation, even when the innovation brings apparent advantages. This quantitative, correlational study used secondary analysis to investigate the association between the location of a province, the specialization of a physician, and the type of dispensed insulin glargine prescriptions. A multinomial logistic regression showed that the specialization of a physician was associated with the type of dispensed insulin glargine prescriptions in South Africa ($p < .001$). The findings from this study support the need for educational interventions among physicians and policy implementation by policymakers. Implications for positive social change include supporting alternative, cost-effective biosimilar insulin glargine and broadening access to more affordable treatment choices for patients with diabetes. Furthermore, this study could impact public health practice by emphasizing the need for further studies on physicians using a longitudinal study design to understand how their biosimilar prescribing behavior changes over time.

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Dedication

My doctoral study is dedicated to my dad, Sockalingum Pillay; mum, Vasantha Pillay; brother, Manogaren Pillay; husband, Jeethan Rambuggan; and son, Shivaan Rambuggan. Your belief in me inspired me to embark on this doctoral journey, and your ongoing support helped me to see it through to completion successfully. Thank you, my dear family. Lots of love to you all.

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Table of Contents

List of Tables

List of Figures

Section 1: Foundation of the Study and Literature Review

Introduction

In South Africa, the increase in the prevalence of diabetes and the unaffordable price of insulin is a major public health issue causing people to die from this disease (Grundlingh et al., 2022). Insulin is an essential treatment for diabetes as it replaces endogenous insulin when the body can no longer produce or is producing insufficient quantities of it (Ahmad, 2014). Many categories of insulins exist, such as originator insulin and biosimilar insulin, to treat diabetes (Moorkens et al., 2017). These insulin injections are biological medicines made from living cells or tissues (American Diabetes Association, 2020). Originator insulins, which are the first insulins of their kind approved by the country's regulatory agency for use by the population, are very expensive and unaffordable for patients in developing countries (Ahmad, 2014; Knox, 2020; White & Goldman, 2019). However, biosimilar insulins, which are insulins that are similar to the originator in terms of safety, efficacy, and quality, enter the market when the originator insulin comes off patent and can be used as an alternative to expensive originator insulins, as they are more cost-effective, affording patients the opportunity for cheaper alternate treatment and broadening treatment access (Aapro et al., 2018; Aladul et al., 2018; Barcina Lacosta et al., 2022, Blankart & Arndt, 2020; Gani et al., 2018).

Biosimilar insulins, however, are not generic medicines. Generic medicines have an identical active ingredient to the originator medicine, and manufacturing companies can replicate the active ingredient, such as for nonbiological products (i.e., tablets; Gamez-Belmonte et al., 2018). Biosimilars such as insulins, on the other hand, are

manufactured in living organisms such as bacteria and yeast (Gamez-Belmonte et al., 2018). They cannot be exactly replicated, which creates constraints in producing identical copies of the originator medicine (Gamez-Belmonte et al., 2018). Therefore, biosimilar insulins are similar to but not exact copies of the originator medicine.

It is concerning that it is not known whether the South African population has access to alternative biosimilar insulin in a country where 1 in 9 adults are living with diabetes and 96,000 diabetes-related deaths were registered in 2021, making it the country with the highest diabetes prevalence on the African continent (Grundlingh et al., 2022; International Diabetes Federation, 2021). The rationale for conducting this study was to assess the accessibility of alternative and affordable biosimilar insulin glargine for the population in South Africa, a country plagued by diabetes (Grundlingh et al., 2022). Increasing the uptake of alternative and affordable biosimilar insulin glargine will improve the management of diabetes and its complications (Shao et al., 2023). The uptake of biosimilar and originator insulin glargine in South Africa will translate into significant positive social change among public health practitioners and healthcare professionals in improving the utilization of alternative biosimilar insulin in the country. In particular, they may be able to use this study's information to inform policymakers to formulate policies that support the uptake of biosimilar insulins for all populations in the different provinces of South Africa.

Furthermore, healthcare professionals can be supported through educational strategies to better manage patients with diabetes. By taking these actions, public health practitioners and healthcare professionals may be able to improve the overall health of

patients with diabetes, ensuring that insulin is made available to all populations in South Africa at affordable prices, resulting in lower morbidity and mortality at the population level and improving population health and the health of communities in a country where diabetes has become a silent killer (World Health Organization African Region, 2023).

This study assessed the uptake of biosimilar and originator insulin glargine in South Africa. The study investigated the associations between the location of a province, the specialization of a physician, and the uptake of biosimilar and originator insulin glargine, measured by the type of dispensed insulin glargine prescriptions in this setting. The location of a province included the urban and rural locations of the nine South African provinces, while the specialization of a physician included specialists and nonspecialists who were pediatricians, general medical practitioners, family physicians, diabetes specialists, and cardiologists.

In this section, I discuss the problem statement, purpose, research questions, theoretical framework, and nature and significance of the study. Additionally, the literature review related to the key variables and constructs of the study is also presented.

Background

Diabetes is known to be one of the most prevalent noncommunicable diseases globally, with developing countries such as South Africa seeing a substantial increase from 4.5% to 12.7% in 2010 and 2019, respectively (Grundlingh et al., 2022). According to Saeed et al. (2022) and Satheesh et al. (2019), insulin is an absolute necessity to treat diabetes, yet the availability and restricted access to insulin are an issue in several parts of the world due to unaffordable prices being a problem.

In a cross-sectional survey, Gani et al. (2018) found that in four Asian countries, originator insulins were very expensive, resulting in people with diabetes being unable to afford them and denying patients access to lifesaving treatment. Biosimilars, on the other hand, were alternatives that were up to 35% cheaper than the originator medicines, providing an opportunity for the population to save on expensive medication while allowing them expanded access to treatment (Aapro et al., 2018; Barcina Lacosta et al., 2022; Blankart & Arndt, 2020; Gani et al., 2018). However, despite the affordability and growing number of biosimilars approved globally for patients, a cohort study by Lund Hansen et al. (2021) and a longitudinal study by Tachov et al. (2021) found that biosimilar uptake in Nordic countries and Bulgaria was very low. Furthermore, a qualitative study by Moorkens et al. (2020) found that biosimilar uptake was much lower in the eastern parts of Germany compared to the western parts, indicating that biosimilar uptake can vary significantly between regions of the same country. In a cross-sectional study, Aladul et al. (2018) also found that even though biosimilars created affordability and broadened access for many more patients to lifesaving therapy, their adoption by physicians and patients in the United Kingdom was limited due to a lack of knowledge of biosimilars and safety concerns.

Insulin therapy is a vital lifesaving treatment for diabetes (Kurtzhals & Gough, 2021). However, to get good insulin control, patients first need access to insulin treatment, and physicians provide this access. Physicians are the key decision-makers who recommend the type of medicine to be used and decide whether to prescribe the originator or the biosimilar insulin (Birkner & Blankart, 2022). However, a cross-

sectional survey by Krstic et al. (2022) found that the knowledge, attitudes, and utilization of physicians and specialists regarding biosimilars varied in Switzerland, and even though specialists in rheumatology, gastroenterology, and immunoallergology were aware of and confident with the use of biosimilars, general physicians still lacked an understanding of biosimilars in relation to the originator medicine. In a cross-sectional survey, Hu et al. (2022) also found that physicians' and patients' lack of knowledge and negative attitudes and beliefs toward biosimilars had resulted in their low uptake in China.

Although the uptake of biosimilar medicines in diabetes and other therapeutic areas is well known and documented in other parts of the world, mainly through cross-sectional studies and systematic literature reviews, it is not known whether the South African population has access to alternative biosimilar insulin treatment in a country plagued by diabetes (Chong et al., 2022; Cobilinschi et al., 2019; Dadkhahfar et al., 2021; El Zorkany et al., 2018; Frantzen et al., 2019; Halimi et al., 2020; Khoo et al., 2022; Mysler et al., 2021; Richter et al., 2023; Yossef et al., 2022).

The gap in knowledge that this study addressed was that no research had been conducted to assess the uptake of the first analog biosimilar insulin glargine for diabetes in this setting. This study's uniqueness lies in the fact that such a study, highlighting the impact of the dispensed prescription activity on the varying uptake of biosimilar and originator insulin glargine, had not yet been performed in the South African setting. Therefore, this study was needed to identify the extent to which the first analog biosimilar insulin, insulin glargine, which was approved in South Africa in 2016, is being

used to alleviate diabetes and its complications in its population. This was the first study to assess the uptake of biosimilar and originator insulin glargine among physicians in South Africa in key areas surrounding biosimilars.

Problem Statement

Although researchers have investigated the uptake of biosimilar medicines in diabetes and other therapeutic areas in other parts of the world, the issue of biosimilar insulin alternatives for diabetes treatment has not been explored in South Africa, where diabetes is rampant. The problem is that it is not known whether the population in South Africa has access to alternative biosimilar insulin for the treatment of diabetes, in a country where diabetes was the leading cause of death in females in 2016 and the second leading cause of death in 2017 (Grundlingh et al., 2022). According to Saeed et al. (2022), the unpredictable use of biosimilar insulin is limiting the accessibility of affordable lifesaving medicines for the population, which will result in the loss of lives of those living in poor, developing countries, such as South Africa. It is concerning that it is not known whether the South African population has access to alternative biosimilar insulin in a country where 1 in 9 adults are living with diabetes and 96,000 diabetes-related deaths were registered in 2021, making it the country with the highest diabetes prevalence in the African continent (Grundlingh et al., 2022; International Diabetes Federation, 2021). Therefore, this study built upon previous research findings by expanding biosimilar knowledge to include South Africa's population regarding the uptake of alternative biosimilar insulin glargine in diabetes treatment among different specializations of a physician and across the different provinces.

Purpose of Study

The purpose of this quantitative study was to assess the uptake of biosimilar and originator insulin glargine in South Africa by examining whether there was an association between the location of a province, the specialization of a physician, and the type of insulin glargine dispensed prescriptions. Uptake in this study was broken down into the type of pharmacy-dispensed prescriptions of insulin glargine so that it could be used to determine the utilization pattern among different physician specializations, especially when different presentations of the same medicine were available. The independent variables included (a) the location of a province (urban, rural), and (b) the specialization of a physician (diabetes specialist, general medical practitioner, pediatrician, cardiologist, or family physician). The dependent variable was the type of dispensed insulin glargine prescription (originator, biosimilar, both) for the full-year period of 2018. Since biosimilar insulin glargine was registered and launched in the South African market in 2016, by 2018, the product would have been well-established and would have started penetrating the market.

The main reason for conducting this quantitative study was to assess whether the South African population had access to alternative biosimilar insulin glargine. Biosimilar insulin glargine is a long-acting insulin analog approved for use in adults and children with diabetes, where insulin treatment is required (Lilly, 2022). It became available in South Africa in 2016 after losing its patency in 2014 (IQVIA, 2020; Tucker, 2015). Furthermore, because the decision to prescribe an originator or biosimilar is at the

discretion of the physician, it is important to determine whether physicians will choose to prescribe an originator or biosimilar when both options are available.

Findings from this study may result in collaboration and communication initiatives among universities, the Department of Education, the Department of Health, public health practitioners, and pharmaceutical companies and may help inform policymakers in implementing policies in support of the uptake of biosimilar insulin treatment for all populations in South Africa. It may also result in the formulation of educational strategies to support healthcare professionals in better-managing patients with diabetes.

Research Questions and Hypotheses

The research questions (RQs) and hypotheses were as follows:

Research Question 1: Is there an association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa?

*Ho*1 – There is no association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa.

*Ha*1 – There is an association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa.

Research Question 2: Is there an association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa?

*Ho*2 – There is no association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa.

*Ha*2 – There is an association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa.

The independent variable for Research Question 1 was the location of a province (i.e., urban or rural). The level of measurement for this variable was nominal. The dependent variable was the type of dispensed insulin glargine prescriptions (i.e., biosimilar, originator, or both) for the full-year period of 2018, and the level of measurement was nominal.

The independent variable for Research Question 2 was the specialization of a physician (i.e., family physicians, general medical practitioners, diabetes specialists, pediatricians, and cardiologists). The level of measurement for this variable was nominal. The dependent variable was the type of dispensed insulin glargine prescription (i.e., biosimilar, originator, or both) for the full-year period of 2018, and the level of measurement was nominal.

Theoretical Foundation of Study

The theoretical foundation of this study was the diffusion of innovation theory developed by E. M. Rogers in 1962. The major hypothesis of the diffusion of innovation theory is how new innovations spread throughout societies from the time they are introduced until they become widely adopted (Rogers, 1962). This theory also seeks to explain the reasons why new innovations are adopted and why it takes long periods to adopt them (Rogers, 1962).

Due to the introduction of an innovative biological medicine called biosimilars, researchers have used the diffusion of innovation theory to understand the acceptance and

adoption of this new treatment (Rogers, 1962). Hayden (2019) and Khan et al. (2020) used the constructs of this theory to explain the adoption of the new treatment of biosimilars by physicians. The constructs of this theory include innovation, relative advantage, trialability, compatibility, confirmation, communication channel, complexity, social system, and knowledge (Hayden, 2019). According to the construct of innovation, biosimilars are a new type of treatment used to treat life-threatening diseases (Khan et al., 2020). The relative advantage that biosimilars have over originator medicines is that they are more cost-effective, making them affordable and expanding treatment access (Khan et al., 2020). However, the trialability of biosimilars without risk is limited because physicians are concerned with biosimilars not being the same as the originator in terms of safety, efficacy, and quality, which makes them reluctant to change patients from an already effective originator medicine to a biosimilar medicine (Khan et al., 2020). Also, the advantages of biosimilars over originators are not aligned with physicians' beliefs and values, showing an incompatibility between the innovation and the adopters' values (Khan et al., 2020). Additionally, conflicting views over biosimilar safety continue to exist among physicians (Khan et al., 2020). Such a lack of confirmation creates uncertainty among physicians in adopting the use of biosimilars (Khan et al., 2020). According to Khan et al., there are several communication channels used to share biosimilar information, such as key opinion leaders, healthcare professionals, and the media. However, biosimilar use also requires a mindset shift among physicians (Khan et al., 2020). The current literature shows gaps in physician knowledge regarding the use of biosimilars (Khan et al., 2020). The social system surrounding the uptake of biosimilars

also affects multiple entities such as patients, physicians, pharmacists, and healthcare organizations (Khan et al., 2020).

The connection between the diffusion of innovation theory and this study is that it shows how this theory can be used to understand physicians' adoption of innovative medicines (Rogers, 1962). Because this theory states that it is often quite difficult to accept an innovation, even when the innovation brings apparent advantages (Rogers, 1962), it led to this investigation of evaluating and understanding the acceptance and uptake of innovative biosimilar insulin glargine for the treatment of diabetes in South Africa. This theory relates to the current study, which addressed introducing an innovative treatment of biosimilar insulin glargine into the South African market and evaluating its adoption or rejection into the market over time. The research questions built upon this theory by evaluating the type of dispensed insulin glargine prescriptions and determining whether physicians accept biosimilar insulins and are early adopters or laggards when it comes to the uptake of biosimilar insulin glargine (Rogers, 1962).

The application of theories to public health issues is important because they explore ways of understanding a health problem, assessing health behavior, and creating new interventions (Alderson, 1998). They can be used in the planning of research and in identifying the most appropriate target audiences (Alderson, 1998). Theories shape the way researchers collect and interpret data (Alderson, 1998). They also influence how data are analyzed and used (Alderson, 1998). In this way, theory helps in understanding the reasons why people engage in certain health behaviors, assists researchers in determining what to know before developing health interventions, and suggests how

to develop strategies to reach target audiences with a meaningful impact (Alderson, 1998).

However, the limitations of theories on public health issues are that they are designed to be simple explanations even though in reality the issues may be much more complex (Viera, 2023). Furthermore, theories may limit a researcher's view, causing them to miss out on certain concepts that are not defined by theories (Viera, 2023). Common types of limitations of theories include restricting the scope of a study and limiting the quantity, diversity, and representativeness of the data (Viera, 2023).

Additionally, the constructs of the social system, communication channel, and knowledge from the diffusion of innovation theory were key as part of my community health intervention plan. My community health intervention plan uses a multisectoral approach and will be diffused through the social system of primary healthcare clinics, the local Department of Health, universities, pharmaceutical companies, the Department of Education, and policymakers (Frieden, 2015). The social system requires building collaborative partnerships among many entities working in this area, namely, physicians, patients, nurses, pharmacists, facility managers at primary healthcare clinics, lecturers from universities, clinical researchers from pharmaceutical companies, and educators from the Department of Health (Trickett et al., 2011). Communication between pharmaceutical companies, universities, and the Department of Education will result in robust educational interventions on biosimilar medicines, empowering physicians, patients, and other healthcare professionals with the knowledge they require to make informed decisions about treatment options (Trickett et al., 2011). The Department of

Health in collaboration with policymakers can form partnerships to evaluate the advantages of cost-effective alternative biosimilar insulin treatment from an economic standpoint, thereby formulating policies that support the uptake of biosimilar insulins and broadening access to alternative affordable treatment opportunities for patients (Marmot, 2005; Galea et al., 2013).

Nature of Study

Using the nationally representative pharmacy-dispensed prescription data for insulin glargine for the full-year period of 2018, a quantitative, secondary data analysis with a nonexperimental, correlational design was employed to assess the uptake of biosimilar and originator insulin glargine in South Africa (Babbie et al., 2017). The rationale for choosing a quantitative, correlational study design was that this design could test for expected relationships between and among variables (Gerstman, 2015). Additionally, an experimental design was not adopted to look at the relationship between the prescribing behavior of physicians from different specializations across the provinces of South Africa because it would have been difficult and unethical to randomly assign physicians to prescribe biosimilar insulins over originator insulins.

The study population consisted of physicians from different specializations across the nine provinces of South Africa treating patients with diabetes (Reference Company, 2022a). Therefore, physicians' specializations included specialists and nonspecialists who predominantly prescribed insulin glargine, namely, family physicians, general medical practitioners, diabetes specialists, pediatricians, and cardiologists (Reference Company, 2022a).

The nationally dispensed prescription data for the full-year period of 2018 was collected from a reference medical company in South Africa that routinely collects prescription information from pharmacy vendors (Reference Company, 2022a). Data were identified through the software used at the pharmacy level, where all prescriptions collected at retail pharmacies were captured and dispensed (Reference Company, 2022a). The prescription-level data that were entered into the software at pharmacies are routinely collected by the pharmacy vendors and sent to the reference medical company in South Africa to create the dispensed prescription datasets (Reference Company, 2022a). The national pharmacy-dispensed dataset for 2018 for insulin glargine was obtained privately, and permission was obtained from the reference medical company to retrieve this information because these databases were not in the public domain. Furthermore, the study data were analyzed using SPSS V. 28.0, as this statistical program allowed for descriptive and inferential analysis to answer the study's research questions.

The variables that were assessed were (a) the location of a province (urban, rural), (b) the specialization of a physician (diabetes specialist, general medical practitioner, pediatrician, cardiologist, or family physician), and (c) the type of dispensed insulin glargine prescriptions (biosimilar, originator, or both) for the full-year period of 2018. Table 1 includes definitions of the key variables and their levels of measurement in the study. A Pearson chi-square test and multinomial logistic regression were used to examine the effects of the variables to determine which variables had statistical significance on the type of dispensed insulin glargine prescriptions.

Table 1

Definition and Levels of Measurement of Key Variables

Variable	Definition	Level of measurement
Insulin Type	Type of dispensed insulin glargine prescriptions	Nominal
Physician Specialization	Specialization of a physician	Nominal
Province	Location of a province	Nominal

Literature Search Strategy

The literature search strategy involved an extensive search of recent literature over the last 5 years, from the year 2018 to 2023, to ensure that current and relevant information was being used. This literature review consisted of published peer-reviewed studies available in English only. The databases that were searched included Thoreau, Science Direct, Sage Journals, MEDLINE/PubMed, CINAHL, APA PsycInfo, SocIndex, Academic Search, Social Sciences Citation Index, Education Source, ERIC, IEEE Xplore, Emerald Insight, and Directory of Open Access Journals. The keywords that were used to search the databases included *diabetes, risk factors, chronic disease, biosimilars, insulin glargine, insulin use, knowledge, attitude, beliefs, behavior, patient access, affordability, utilization, urban areas, rural areas, healthcare providers,* and *South Africa.*

Literature Review Based on Key Variables/Key Concepts

Diabetes

Diabetes is known to be a very common and prevalent noncommunicable disease globally (Godman et al., 2021a; Saeed et al., 2022, Swain et al., 2022). In a systematic

review of health authority databases, Godman et al. (2021a) found that Europe has approximately 59 million people with diabetes, a figure that is expected to rise to 68 million by 2045. Additionally, a cross-sectional study by Saeed et al. (2022) found that approximately 629 million people globally will have diabetes by 2045 and diabetes-related deaths will almost double by 2025. Satheesh et al. (2019) also conducted a mixed-methods study and found that in developing countries such as India and Pakistan, diabetes ranked as one of the top 10 most prevalent diseases. South Africa has also seen a drastic rise in diabetes prevalence, where 1 in every 9 adults has diabetes, making South Africa the country with the highest diabetes prevalence in the African continent (Grundlingh et al., 2022; International Diabetes Federation, 2021). In 2021, South Africa registered approximately 96,000 deaths due to diabetes (International Diabetes Federation, 2021). Furthermore, systematic reviews conducted by Achoki et al. (2022) and a cross-sectional study by Mutyambizi et al. (2019) found that noncommunicable diseases were envisioned to be the main cause of death in Africa by the year 2030.

Risk Factors for Diabetes in South Africa

The risk factors for diabetes have significantly increased in South Africa over the past years. A cross-sectional study by Sidahmed et al. (2023) found that rapid urbanization has been accompanied by an increase in the consumption of energy-dense foods and a lack of physical activity. Furthermore, a systematic review of cross-sectional studies by Pheiffer et al. (2021) stated that these factors have contributed to a rapid increase in obesity, with 69% of females and 39% of males in South Africa being overweight or obese. Obesity is a major precursor to diabetes and accounts for

approximately 87% of diabetes cases in South Africa (Pheiffer et al., 2021). In African countries, being overweight is seen as a sign of high socioeconomic status and wealth (Pheiffer et al., 2021). Furthermore, physical activity is associated with masculinity instead of a healthy lifestyle in many African cultures and is not preferable for females (Pheiffer et al., 2021).

Categories of Insulin

Today's insulin market contains different categories of insulin (Flaherty, 2022). These categories include originator insulins and biosimilar insulins (Flaherty, 2022).

Originator Insulins

Systematic literature reviews by White and Goldman (2019) stated that originator insulins are the first insulin product of their kind that a country's national regulatory agency approves for use by the country's population. According to Chaplin (2021), originator medicines are patented for approximately 20 years so that they can be marketed exclusively and are protected from competition by other companies with the same molecule. Because they are the first product in the market, prices can be negotiated with the state, making originator insulins very expensive and unaffordable (Chaplin, 2021). Originator insulins are also used as reference products during the licensing process of biosimilar insulins. For example, a biosimilar human insulin will use the respective originator human insulin as its reference medicine when applying for registration of the product to the country's national regulatory agency. Similarly, a biosimilar analog insulin will use the respective originator analog insulin as its reference medicine when applying for registration.

Biosimilar Insulins

Biosimilar insulins are insulins that are similar to but not exact copies of the originator insulin in terms of their safety, efficacy, and equality (Chaplin, 2021; Gani et al., 2018; Mansell et al., 2019). According to a cross-sectional qualitative study by Aladul et al. (2018), biosimilar insulins can be used as an alternative to expensive originator insulins, supporting access to affordable therapy. When the patent of the originator insulin expires, other manufacturers can produce similar insulins, called biosimilars, allowing for affordable, lower-priced insulins to enter the market and broaden treatment access for patients (Marotto et al., 2019; Satheesh et al., 2019; Tachkov et al., 2021; Tinsley et al., 2018; Yang et al., 2021). However, biosimilar insulins differ slightly in the manufacturing process from their originator medicine, resulting in variations across batches that are manufactured (Chaplin, 2021). Because they are produced using a different manufacturing process from their originator, this could result in more adverse effects, causing severe immunological reactions (Chaplin, 2021).

A retrospective, quantitative, longitudinal study by Tachov et al. (2021) found that despite these safety concerns, the first biosimilar insulin, insulin glargine, became available in the European Union and most European countries in 2015. In 2016, insulin glargine became available in South Africa (IQVIA, 2020). Additionally, a systematic review conducted by White and Goldman (2019) stated that the hope is that the availability of innovative biosimilar insulins will be seen as an opportunity to make insulin more affordable and expand treatment access to patients.

Types of Insulin

Insulins have evolved over the years (Griffith, 2021). Traditionally, insulin came from animals (Griffith, 2021). However, in recent years, most people have received insulin that is engineered in the laboratory. The two types of laboratory-made insulins are human insulins and insulin analogs (Griffith, 2021).

Animal Insulin

Animal insulin was made from the pancreas of cows and pigs. Up until the 1980s, people with diabetes received animal insulin (Griffith, 2021). However, these insulins contained many impurities leading to allergic reactions (Bolli et al., 2022).

Human Insulin

Human insulin is a type of insulin manufactured in laboratories to mimic the insulin made by the body (Griffith, 2021). Initially, human insulin was extracted from the pancreas of human cadavers, and this insulin had less predictability over blood sugar levels (Hilgenfeld et al., 2014). However, due to the limited availability of insulin, a synthetic version of human insulin began being produced in the 1980s and was preferred over animal insulin (Flaherty, 2022; Hilgenfeld et al., 2014).

Analog Insulin

Analog insulins were made using the same process as human insulin but were genetically altered to act differently in the body so that they could be absorbed more quickly and work faster in lowering blood glucose levels (Flaherty, 2022; Griffith, 2021). As such, they have been replacing many human insulin prescriptions since the 2000s (Flaherty, 2022).

Groups of Insulin

There are three main groups of insulins, namely fast-acting, intermediate-acting, and long-acting insulin (Centers for Disease Control and Prevention [CDC], 2022). These insulins are classified by their onset of action and duration in the body (CDC, 2022).

Fast-Acting Insulin

Fast-acting insulin is absorbed rapidly into the bloodstream. It acts within 30 minutes, has a duration of 3 to 6 hours, and is taken half an hour to 1 hour before a meal (CDC, 2022).

Intermediate-Acting Insulin

Intermediate-acting insulin has a slower absorption into the bloodstream and lasts longer. It acts within 2 to 4 hours, has a duration of 12 to 18 hours, and provides insulin cover for half the day or overnight (CDC, 2022).

Long-Acting Insulin

Long-acting insulin is absorbed slowly into the bloodstream. It acts within 2 hours, lasts up to 24 hours, and provides insulin coverage for the entire day (CDC, 2022).

Cost of Originator Insulins

A mixed methods approach by Godman et al. (2021c) and Satheesh et al. (2019), a survey study design by Miller et al. (2023), and a retrospective review by Iacullo et al. (2018) and Luukkanen et al. (2022) found that the high cost of originator biological medicines is a concern, making originator insulins unaffordable to patients with diabetes in many developed and developing countries. According to Knox (2022), insulin prices are exorbitant, costing patients up to $900 per month. Therefore, patients suffer from

these high prices, resulting in 1 in 4 people with diabetes rationing their insulin, which can lead to devastating consequences of severe complications and death. The highly priced originator biological medicines are threatening healthcare (Godman et al., 2021b). Godman et al. (2021b) stated that the high prices of originator biological medicines have made them unaffordable and inaccessible for patients in lower and middle-income countries, such as South Africa, denying them access to lifesaving treatment and raising concerns about their affordability in developing countries.

Cost of Biosimilar Insulins

Systematic reviews by Blankart and Arndt (2020) and Sarnola et al. (2020) found that since the licensing of biosimilars does not require clinical trials by the national regulatory agency, biosimilars can be brought to the market at more affordable prices for patients than the originator, allowing biosimilar insulins to enter the market at up to 35% cheaper than the originator insulin. When biosimilars were first introduced in the United Kingdom, the per-unit price for biosimilar insulin glargine was £7.06, which offered a 15% saving on the £8.30 originator insulin glargine (Chaplin, 2021). In South Africa, biosimilar insulin glargine also offered 15% savings compared to the originator (Ferreri, 2022). A systematic literature review by Barcina Lacosta et al. (2022) and a longitudinal study by Tachov et al. (2021) found that the price decrease of biosimilars offered much-needed affordability and accessibility to treatment for diabetes patients. Secondary research conducted by Aapro et al. (2018), Gaffney et al. (2019), and Tamer et al. (2019) found that in Europe, the availability of biosimilars over the past 10 years has provided an opportunity to save on expensive medication while being able to improve treatment

access to patients, making affordability the key reason for biosimilar uptake throughout Europe. Even healthcare providers consider affordability the main advantage of biosimilars (Lobo & Rio-Álvarez, 2021). However, in South Africa, it is still not known whether the population has access to alternative and affordable biosimilar insulins. A cross-sectional study by Aladul et al. (2018) and systematic reviews conducted by Godman et al. (2021a), Hayes et al. (2022), and Luukkanen et al. (2022) stated that improving biosimilar use is becoming vital as they can create access to affordable medicines for the population.

Accessibility and Affordability of Insulin

According to Saeed et al. (2022) and Satheesh et al. (2019), insulin treatment is essential in saving the lives of people with diabetes. However, a cross-sectional study by Saeed et al. (2022) found that in seven low- to middle-income countries, the exorbitant price of insulin restricts access to insulin treatment. Because the cost of diabetes treatment is constantly rising, there are major concerns with the affordability of insulin used for the treatment of diabetes (Chaplin, 2021; Godman et al., 2021a; Tachkov et al., 2021). Furthermore, a cross-sectional study by Gani et al. (2018) found that diabetes and its complications were becoming very costly, resulting in $465 billion being spent on diabetes, worldwide, in 2011. Also, the expenditure on insulin tripled per patient from $231.48 in 2002 to $736.09 in 2013. In 2017, systematic reviews of articles and studies by White and Goldman (2019) estimated that healthcare expenditures for insulin alone were almost $15 billion for people suffering from diabetes.

Furthermore, in systematic reviews of health authority databases, Godman et al. (2021a) found that almost one-fifth of Europe's health spend is paid out of pocket by patients, affecting those with low income, and leading to catastrophic consequences for patients. Similarly, mixed-methods studies by Grundlingh et al. (2022) and Satheesh et al. (2019) found that in India and South Africa, the public health systems are underfunded, offering limited healthcare coverage to most people, thereby driving patients with diabetes to the private sector to receive healthcare by paying out of pocket. A survey design study by Inotai et al. (2018) also stated that there was a significant unmet need for more affordable biological treatments. Therefore, overcoming limitations of accessibility and affordability of insulins is vital for developing countries; otherwise, the cost of inaccessibility of insulin will be paid for by the loss of the lives of those living in poorer countries, such as South Africa (Saeed et al., 2022).

Policies

According to de Assis et al. (2018), Kabir et al. (2018), and Nabhan et al. (2018), there is a need for more updated regulations for biosimilars to offer patients more options for treatment. Without active policies for use, the promise of biosimilars is apt to fall short (de Mora, 2019). Daniel et al. (2020) conducted systematic reviews of studies, reports, and surveys and found that policies need to be implemented to help cheaper alternative medicines come to market faster. A cross-sectional study by Barbier et al. (2021) and a longitudinal study by Birkner and Blankart (2022) found that policies were facilitators for enhancing the uptake of biosimilars. Since the affordability of biosimilars alone may not be sufficient to increase the uptake of biosimilars, educational initiatives

need to be implemented in parallel to drive greater biosimilar uptake (Gaffney et al., 2019; Okoro, 2021). In a quasi-experimental study, Saborido-Cansino et al. (2019) found that intervention strategies aimed at training and information were found to influence the uptake of biosimilar medicines. Furthermore, an experimental study by Ismailov et al. (2019) found that when physicians and patients were provided with educational initiatives, they demonstrated a good level of knowledge of biosimilars. Therefore, because physician and patient acceptance of biosimilars remain a significant barrier to their uptake, educational strategies to improve their understanding of biosimilars can enhance their acceptance of biosimilars and result in a smooth adoption of these medicines (Garg et al., 2021; Gasteiger et al., 2022; Haghnejad et al., 2020; Janjigian et al., 2018; Oskouei et al., 2021; Vandenplas et al., 2021a).

Patients' Knowledge, Attitudes, and Perceptions Toward Biosimilars

A patient's acceptance and adoption of biosimilars rely on several factors, such as their knowledge, attitudes, beliefs, and concerns about the medicine as well as support from their physicians because patients depend on their physicians to prescribe the best medicine for them (Khoo et al., 2023, Scherlinger et al. 2019). However, cross-sectional studies by Frantzen et al. (2019), Khoo et al. (2022), and Yossef et al. (2022); an experimental study by Gall et al. (2022); a survey design study by Garcia et al. (2021); and a qualitative study by Varma et al. (2022) found that patients lacked knowledge about biosimilars, had never heard about them, had misconceptions about them, or struggled to understand them. In a survey design study, Gibofsky et al. (2022) found that even though patients understood the affordability of biosimilars, they lacked confidence

that the biosimilar would treat their disease as effectively as the originator medicine and felt that it would cause more side effects. Patients' perceptions of biosimilars being unsafe have led to their concerns about being changed from an originator to a biosimilar (Gasteiger et al., 2021). According to Hu et al. (2022), such a lack of patient knowledge about biosimilars has led to the inadequate uptake of these medicines. A survey design study by Macaluso et al. (2020) found that some patients lacked confidence in biosimilars, while a cross-sectional study by Dadkhahfar et al. (2021) found that other patients felt very favorable toward them. Additionally, a semi-qualitative study by Cohen et al. (2020), a systematic literature review by Vandenplas et al. (2020), a survey study by Vandenplas et al. (2022), and an experimental study by Young et al. (2022) found that some patients felt comfortable and were willing to switch to biosimilars provided their physician sufficiently supported them, and if both patient and physician agreed upon it. Furthermore, survey design studies by Azevedo et al. (2018) and Quinlivan et al. (2022) found that even though some patients had limited knowledge about biosimilars, they still had positive attitudes towards them and were receptive to their use.

Physicians' Knowledge, Attitudes, and Perceptions Toward Biosimilars

Several survey design studies by Belokoneva (2019), Karateev and Gibofsky et al. (2022), and Robinson et al. (2018), found that while physicians recognized the benefits of biosimilars due to their affordability and broadening access to alternative treatments, physicians lacked an understanding of biosimilars in relation to its reference biologic, safety, efficacy, and switching. Furthermore, a survey study by Demirkan et al. (2022) and an observational study by van Adrichem et al. (2022) found that some physician's

knowledge and beliefs were favorable toward the switching from originator to biosimilar and deemed it successful in many patients, while, on the other hand, pediatricians were hesitant to perform the switch in children because of concerns with biosimilar safety and efficacy. According to survey design studies by Feldman & Reilly (2020), Krstic et al. (2022), and Park et al. (2019), even though physicians had increased their familiarity with biosimilars, they were not comfortable using them for patients already stable on the originator or even in general. Furthermore, a cross-sectional study by Omair et al. (2022) and a survey by Resende et al. (2021) found that physicians had negative opinions toward switching which posed a barrier to biosimilar uptake. Also, many physicians had a low understanding of biosimilars and required more education about them (Aronson et al., 2018; Barbier et al. 2020a; Barbier et al., 2021; Cook et al., 2019; Gürler et al., 2022; Hadoussa et al., 2020; Poon et al., 2021). In a survey study design, Kolbe et al. (2021) found that a low level of physician knowledge of biosimilars has led to hesitancy to utilize them. On the other hand, an experimental study by Ismailov et al. (2018) found that some clinicians had a good understanding of biosimilars and showed an interest in learning more. A systematic review by Sarnola et al. (2020) also found that physicians varied significantly in their knowledge and attitudes toward biosimilar medicines and even though some physicians looked at them positively, their utilization was still low. Another survey study by Gibofsky and McCabe (2021) found that it is important to understand the level of physicians' knowledge of biosimilars, as it is anticipated that they will require more education about biosimilars before they are comfortable using them for their patients.

Safety, Quality, and Efficacy of Biosimilars

Even though many biosimilars are being approved for patient use, safety, and efficacy concerns were identified as barriers to their uptake (Barbier et al., 2020b; Fahmi et al., 2022; Frank et al., 2018; Khan et al., 2020; Liu et al., 2021; Schachne et al., 2021). A qualitative descriptive study by Chew et al. (2022), a cross-sectional study by Cobilinschi et al. (2019), and systematic literature reviews by El Zorkany et al. (2018) and Halimi et al. (2020) found that there were perceptions among physicians and patients that biosimilars lacked safety and efficacy compared to the originator and were afraid to switch to a biosimilar. On the other hand, a pragmatic study by Boone et al. (2018), observational studies by Kapoor et al. (2019) and Piezzo et al. (2021), a single-center study by Mohan et al. (2023), and experimental studies by Aravind et al. (2022), Perry et al. (2019), and Shah et al. (2021) found that biosimilars demonstrated similar safety and efficacy as the originator. Additionally, an experimental study by Graham-Clarke et al. (2020), a post-marketing surveillance study by Kurki et al. (2021), and a cross-sectional study by Richter et al. (2023) found that even though biosimilar medicines had a well-documented safety profile, many healthcare providers and patients were still doubtful about their safety and most physicians and patients still preferred to use the originator.

Furthermore, a cross-sectional study by Chong et al. (2022), a cohort study by Herndon et al. (2021), and a systematic literature review by Mysler et al. (2021) found that even specialists who were satisfied with biosimilar safety and efficacy still preferred to use the originator medicine instead of the biosimilar. According to a multinational survey conducted by Park et al. (2020), even though physicians are currently reluctant to

use biosimilars, in the future, many biosimilars due to their safety, and efficacy being similar to the originator, will be used to treat many chronic conditions.

Biosimilar Uptake

In a longitudinal study, Tachkov et al. (2021) found that biosimilar insulin usage was very low compared to its originator insulin, globally, with only 7.4% of patients being treated with biosimilar insulin in 2018. Similarly, in the United Kingdom, there was a reluctance among physicians and patients to embrace this innovation (Chaplin, 2021). Also, a cross-sectional study by Mansell et al. (2019) found that Canada was not the only country with a slow uptake of biosimilar**s**. An experimental study by Helfgott et al. (2020) found that in the United States, originators were preferred to be used early on as the first choice of treatment in rheumatoid arthritis rather than biosimilars.

However, a comparative analysis by Labdi et al. (2023) found that there was an increase in the use of the biosimilar over time. Also, a cross-sectional study by Gani et al. (2018), a cohort study by Lund Hansen et al. (2021), and a retrospective study by Socal et al. (2020) found that while Sweden, Germany, Asia, the United States, and Nordic countries observed a faster uptake of biosimilars**,** Italy, France, Ireland, and the United Kingdom lagged behind. Furthermore, a systematic literature review performed by Moorkens et al. (2020) and a mixed-method study by Vandenplas et al. (2021b) found that the Belgian and German markets also had low biosimilar uptake, suggesting a malfunctioning market for biosimilar insulin. Some European countries and even the United States had not even launched biosimilar insulin glargine despite its affordability, limiting its overall utilization and creating concerns about the availability and use

of biosimilar insulin glargine amongst the population (Godman et al., 2021a; Zhai et al.,2019). Furthermore, physicians' understanding, knowledge, attitudes, and beliefs of biosimilar medicines are important factors in their uptake because patients rely on their physicians for support when being initiated or switched to biosimilar treatment (Karateev et al., 2019). In a sociological study, Scherlinger et al. (2019) found that biosimilar usage by patients was much higher when physicians had good opinions about them. However, a retrospective patient chart study by Eric (2020), a quantitative study by Finch et al. (2019), and a systematic literature review by Hair et al. (2022) found that physician's and patient's comfort with originators posed a problem with using biosimilars in that, even though some patients were using biosimilars, the majority of patients were still using the originator. According to Okoro et al. (2021), biosimilar acceptance and adoption will improve as physicians and patients increase their knowledge of biosimilars and the role they play in patient care.

Rationale for Selection of Variables

Based on the above-mentioned literature, the rationale for choosing the study variables namely: (a) the location of a province (urban, rural), (b) the specialization of a physician (diabetes specialist, general medical practitioner, pediatrician, cardiologist, or family physician), and (c) the type of dispensed insulin glargine prescriptions, i.e., (biosimilar, originator, or both) for the full year period of 2018 were as follows. Biosimilar insulin glargine was registered and launched in the South African market in 2016. Therefore, by the year 2018, the product would have been well-established in the market, and physicians and patients would have become aware of it and may have started

using it. Additionally, biosimilar insulin glargine was the first modern biosimilar insulin to enter the South African market in 2016 (IQVIA, 2020). The location of provinces was selected because it was found that different regions within the same country, as was the case in Germany had varied biosimilar uptake and urban and rural locations can also impact biosimilar uptake as they have different socioeconomic statuses (Moorkens et al., 2020). Finally, a physician's specialization was chosen because different types of physicians were found to have different knowledge and understanding of biosimilar medicines (Krstic et al., 2022).

Definitions

The independent variables were the location of a province and the specialization of a physician in South Africa. The dependent variable was the type of dispensed insulin glargine prescriptions, i.e., biosimilar, originator, or both, for the year 2018. The province is a categorical variable that is assessed by whether a province is urban or rural. The specialization of a physician is categorized as a categorical variable: diabetes specialist, general medical practitioner, pediatrician, cardiologist, or family physician. The type of dispensed insulin glargine prescriptions for 2018 is a categorical variable with three groups categorized as an originator, biosimilar, or both. The level of measurement for all the variables in the study is nominal. Table 2 consists of the operational definitions of the variables that will be assessed in this research including the variable types, coding, and level of measurements.

Table 2

Operational Definitions of Key Variables

Variable	Variable label	Data code	Level of measurement
Insulin Type	Type of dispensed insulin glargine prescriptions	Biosimilar = 1 Both = 2 Originator = 3	Nominal
Physician Specialization	Specialization of a physician	Cardiologist = 1 Diabetes Specialist = 2 Family Physician = 3 General Medical Practitioner = 4 Pediatrician = 5	Nominal
Province	Location of a province	Rural = 1 Urban = 2	Nominal

Dispensed prescriptions: The dispensed prescriptions are defined as retail pharmacy-dispensed prescriptions for insulins (Reference Company, 2022a). The dispensed insulins consist of the type of dispensed insulin glargine prescriptions, i.e., biosimilar, originator, or both for the full year period of 2018.

Biologics: A biologic medicine is a medicine derived from living organisms, such as living cells and tissues (American Diabetes Association, 2020; South African Health Products Regulatory Authority, 2014). They are large molecules made in plant or animal cells using biotechnology (Flaherty, 2022). Originator and biosimilar insulin glargine are both biologic medicines.

Originator: An originator is defined as an innovator product licensed by a national regulatory agency based on a full registration dossier (SAHPRA, 2014). The originator medicine consists of insulin glargine.

Biosimilar: A biological medicine that is similar, but not an exact copy of the originator medicine regarding its quality, safety, and efficacy (SAHPRA, 2014). The biosimilar consists of biosimilar insulin glargine.

Reference medicine: The reference medicine is the originator medicine which is used as the comparator for the biosimilar medicine to prove similar safety, efficacy, and quality to the originator (SAHPRA, 2014). The reference medicine is the originator insulin glargine.

Urban: Urban is defined as an ordinary town or city area within proclaimed formal structures (adapted from the Department of Statistics South Africa website, 2001). The urban provinces of South Africa consist of the Free State, Gauteng, Northern Cape, and Western Cape.

Rural: Rural is defined as a village or settlement without a local authority, with formal and semiformal dwellings (adapted from the Department of Statistics South Africa website, 2001). The rural provinces of South Africa consist of the Eastern Cape, KwaZulu Natal, Limpopo, Mpumalanga, and North-West.

Specialist: A medical practitioner registered as a specialist in a speciality or subspeciality (adapted from the Health Professionals Council of South Africa website, 2001). The specialists consist of cardiologists, pediatricians, and diabetes specialists.

Nonspecialist: A physician broadly trained in medicine, who is the primary contact for patients (adapted from the Intercare website, 2019). The nonspecialists consist of family physicians and general medical practitioners.

Assumptions

The national pharmacy-dispensed prescription dataset for 2018 includes the type of dispensed insulin glargine prescriptions, the specialization of a physician, and the location of a province. This study assumed the following:

- Dispensed prescription data accurately documented the type of insulin glargine dispensed at retail pharmacies, i.e., biosimilar or originator.
- Specialization of a physician was clearly identified in all dispensed prescription cases.
- Data was entered efficiently and effectively with minimal errors.

This assumption needed to be stated because it is not possible to determine whether all pharmacists entered the correct prescription data into the system. Taking these assumptions into consideration enhances the study's validity.

Scope and Delimitations

Due to insufficient knowledge regarding the uptake of biosimilar insulins in South Africa, this study focused explicitly on assessing the uptake of biosimilar and originator insulin glargine among physicians in the urban and rural provinces of this country. The study population consisted of physicians from different specializations across South Africa treating patients with diabetes (Reference Company, 2022a). The physician's specializations included specialists and nonspecialists, namely, family physicians, general medical practitioners, diabetes specialists, pediatricians, and cardiologists who were predominantly prescribers of insulin, and the dataset excluded physicians from specializations that were not primary prescribers of insulin.

The diffusion of innovation theory which is the theoretical framework guiding this study has also been used in previous studies to investigate the uptake of biosimilar medicines (Khan et al., 2020). The health belief model is also related to the area of this study and suggests that a person or in the case of this study, a physician will perform a health-related action, such as the prescribing of alternative medicines, if the physician feels that a side-effect can be avoided, or perceives that the benefits of partaking in the new behavior of adopting biosimilar medicines into his or her practice will improve a patient's medical condition or related symptoms (Albashtawy et al., 2016). However, the health belief model focuses more on the knowledge, beliefs, and attitudes of individuals and does not consider economic factors that promote the recommended action such as prescribing cheaper alternative insulins to expand treatment access, as is the case in this study (Hayden, 2019). Therefore, the health belief model was not investigated.

Based on the scope of this study, the delimitations of this study include:

- This study was delimited to a quantitative study.
- Only secondary data was used.
- The study was delimited to the variables present in the dataset selected for this study.
- The study was delimited to the information collected by the data collectors.
- The study was delimited by the time of dispensation of the insulin glargine prescriptions from 01/01/2018 to 31/12/2018.

Furthermore, to be able to generalize findings across people and settings, the results should not be limited to a single population. Data from the nationally

representative pharmacy-dispensed prescription dataset, 2018, for insulin glargine, was population-level data generalizable to the South African population only and therefore restricts the findings to the South African population.

Limitations

A limitation of this study was the use of secondary data which was not specifically collected for this study. Therefore, some socio-demographic variables that could have added value to the study, such as physicians' age and gender, were not in the dataset. When interpreting the analysis of pharmacy dispensation data, it was also important to consider that multiple physicians with different levels of expertise are contributing to the prescribing data. Therefore, while pharmacy-dispensed prescription data may include information on the specialization of a physician, it did not contain information on the number of years of experience (Stein et al., 2014). Another limitation was the analysis of data that consisted of dispensed insulin glargine only, making prescribed but never dispensed cases unobservable. Additionally, findings from insulin glargine were not generalizable to other biosimilars, especially those used to treat other medical conditions.

Furthermore, I used a total sample of South African physicians who met the study criteria to address external validity, thereby, eliminating sampling bias. The data I used was from existing records of pharmacy-dispensed prescription data among physicians from different specializations across the provinces of South Africa to increase external validity. Also, when people sometimes know that they have been chosen for a study, they may change their behavior to allow researchers to obtain the conclusion that they expect.

However, this was not the case for this study, because the insulin data was obtained from nationally dispensed pharmacy data and not directly from the physicians.

Significance

This study could potentially contribute knowledge to South Africa's public health organizations and practitioners regarding the uptake of alternative biosimilar insulin glargine for diabetes treatment in South Africa. Furthermore, findings from this study can be used to inform policymakers, resulting in educational strategies being formulated to support healthcare professionals in better-managing patients with diabetes and resulting in the implementation of policies to ensure access to affordable biosimilar insulin treatment for patients. Findings from this study can also provide important information to physicians when making decisions for newly diagnosed patients with diabetes and can be used to justify the attention needed for diabetes treatment. Information from this study can also advise patients with diabetes about other affordable options to treat their diabetes. This is critical in improving the overall health of patients with diabetes and ensuring that insulin is made available to all populations in South Africa at affordable prices, resulting in lower morbidity and mortality at the population level.

Summary and Conclusion

From the existing literature, this study identified the increased prevalence of diabetes and the unaffordability of insulin as a major concern for public health and further emphasized the severity of the problem in South Africa where the availability of alternative affordable biosimilar insulin is unknown in a country that has the highest

prevalence of diabetes in the African continent (Grundlingh et al., 2022; Saeed et al., 2022; Satheesh et al., 2019).

Although some factors, such as physician and patient knowledge, attitude, and beliefs of biosimilars in diabetes and other therapeutic areas have been identified as barriers to biosimilar uptake in many parts of the world, more research is needed to account for other factors that tend to affect biosimilar uptake in low-and-middle-income countries, such as South Africa. Therefore, due to the lack of data on biosimilar insulin glargine usage in South Africa, this research investigated the uptake of alternative biosimilar insulin glargine in relation to the location of provinces and the specialization of a physician in this study setting using a quantitative methodology. This study also extended knowledge in the discipline by including South Africa's population regarding the uptake of alternative biosimilar insulin glargine treatment. This investigation was important to identify effective policies and strategies to support the uptake of biosimilars, making insulin available and affordable to all populations in South Africa and improving population health.

While this section describes the foundation of the study and the literature review, section 2 will discuss the study's research design, data collection methods, methodology, data analysis plan, threats to validity, and ethical procedures that were used to evaluate the uptake of biosimilar and originator insulin glargine among physicians for the treatment of diabetes in South Africa and to address the literature gap.

Section 2: Research Design and Data Collection

Introduction

The purpose of this quantitative study was to assess the uptake of biosimilar and originator insulin glargine among physicians in South Africa by examining whether there was an association between the location of a province, specialization of a physician, and type of dispensed insulin glargine prescriptions (i.e., biosimilar, originator, or both). Furthermore, this study helped in obtaining a better understanding of a new yet grey area of the South African population's access to alternative biosimilar insulin glargine and to determine whether physicians chose the originator or biosimilar insulin when both were available. This section details the dataset selected for the study, the research design, data collection, and methodology. The operational definitions of each variable and sampling methods are also presented. Furthermore, this section explains how the data analysis plan was conducted, describes threats to validity, and explains the ethical procedures used in this study.

Research Design and Rationale

This study used a secondary analysis of pharmacy-dispensed prescription data with a nonexperimental, quantitative, correlational design to determine whether there was an association between the location of a province, specialization of a physician, and the type of dispensed insulin glargine prescriptions (i.e., biosimilar, originator, or both) in South Africa. This type of research design was used due to the nature of the data collection procedures for the nationally representative pharmacy-dispensed insulin glargine data for the full-year period of 2018. A quantitative research design was used

because quantitative research designs help to understand the nature of a relationship between two variables that cannot be manipulated (Burkholder et al., 2020). A qualitative design did not apply to this study because these designs are exploratory in nature and involve the analysis of narratives (Burkholder et al., 2020). This research design was also nonexperimental because the variables were not manipulated and there was no random assigning of participants to treatment and control groups (Burkholder et al., 2020). Also, data were not collected at a single point in time for this study; therefore, a cross-sectional design was not appropriate. The secondary analysis of pharmacy-dispensed prescription data was convenient as there were no resource or expense issues involved. The use of secondary data was cost-effective, efficient in saving time, and allowed for ready-to-use information. Furthermore, a correlational design was used as the quantitative design of choice because the study's goal was to identify the association between the independent variables and the dependent variable (Burkholder et al., 2020).

The study design was appropriate as it effectively answered the research questions for this study. For RQ1, I investigated how the location of a province as the independent variable was associated with the type of dispensed insulin glargine prescriptions in South Africa. RQ2 investigated how a physician's specialization was associated with the type of dispensed insulin glargine prescriptions in South Africa.

This design was implemented using existing secondary data (i.e., nationally representative pharmacy-dispensed insulin glargine data) for the full-year period of 2018, from a reference medical company in South Africa, to support the study's quantitative design (Reference Company, 2022b). The nationally representative pharmacy-dispensed

insulin glargine dataset for the full year period of 2018 was selected for this study as the data were collected to assess the utilization of medicines such as insulins.

The independent variables included (a) the location of a province and (b) the specialization of a physician; the dependent variable was the type of dispensed insulin glargine prescriptions (i.e., biosimilar, originator, or both) for the full-year period of 2018. Statistical analysis was used to determine the relationship between variables for this study's correlational research design (Creswell & Creswell, 2018).

A correlational, secondary analysis study design was aligned with the study's research strategy needed to advance knowledge in the discipline, specifically using the correlational design to test for expected relationships between and among variables (Gerstman, 2015). Additionally, this choice of design is consistent with other studies that have investigated the uptake of biosimilar medicines in countries such as Asia, Germany, Australia, the United States, and India (Blankart & Arndt, 2020; Godman et al., 2021c; Helfgott et al., 2020; Khoo et al., 2023; Labdi et al., 2023; Mohan et al., 2023).

Methodology

Population

The study population consisted of physicians who were specialists and nonspecialists from the rural and urban provinces of South Africa treating patients with diabetes (Reference Company, 2022a). Physicians' specializations included those that predominantly prescribed insulin, namely, family physicians, general medical practitioners, diabetes specialists, pediatricians, and cardiologists, and excluded physicians from specialization areas that were not primary prescribers of insulin

(Reference Company, 2022a). Data were collected by a reference medical company in South Africa with a total sample of physicians taken from pharmacy dispensation systems (Reference Company, 2022a). The sample size of physicians who prescribed biosimilar or originator insulin glargine in the year 2018 was approximately 5,907 (Reference Company, 2022a). I chose the full-year period of 2018 because the biosimilar insulin glargine would have been well-established in the market, and physicians would have become aware of it and started using it with their patients. Therefore, during the full-year period of 2018, I would expect the dispensation of insulin glargine prescription data from pharmacies to be more accurate.

Sampling and Sampling Procedures

The data were obtained electronically from a reference medical company on variables including drug characteristics from prescriptions collected routinely by pharmacies across the nine provinces of South Africa (Reference Company, 2022a). Data were collected through the software used at the pharmacy level (Reference Company, 2022a). The prescription-level data were entered by pharmacies into the software and were collected routinely by the reference medical company in South Africa to create the secondary dataset (Reference Company, 2022a). Therefore, no data collection instrument was used for this study.

For this study, total population sampling was used, whereby the total sample of physicians in South Africa who met the study criteria was used to address external validity, thereby eliminating sampling bias. This type of purposive sampling includes the use of the total population that has specific traits (Laerd Dissertation, 2012a). For this

study, all the data obtained from the reference medical company that captured insulin glargine prescriptions dispensed for the full year of 2018 were used. The data were drawn from specializations that prescribe insulins because the effectiveness of this type of nonprobability sampling lies in having experts within a certain cultural domain (Tongco, 2007). The data I used were from existing records of pharmacy-dispensed prescription data among physicians from different specializations across the provinces of South Africa, which will increase external validity. Also, when people sometimes know that they have been chosen for a study, they may change their behavior to allow researchers to obtain the conclusion that they expect. However, this was not the case in this study, because the insulin data were captured from the pharmacy-dispensed prescriptions, which served as the source document for the data and were not taken directly from the physicians (Reference Company, 2022a).

The data sample included physicians who were specialists and nonspecialists from the rural and urban provinces of South Africa treating patients with diabetes (Reference Company, 2022a). Physicians' specializations included those that predominantly prescribe insulin, namely, family physicians, general medical practitioners, diabetes specialists, pediatricians, and cardiologists, and excluded physicians from specializations that were not primary prescribers of insulin (Reference Company, 2022a).

The dataset was obtained by contacting the reference medical company and providing occupation details, contact information, and the information needed for the study (Reference Company, 2022a). A data-sharing agreement for academic purposes was then signed confirming that the user would be provided access to the dataset for

study purposes. Once the agreement was signed, the dataset was provided by the reference medical company to the user. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IQVIA Solutions (Pty) Ltd or any of its affiliated or subsidiary entities (Reference Company, 2023c).

The organization from which the secondary dataset was obtained is a global provider of analytical data to the life sciences industry that brings together experts within the healthcare sector to help customers make well-informed decisions to improve patient outcomes (Reference Company, 2022a). It did not have any biased reasons for providing the information. The datasets constitute one of the reference medical company's data assets that are collected and provided to the South African healthcare industry for academic and commercial purposes (Reference Company, 2022a). Because the company is an American multinational company with affiliates around the world providing data to industries involved in health information technology and clinical research, the information is more likely to be reliable and valid, and one can, therefore, trust the data that were provided.

The dataset includes real transactions at presummarized levels to protect the confidentiality of physicians and patients. The total sample of pharmacy-dispensed insulin glargine data includes information on the type of dispensed insulin glargine prescriptions, physicians' specialization area, and the location of a province (Reference Company, 2022a). Data were confined to these characteristics to determine the association between the location of a province, the specialization of a physician, and the type of dispensed insulin glargine prescriptions. Also, the nationally representative

pharmacy-dispensed prescription dataset for the full year of 2018 was the best source for this study as it had all the necessary variables needed to perform this study.

Data Access

The nationally representative pharmacy-dispensed insulin glargine dataset for 2018 was obtained privately. Permission was obtained from the reference medical company to retrieve the information that it collected from the pharmacy vendors.

Power Analysis

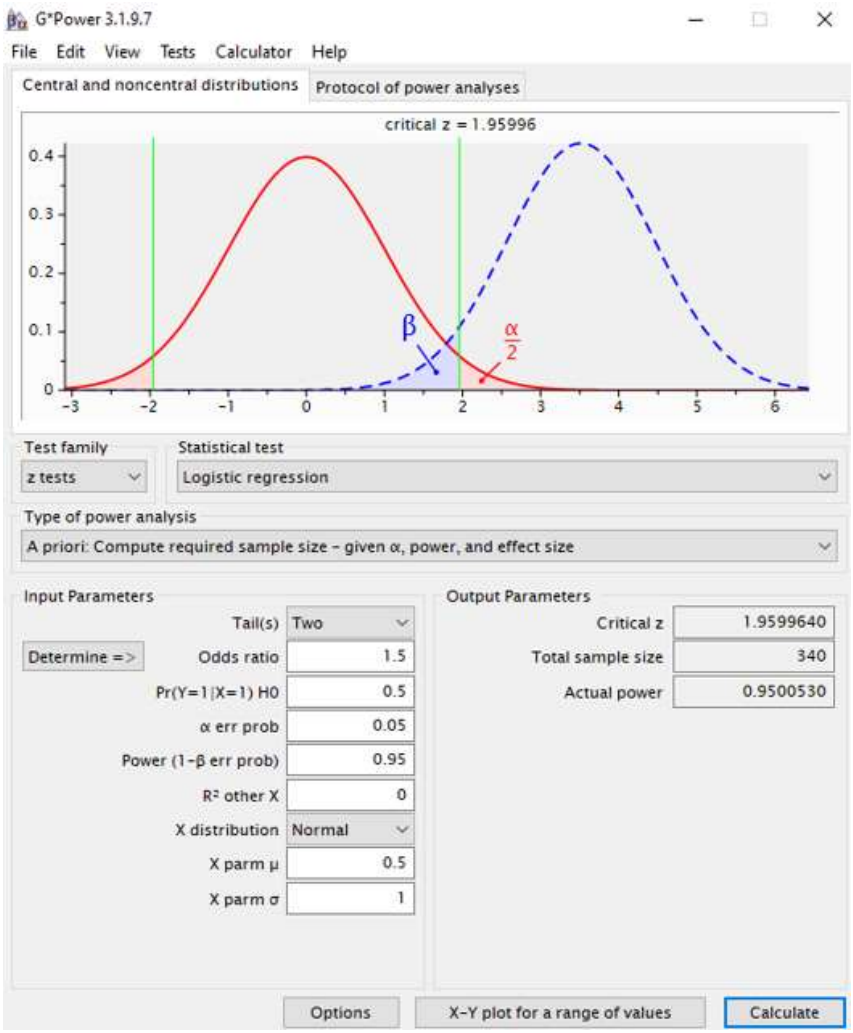
A power analysis was conducted to assess the needed sample size to understand differences in the uptake of insulin glargine (Mysiak, 2020). Inappropriate sample sizes or powers may lead to inaccurate outcomes (Kang, 2021). A sample size that is too small may lead to a large effect, but this large effect could be because of random variations (Kang, 2021). Alternately, too large a sample size may result in statistical significance, even if there is no meaningful difference (Kang, 2021). Too small a sample size may also result in a low power that cannot answer the research questions (Kang, 2021). Therefore, a sufficient sample size is significant in supporting the study's internal validity and generalizability of the results (Vasileiou et al., 2018).

To perform a sample size calculation and power analysis, the effect size, power (1-β), significance level (α), and type of statistical analysis were required (Kang, 2021). For this study, the statistical software G*Power v 3.1.9.7 was used to conduct an a priori power analysis to establish the minimum required sample size (Mysiak, 2020). An alpha of .05 is a common practice used in research, indicating that there is less than a 5% chance that the null hypothesis is correct (Mysiak, 2020). Studies also show that it is generally

well-accepted to use a power of .95 because there will be a 95% chance of obtaining statistical significance (Mysiak, 2020). Therefore, a logistic regression statistical test was used to detect a medium effect size for this power analysis with an odds ratio of 1.5, a significance level (α) of .05, and 95% power (1-β; Mysiak, 2020). The minimum required sample size was 340 (Mysiak, 2020). Figure 1 shows the parameters used to estimate the minimum required sample to conduct a logistic regression test.

Figure 1

Logistic Regression for Sample Size



If effect size, power (1-β), significance level (α), and type of statistical analysis are unknown, research shows that a well-used rule of thumb is to have at least 10 observations per independent variable, which for this study implies having a minimum required sample size of 10 x 2 = 20 observations (Riley et al., 2019). One hundred and eighty observations will be needed to achieve a power of 95%, considering the average of the two estimations of the minimum sample size.

Furthermore, the statistical power of the study depends on the effect size and sample size. The effect size shows the strength of relationships. While a type I error is the error of rejecting a null hypothesis when it is true, a type II error is the error of accepting a null hypothesis when the alternative hypothesis is true (Kang, 2021). If the results of a statistical analysis are nonsignificant, it could be due to correctly accepting the null hypothesis when the null hypothesis is true or erroneously accepting the null hypothesis when the alternative hypothesis is true (Kang, 2021). The latter occurs when the research method does not have enough power (Kang, 2021). Therefore, it is important to calculate sample size and consider power when planning studies (Kang, 2021). In this study, a medium effect size was used because the literature shows that large effect sizes require smaller sample sizes because they are obvious for the analysis to find, while small effect sizes require larger sample sizes as smaller effect sizes are harder to find (Mysiak, 2020).

Operationalization of Constructs

This study did not use any instruments for data collection because secondary data collected by a reference medical company in South Africa were used (Reference Company, 2022a). The study variables were operationalized to make the data analysis

possible. The variables that were assessed in the study were the location of a province, the specialization of a physician, and the type of dispensed insulin glargine prescriptions. The type of dispensed insulin glargine prescriptions is a categorical variable categorized into three groups (i.e., biosimilar, originator, or both). The level of measurement for the insulin type variable is categorical. The physician's specialization is categorized as a categorical variable: diabetes specialist, general medical practitioner, pediatrician, cardiologist, or family physician. The location of a province is a categorical variable that is assessed by whether a province is rural or urban. Table 3 is a summary of the operationalization of the variables that were assessed in this research, including the variable types and level of measurements.

Table 3

Operationalization and Coding of Key Variables

Variable	Variable label	Operationalization
Insulin Type	Type of dispensed insulin glargine prescriptions	Categorical variable (nominal). Categorized as 1 = Biosimilar, 2 = Both, 3 = Originator
Physician Specialization	Specialization of a physician	Categorical variable (nominal). Categorized as: 1 = Cardiologist, 2 = Diabetes Specialist, 3 = Family Physician, 4 = General Medical Practitioner, 5 = Pediatrician
Province	Location of a province	Categorical variable (nominal). Categorized as: 1 = Rural or 2 = Urban

Data Analysis Plan

The data used for this study was obtained with permission from a reference medical company in South Africa (Reference Company, 2022b). The data includes nationally representative pharmacy-dispensed prescription data, which serves as the source document for the data. The dataset contains full dispensation information as per the academic agreement which includes the location of the provinces, a physician's specialization, and the type of dispensed insulin glargine prescriptions, i.e., biosimilar, originator, or both. I checked and made sure that there was no missing data provided as part of the secondary dataset. I also did not envisage that the dataset would require cleaning of missing data or duplicate cases as it was pharmacy-dispensed information from validated software systems, so if there were missing fields, then this means that the data was not available on the prescription at the point of dispensation (Reference Company, 2022b). However, I still reviewed the secondary dataset for missing data. Maintaining open communication with the reference medical company would allow me to complete missing data quickly if needed. However, no missing data was found within the dataset provided by the reference medical company and therefore no data was excluded. Not having any missing data prevented potential sample bias and the need to replace missing information.

As stated in Section 1, the research questions and associated hypotheses that guided this study are:

Research Question 1: Is there an association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa?

*Ho*1 – There is no association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa.

*Ha*1 – There is an association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa.

Research Question 2: Is there an association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa?

*Ho*2 – There is no association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa.

*Ha*2 – There is an association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa.

The data analysis involves descriptive and inferential analysis. The descriptive analysis allows the data to be visualized and interpreted easily through the use of numerical summaries (Gertsman, 2015). Frequencies, which describe the distribution of counts were used for the nominal variables in the study (Gertsman, 2015). These measures were important when analyzing the study as they described the factors that influence the uptake of biosimilar insulin glargine within the study setting.

The inferential statistics for Research Questions 1 and 2 included the use of bivariate and multivariate analyses. The bivariate analysis for the independent variables (the location of a province and the specialization of a physician) was the Pearson Chi-square test because these variables were categorical. The multivariate analysis for the dependent and independent variables was multinomial logistic regression because the dependent variable was categorical with three groups.

Multinomial logistic regression was used to assess the impact of one or more independent variables on the dependent variable (Robinson, 2021). It also predicted how much variance is accounted for in a single response by a set of independent variables (Robinson, 2021). The results were interpreted using the odds ratio with a 95% confidence interval (Robinson, 2021). The expected B coefficient, Exp(B), and confidence intervals (CI) provide the change in the odds for each increase in one unit of the predictor variables (Laerd Statistics, 2018). Cox & Snell R Square, Nagelkerke R Square, and McFadden provide an idea of the amount of variation that can be explained by the model (Robinson, 2021). The statistical significance of each predictor variable was determined using the Wald test and test significance (Laerd Statistics, 2018). No further procedures were used to account for multiple statistical tests since the multinomial logistic regression analysis per se did not demand post hoc tests.

The assumptions for multinomial logistic regression include that the dependent variable must be nominal and have more than two groups (Laerd Statistics, 2018). There must be one or more independent variables that are nominal, ordinal, or continuous, including dichotomous variables (Laerd Statistics, 2018). The dependent variable must have mutually exclusive and exhaustive categories and there should be independence of observations (Laerd Statistics, 2018). There must be no multicollinearity and no outliers. If there are independent variables that are continuous independent variables, then there must be a linear relationship between these variables and the logit transformation of the dependent variable (Laerd Statistics, 2018). However, there were no continuous independent variables in this study. The residuals from Mahalanobis distances tell us

about outliers for multinomial regression. The correlation coefficient indicates if there is multicollinearity in the model. As a general rule, if the tolerance is above 0.1 then this indicates no multicollinearity and the assumption would, therefore, be met (Robinson, 2021).

If one or more of these assumptions are violated, then the following actions can be taken. If there is multicollinearity, a decision will be made as to which independent variable is more important to keep in the model and which one to remove (Robinson, 2021). Similarly, with the outliers, the outliers with little effect can be retained, and those with strong influence will be removed (Robinson, 2021).

The study data was analyzed using SPSS V. 28.0. for results since this statistical program allows for descriptive and inferential analysis to be conducted to answer the study's research questions.

Threats to Validity

According to Babbie (2017), validity refers to how accurately measures reflect what they were meant to measure. While internal validity is the extent to which you can be highly confident that a cause-and-effect relationship of a study was not affected by other factors, external validity is the extent to which findings can be generalized to different groups of people or settings (Babbie, 2017). Construct validity, on the other hand, refers to whether the operational definition of a variable reflects the true theoretical meaning of a construct under investigation.

Threats to internal validity occur when influences other than the independent variables can explain study results (Pourhoseingholi, Baghestani, & Vahedi, 2012).

Confounding variables may influence the dependent variable and can be a threat when making assumptions about the association between the variables of interest. However, there were no confounding variables in this study.

Threats to external validity can compromise the generalizability of the study's results. To address external validity, I used a total sample of physicians who met the study criteria, eliminating sampling bias. This resulted in wide coverage and a better representation of the population of interest and provided more accurate results. Also, when people sometimes know that they have been chosen for a study, they may change their behavior to allow researchers to obtain the conclusion that they expect. However, this was not the case in this study, because the insulin data was captured from pharmacy-dispensed prescriptions, which served as the source document for the data and was not obtained directly from the physicians, thereby eliminating the Hawthorne effect (Reference Company, 2022a). Furthermore, to be able to generalize findings across people and settings, the results should not be limited to a single population. Data from the nationally representative pharmacy-dispensed prescription dataset, 2018, for insulin glargine, is population-level data generalizable to the South African population only and will, therefore, restrict the findings to the South African population.

Threats to construct validity is poor construct definition (Laerd Dissertation, 2012b). Therefore, clear definitions of the cause-and-effect variables were provided in this study to reduce jargon that could create confusion for the audience (Laerd Dissertation, 2012b). In this research, the cause constructs are the independent variables of the location of a province, and the specialization of a physician. The effect construct is

the dependent variable of the uptake of biosimilar and originator insulin glargine, measured by the type of dispensed insulin glargine prescriptions, i.e., biosimilar, originator, or both, for the full year period of 2018. The construct for this study is prescribing behavior, and this was assessed in this study using measurable variables to ensure that this study has strong construct validity.

Ethical Procedures

The nationally representative pharmacy-dispensed prescription dataset for insulin glargine, 2018, was used to answer this study's research questions (Reference Company, 2022b). It is important to note that this study requires permission to collect data from the reference medical company in South Africa because the data is not publicly available.

To access the secondary dataset, I contacted the reference medical company in South Africa, discussed my research topic, and mentioned the data I would require for the study. After obtaining detailed information from the reference medical company, I completed, signed, and e-mailed the academic agreement provided via e-mail. Once I received the data file, I saved it on a personal flash drive with password protection which was kept in a locked box and the data will be deleted from the device after the completion of the study as stipulated by Walden University's IRB guidelines.

Additionally, this study sought IRB approval from Walden University before starting the analysis of this study. The data agreement to gain access to the secondary dataset and other required documentation and information was included in the IRB application.

Furthermore, the secondary dataset that was used in this study was de-identified and anonymized upon receipt. They did not contain any personal information or any details that could potentially make it possible to identify the participants that the data came from. Since the reference medical company follows the Protection of Personal Information Act (POPIA), it protects the privacy of all its customers whose personal information may be processed by them to perform their services and business operations (IQVIA, 2023b). Therefore, the reference medical company that provides the secondary dataset included real transactions at presummarized levels to protect the confidentiality of participants (Reference Company, 2022a). The information was de-identified for research purposes, primarily in connection with academic partners as is the case of this study, where the participant's details were anonymized (Reference Company, 2022a). Furthermore, the datasets are stored on the reference company's server in South Africa and all data is security encrypted (IQVIA, 2023a).

Since this study used a secondary dataset, the ethical issues were minimal due to indirect contact with the target population. However, a potential ethical concern about the use of secondary data involves potential harm to participants by re-using any data containing personal information (Tripathy, 2013). This can be addressed by ensuring that the secondary data is anonymized and de-identified so that the risk of harm to the participants is greatly reduced (Tripathy, 2013). Secondly, participants who provided data for the original study may have only given consent for the use of their data in that study and not for future use (Tripathy, 2013). Therefore, the researcher needs to ensure that the original consent form makes provision for the analysis of secondary data for future use

and that the secondary study obtains approval from the ethics committee (Tripathy, 2013).

Summary

This study aimed to investigate the possibility of an association between the predictor variables of the location of a province and specialization of a physician with the outcome variable of the uptake of insulin glargine measured by the type of dispensed insulin glargine prescriptions, i.e., biosimilar, originator, or both in South Africa. This is a quantitative study that adopted a correlational, secondary data analysis design. The research design, methodology, and data analysis plan were based on the nationally representative pharmacy-dispensed prescription dataset for insulin glargine for the full year period of 2018 provided by a reference medical company in South Africa (Reference Company, 2022b). The Chi-square test and multinomial logistic regression analysis were used to analyze and interpret the relationships among the defined variables, provided all the assumptions were met. The next section of this study will interpret and discuss the study results and findings obtained after implementing the research methods described in this section.

Section 3: Presentation of the Results and Findings

Introduction

In South Africa, the increase in the prevalence of diabetes and the unaffordability of insulin constitutes a major public health problem causing people to die from this disease (Grundlingh et al., 2022). Assessing the accessibility of alternative and affordable biosimilar insulin glargine to the South African population in a country plagued by diabetes is essential (Grundlingh et al., 2022). Therefore, this study's purpose was to assess the uptake of biosimilar and originator insulin glargine in South Africa by examining whether there was an association between the location of a province, the specialization of a physician, and the type of dispensed insulin glargine prescriptions (i.e., biosimilar, originator, or both). Section 3 shows the results of the statistical analysis from the nationally representative pharmacy-dispensed prescription data for insulin glargine that were collected for the full-year period of January 2018 to December 2018 using SPSS software V. 28.0. The Pearson chi-square test and multinomial logistic regression were used to address Research Question 1 and Research Question 2. This section provides the descriptive and statistical results for each research question at a statistical significance of $p < .05$.

The research questions and hypotheses for this study were as follows:

Research Question 1: Is there an association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa?

*Ho*1 – There is no association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa.

*Ha*1 – There is an association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa.

Research Question 2: Is there an association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa?

*Ho*2 – There is no association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa.

*Ha*2 – There is an association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa.

Accessing the Secondary Dataset

Timeframe of the Dataset

The nationally dispensed prescription data for insulin glargine that were collected for the full-year period of January 2018 to December 2018 were obtained electronically from a reference medical company in South Africa that routinely collects prescription information from pharmacy vendors (Reference Medical Company, 2022a). The data were collected to assess the uptake of medicines, such as insulins, and were collected through the software used at the pharmacy level, where all prescriptions collected at retail pharmacies were captured and dispensed (Reference Medical Company, 2022a). The prescription-level data that were entered into the software at pharmacies were routinely collected by the pharmacy vendors and sent to the reference medical company in South Africa to create the dispensed prescription datasets (Reference Medical Company, 2022a). Therefore, no data collection instrument was used for this study.

The nationally representative pharmacy-dispensed dataset for insulin glargine for 2018 was obtained privately, and permission was obtained from the reference medical company to retrieve this information because the content of these databases was not publicly available. The dataset was obtained by contacting the reference medical company and providing information including contact details, occupation details, and a summary of the information needed (Reference Medical Company, 2022a). A data-sharing agreement for academic purposes was then signed confirming that the user would be provided access to the dataset for study purposes.

Once the agreement was signed, and after I had obtained IRB approval (01-02-24-0997143), the dataset was provided by the reference medical company. The file was precleaned for missing data by the reference medical company before being made available for use, and the dataset was a complete set containing full dispensation information, as per the agreement, including the location of a province, specialization of a physician, and the type of dispensed insulin glargine prescriptions. Therefore, no missing data were found within the dataset provided by the reference medical company, and no data were excluded. The lack of missing data ensured that there was no potential bias within the sample and that there was no need to replace the missing information.

Discrepancies from Section 2

In Section 2, the sample size indicated was estimated to be $N = 5{,}907$ because the dataset was not in the public domain and included physician specializations that predominantly prescribe insulin, namely, family physicians, general medical practitioners, diabetes specialists, pediatricians, and cardiologists. However, once the

actual dataset was obtained privately for 2018, the total number of prescribers for insulin glargine for 2018 was 5,899.

Sample Representativeness of the Population of Interest

The study population consisted of specialist and nonspecialist physicians from different specializations across South Africa treating patients with diabetes (Reference Medical Company, 2022a). The physicians' specializations included family physicians, general medical practitioners, diabetes specialists, pediatricians, and cardiologists who were predominantly prescribers of insulin and excluded physicians from specialization areas that were not primary prescribers of insulin (Reference Medical Company, 2022a). The nationally dispensed prescription data for insulin glargine that were collected for the full-year period of January 2018 to December 2018 served as the source document for the data (Reference Medical Company, 2022a). Total population sampling was used, whereby the total sample of physicians in South Africa who met the study criteria was used to address external validity, thereby eliminating sampling bias. This resulted in wide coverage and a better representation of the population of interest and provided more accurate results. The total sample size of physicians who prescribed biosimilar or originator insulin glargine in the year 2018 was 5,899 (Reference Medical Company, 2022a). Total population sampling is a type of purposive sampling whereby the total population being examined has a particular set of characteristics (Laerd Dissertation, 2012a). Therefore, the data were drawn from specializations that prescribe insulins because this type of nonprobability sampling is most effective when one needs to study a certain cultural domain with experts within it (Tongco, 2007). Furthermore, data from the

nationally representative pharmacy-dispensed prescription dataset for 2018 for insulin glargine was population-level data generalizable to the South African population only and therefore restricted the findings to the South African population.

Baseline Descriptives and Characteristics of the Sample

The dataset used in the study provides comprehensive insight into certain essential variables relevant to the research objectives, and the frequency statistics provide characteristics of the sample. Univariate analysis was performed for the independent variables and outcome variables as described below.

Independent Variable: Specialization of a Physician

Table 4 displays the frequency table for the independent variable, the specialization of a physician, within South Africa for the 2018 nationally dispensed prescription data for insulin glargine. The variable, specialization of a physician, has five categories (i.e., cardiologist, family physician, general medical practitioner, diabetes specialist, and pediatrician). From Table 5, 81.9% of physicians were general medical practitioners, 12.5% were diabetes specialists, 2.7% were cardiologists, 2.0% were pediatricians, and 0.8% were family physicians.

Independent Variable: Location of a Province

Table 4 displays the frequency table for the independent variable, the location of a province in South Africa. The variable, provinces, has two categories (i.e., rural or urban). The rural provinces include the Eastern Cape, KwaZulu Natal, Limpopo, Mpumalanga, and North-West Province, and the urban provinces include the Free State,

Gauteng, Northern Cape, and Western Cape Province. From Table 4, 40.3% of the provinces are rural, while 59.7% of the provinces are urban.

Dependent Variable: Type of Dispensed Insulin Glargine Prescriptions

Table 4 displays the frequency table for the dependent variable, the type of dispensed insulin glargine prescriptions. Insulin glargine was categorized according to three groups (i.e., biosimilar, originator, or both). From Table 4, 57.3% of dispensed insulin glargine prescriptions were for the originator, 7.8% were for the biosimilar, and 34.8% were for both the originator and biosimilar.

Table 4

Frequency Distribution for the Independent and Dependent Variables

	N	%
Cardiologist	159	2.7
Diabetes Specialist	740	12.5
Family Physician	50	0.8
General Medical Practitioner	4,831	81.9
Pediatrician	119	2.0
Rural	2,377	40.3
Urban	3,522	59.7
Biosimilar	463	7.8
Originator	3,383	57.3
Both	2,053	34.8

Statistical Assumptions

The Pearson chi-square test was used to test associations between two variables and was organized in a bivariant table (Frankfort-Nachmias & Leon Guerrero, 2018). There are several assumptions made when using the Pearson chi-square test:

- The dependent variable and independent variable should be measured at an ordinal or nominal level.
- The dependent and independent variables should consist of two or more categorical, independent groups.
- The categories of the variables must be mutually exclusive.
- The expected cell count must not be less than five in any cell.

For the Pearson chi-square test, the expected cell count was less than five when five categories of the independent variable, the specialization area of a physician, were used. Because this assumption for the Pearson chi-square test was violated, the transform and recode features were used to dichotomize the independent variable, specialization of a physician, into two categories: “specialist” and “nonspecialist,” whereby 1 = nonspecialist and 2 = specialist, to meet the assumption, allow for a better spread of the data, and ensure that there were more than five counts per cell. The specialist category consisted of cardiologists, pediatricians, and diabetes specialists while the nonspecialist category consisted of family physicians and general medical practitioners.

The multinomial logistic regression test was used to test the influence of the independent variables on the dependent variable (Laerd Statistics, 2018). There are several assumptions made when using the multinomial logistic regression test (Laerd Statistics, 2018):

- The dependent variable must be nominal and have more than two groups.
- There must be one or more independent variables that are nominal, ordinal, or continuous, including dichotomous variables.

- The dependent variable must have mutually exclusive and exhaustive categories.
- There must be independence of observations.
- There must be an absence of multicollinearity.
- There must be no outliers.

The dependent variable, the type of dispensed insulin glargine prescriptions, was a categorical variable with three groups (biosimilar, originator, or both) and was a nonordinal variable. The dependent variable also had mutually exclusive and exhaustive categories. The independent variable of interest was the location of a province and the specialization of a physician, and both variables were dichotomous. This model does not assume that the variables have linearity, are normally distributed, or have homoscedasticity. As a result, the Pearson chi-square test and multinominal logistic regression were the best fit to predict the dependent variable.

I assessed multicollinearity using SPSS-generated correlation coefficients. As a general rule, if the tolerance is above 0.1, this indicates no multicollinearity, and the assumption would, therefore, be met (Robinson, 2021). The correlation coefficient observed between different variables was 0.985, indicating that the independent variables were not highly correlated with each other. I also tested multicollinearity using the VIF, where values of 10 or larger were considered an issue and would violate the assumption. The VIF value was 1.015. Therefore, both tests confirmed the absence of multicollinearity, and the independent variables were not highly correlated to each other. I assessed the presence of strongly influential outliers by looking at the residuals and

found no strong outliers. The maximum value for Mahalanobis distances was 7.036. Using a chi-square statistic, the critical value for chi-square with a degree of freedom of 1 at a *p*-value < .005 was 7.88. Because the maximum distance of 7.036 did not exceed 7.88, this indicates that there were no outliers.

Therefore, all the assumptions for the Pearson chi-square test and multinomial logistic regression analysis as mentioned above were met in this data analysis.

Results by Research Question

Research Question 1

Research Question 1: Is there an association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa?

*Ho*1 – There is no association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa.

*Ha*1 – There is an association between the location of provinces and the type of dispensed insulin glargine prescriptions in South Africa.

Bivariate Analysis

The Pearson chi-square test was used to examine the association between the location of a province and the uptake of biosimilar and originator insulin glargine, measured by the type of dispensed insulin glargine prescriptions. The crosstabulation matrix from Table 5 indicated that provinces that were classified as rural had a higher uptake of originator insulin glargine than urban provinces. Specifically, more than half (58.8%) of the provinces with higher dispensed prescriptions of originator insulin glargine were rural provinces and 56.4% were urban provinces. Also, provinces that were

classified as urban provinces had the lowest uptake of biosimilar insulin glargine. Specifically, 7.8% of the provinces with the lowest dispensed prescriptions of biosimilar insulin glargine were urban provinces and 7.9% were rural provinces.

Table 5

Results of Crosstabs for Location of a Province and the Type of Dispensed Insulin Glargine Prescriptions

Insulin Type* Location of Province Crosstabulation

		Location of Province				Total	
		Rural		Urban			
		N	%	*N*	%	*N*	%
Insulin Type	Biosimilar	188	7.9	275	7.8	463	7.8
	Both	792	33.3	1,261	35.8	2,053	34.8
	Originator	1,397	58.8	1,986	56.4	3,383	57.3
Total		2,377	100.0	3,522	100.0	5,899	100.0

Table 6 indicates that the association between the location of provinces and the type of dispensed insulin glargine prescriptions was not significant X^2 (2, N = 5,899) = 3.940, p = .139. Since, at the alpha level of .05, there is no significant association between the location of a province and the type of dispensed insulin glargine prescriptions, the null hypothesis was retained (Frankfort-Nachmias & Leon Guerrero, 2018).

Table 6

Pearson Chi-Square Test for Location of a Province and the Type of Dispensed Insulin Glargine Prescriptions

	Value	df	Asymptotic significance (2-sided)
Pearson chi-square	3.940 [a]	2	.139
Likelihood ratio	3.949	2	.139
Linear-by-linear association	1.816	1	.178
N of valid cases	5,899		

[a] 0 cells (,0%) have expected count less than 5. The minimum expected count is 186,57.

Phi and Cramer's V test indicates the strength of this association (Laureate Education, 2016). A value of 0 indicates no relationship, and a value of 1 indicates a strong relationship (Laureate Education, 2016). Since Table 7 indicates a value of .026, this means there was a very weak relationship between the two variables.

Table 7

Symmetric Measures for Location of a Province and the Type of Dispensed Insulin Glargine Prescriptions

		Value	Approximate significance
Nominal by nominal	Phi	.026	.139
	Cramer's *V*	.026	.139
N of valid cases		5,899	

Research Question 2

Research Question 2: Is there an association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa?

*Ho*2 – There is no association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa.

*Ha*2 – There is an association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa.

Bivariate Analysis

There was a total of 5,899 physicians who were either specialists or nonspecialists prescribing insulins. The Pearson chi-square test was used to examine the association between the specialization of a physician and the uptake of biosimilar and originator insulin glargine, measured by the type of dispensed insulin glargine prescriptions. The transform and recode features were used to dichotomize the independent variable, the specialization of a physician, into two categories: “specialist” and “nonspecialist” to allow for a better spread of the data and ensure there were more than five counts per cell.

The crosstabulation matrix from Table 8 indicated that the dispensed insulin glargine prescriptions for the originator came mostly from physicians who were classified as nonspecialists compared to those who were classified as specialists. Specifically, the dispensed insulin glargine prescriptions for the originator came from more than half (60.1%) of the nonspecialists and 44.2% who were specialists. Also, the dispensed insulin glargine prescriptions for the biosimilar were the least from physicians who were classified as specialists. Specifically, the dispensed insulin glargine prescriptions for the biosimilar came from 7% of specialists and 8% of nonspecialists. Furthermore, the dispensed insulin glargine prescriptions for both, the originator and biosimilar came mostly from specialists (48.8%), while 31.9% were from nonspecialists.

Table 8

Results of Crosstabs for Specialization of a Physician and the Type of Dispensed Insulin Glargine Prescriptions

Insulin Type * Specialization of a Physician Crosstabulation

		Specialization of a Physician				Total	
		Nonspecialist		Specialist			
		N	%	*N*	%	*N*	%
Insulin Type	Biosimilar	392	8.0	71	7.0	463	7.8
	Both	1,556	31.9	497	48.8	2,053	34.8
	Originator	2,933	60.1	450	44.2	3383	57.3
Total		4,881	100.0	1,018	100.0	5,899	100.0

Table 9 showed that the association between the specialization of a physician and the type of dispensed insulin glargine prescriptions was significant overall X^2 (2, N=5,899) = 107.74, $p < .001$. Using the Pearson Chi-square test, these results show that there is an association between the specialization of a physician and the type of dispensed insulin glargine prescriptions. As a result, the null hypothesis was rejected, and the alternative hypothesis was accepted.

Table 9

Pearson Chi-Square Test for Specialization of a Physician and the Type of Dispensed Insulin Glargine Prescriptions

	Value	*df*	Asymptotic significance (2-sided)
Pearson chi-square	107.738 [a]	2	< .001
Likelihood ratio	104.221	2	< .001
Linear-by-linear association	45.509	1	< .001
N of valid cases	5899		

[a] 0 cells (,0%) have expected count less than 5. The minimum expected count is 79,90.

Also, Phi and Cramer's V test indicated the strength of this association (Laureate Education, 2016). Since Table 10 indicates a value of .135, we can conclude that even though there is an association between the specialization of a physician and the type of dispensed insulin glargine prescriptions, which is statistically significant at the .05 level, it is a very weak association.

Table 10

Symmetric Measures for Specialization of a Physician and the Type of Dispensed Insulin Glargine Prescriptions

		Value	Approximate significance
Nominal by nominal	Phi	.135	< .001
	Cramer's *V*	.135	< .001
N of valid cases		5,899	

Multivariate Analysis

To address the research question: Is there an association between the location of a province, the specialization of a physician, and the type of dispensed insulin glargine prescriptions in South Africa, a multinomial logistic regression analysis was performed to model the relationship between the independent variables (location of a province, specialization of a physician) and the dependent variable, uptake of biosimilar and originator insulin glargine measured by the type of dispensed insulin glargine prescriptions. A p-value of <.05 was considered significant. The independent variables, which were nominal, were the factors in the multinomial logistic regression analysis. In the study, the location of a province (a nominal variable) and the specialization of a

physician (a nominal variable) were treated as factors. SPSS statistics automatically defaulted the settings to the last category to be selected as the reference category. However, this study selected the first category as the reference category. Table 11 shows the reference categories used for the multinomial logistic regression analysis. The independent variable, the location of a province, was a dichotomous variable coded as 1=rural and 2=urban. The independent variable, the specialization of a physician, was also a dichotomous variable coded as 1=nonspecialist and 2=specialist. The dependent variable, the type of dispensed insulin glargine prescriptions, was a nominal variable coded as 1=biosimilar, 2=both, and 3=originator.

Table 11

Reference Categories Used for Multinomial Logistic Regression

Variable	Reference category
Location of a province (IV)	Rural
Specialization of a physician (IV)	Nonspecialist
Type of dispensed insulin glargine prescriptions (DV)	Biosimilar

Table 12 is the case processing table containing the dependent variable and independent variables. The number under the N column provides the number of observations fitting the description in the first column. The proportion of valid responses for each category is listed under the marginal percentage. Table 12 shows 5,899 valid cases, with zero missing cases. Finally, the subpopulation is a piece of information provided by the case processing table showing a total of 4 subpopulations in the data.

Table 12

Case Processing Summary Table

		N	Marginal percentage (%)
Type of dispensed insulin glargine prescriptions	Biosimilar	463	7.8
	Both	2,053	34.8
	Originator	3,383	57.3
Location of a province	Rural	2,377	40.3
	Urban	3,522	59.7
Specialization of a physician	Nonspecialist	4,881	82.7
	Specialist	1,018	17.3
Valid		5,899	100.0
Missing		0	
Total		5,899	
Subpopulation		4	

Table 13 is the Model Fitting Table which indicates whether the variables that were added, statistically significantly improved the model compared to the intercept alone (i.e., with no variables added) using an alpha less than .05. The logistic regression model was statistically significant ($\chi 2 = 104.750$, $p<.001$) as shown in the table. The results mean that the full model statistically significantly predicts the dependent variable, the type of dispensed insulin glargine prescriptions, better than the intercept-only model alone.

Table 13

Model Fitting Table

	Model fitting criteria			Likelihood ratio tests		
Model	AIC	BIC	-2 log likelihood	Chi-square	*df*	Sig.
Intercept only	171.791	185.156	167.791			
Final	75.041	115.136	63.041	104.750	4	< .001

The Pseudo *R* Square indices in Table 14 indicate the proportion of variance that can be explained by the model using Cox and Snell, Nagelkerke, and McFadden. The indices from Cox and Snell (.018) Nagelkerke (.021), and McFadden (.010) confirmed that the model accounts for 1.0 % to 2.1% of the variance. These low values show that the independent variables do not explain much of the variation of the dependent variable.

Table 14

Pseudo R-Square Table

Cox and Snell	.018
Nagelkerke	.021
McFadden	.010

The Likelihood Ratio Test shows which of the independent variables are statistically significant. It provides an overview of how well the independent variables contribute to the model using an alpha = .05 (Laerd Statistic, 2018). In Table 15, the location of a province (p = .768) was not statistically significant while the specialization of a physician (p =<.001) was statistically significant. The result shows that only the predictor of specialization of a physician contributed significantly to the final model.

Table 15

Likelihood Ratio Tests Table

	Model fitting criteria			Likelihood ratio tests		
Effect	AIC of reduced model	BIC of reduced model	-2 log likelihood of reduced model	Chi-square	*df*	Sig.
Intercept	75.041	115.136	63.041[a]	.000	0	.
Location of a province	71.570	98.300	63.570	.529	2	.768
Specialization of a physician	171.842	198.572	163.842	100.801	2	<.001

Note. The chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0.

[a] This reduced model is equivalent to the final model because omitting the effect does not increase the degrees of freedom.

Table 16 presents the parameter estimates which are also known as the coefficients of the model. Each dummy variable has a coefficient for the location of a province variable and the specialization of a physician variable. As there were three categories of the dependent variable (biosimilar, originator, or both), the table shows two sets of logistic regression coefficients. The first set of coefficients is found in the "Both" row (representing the comparison of both the biosimilar and originator category to the reference category of Biosimilars only). The second set of coefficients is found in the "Originator" row (this time representing the comparison of the Originator-only category to the reference category of Biosimilars only). From Table 16 “Location of a Province"

for both sets of coefficients is not statistically significant (Wald = .064, *P* = .800) and (Wald = .023, *P* = .879) respectively at an alpha level of .05. For "Specialization of a Physician" the first sets of coefficients which are found under the “Both” category is statistically significant (Wald = 16.202, *P* < .001) while the second set of coefficients is not statistically significant (Wald = 1.374, *P* = .241) at an alpha level of .05. Therefore, the only coefficient that is statistically significant is for the specialization of a physician variable under the second set of coefficients for the “Both” category. It is [Specialization of a Physician = 1 (nonspecialist] (*p* < .001), which is a dummy variable representing the comparison between a "nonspecialist" and "specialist" regarding dispensed insulin glargine prescriptions. The 95 % confidence interval with an odds ratio (Lower Bound .433 and Upper Bound .749) is less than one. Hence, the model has less risk of prescribing both, rather than prescribing the biosimilar only. The sign of the coefficient is negative (b = -.563), indicating that nonspecialists compared to specialists are less likely to prescribe both the biosimilar and originator rather than the biosimilar only. Specifically, the odds for nonspecialists are approximately 43.1% lower than the odds for specialists to prescribe both instead of the biosimilar.

Therefore, for Research Question 1, based on the results of the multinomial logistic regression test, the null hypothesis is accepted, denoting, that there is no significant association between the location of a province and the type of dispensed insulin glargine prescriptions in South Africa. For Research Question 2, based on the results of the multinomial logistic regression test, the null hypothesis is rejected,

denoting, that there is a significant association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa.

Table 16

Parameter Estimate Table: Type of Dispensed Insulin Glargine Prescriptions

Type of dispensed insulin glargine prescriptions [a]		B	Std. Error	Wald	*df*	Sig.	Exp(B)	95% confidence interval for Exp(B) Lower bound	Upper bound
Both	Intercept	1.953	.130	225.421	1	< .001			
	[Location of a province = 1 (Rural)]	-.027	.106	.064	1	.800	.974	.791	1.198
	[Location of a province = 2 (Urban)]	0[b]	.	.	0	.	.	.	.
	[Specialization of a physician = 1 (Nonspecialist)]	-.563	.140	16.202	1	< .001	.569	.433	.749
	[Specialization of a physician = 2 (Specialist)]	0[b]	.	.	0	.	.	.	.
Originator	Intercept	1.842	.131	198.796	1	< .001			
	[Location of a province=1 (Rural)]	.015	.102	.023	1	.879	1.016	.832	1.239
	[Location of a province=2 (Urban)]	0[b]	.	.	0	.	.	.	.
	[Specialization of a physician=1 (Nonspecialist)]	.164	.139	1.374	1	.241	1.178	.896	1.548
	[Specialization of a physician=2 (Specialist)]	0[b]	.	.	0	.	.	.	.

[a] The reference category is biosimilar. [b] This parameter is set to zero because it is redundant.

Summary

The secondary data collected for this research was used to determine whether an association exists between the dependent variable which was the uptake of biosimilar and originator insulin glargine, measured by the type of dispensed insulin glargine

prescriptions, and the independent variables, i.e., the location of a province and the specialization of a physician. The findings from this study can be used to inform physicians, healthcare professionals, and policymakers about the uptake of affordable alternative biosimilar insulin glargine treatment as they make prescribing and formulary decisions that affect the health outcomes of patients.

Performing this quantitative study confirms the need for ongoing future studies involving newly qualified physicians and healthcare professionals as they navigate the healthcare system of unaffordable insulin therapy and start to prescribe insulin to patients.

The nationally dispensed prescription data for insulin glargine that was collected for the full year period of 2018 was analyzed using IBM SPSS V. 28.0. The prescription data from 5,899 physicians in South Africa was used in this study's analysis, and the results were presented using tables and figures. The data needed to be recoded to meet the assumptions of the Pearson Chi-square test and a descriptive analysis of the variables was also conducted. The descriptive analysis showed that most of the physicians were nonspecialists, i.e., general medical practitioners, the majority of the provinces were of urban location, and the type of dispensed insulin glargine prescriptions was mostly for the originator and least for the biosimilar.

This section also gave a detailed evaluation of the statistical results for each research question. In summary, a Pearson chi-square test and multinomial logistic regression analysis were used to evaluate the two research questions. For Research Question 1, both the Pearson chi-square test and multinomial logistic regression analysis

indicated that the location of a province was not significantly associated with the type of dispensed insulin glargine prescriptions in South Africa. For Research Question 2, both the Pearson chi-square test and multinomial logistic regression analysis indicated that the specialization of a physician was significantly associated with the type of dispensed insulin glargine prescriptions in South Africa.

Section 4 will include an interpretation of the findings and how the findings relate to the literature review presented in Section 1, the appropriateness to the theoretical framework, the study's limitations, recommendations for future research, and social change implications.

Section 4: Application to Professional Practice and Implications for Social Change

Introduction

The purpose of this quantitative, nonexperimental, correlational study was to assess the uptake of biosimilar and originator insulin glargine among physicians in South Africa by examining whether there is an association between the location of a province, specializations of a physician, and the type of dispensed insulin glargine prescriptions (i.e., biosimilar, originator, or both). Furthermore, this study helped gain further understanding of a new yet grey area of the South African population's access to alternative biosimilar insulin glargine and determine whether physicians chose the originator or biosimilar insulin when both were available.

This study was conducted to inform policymakers to formulate policies that support the uptake of biosimilar insulins to all populations in the different provinces of South Africa. Furthermore, healthcare professionals can be supported through educational strategies to better manage patients with diabetes and ensure access to affordable biosimilar insulin treatment for patients through the implementation of policies. Findings from this study can also provide important and necessary information used for making informed decisions for patients diagnosed with diabetes and will justify the attention needed for diabetes treatment. These findings can also inform patients with diabetes about affordable and alternative options to manage their diabetes. By taking these actions, policymakers, public health practitioners, and healthcare professionals may be able to improve the overall health of patients with diabetes, ensuring that insulin is made available to all populations in South Africa at affordable prices, resulting in lower

morbidity and mortality at the population level and improving population health and the health of communities in a country where diabetes is rampant (World Health Organization African Region, 2023).

The data for this study were analyzed using the Pearson chi-square test and multinominal logistic regression analysis using the nationally representative pharmacy-dispensed prescription data for the full-year period of 2018 for insulin glargine (Babbie et al., 2017). The independent variables included (a) the location of a province (urban, rural) and (b) the specialization of a physician (diabetes specialists, general medical practitioners, pediatricians, cardiologists, and family physicians). The dependent variable was the uptake of biosimilar and originator insulin glargine, measured by the type of dispensed insulin glargine prescriptions (originator, biosimilar, both) for the full-year period of 2018.

Descriptive analysis showed that most of the physicians (81.9%) were general medical practitioners, 12.5% were diabetes specialists, 2.7% were cardiologists, 2.0% were pediatricians, and 0.8% were family physicians. The majority of the provinces were urban (59.7%), while 40.3% of the provinces were rural. Also, 57.3% of dispensed insulin glargine prescriptions were for the originator, 34.8% were for both the originator and biosimilar, and 7.8% were for the biosimilar.

Statistical analysis using the Pearson chi-square test showed that provinces that were classified as rural had a higher uptake of originator insulin glargine than urban provinces. Specifically, more than half (58.8%) of the provinces with higher dispensed prescriptions of originator insulin glargine were rural provinces and 56.4% were urban

provinces. Also, provinces that were classified as urban provinces had the lowest uptake of biosimilar insulin glargine. Specifically, 7.8% of the provinces with the lowest dispensed prescriptions of biosimilar insulin glargine were urban provinces and 7.9% were rural provinces. Additionally, the dispensed insulin glargine prescriptions for the originator came mostly from physicians who were classified as nonspecialists compared to those who were classified as specialists. Specifically, the dispensed insulin glargine prescriptions for the originator came from more than half (60.1%) of the nonspecialists and 44.2% who were specialists. Also, the dispensed insulin glargine prescriptions for the biosimilar were the least from physicians who were classified as specialists. Specifically, the dispensed insulin glargine prescriptions for the biosimilar came from 7% of specialists and 8% of nonspecialists. Furthermore, the dispensed insulin glargine prescriptions for both, the originator and biosimilar came mostly from specialists (48.8%), while 31.9% were from nonspecialists.

Finally, statistical analysis using multinomial logistic regression showed no statistically significant association between the location of a province and the type of dispensed insulin glargine prescriptions in South Africa. However, analysis of the dataset for the specialization of a physician showed statistical significance between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa. The logistic regression model was also statistically significant ($\chi 2 = 104.750$, $p < .001$). More specifically, as shown in Table 16 in Section 3, under the odds ratio, the odds for nonspecialists [Exp(B) = .569] were approximately 43.1% lower than

the odds for specialists to prescribe both the biosimilar and originator insulin glargine instead of the biosimilar only.

Findings in Relation to the Literature

Uptake of Biosimilar and Originator Insulin Glargine by Specialization

Consistent with the literature, I found that a physician's specialization was significantly associated with the uptake of biosimilar and originator insulin glargine. Global studies have shown that biosimilar utilization by physicians varied, limiting their uptake, and studies by Graham-Clarke et al. (2020), Kurki et al. (2021), and Richter et al. (2023) found that many healthcare providers still preferred the originator. This was consistent with my study, whereby in South Africa, the utilization of biosimilar and originator insulin glargine also varied among physicians (i.e., 57.3% of dispensed insulin glargine prescriptions were for the originator, 7.8% were for the biosimilar, and 34.8% were for both the originator and biosimilar).

Also, Krstic et al. (2022) found that the specialists' and nonspecialists' use of biosimilars varied in other countries, such as Switzerland and even though specialists in rheumatology, gastroenterology, and immunoallergology were familiar with biosimilars and were confident in using them, the nonspecialist (i.e., general physicians) still lacked an understanding of biosimilars in relation to the originator medicine. Contrary to the literature, in South Africa, physicians who were classified as nonspecialists (general medical practitioners, family physicians) were more likely to prescribe biosimilar insulin glargine than those who were specialists (cardiologists, pediatricians, diabetes

specialists). Even though nonspecialists were mostly prescribing biosimilars, the uptake was still very low (8.0%) compared to the originator (60.1%).

Additionally, studies by Chong et al. (2022), Herndon et al. (2021), and Mysler et al. (2021) found that even specialists who were not concerned about biosimilar safety still preferred to use the originator medicine instead of the biosimilar. This was consistent with this study, whereby specialists were more likely to prescribe the originator (44.2%) compared to the biosimilar (7.0%). However, to extend the knowledge in the discipline, this study showed that in South Africa, specialists were more likely to prescribe both the originator and biosimilar (48.8%) instead of the biosimilar only (7.5%). Also, the odds for nonspecialists were approximately 43.1% lower than the odds for specialists to prescribe both the biosimilar and originator insulin glargine instead of the biosimilar only.

Finally, Tachkov et al. (2021) found that biosimilar insulin has not been widely used compared to its originator insulin worldwide. Even in the United Kingdom, there was a reluctance among physicians to embrace this innovation (Chaplin, 2021). This is consistent with this study, which shows that even in South Africa, the uptake of biosimilar insulin glargine is low (7.8%) compared to its originator (57.3%). Park et al. (2020) stated that physicians were reluctant to use biosimilars, which is consistent with this study and shows that physicians in South Africa are also laggards and slow in adopting the use of biosimilars.

Uptake of Biosimilar Insulin Glargine in Different Parts of a Country

Moorkens et al. (2020) found that biosimilar uptake was much lower in the eastern parts of Germany compared to the western parts, indicating that biosimilar uptake can vary significantly between regions of the same country. This was contrary to what was found in this study. Despite biosimilar uptake being lower in urban provinces (Free State, Gauteng, Northern Cape, and Western Cape) compared to the rural provinces (Eastern Cape, KwaZulu Natal, Limpopo, Mpumalanga, and North-West) in South Africa, no statistically significant association was found for the uptake of biosimilar and originator insulin glargine by location of provinces.

Analyzing and Interpreting the Findings with Regard to the Theoretical Framework

For this research study, I referenced the diffusion of innovation theory. As it applies to the diffusion of innovation theory, I considered the role that innovation plays in treating medical conditions, i.e., diabetes. Additionally, with regard to early adopters or laggards, I took into account the uptake of the innovation of biosimilar insulin glargine amongst physicians in South Africa and discussed the findings in light of this theory. Even though in reality, I did not test any variables for the diffusion of innovation theory, conceptually, there are aspects of this study that looked at this theory.

The diffusion of innovation theory is based on how new innovations spread throughout societies from the time they are introduced until they become widely adopted and states that it is often quite difficult to accept an innovation, even when the innovation brings apparent advantages (Rogers, 1962). Certain innovations may have an advantage over what currently exists. Due to biosimilar insulin glargine being an affordable

alternative to expensive originators, it could broaden access to treatment for people suffering from diabetes.

This study's results indicated that the social constructs of innovation, relative advantage, and time were associated with the uptake of biosimilar insulin glargine. As it applies to this study, the diffusion of innovation theory was used to examine the uptake of biosimilar insulin glargine by physicians in South Africa by evaluating the type of dispensed insulin glargine prescriptions. The results of this study supported this theory and indicated that the innovation of biosimilar insulin glargine, even though it had the relative advantage of cost-effectiveness, had a low uptake over two years from the time it was launched into the market. It was difficult to get this innovation adopted into the market despite its advantages. A physician's acceptance of innovative biosimilars was low in South Africa based on the type of insulin glargine being prescribed. This low adoption shows that physicians in South Africa are laggards rather than early adopters of biosimilar insulin glargine and they continue to rely on the traditional, originator insulin glargine until it is no longer available or unless they are forced to adopt the new innovation (Rogers, 1962).

Limitations of the Study

This quantitative, correlational, secondary analysis study design used the nationally representative pharmacy-dispensed prescription data for the full-year period of 2018 for insulin glargine to assess the association between the location of a province, specialization of a physician, and type of dispensed insulin glargine prescriptions in South Africa (Babbie et al., 2017).

The first limitation of this study was related to the use of secondary data that were not collected to specifically answer my research hypotheses. Therefore, I had no control over the methodology used to collect the data and their reliability in answering my specific research questions. The dataset lacked some variables that may have added value to the study, such as demographic factors of physicians' age and gender, which were not in the dataset. When interpreting the analysis of pharmacy-dispensed prescription data, it was also important to consider that multiple physicians with different levels of expertise were contributing to the prescribing data. However, while pharmacy-dispensed prescription data included information on the specialization of a physician, it did not contain information on the number of years of experience the physician possessed (Stein et al., 2014).

The second limitation was the design of the study. This quantitative, correlational study design was used to test for expected relationships between and among variables but did not relate to causation (Gerstman, 2015). It also analyzed data over one year and could not show changes in uptake over many consecutive years. Also, the way the variables were given in the dataset was mostly nominal; this was a limitation of the proposed statistical analysis plan of multiple linear regression, which needed continuous variables. Therefore, I had to change the analysis plan from multiple linear regression to multinomial logistic regression. Furthermore, the control variable (i.e., the length of time that an insulin was on the market) could not be used as initially planned because there was no difference in the length of time that the insulin was on the market for urban and

rural provinces and the specialization of physicians. Therefore, the control variable had to be removed from the analysis.

A third limitation of this study was related to the generalization of the results across other settings. To be able to generalize findings across people and settings, the results should not be limited to a single population. Data from the nationally representative pharmacy-dispensed prescription dataset for 2018 for insulin glargine are population-level data generalizable to the South African population only and will, therefore, restrict the findings to the South African population.

Recommendations for Future Research

The research study investigated the association between the location of a province, the specialization of a physician, and the type of dispensed insulin glargine prescriptions in South Africa. However, this study lacked demographic variables and control variables, such as the age and gender of a physician as well as variables that could be valuable to this study, such as the number of years of experience of a physician. As a result, I recommend that future studies use additional sociodemographic variables and control variables to investigate if the effect of a physician's age, gender, and years of experience impacts the uptake of biosimilar and originator insulin glargine significantly. The use of these additional factors may provide more context on the uptake of biosimilar insulin glargine among physicians in South Africa. Also, the inclusion of control variables in future studies will enhance the study's internal validity while controlling for other extraneous variables (Burkholder et al., 2020).

For this study, a correlational design was chosen as it could be performed quickly and conveniently. However, another recommendation for future studies is to implement a longitudinal study design. By using a longitudinal study design, researchers could better understand how the prescribing behavior of a physician may change over time. Furthermore, future studies should focus on newly qualified physicians and the uptake of biosimilar insulin glargine. This will help design and implement educational initiatives targeted at entry-level physicians. Newly qualified physicians may not be familiar with the differences between originator and biosimilar medicines, as this is a fairly new and complex area. As a result, an educational intervention targeting newly qualified physicians will help them understand biosimilars and their advantages. Therefore, future research should explore the uptake of biosimilar insulins among physicians who are prescribing insulins and who identify as newly qualified physicians. Finally, a recommendation for future research is related to the generalizability of the findings. Researchers could conduct this study in other countries on the African continent and compare the results of the studies.

Application to Professional Practice and Implications for Social Change

Professional Practice

Physicians are the first point of contact for patients in the treatment of diabetes, which requires the prescription of scheduled insulin treatment. A patient's acceptance of any type of insulin is reliant on their physician's knowledge and support about the medicine because patients depend heavily on their physicians to prescribe the most appropriate medicine for them (Khoo et al., 2023; Scherlinger et al. 2019). Physicians

need to be able to explain to patients about biosimilar insulins, especially how they compare and differ from the originator.

This study's findings can be helpful for physicians, patients, policymakers, and other key stakeholders since there was a statistically significant association between the specialization of a physician and the uptake of biosimilar and originator insulin glargine, measured by the type of dispensed insulin glargine prescriptions. Therefore, physicians and other stakeholders should address physicians' uptake of biosimilar insulin glargine to broaden treatment access.

For physicians to be able to improve the uptake of biosimilar insulin glargine with their patients they first need to be empowered with knowledge of the biosimilar. Also, access to medicine requires a multidisciplinary team approach and physicians play a key role as prescribers in this process. At an academic level for upcoming physicians and a continuing professional development level for qualified physicians, Universities, and the Department of Education with assistance from pharmaceutical companies can implement educational interventions on biosimilar medicines to increase physicians' knowledge and awareness of biosimilar insulins. Such educational interventions can help physicians with the knowledge they require to make informed decisions about affordable alternative treatment options for patients with diabetes (Trickett et al., 2011). This is important in addressing the public health problem of access to lifesaving treatment for all populations in South Africa and reducing the economic burden associated with diabetes treatment.

Positive Social Change

This study's findings may lead to positive social change implications by formulating policies and educational strategies to support the uptake of biosimilar insulin glargine, making insulin available to all populations in South Africa, and resulting in lower morbidity and mortality at the population level.

Specifically, the findings from the current study may help policymakers, healthcare professionals, the Department of Health and the Department of Education understand the uptake of affordable alternative insulin for the treatment of diabetes in South Africa. Having a better understanding of the uptake of biosimilar and originator insulin glargine in South Africa will translate into significant positive social change among public health practitioners and healthcare professionals in improving the utilization of alternative biosimilar insulin in the country. Specifically, public health practitioners can use this study's information to inform policymakers to formulate policies that support the uptake of biosimilar insulins to all populations in the different provinces of South Africa. Also, the Department of Health in collaboration with policymakers can form partnerships to evaluate the advantages of cost-effective alternative biosimilar insulin treatment from an economic standpoint, thereby formulating policies that support the uptake of biosimilar insulins and broadening access to alternative affordable treatment opportunities for patients (Marmot, 2005; Galea et al., 2013).

Furthermore, healthcare professionals can be supported through educational strategies to better manage patients with diabetes. By taking these actions, public health practitioners and healthcare professionals may be able to enhance the health of patients

with diabetes, ensuring that insulin is made available to all populations in South Africa at affordable prices, and improving population health and the health of communities in the country.

Conclusion

This quantitative, correlational study, examined the relationship between the location of a province, the specialization of a physician, and the uptake of biosimilar and originator insulin glargine, measured by the type of dispensed insulin glargine prescriptions in South Africa. Descriptive analysis showed that the type of dispensed insulin glargine prescriptions for biosimilar insulin glargine was lower than for the originator insulin glargine, indicating a low uptake of biosimilar insulin glargine among physicians in South Africa. Additionally, multinomial logistic regression analysis showed that there was a significant association between the specialization of a physician and the type of dispensed insulin glargine prescriptions in South Africa but not for the location of a province. Even though the results showed that nonspecialists compared to specialists were less likely to prescribe both the biosimilar and originator compared to the biosimilar only, the type of dispensed insulin glargine prescriptions for the biosimilar was still very low by nonspecialists.

Studies have indicated that globally biosimilar insulin has not been widely used compared to its originator insulin and biosimilar uptake was slow across many countries and therapeutic areas. Studies have also indicated that there was a reluctance among physicians to embrace this innovation and that a physician’s comfort with originators posed a problem with using biosimilars for their patients to the extent that, even though

some patients were prescribed biosimilars, the majority of patients were still prescribed the originator.

The application of the diffusion of innovation theory was important in understanding the utilization of biosimilar insulin glargine in the South African population. This theory was used to examine the uptake of biosimilar insulin glargine by physicians in South Africa by evaluating the type of dispensed insulin glargine prescriptions in the country. The results of this study supported this theory and found that the innovation of biosimilar insulin glargine, even though it had the relative advantage of cost-effectiveness, had a low uptake over the two years from the time it was launched into the market. It was difficult to get this innovation adopted despite its advantages. A physician's acceptance of innovative biosimilar insulin was low in South Africa based on the type of insulin glargine being prescribed. This low adoption showed that physicians in South Africa are laggards rather than early adopters of biosimilar insulin glargine and continue to rely on the traditional, originator insulin glargine until it is no longer available or unless they are forced to adopt the new innovation (Rogers, 1962).

Therefore, this study was conducted to inform policymakers to formulate policies that support the uptake of biosimilar insulins to all populations in the different provinces of South Africa. Furthermore, healthcare professionals can be supported through educational strategies to better manage patients with diabetes and to broaden access to alternative biosimilar insulin treatment for patients through the implementation of policies. Such policy changes and interventions can help improve population health and the health of communities in a country where diabetes has become a silent killer.

References

Aapro, M., Krendyukov, A., Schiestl, M., & Gascón, P. (2018). Epoetin biosimilars in the treatment of chemotherapy-induced anemia: 10 years' experience gained. *BioDrugs*, *32*, 129-135. https://doi.org/10.1007/s40259-018-0262-9

Achoki, T., Sartorius, B., Watkins, D., Glenn, S. D., Kengne, A. P., Oni, T., Wiysonge, C. S., Walker, A., Adetokunboh, O. O., Babalola, T. K., Bolarinwa, O. A., Claassens, M. M., Cowden, R. G., Day, C. T., Ezekannagha, O., Ginindza, T. G., Iwu, C. C. D., Iwu, C. J., Karangwa, I., … Naghavi, M. (2022). Health trends, inequalities, and opportunities in South Africa's provinces, 1990–2019: Findings from the Global Burden of Disease 2019 Study. *Journal of Epidemiology and Community Health*, *76*(5), 471-481. https://doi.org/10.1136/jech-2021-217480

Ahmad, K. (2014). Insulin sources and types: A review of insulin in terms of its mode on diabetes mellitus. *Journal of Traditional Chinese Medicine*, *34*(2), 234-237. https://doi.org/10.1016/S0254-62(14)60084-4

Aladul, M. I., Fitzpatrick, R. W., & Chapman, S. R. (2018). Healthcare professionals' perceptions and perspectives on biosimilar medicines and the barriers and facilitators to their prescribing in the UK: A qualitative study. *BMJ Open*, *8*(11), Article e023603. https://doi.org/10.1136/bmjopen-2018-023603

Albashtawy, M., Gharaibeh, H., Alhalaiqa, F., Batiha, A. M., Freij, M., Saifan, A., Al-Awamreh, K., Hamadneh, S., Al-Kloub, M., & Khamaiseh, A. (2016). The health belief model's impacts on the use of complementary and alternative medicine by

parents or guardians of children with cancer. *Iranian Journal of Public Health*, *45*(5), 708-709. https://www.ncbi.nlm.nih.gov/pmc/articlesPMC4935720/

Alderson, P. (1998). The importance of theories in health care. *BMJ*, *317*(7164), 1007-1010. https://doi.org/10.1136/bmj.317.7164.1007

American Diabetes Association. (2020). *Insulin is now a biologic—What does that mean?* https://diabetes.org/blog/insulin-now-biologic-what-does-mean

Aravind, S. R., Singh, K. P., Aquitania, G., Mogylnytska, L., Zalevskaya, A. G., Matyjaszek-Matuszek, B., Wernicke-Panten, K., Nguyên-Pascal, M.-L., Pierre, S., Rotthaeuser, B., Kramer, D., & Mukherjee, B. (2022). Biosimilar insulin aspart premix SAR341402 Mix 70/30 versus originator insulin aspart Mix 70/30 (NovoMix 30) in people with diabetes: A 26-week, randomized, open-label trial (GEMELLI M). *Diabetes Therapy*, *13*(5), 1053-1071. https://doi.org/10.1007/s13300-022-01255-7

Aronson, J. K., Goldacre, B., & Ferner, R. E. (2018). Prescribing biosimilars. *BMJ*, *362*. https://doi.org/10.1136/bmj.k3141

Azevedo, A., Bettencourt, A., Selores, M., & Torres, T. (2018). Biosimilar agents for psoriasis treatment: The perspective of Portuguese patients. *Acta Médica Portuguesa*, *31*(9), 496-500. https://doi.org/10.20344/amp.10127

Babbie, E. (2017). *Basics of social research* (7th ed.). Cengage Learning.

Barbier, L., Simoens, S., Vulto, A. G., & Huys, I. (2020a). European stakeholder learnings regarding biosimilars: Part I—Improving biosimilar understanding and adoption. *BioDrugs*, *34*, 783-796. https://doi.org/10.1007/s40259-020-00452-9

Barbier, L., Simoens, S., Vulto, A. G., & Huys, I. (2020b). European stakeholder learnings regarding biosimilars: Part II—Improving biosimilar use in clinical practice. *BioDrugs, 34*, 797-808. https://doi.org/10.1007/s40259-020-00440-z

Barbier, L., Vandenplas, Y., Simoens, S., Declerck, P., Vulto, A. G., & Huys, I. (2021). Knowledge and perception of biosimilars in ambulatory care: A survey among Belgian community pharmacists and physicians. *Journal of Pharmaceutical Policy and Practice, 14*(1), 1-16. https://doi.org/10.1007/s11096-021-01243-0.

Barcina Lacosta, T., Vulto, A. G., Huys, I., & Simoens, S. (2022). Evaluating the benefits of TNF-alfa inhibitor biosimilar competition on off-patent and on-patent drug markets: A Southern European analysis. *Frontiers in Pharmacology, 13*, Article 1031910. https://doi.org/10.3389/fphar.2022.1031910

Birkner, B., & Blankart, K. E. (2022). The Effect of biosimilar prescription targets for erythropoiesis-stimulating agents on the prescribing behavior of physicians in Germany. *Value in Health, 25*(9), 1528-1538. https://doi.org/10.1016/j.jval.2022.03.005

Blankart, K. E., & Arndt, F. (2020). Physician-level cost control measures and regional variation of biosimilar utilization in Germany. *International Journal of Environmental Research and Public Health, 17*(11), Article 4113. https://doi.org/10.3390/ijerph17114113

Bolli, G. B., Cheng, A. Y., & Owens, D. R. (2022). Insulin: Evolution of insulin formulations and their application in clinical practice over 100 years. *Acta Diabetologica, 59*(9), 1129-1144. https://doi.org/10.1007/s00592-022-01938-4

Boone, N. W., Liu, L., Romberg-Camps, M. J., Duijsens, L., Houwen, C., Van Der Kuy, P. H. M., ... & van Bodegraven, A. A. (2018). The nocebo effect challenges the non-medical infliximab switch in practice. *European Journal of Clinical Pharmacology*, *74*, 655-661. https://doi.org/10.1007/s00228-018-2418-4

Burkholder, G. J., Cox, K. A., Crawford, L. M., & Hitchcock, J. H. (Eds.). (2020). *Research designs and methods: An applied guide for the scholar-practitioner*. Thousand Oaks, CA: Sage.

Centers for Disease Control and Prevention. (2022). Types of Insulin. https://www.cdc.gov/diabetes/basics/type-1-types-of-insulin.html

Chaplin, S. (2021). Biosimilar insulins: will switching soon be the norm? *Practical Diabetes*, *38*(4), 17-20. https://doi/org/10.1002/pdi.2346

Chew, C., Aguiar, M., Bansback, N., Law, M. R., & Harrison, M. (2022). Patient perspectives on the British Columbia Biosimilars Initiative: a qualitative descriptive study. *Rheumatology International*, *42*(10), 1831-1842. https://doi.org/10.1007/s00296-021-04874-8

Chong, S. C., Rajah, R., Chow, P. L., Tan, H. C., Chong, C. M., Khor, K. Y., ... & Tan, W. Y. (2022). Perspectives toward biosimilars among oncologists: A Malaysian survey. *Journal of Oncology Pharmacy Practice*, 10781552221104773. https://doi.org/10.1177/10781552221104773

Cobilinschi, C., Opris-Belinski, D., Codreanu, C., Ionescu, R., Mihailov, C., Parvu, M., ... & Ionescu, R. (2019). SAT0688 Patient State of Knowledge on Biosimilars-Do

Physicians Need to Improve Education Skills? *Annals of the Rheumatic Diseases, 78*, 1446-1447. http://dx.doi.org/10.1136/annrheumdis-2019-eular.6300

Cohen, A. D., Vender, R., Naldi, L., Kalb, R. E., Torres, T., Rajagopalan, M., ... & Young, H. S. (2020). Biosimilars for the treatment of patients with psoriasis: A consensus statement from the Biosimilar Working Group of the International Psoriasis Council. *JAAD International*, *1*(2), 224-230. https://doi.org/10.1016/j.jdin.2020.09.006

Cook, J. W., McGrath, M. K., Dixon, M. D., Switchenko, J. M., Harvey, R. D., & Pentz, R. D. (2019). Academic oncology clinicians' understanding of biosimilars, and information needed before prescribing. *Therapeutic Advances in Medical Oncology*, *11*, 1758835918818335. https://doi.org/10.1177/1758835918818335

Creswell, J. W., & Creswell, J. D. (2018). *Research design: Qualitative, Quantitative, and Mixed Methods Approach* (5th ed.). Thousand Oaks, CA: Sage.

Dadkhahfar, S., Ohadi, L., Rahimi, Y., Robati, R. M., Shekarabi, M., Zargari, O., & Shahidi-Dadras, M. (2021). Patients' perception, and adherence to treatment with biosimilar adalimumab in psoriasis. *Dermatologic Therapy*, *35*(2), e15227-e15227. https://doi.org/10.1111/dth.15227

Daniel, H., Serchen, J., Cooney, T. G., & Health and Public Policy Committee of the American College of Physicians*. (2020). Policy recommendations to promote prescription drug competition: A position paper from the American College of Physicians. *Annals of Internal Medicine, 173*(12), 1002-1003. https://doi.org/10.7326/M19-3773

de Assis, M. R., & Pinto, V. (2018). Strengths and weaknesses of the Brazilian regulation on biosimilars: a critical view of the regulatory requirements for biosimilars in Brazil. *Therapeutic Advances in Musculoskeletal Disease*, *10*(12), 253-259. https://doi.org/10.1177/1759720X18809683

Demirkan, F. G., Sönmez, H. E., Lamot, L., Akgün, Ö., Sözeri, B., Ayaz, N. A., & PeRA-Research Group. (2022). Embracing Change: An International Survey Study on the Beliefs and Attitudes of Pediatric Rheumatologists Towards Biosimilars. *BioDrugs*, *36*(3), 421-430. https://doi.org/10.1007/s40259-022-00526-w

de Mora, F. (2019). Biosimilars: a value proposition. *BioDrugs*, *33*(4), 353-356. https://doi.org/10.1007/s40259-019-00360-7

Department of Statistics South Africa. (2001). Consensus 2001. https://www.statssa.gov.za/?page_id=5134

El Zorkany, B., Al Ani, N., Al Emadi, S., Al Saleh, J., Uthman, I., El Dershaby, Y., ... & Al Moallim, H. (2018). Biosimilars in rheumatology: recommendations for regulation and use in Middle Eastern countries. *Clinical Rheumatology*, *37*(5), 1143-1152. https://doi.org/10.1007/s10067-018-3982-9

Eric, J. (2020). P046 Though Biosimilar Infliximab Prescribing in Inflammatory Bowel Disease Has Increased, Branded Infliximab Continues to Be Prescribed More Often. *Official Journal of the American College of Gastroenterology ACG*, *115*, S12. https://doi.org/10.14309/01.ajg.0000722980.69306.ba

Fahmi, H. L., Al-Jumaili, A. A., & Younus, M. M. (2022). The whole experience of public hospital physicians from several specialties with biopharmaceutical effectiveness, safety, adverse drug reactions, and interchangeability: A qualitative study. *Exploratory Research in Clinical and Social Pharmacy, 7*. https://doi.org/10.1016/j.rcsop.2022.100162

Feldman, M., & Reilly, M. S. (2020). European prescribers' attitudes and beliefs on biological prescribing and automatic substitution. *Generics and Biosimilars Initiative Journal, 9*(3), 116-125. https://doi.org/10.5639/gabij.2020.0903.020

Ferreri, D. (2022). Basaglar is not associated with lower out-of-pocket costs than the reference product. https://www.centerforbiosimilars.com/view/basaglar-is-not-associated-with-lower-out-of-pocket-costs-than-the-reference-product

Finch, L., Colasante, W., Dehnen, J., Alexander, R., & Collins, S. (2019). PBI8 Unknown. *Value in Health, 22,* S419. https://doi.org/10.1016/j.jval.2019.09.112

Flaherty, J. (2022). The Differences between Biosimilar, Human, and Analog Insulins. https://beyondtype1.org/biosimilar-human-analog-insulin-differences/

Frank, R. G. (2018). Friction in the path to use of biosimilar drugs. *New England Journal of Medicine, 378*(9), 791-793. https://doi.org/10.1056/NEJMp1714908

Frankfort-Nachmias. C., Leon-Guerrero, A., & Davis, G. (2020). *Social Statistics for a Diverse Society* (9th ed.). Sage Publications.

Frantzen, L., Cohen, J. D., Tropé, S., Beck, M., Munos, A., Sittler, M. A., ... & Sordet, C. (2019). Patients’ information and perspectives on biosimilars in rheumatology: a

French nationwide survey. *Joint Bone Spine*, *86*(4), 491-496. https://doi.org/10.1016/j.jbspin.2019.01.001

Frieden, T. R. (2015). The future of public health. *New England Journal of Medicine*, *373*(18), 1748-1754. https://doi.org/10.1056/NEJMsa1511248

Gaffney, A., Cadi-Tazi, A., & Ribeiro, A. (2019). PBI57 Payer and Physician Dynamics Surrounding Biosimilar Access in the EU. *Value in Health*, *22*, S427. https://doi.org/10.1016/j.jval.2019.09.161

Galea, S., & Annas, G. J. (2016). Aspirations and strategies for public health. *JAMA*, *315*(7), 655-656. https://doi.org/10.1001/jama.2016.0198

Gall, S., Kiltz, U., Kobylinski, T., Andreica, I., Vaupel, K., Waldecker, C., ... & Braun, J. (2022). Patient knowledge about biosimilars and satisfaction with the education provided by rheumatologists or nurse specialists in a biosimilar multi-switch scenario–The perception study. In *Seminars in Arthritis and Rheumatism*, *57*, 152119. https://doi.org/10.1016/j.semarthrit.2022.152119

Gamez-Belmonte, R., Hernandez-Chirlaque, C., Arredondo-Amador, M., Aranda, C. J., Gonzalez, R., Martinez-Augustin, O., & de Medina, F. S. (2018). Biosimilars: Concepts and controversies. *Pharmacological Research*, *133*, 251-264. https://doi.org/10.1016/j.phrs.2018.01.024

Gani, L., Lau, E., Luk, A., Sobrepena, L., Tran, Q. K., Kesavadev, J., ... & JADE Collaborative Study Group. (2018). Cross-sectional survey of biosimilar insulin utilization in Asia: The Joint Asia Diabetes Evaluation Program. *Journal of Diabetes Investigation*, *9*(6), 1312-1322. https://doi.org/10.1111/jdi.12843

Garcia, K. S., Facas, B. P., Machado, M. B., Teixeira, F. V., Avedano, L., Lönnfors, S., ... & Queiroz, N. S. F. (2021). Biosimilar knowledge and viewpoints among Brazilian inflammatory bowel disease patients. *Therapeutic Advances in Gastroenterology*, *14*, 17562848211013249. https://doi.org/10.1177/17562848211013249

Garg, M., Chatterjee, A., & Chambers, C. R. (2021). Education strategy for the implementation of oncology biosimilars essential for operational and patient safety in Alberta, Canada. *Journal of Oncology Pharmacy Practice*, *27*(5), 1189-1194. https://doi.org/10.1177/10781552211007535

Gasteiger, C., Lobo, M., Dalbeth, N., & Petrie, K. J. (2021). Patients' beliefs and behaviors 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

Gasteiger, C., & Petrie, K. J. (2022). Moving forward: Implementing health psychology research to improve patient acceptance of biosimilars. *Research in Social and Administrative Pharmacy*, *18*(10), 3860-3863. https://doi.org/10.1016/j.sapharm.2022.03.009

Gerstman, B. Burt. (2015). *Basic Biostatistics* (2nd ed). San Jose, California: Jones & Bartlett Learning

Gibofsky, A., & McCabe, D. (2021). US rheumatologists' beliefs and knowledge about biosimilars: a survey. *Rheumatology*, *60*(2), 896-901. https://doi.org/10.1093/rheumatology/keaa502

Gibofsky, A., Evans, C., & Strand, V. (2022). Provider and patient knowledge gaps on biosimilars: insights from surveys. *The American Journal of Managed Care*, *28*(12), 227-233. https://doi.org/10.37765/ajmc.2022.89297

Godman, B., Wladysiuk, M., McTaggart, S., Kurdi, A., Allocati, E., Jakovljevic, M., ... & Wettermark, B. (2021a). Utilization trend of long-acting insulin analogs including biosimilars across Europe: findings and implications. *BioMed Research International*, *2021*. https://doi.org/10.1155/2021/9996193

Godman, B. (2021b). Biosimilars are becoming indispensable in the management of multiple diseases although concerns still exist. *Bangladesh Journal of Medical Science*, *20*(1), 5-10. https://doi.org/10.3329/bjms.v20i1.50338

Godman, B., Haque, M., Leong, T., Allocati, E., Kumar, S., Islam, S., ... & Jakovljevic, M. (2021c). The Current Situation Regarding Long-Acting Insulin Analogues Including Biosimilars Among African, Asian, European, and South American Countries; Findings and Implications for the Future. *Frontiers in Public Health*, *9*, 636. https://doi.org/10.3389/fpubh.2021.671961

Graham-Clarke, P. L., Hauber, B., Boeri, M., Leonardi, F., Burge, R. T., Fernandez, M., ... & Florez, S. (2020). Patient Preferences for Biologic and Biosimilar Osteoporosis Treatments in Colombia. *Patient Preference and Adherence*, 1049-1064. https://doi.org/10.2147/PPA.S250745

Griffith, M.L. (2021). What to Know About Human Insulin and How it Works. https://www.healthline.com/health/diabetes/human-insulin

Grundlingh, N., Zewotir, T. T., Roberts, D. J., & Manda, S. (2022). Assessment of prevalence and risk factors of diabetes and pre-diabetes in South Africa. *Journal of Health, Population, and Nutrition*, *41*(1), 1-12. https://doi.org/10.1186/s41043-022-00281-2

Gürler, F., Kasım, D. D., Kurt İnci, B., Sütçüoğlu, O., Ünsal, O., Aslan, V., ... & Yazıcı, O. (2022). Current status of biosimilars in Turkey: A survey among medical oncologists. *Journal of Oncology Pharmacy Practice*, *28*(7), 1516-1523. https://doi.org/10.1177/10781552211031643

Hadoussa, S., Bouhlel, M., Soussi, M. A., Drira, C., Hadoussa, M., & Khrouf, M. R. (2020). Perception of hematologists and oncologists about the biosimilars: A prospective Tunisian study based on a survey. *Journal of Oncology Pharmacy Practice*, *26*(1), 124-132. https://doi.org/10.1177/1078155219848817

Haghnejad, V., Le Berre, C., Dominique, Y., Zallot, C., Guillemin, F., & Peyrin-Biroulet, L. (2020). Impact of a medical interview on the decision to switch from originator infliximab to its biosimilar in patients with inflammatory bowel disease. *Digestive and Liver Disease*, *52*(3), 281-288. https://doi.org/10.1016/j.dld.2019.09.012

Hair, J., Maryon, T., & Lieneck, C. (2022). Identification of Barriers Preventing Biosimilar Oncology Medication Adoption. *Medicina*, *58*(11), 1533. https://doi.org/10.3390/medicina58111533

Halimi, V., Daci, A., Ancevska Netkovska, K., Suturkova, L., Babar, Z. U. D., & Grozdanova, A. (2020). Clinical and regulatory concerns of biosimilars: a review

of the literature. *International Journal of Environmental Research and Public Health*, *17*(16), 5800. https://doi.org/10.3390/ijerph17165800

Hayden, J. (2019). Introduction to health behavior theory. Jones & Bartlett Publishers.

Hayes, K. N., Mor, V., & Zullo, A. R. (2022). Electronic health records to rapidly assess biosimilar uptake: an example using insulin glargine in a large US nursing home cohort. *Frontiers in Pharmacology*, *13*, 855598. https://doi.org/10.3389/fphar.2022.855598

Health Professionals Council of South Africa. (2001). Health Professions Act 56 of 1974. https://www.hpcsa.co.za/Content/upload/professional_boards/mdb/regulations/REGULATIONS%20RELATING%20TO%20THE%20SPECIALITIES%20AND%20SUBSPECIALITIES%20IN%20MEDICINE%20AND%20DENTISTRY.pdf

Helfgott, S., Radtchenko, J., Soloman, N., Huston, K. K., Singh, J., & Edgerton, C. (2020, October). Real-World Utilization of Infliximab (IFX) and Its Biosimilars in Patients (Pts) with Rheumatoid Arthritis (RA) Since the First Biosimilar Approval in the US. *Arthritis & Rheumatology*, *13*. https://americanrheum.com/wp-content/uploads/ACR-2020-RW-Utilization-of-Biosimilars-10052020-fc.pdf

Herndon, K., Braithwaite, J., Berry, B., & Bourget, K. (2021). Biosimilar perceptions among healthcare professionals and commercial medical benefit policy analysis in the United States. *BioDrugs*, *35*, 103-112. https://doi.org/10.1007/s40259-020-00463-6

Hilgenfeld, R., Seipke, G., Berchtold, H., & Owens, D. R. (2014). The evolution of insulin glargine and its continuing contribution to diabetes care. *Drugs*, *74*, 911-927. https://doi.org/10.1007/s40265-014-0226-4

Hu, Y., Song, Z., Jiang, D., Zhuo, L., Cheng, Y., & Zhao, R. (2022). Knowledge, attitudes, and practice of healthcare providers, healthcare regulatory practitioners and patients toward biosimilars in China: Insights from a nationwide survey. *Frontiers in Pharmacology*, *13*, 876503. https://doi.org/10.3389/fphar.2022.876503

Iacullo, J., Kunzler, E., Ezaldein, H. H., & Scott, J. F. (2018). Prescribing trends for biologic drugs among Ohio dermatologists. *Dermatology Online Journal*, *24*(7). https://doi.org/10.5070/D3247040911

Inotai, A., Csanadi, M., Petrova, G., Dimitrova, M., Bochenek, T., Tesar, T., ... & Kalo, Z. (2018). Patient access, unmet medical need, expected benefits, and concerns related to the utilization of biosimilars in Eastern European countries: a survey of experts. *BioMed Research International*, *2018*. https://doi.org/10.1155/2018/9597362

Intercare. (2019). Physicians as Medical Specialist. https://www.intercare.co.za/article/physicians-as-medical-specialists

International Diabetes Federation. (2021). With 1 in 9 adults living with diabetes, South Africa has highest diabetes prevalence in Africa. https://www.idf.org/index.php?option=com_attachments&task=download&id=2642:WDD2021_SOUTH_AFRICA

IQVIA. (2020). Realizing Biosimilar Potential in the Middle East & Africa. https://www.iqvia.com/-/media/iqvia/pdfs/mea/white-paper/biosimilar_iqvia-whitepaper_final.pdf

IQVIA Solutions, South Africa. (2022a). Codebook: January 2018 to December 2018.

IQVIA Solutions, South Africa (2022b). Dataset: January 2018 to December 2018.

IQVIA. (2023a). Real World Datasets. https://www.iqvia.com/solutions/real-world-evidence/real-world-data-and-insights

IQVIA. (2023b). IQVIA Privacy Policy (The "Policy"). https://www.iqvia.com/about-us/privacy/privacy-policy#

IQVIA Solutions, South Africa (2023c). Academic Agreement: December 2023.

Ismailov, R. M., & Khasanova, Z. D. (2018). Biosimilar knowledge among oncology/hematology team members in Colorado, USA: an educational initiative and follow-up survey. *BioDrugs*, *32*, 499-506. https://doi.org/10.1007/s40259-018-0301-6

Ismailov, R. M., Khasanova, Z. D., & Gascon, P. (2019). Knowledge and awareness of biosimilars among oncology patients in Colorado, USA. *Future Oncology*, *15*(22), 2577-2584. https://doi.org/10.1007/s00296-020-04576-7

Janjigian, Y. Y., Bissig, M., Curigliano, G., Coppola, J., & Latymer, M. (2018). Talking to patients about biosimilars. *Future Oncology*, *14*(23), 2403-2414. https://doi.org/10.2217/fon-2018-0044

Kabir, E. R., Moreino, S. S., & Sharif Siam, M. K. (2018). An empirical analysis of the perceived challenges and benefits of introducing biosimilars in Bangladesh: a paradigm shift. *Biomolecules, 8*(3), 89. https://doi.org/10.3390/biom8030089

Kang, H. (2021). Sample size determination and power analysis using the G* Power software. *Journal of Educational Evaluation for Health Professions, 18*. https://doi.org/10.3352/jeehp.2021.18.17

Kapoor, S., Kaushik, V. V., Jain, R., Rao, V. K., & Gharia, M. (2019). Real-life tolerability and effectiveness of Adalimumab biosimilar in Ankylosing spondylitis: The Adalimumab biosimilar patient registry data. *ACR Open Rheumatology, 1*(8), 480-484. https://doi.org/10.1002/acr2.11067

Karateev, D., & Belokoneva, N. (2019). Evaluation of physicians' knowledge and attitudes towards biosimilars in Russia and issues associated with their prescribing. *Biomolecules, 9*(2), 57. https://doi.org/10.3390/biom9020057

Khan, D., Luig, T., Mosher, D., & Campbell-Scherer, D. (2020). Lessons from International Experience with Biosimilar Implementation: An Application of the Diffusion of Innovations Model. *Healthcare Policy*, 15(3), 16-27. https://doi.org/10.12927/hcpol.2

Khoo, T., Sidhu, N., Marine, F., Lester, S., Quinlivan, A., Rowett, D., ... & Hill, C. L. (2022). Perceptions towards biologic and biosimilar therapy of patients with rheumatic and gastroenterological conditions. *BMC Rheumatology*, *6*(1), 1-10. https://doi.org/10.1186/s41927-022-00309-4

Knox, R. (2020). Insulin insulated: barriers to competition and affordability in the United States insulin market. *Journal of Law and the Biosciences*, *7*(1), lsaa061. https://doi.org/10.1093/jlb/lsaa061

Kolbe, A. R., Kearsley, A., Merchant, L., Temkin, E., Patel, A., Xu, J., & Jessup, A. (2021). Physician understanding and willingness to prescribe biosimilars: findings from a US national survey. *BioDrugs*, *35*, 363-372. https://doi.org/10.1007/s40259-021-00479-6

Krstic, M., Devaud, J. C., Sadeghipour, F., & Marti, J. (2022). Current Expertise, Opinions, and Attitude toward TNF-α Antagonist Biosimilars among Physicians: A Self-Administered Online Survey in Western Switzerland. In *Healthcare*, *10*(11), 2152. https://doi.org/10.3390/healthcare10112152

Kurki, P., Barry, S., Bourges, I., Tsantili, P., & Wolff-Holz, E. (2021). Safety, immunogenicity, and interchangeability of biosimilar monoclonal antibodies and fusion proteins: a regulatory perspective. *Drugs*, *81*(16), 1881-1896. https://doi.org/10.1007/s40265-021-01601-2

Kurtzhals, P., & Gough, S. C. (2021). The contributions of insulin to science in medicine. *Diabetic Medicine*, *38*(12). https://doi.org/10.1111/dme.14623

Labdi, B. A., Elbeshbeshy, R. A., Winkler, M., Johnson, S. G., & Attridge, R. L. (2023). Rituximab Reference vs Biosimilar Utilization for Oncology vs Nononcology Indications. *American Journal of Managed Care*, *29*(11). https://doi.org/10.37765/ajmc.2023.89461

Laerd Dissertation. (2012a). Purposive Sampling. https://dissertation.laerd.com/purposive-sampling.php

Laerd Dissertation. (2012b). Threats to Construct Validity. https://dissertation.laerd.com/construct-validity-p2.php#:~:text=The%20definitions%20of%20constructs%20that,construct%20(Nunnally%2C%201978)

Laerd Statistics. (2018). Multinomial Logistic Regression using SPSS Statistics. https://statistics.laerd.com/spss-tutorials/multinomial-logistic-regression-using-spss-statistics.php

Laureate Education. (2016). *Bivariate categorical tests* [Video file]. Baltimore, MD: Author.

Lilly. (2022). Basaglar. https://www.basaglar.com/hcp

Liu, Y. (2021). Utilizing oncology biosimilars to minimize the economic burden associated with cancer treatment: managed care considerations. *The American Journal of Managed Care*, *27*(14 Suppl). 10.37765/ajmc.2021.88734. https://doi.org/10.37765/ajmc.2021.88734

Lobo, F., & Río-Álvarez, I. (2021). Barriers to Biosimilar Prescribing Incentives in the Context of Clinical Governance in Spain. *Pharmaceuticals*, 14(3), 283. https://doi.org/10.3390/ph14030283

Lund Hansen, R., Schoedt Jørgensen, T., Dreyer, L., Hetland, M. L., Glintborg, B., Askling, J., ... & Kristensen, L. E. (2021). Inflammatory hallmarks of lesser prominence in psoriatic arthritis patients starting biologics: a Nordic population-

based cohort study. *Rheumatology*, *60*(1), 140-146. https://doi.org/10.1093/rheumatology/keaa237

Luukkanen, S. V., Tolonen, H. M., Airaksinen, M., & Saarukka, L. S. (2022). The Price and Market Share Evolution of the Original Biologics and Their Biosimilars in Finland. *BioDrugs*, *36*(4), 537-547. https://doi.org/10.1007/s40259-022-00540-y

Macaluso, F. S., Leone, S., Previtali, E., Ventimiglia, M., Armuzzi, A., & Orlando, A. (2020). Biosimilars: The viewpoint of Italian patients with inflammatory bowel disease. *Digestive and Liver Disease*, *52*(11), 1304-1309. https://doi.org/10.1016/j.dld.2020.07.028

Mansell, K., Bhimji, H., Eurich, D., & Mansell, H. (2019). Potential cost-savings from the use of the biosimilars filgrastim, infliximab, and insulin glargine in Canada: a retrospective analysis. *BMC Health Services Research*, *19*, 1-8. https://doi.org/10.1186/s12913-019-4680-2

Marmot, M. (2005). Social determinants of health inequalities. *The Lancet*, *365*(9464), 1099-1104. https://doi.org/10.1016/S0140-6736(05)74234-3

Marotto, D., Ceribelli, A., & Puttini, P. S. (2019). Biosimilars: New guns for the treatment of rheumatological patients? *Beyond Rheumatology*, *1*(1), 15-21. https://doi.org/10.4081/br.2019.3

Miller, T., Savill, K. Z., Brown, M., Jeune-Smith, Y., & Feinberg, B. (2023). HSD7 Prescribing Behavior Among Community Oncologists for Generics/Biosimilars While Considering Costs or Financial Toxicity When Treating Cancer. *Value in Health*, *26*(6), S239-S240. https://doi.org/10.1016/j.jval.2023.03.1316

Mohan, A., Komakula, S., Murali, S., Anand, P., Shah, D., Vishnu, V. Y., ... & Bhatia, R. (2023). Biosimilar tenecteplase versus alteplase in acute ischemic stroke: A real world study. *Annals of Indian Academy of Neurology*, *26*(1), 54. https://doi.org/10.4103/aian.aian_754_22

Moorkens, E., Meuwissen, N., Huys, I., Declerck, P., Vulto, A. G., & Simoens, S. (2017). The market of biopharmaceutical medicines: a snapshot of a diverse industrial landscape. *Frontiers in Pharmacology*, 314. https://doi.org/10.3389/fphar.2017.00314

Moorkens, E., Barcina Lacosta, T., Vulto, A. G., Schulz, M., Gradl, G., Enners, S., ... & Simoens, S. (2020). Learnings from regional market dynamics of originator and biosimilar infliximab and etanercept in Germany. *Pharmaceuticals*, *13*(10), 324. https://doi.org/10.3390/ph13100324

Mutyambizi, C., Booysen, F., Stokes, A., Pavlova, M., & Groot, W. (2019). Lifestyle and socio-economic inequalities in diabetes prevalence in South Africa: A decomposition analysis. *PloS One*, *14*(1), e0211208. https://doi.org/10.1371/journal.pone.0211208

Mysiak, K. (2020). The Relationship between Significance, Power, Sample Size & Effect Size. https://towardsdatascience.com/the-relationship-between-significance-power-sample-size-effect-size-899fcf95a76d

Mysler, E., Azevedo, V. F., Danese, S., Alvarez, D., Iikuni, N., Ingram, B., ... & Peyrin-Biroulet, L. (2021). Biosimilar-to-biosimilar switching: what is the rationale and

current experience? *Drugs*, *81*(16), 1859-1879. https://doi.org/10.1007/s40265-021-01610-1

Nabhan, C., Valley, A., & Feinberg, B. A. (2018). Barriers to oncology biosimilars uptake in the United States. *The Oncologist*, *23*(11), 1261-1265. https://doi.org/10.1634/theoncologist.2018-0066

Okoro, R. N. (2021). Biosimilar medicines uptake: The role of the clinical pharmacist. *Exploratory Research in Clinical and Social Pharmacy*, *1*, 100008. https://doi.org/10.1016/j.rcsop.2021.100008

Omair, M. A., Almadany, R., Omair, M. A., Al Rayes, H., Almalag, H. M., & Alshamsan, A. (2022). Perception of biosimilar biologics and non-medical prescription switching among rheumatologists: a Saudi society for rheumatology initiative. *Saudi Pharmaceutical Journal*, *30*(1), 39-44. https://doi.org/10.1016/j.jsps.2021.10.012

Oskouei, S. T., & Kusmierczyk, A. R. (2021). Biosimilar uptake: the importance of healthcare provider education. *Pharmaceutical Medicine*, *35*(4), 215-224. https://doi.org/10.1007/s40290-021-00396-7

Park, S. K., Moon, W., Kim, E. S., Park, S. H., & Park, D. I. (2019). Knowledge and viewpoints on biosimilar monoclonal antibodies among Asian physicians: comparison with European physicians. *The Korean Journal of Gastroenterology*, *74*(6), 333-340. https://doi.org/10.4166/kjg.2019.74.6.333

Park, S. H., Park, J. C., Lukas, M., Kolar, M., & Loftus, E. V. (2020). Biosimilars: concept, current status, and future perspectives in inflammatory bowel diseases. *Intestinal Research*, *18*(1), 34-44. https://doi.org/10.5217/ir.2019.09147

Perry, D., Ton, J., & Kolber, M. R. (2019). Biosimilars versus biologics for inflammatory conditions. *Canadian Family Physician*, *65*(9), 636-636. https://www.cfp.ca/content/65/9/636.short

Pheiffer, C., Pillay-van Wyk, V., Turawa, E., Levitt, N., Kengne, A. P., & Bradshaw, D. (2021). Prevalence of type 2 diabetes in South Africa: a systematic review and meta-analysis. *International Journal of Environmental Research and Public Health*, *18*(11), 5868. https://doi.org/10.3390/ijerph18115868

Piezzo, M., D'Aniello, R., Avallone, I., Barba, B., Cianniello, D., Cocco, S., ... & Maiolino, P. (2021). Uptake of trastuzumab biosimilars for the treatment of her2-positive breast cancer: A real-world experience from a cancer center. *Pharmaceuticals*, *13*(5), 684. https://doi.org/10.3390/pharmaceutics13050684

Poon, S. Y. K., Hsu, J. C., Ko, Y., & Chiang, S. C. (2021). Assessing knowledge and attitude of healthcare professionals on biosimilars: A national survey for pharmacists and physicians in Taiwan. In *Healthcare*, *9*(11), 1600. https://doi.org/10.3390/healthcare9111600

Pourhoseingholi, M. A., Baghestani, A. R., & Vahedi, M. (2012). How to control confounding effects by statistical analysis. *Gastroenterology and hepatology from bed to bench*, *5*(2), 79. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017459/

Quinlivan, A., Lester, S., Barrett, C., Whittle, S., Rowett, D., Black, R., ... & Hill, C. (2022). Attitudes of Australians with inflammatory arthritis to biologic therapy and biosimilars. *Rheumatology Advances in Practice*, *6*(3), rkac099. https://doi.org/10.1093/rap/rkac099

Resende, H. M., Ladislau, L., Cardoso, A. C. F., Brandão, J. D. P., Assis, B. R., Cardoso, P., ... & Castilho, V. (2021). Biosimilar use in breast cancer treatment: A national survey of Brazilian oncologists' opinions, practices, and concerns. *JCO Global Oncology*, *7*, 1316-1324. https://doi.org/10.1200/GO.20.00649

Richter, V., Cohen, D. L., Bermont, A., Shalem, T., Broide, E., & Shirin, H. (2023). The Perception among Israeli Gastroenterologists Regarding Treatment of Patients with Biosimilar Medications. *Medicina*, *59*(3), 523. https://doi.org/10.3390/medicina59030523

Riley, R. D., Snell, K. I., Ensor, J., Burke, D. L., Harrell Jr, F. E., Moons, K. G., & Collins, G. S. (2019). Minimum sample size for developing a multivariable prediction model: PART II-binary and time-to-event outcomes. *Statistics in Medicine*, *38*(7), 1276-1296. https://doi.org/10.1002/sim.7992

Robinson, K. (2018). Revealing and addressing knowledge gaps regarding biosimilars in rheumatology practice with targeted continuing education and patient surveys. *Arthritis Rheumatol,70* (9). https://acrabstracts.org/abstract/revealing-and-addressing-knowledge-gaps-regarding-biosimilars-in-rhematology-practice-with-targeted-continuing-education-and-patient-surveys/.

Robinson, D. (2021). Binary Logistic Regression on SPSS with Assumption Checks and APA-Style Write Up. https://www.youtube.com/watch?v=sQdbwrTS2Lc

Rogers, E.M. (1962). *Diffusion of Innovations*. New York, Free Press of Glencoe, RS(*N*).

Saborido-Cansino, C., Santos-Ramos, B., Carmona-Saucedo, C., Rodríguez-Romero, M. V., González-Martín, A., Palma-Amaro, A., ... & Sánchez-Fidalgo, S. (2019). Effectiveness of an intervention strategy in the biosimilar glargine prescription pattern in primary care. *Atencion Primaria*, *51*(6), 350-358. https://doi.org/10.1016/j.aprim.2018.02.012

Saeed, A., Lambojon, K., Saeed, H., Saleem, Z., Anwer, N., Aziz, M. M., ... & Babar, Z. U. D. (2022). Access to Insulin Products in Pakistan: A National Scale Cross-Sectional Survey on Prices, Availability, and Affordability. *Frontiers in Pharmacology*, *939*. https://doi.org/10.3389/fphar.2022.820621

Sarnola, K., Merikoski, M., Jyrkkä, J., & Hämeen-Anttila, K. (2020). Physicians' perceptions of the uptake of biosimilars: a systematic review. *BMJ Open*, *10*(5), e034183. https://doi.org/10.1136/bmjopen-2019-034183.

Satheesh, G., Unnikrishnan, M. K., & Sharma, A. (2019). Challenges constraining availability and affordability of insulin in Bengaluru region (Karnataka, India): Evidence from a mixed-methods study. *Journal of Pharmaceutical Policy and Practice*, *12*(1), 1-11. https://doi.org/10.1186/s40545-019-0190-1

Schachne, J. M., Durbin, L. L., Lacher, C. R., Sangha, M., Mone, A., & Swaminath, A. (2021). Ideal Vial Size for Infliximab in the Treatment of Inflammatory Bowel

Disease: An Analysis of Pharmaceutical Waste and Physician Opinions. *Crohn's & Colitis 360*, *3*(4). https://doi.org/10.1093/crocol/otab071

Scherlinger, M., Langlois, E., Germain, V., & Schaeverbeke, T. (2019). Acceptance rate and sociological factors involved in the switch from originator to biosimilar etanercept (SB4). In *Seminars in Arthritis and Rheumatism*, *48*(5), 927-932. https://doi.org/10.1016/j.semarthrit.2018.07.005

Shah, V. N., Franek, E., Wernicke-Panten, K., Pierre, S., Mukherjee, B., & Sadeharju, K. (2021). Efficacy, safety, and immunogenicity of insulin aspart biosimilar SAR341402 compared with originator insulin aspart in adults with diabetes (GEMELLI 1): a subgroup analysis by prior type of mealtime insulin. *Diabetes Therapy*, *12*, 557-568. https://doi.org/10.1007/s13300-020-00992-x

Shao, H., Tao, Y., & Tang, C. (2023). Factors influencing bioequivalence evaluation of insulin biosimilars based on a structural equation model. *Frontiers in Pharmacology*, *14*, 1143928. https://doi.org/10.3389/fphar.2023.1143928

Sidahmed, S., Geyer, S., & Beller, J. (2023). Socioeconomic inequalities in diabetes prevalence: the case of South Africa between 2003 and 2016. *BMC Public Health*, *23*(1), 324. https://doi.org/10.1186/s12889-023-15186-w

Socal, M. P., Anderson, K. E., Sen, A., Bai, G., & Anderson, G. F. (2020). Biosimilar uptake in Medicare Part B varied across hospital outpatient departments and physician practices: the case of filgrastim. *Value in Health*, *23*(4), 481-486. https://doi.org/10.1016/j.jval.2019.12.007

South African Health Products Regulatory Authority. (2014). Biosimilar medicines Quality, Non-clinical and Clinical Requirements. SAHPRA-BIOSIMILARS-MEDICINES-GUIDANCE.pdf

Stein, J. D., Lum, F., Lee, P. P., Rich III, W. L., & Coleman, A. L. (2014). Use of health care claims data to study patients with ophthalmologic conditions. *Ophthalmology*, *121*(5), 1134-1141. https://doi.org/10.1016/j.ophtha.2013.11.038

Swain, J., Jena, S., Manglunia, A., & Singh, J. (2022). The Journey of Insulin Over 100 Years. *Journal of Diabetology*, *13*(1), 8-15. https://doi.org/10.4103/jod.jod_100_21

Tachkov, K., Mitkova, Z., Milushewa, P., & Petrova, G. (2021). Biosimilar insulins and their impact on prices and utilization of insulins in Bulgaria. In *Healthcare*, *9*(6), 697. https://doi.org/10.3390/healthcare9060697

Tamer, J., Grozev, J., Kamusheva, M., & Petrova, G. (2019). PNS155 access of Bulgarian patients to biosimilar medicines. *Value in Health*, *22*, S787. https://doi.org/10.1016/j.jval.2019.09.2056

Tinsley, S. M., Grande, C., Olson, K., Plato, L., & Jacobs, I. (2018). Potential of biosimilars to increase access to biologics: considerations for advanced practice providers in oncology. *Journal of the Advanced Practitioner in Oncology*, *9*(7), 699. https://doi.org/10.6004/jadpro.2018.9.7.2

Tongco, D.C. (2007). Purposive Sampling as a Tool for Informant Selection. *Ethnobotany Research & Applications, 5*, 147-158.

Trickett, E. J., Beehler, S., Deutsch, C., Green, L. W., Hawe, P., McLeroy, K., ... & Trimble, J. E. (2011). Advancing the science of community-level interventions. *American Journal of Public Health*, *101*(8), 1410-1419. https://doi.org/10.2105/AJPH.2010.300113

Tripathy, J. P. (2013). Secondary data analysis: Ethical issues and challenges. *Iranian Journal of Public Health*, *42*(12), 1478. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4441947/

Tucker, M. E. (2015). Why are there no generic insulins? https://www.medscape.com/viewarticle/841669?form=fpf#vp_2

van Adrichem, R. C., Voorneveld, H. J., Waverijn, G. J., Kok, M. R., & Bisoendial, R. J. (2022). The Non-medical Switch from Reference Adalimumab to Biosimilar Adalimumab is Highly Successful in a Large Cohort of Patients with Stable Inflammatory Rheumatic Joint Diseases: A Real-Life Observational Study. *Rheumatology and Therapy*, *9*(4), 1109-1118. 10.1007/s40744-022-00465-6

Vandenplas, Y., Brown, J., Janssens, B., Lenaerts, S., Pardon, M., Wagman, O., ... & Huys, I. (2020). PBI54 The Role of Patient Education about Biosimilar Medicines: A Systematic Review. *Value in Health*, *23*, S419. https://doi.org/10.1016/j.jval.2020.08.132

Vandenplas, Y., Simoens, S., Van Wilder, P., Vulto, A. G., & Huys, I. (2021a). Informing patients about biosimilar medicines: The role of European patient associations. *Pharmaceuticals*, *14*(2), 117. https://doi.org/10.3390/ph14020117

Vandenplas, Y., Simoens, S., Van Wilder, P., Vulto, A. G., & Huys, I. (2021b). Off-patent biological and biosimilar medicines in Belgium: a market landscape analysis. *Frontiers in Pharmacology*, *12*, 644187. https://doi.org/10.3389/fphar.2021.644187

Vandenplas, Y., Barbier, L., Simoens, S., Van Wilder, P., Vulto, A. G., & Huys, I. (2022). Perceptions about biosimilar medicines among Belgian patients in ambulatory care. *Frontiers in Pharmacology*, *12*, 789640. https://doi.org/10.3389/fphar.2021.789640

Varma, M., Almarsdóttir, A. B., & Druedahl, L. C. (2022). “Biosimilar, so it looks alike, but what does it mean?” A qualitative study of Danish patients' perceptions of biosimilars. *Basic & Clinical Pharmacology & Toxicology*, *130*(5), 581-591. https://doi.org/10.1111/bcpt.13719

Vasileiou, K., Barnett, J., Thorpe, S., & Young, T. (2018). Characterizing and justifying sample size sufficiency in interview-based studies: systematic analysis of qualitative health research over a 15-year period. *BMC Medical Research Methodology*, *18*, 1-18. https://doi.org/10.1186/s12874-018-0594-7

Viera, C. (2023). How to Write Limitations of the Study with Examples. https://www.aje.com/arc/how-to-write-limitations-of-the-study/

White, J., & Goldman, J. (2019). Biosimilar and follow-on insulin: the ins, outs, and interchangeability. *Journal of Pharmacy Technology*, *35*(1), 25-35. https://doi.org/10.1177/8755122518802268

World Health Organization African Region. (2023). Diabetes, a silent killer in Africa. https://files.aho.afro.who.int/afahobckpcontainer/production/files/iAHO_Diabetes_Regional_Factsheet.pdf

Yang, J., Liu, R., Ektare, V., Stephens, J., & Shelbaya, A. (2021). Does biosimilar bevacizumab offer affordable treatment options for cancer patients in the USA? A budget impact analysis from US commercial and Medicare payer perspectives. *Applied Health Economics and Health Policy, 19*, 605-618. https://doi.org/10.1007/s40258-021-00637-5

Yossef, L., Wright, M., Benedict, J., Morris, G. A., McNicol, M., Boyle, B., ... & Maltz, R. M. (2022). Patient and Caregivers' Perspectives on Biosimilar Use in Pediatric Inflammatory Bowel Disease. *Journal of Pediatric Gastroenterology and Nutrition*, *75*(1), 59-63. https://doi.org/10.1097/MPG.0000000000003462

Young, D., Cummings, F., & Latter, S. (2022). Patient perspectives of successful adalimumab biosimilar transitioning in Crohn's disease: an interview study. *European Journal of Hospital Pharmacy*, *31*(2), 143-149. http://dx.doi.org/10.1136/ejhpharm-2022-003371

Zhai, M. Z., Sarpatwari, A., & Kesselheim, A. S. (2019). Why are biosimilars not living up to their promise in the US? *AMA Journal of Ethics*, *21*(8), 668-678. 10.1001/amajethics.2019.668