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A Comparison of the Safety and Efficacy of Three Medical Abortion Protocols

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Abstract

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FFPH, UK Faculty of Public Health, 2018

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Unsafe abortions pose serious threats to women's health. Medical abortion provides safer abortion access to many. The lengthy interval between misoprostol and mifepristone creates multiple barriers for women and providers. A paucity of research exists about medical abortion protocols that allow single day procedures. The efficacy and the safety of 3 medical abortion protocols of varying lengths were explored in this study. A secondary data set of over 55,000 patients from the United Kingdom was retrospectively analyzed using binomial logistic regression. Efficacy results showed no significant difference between the conventional and the simultaneous protocols; when compared to those, the 6- to 8- hour protocol showed a 79% higher risk (*OR* = 0.210, *95% CI* = 0.178 - 0.246) of failure. Safety of the simultaneous protocol was 48% lesser (*OR* = 0.524, *95% CI* = 0.447 - 0.613) and the safety of the 6- to 8- hour protocol 61% lesser (*OR* = 0.386, *95% CI* = 0.304- 0.489) compared to the conventional protocol. The absolute risk of complications or severe adverse events of all protocols (0.98%, 1.97%, and 2.67%) was very low. The results suggest the simultaneous protocol is a viable alternative to the conventional protocol up to 10 weeks' gestation. The results could promote the adoption of the simultaneous protocol by health systems, give millions more women access to safe and effective single day medical abortions, reduce the need for skilled clinicians, and reduce cost burdens for both women and for healthcare systems overall. Implementation of these social changes could make abortion safer globally.

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Dedication

This dissertation is dedicated to all the teachers that have nurtured me and guided me through my life. Starting with my maternal grandfather who paved the way for all my achievements, to the dedicated teachers of my primary, secondary, and high schools who taught me expecting nothing in return but that I learn and flourish. Finally, to the great teachers that formatted my professional education at medical school, and to those who gave me my foreign education through Norway, England, and finally, Walden. I am who I am because of you, because of what you gave me, and the paths that you showed.

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Thank you, Professor Anderson. You were a guiding light in my dissertation journey. From our very first meeting in Atlanta five years ago, until the completion of my degree, you were by my side. Thank you for your support through your own health challenges and through the slow patches that I hit along the way.

Thank you Dr. Margaritis, for your teachings in advanced statistics and your support through my dissertation. You helped me from our first interactions on Blackboard, our conversations in Spain, right until my completing the degree.

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Chapter 1: Introduction to the Study

Introduction

According to Devereux (1954, p. 98), "Abortion is an absolutely universal phenomenon, and it is impossible to construct an imaginary social system in which no woman would ever feel at least compelled to abort". The world saw an estimated 200–220 million pregnancies in the years after 2010 (Vrachnis et al., 2016). Approximately 40% (i.e., 85 million) of these pregnancies were unintended, and over half of the unintended pregnancies (i.e., approximately 40 million pregnancies) were aborted (Sedgh, Singh, & Hussain, 2014). Over half of those 40 million abortions were carried out in an unsafe manner (Sedgh et al., 2014; Vrachnis et al., 2016). In 2015, there were 303,000 maternal deaths globally (Filippi et al., 2016). The World Health Organization (WHO; 1992) defined a maternal death as "the death of a woman whilst pregnant or within 42 days of delivery or termination of pregnancy, from any cause related to, or aggravated by pregnancy or its management, but excluding deaths from incidental or accidental causes" (p. 2). Unsafe abortion has been estimated to cause 4.7% to 15% of the maternal deaths in 2015 (Filippi et al., 2016).

Surgical and medical methods are used for inducing abortion. With prostaglandins, such as misoprostol (MISO), becoming available in the early 1970s and antiprogestins, such as mifepristone (MIFE), in the 1980s, medical abortion (MA), the induction of abortion using medication alone (Gopal et al., 2017) became an alternative to surgical methods (Kulier et al., 2004). MA is safer, cheaper, and less medicalized compared to surgical methods (Simmonds, Beal, & Eagen-Torkko, 2017; Zane, et al.,

2015). Protocols of MIFE and MISO, separated by a dosing interval is the norm for MA (Gatter et al., 2015; Raymond et al., 2013). This interval has remained at 24-to 48-hours over the last 2 decades (Creinin et al., 2004; WHO, 2015), making MA longer than surgical abortion.

In this study, I compared the efficacy and the safety of three MA protocols. The protocols differed based on their dosing intervals between MIFE and MISO while having the same dosages of the two drugs and the same route for administering MISO. The first uses a 24- to 36-hour dosing interval, the second a 6-hour dosing interval, and the third eliminates the interval, with the two drugs being administered simultaneously. The latter two shorter protocols, if found to have acceptable levels of safety and efficacy, could eventually replace the current MA protocol. This could pave the way for MA to become a shorter, simpler procedure and increase access for many more women. If the efficacy and the safety of either of the latter protocols is found to be acceptable, it could replace the conventional protocol and potentially turn MA in to a single day process. That could make MA both more enticing and accessible to millions of women worldwide. Even if the safety and efficacy of the shorter protocols are inferior in comparison, knowing the exact safety and efficacy of those protocols could still allow one or both to be offered as an alternative option to women who seek a safe and convenient MA, following robust counselling on the protocol choices. That too, could make MA more appealing and accessible to millions of women.

I will use this chapter to introduce the study. I will provide a brief overview of the study by explaining the background of the study, the problem statement focused on the

gap that I intended to fill with this study, and the purpose of the study. I will also present the research questions and the hypotheses along with the variables of the study. The theories that were used to guide this study and form its theoretical foundation will then be outlined. Definitions of the different terms related to the field of MA that were used in the study will be included in this chapter. I will also explain the nature of the study and examine its limitations. Finally, I will outline the significance of the study from the perspectives of public health and social change.

Background of the Study

Since MIFE was introduced in France and China more than 2 decades ago, MA with this antiprogestin has expanded rapidly throughout the world. MIFE is now registered in 57 countries (Dunn & Cook, 2014). In the United States, about one fifth of all outpatient abortions are performed medically (Jones & Kooistra, 2011), and in several countries in Europe, the proportion exceeds 60% (Jones & Henshaw, 2002). Many aspects of different MA protocols have been studied at various gestational ages. The next frontier in MA research appears to be the shortening of the process by shortening the dosing interval; however, only 13 studies have explored MA protocols with dosing intervals below 12 hours. Pymar, Creinin, and Schwartz (2001) and Creinin et al. (2004) showed MIFE 200 mg and vaginal MISO 800 μg with a 6- to 8-hour dosing interval has comparable efficacy to the conventional protocol (i.e., 24- to 36-hour dosing interval) at gestational ages below 49 days.

Fox, Creinin, and Harwood (2002) and Guest et al. (2007) showed that comparative efficacy extends up to 63 days of gestation. Creinin et al. (2004), authors of

the first randomized trial, also showed comparable efficacy between the 6-to 8-hour dosing interval and the conventional protocol. Protocols with simultaneous dosing at gestational ages up to 49 days (Li et al., 2006; Li et al., 2011; Murthy, Creinin, Harwood, & Schreiber, 2005), 56 days (Kapp, Borgatta, Ellis, & Stubblefield, 2006), and 63 days (Creinin et al., 2007; Schreiber, Creinin, Harwood, & Murthy, 2005) have been shown to have expulsion rates of approximately 90%. Only Lohr et al. (2007) showed simultaneous dosing to have expulsion rates below 80% at gestational ages up to 63 days. During my exhaustive literature review, I found neither studies that compared more than two protocols nor studies that included more than one short MA protocol. Furthermore, I found no author that had conducted a retrospective analysis of a large data set of MA clients who had the procedure in a non-research setting.

The aforementioned gaps in the literature helped highlight the need for my study. Women, especially in resource-poor countries, need access to the shortest and simplest possible methods available to terminate a pregnancy when they choose to do so. Clinical providers need to offer the simplest and shortest MA options. Their ability to offer a choice in MA protocols to women could increase the percentage of safe abortions done using medical options. Finally, providers need to be able to accurately counsel women on the efficacy and the safety of the MA protocols that they offer. The results of this study could help determine which method is the best for them.

Problem Statement

Unsafe abortion accounts for between 7% and 15% of global maternal deaths (Kassebaum et al., 2014). Of the 213 million pregnancies in world in 2012, 40% were

unintended and over 20% were aborted. More than half of all abortions in the world were unsafe (Sedgh et al., 2014, Vrachnis et al., 2016). MA is the induction of abortion using abortifacient medication alone (Gopal et al., 2017). It is a viable alternative to surgical options that is growing in popularity (Gatter, Cleland, & Nucatola, 2015; Ngo, Park, Shakur, & Free, 2011). MA allows safe, cheaper abortion services in demedicalized settings (Raymond, Shannon, Weaver, & Winikoff, 2013). Regimens of MIFE followed by MISO after a time gap is the norm for MA (Gatter et al., 2015; Raymond et al., 2013). This time gap has remained at 24 hours or more over the last 2 decades (Creinin et al., 2004; WHO, 2015) and makes MA a much longer process than surgical abortion. Furthermore, many countries do not allow the self-use of either drug (Gatter et al., 2015). Due to these reasons, women who want to have a MA are forced to stay in a health facility for over a day, make two or more visits, or take one or both drugs and complete the expulsion with no clinical supervision (Aiken et al., 2017). A shorter time protocol that is just as effective and safe could relieve these burdens.

Despite the future of MA research seeming to lay in finding ways to make MA shorter and simpler, little research has been conducted in this field. I could find only 13 studies that studied MA protocols with dosing intervals of less than 12 hours have been published over the last 15 years. These started with Pymar et al. (2001) studying a 6- to 8-hour dosing interval and ended with Verma et al. (2017) who studied a simultaneous dosing protocol. There are multiple gaps in this body of literature on shorter MA protocols. I could not discover any study that simultaneously compared more than two protocols. I also failed to discover any study that compared the 6-to 8-hour dosing

interval with simultaneous dosing. None of the authors in the 13 short-protocol studies pointed out these areas as requiring further research. The other significant gap was in secondary analyses of real MA patient data of any short MA protocol in any setting. All 13 published studies on short MA protocols were prospective studies, where the authors started gathering data knowing that the clients' outcomes would be analyzed for publication.

In this study, I will present efficacy and safety analyses based, for the first time, on a large, retrospective data set where the women underwent MA without a research setting. Such analyses of large patient data sets could uncover efficacy differences between these protocols administered in a research setting versus in day-to-day clinical practice. Another relevant gap in the literature exists around studies of 6- to 8-hour dosing intervals and simultaneous dosing in the United Kingdom. Guest et al.'s (2007) research represents the only published study that explored the protocol using the 6- to 8-hour dosing interval in the United Kingdom, while Lohr et al. (2007) is the only published UK-based study that explored the simultaneous dosing protocol. Both these studies have relatively small sample sizes, with Guest et al. having 215 women on the 6- to 8-hour dosing interval and Lohr et al. having 120 women in total. The United Kingdom differs from many countries with liberal abortion legislature in that home administration of any abortifacient is not allowed under criminal law (Francome, 2017). Analyzing the safety of the efficacy of both the 6- to 8-hour dosing interval and simultaneous dosing, my study findings could offer information that is of great value to women and healthcare providers in the United Kingdom and should be studied further.

Purpose of the Study

In this study, I employed a quantitative design and used regression analyses to explore the relationships of different MA protocols with different dosing intervals to the efficacy and safety of the procedures resulting from those protocols. In exploring the relationship between a MA protocol and the resulting safety of the procedure, I controlled for factors that have been shown to impact the safety of MAs conducted using MIFE and MISO (i.e., gestational age and the age of the pregnant woman). In exploring the relationship between the MA protocol and the efficacy of the procedure, I controlled for factors that have been shown to impact the efficacy of MAs conducted using MIFE and MISO (i.e., gestational age, maternal age, and the number of past deliveries). Hence, I had one independent variable (i.e., MA protocol, decided by the dosing interval). This variable had three levels (i.e., dosing interval of 24- to 36-hours, dosing interval of 6-to 8-hours, and simultaneous dosing). There were two dependent variables: safety (decided based on whether a given client faced a complication that required healthcare or not) and efficacy (decided based on whether a given client required an intervention to complete evacuation due to MA failure). Each of these variables had two levels (i.e., efficacious or not, and safe or unsafe). There were three control variables. Gestational age and the maternal age at the procedure were controlled for when exploring the relationship between the MA protocol and the safety of the procedure. I controlled for all three (i.e., gestational age, maternal age, and the number of past pregnancies) when exploring the relationship between the MA protocol and the efficacy of the procedure.

Research Questions and Hypotheses

Research Question 1: What is the relationship between the MA protocol time gap (i.e., 6 hours vs. 24 to 36 hours vs. simultaneous) and the safety of the procedure as measured by the percentage of women who experienced a complication that required medical care after controlling for factors that impact the safety of MAs conducted using MIFE and MISO (i.e., gestational age and maternal age)?

$H_0$1: There is no statistically significant relationship between the MA protocol time gap (i.e., 6 hours vs. 24 to 36 hours vs. simultaneous) and the safety of the procedure as measured by the percentage of women who experienced a complication that required medical care after controlling for factors that impact the safety of MAs conducted using MIFE and MISO (i.e., gestational age and maternal age).

H_A1: There is a statistically significant relationship between the MA protocol time gap (i.e., 6 hours vs. 24 to 36 hours vs. simultaneous) and the safety of the procedure as measured by the percentage of women who experienced a complication that required medical care after controlling for factors that impact the safety of MAs conducted using MIFE and MISO (i.e., gestational age and maternal age).

Research Question 2: What is the relationship between the MA protocol time gap (i.e., 6 hours vs. 24 to 36 hours vs. simultaneous) and the efficacy of the procedure as measured by the percentage of women who required a second intervention to complete the expulsion after controlling for factors that impact the

effectiveness of MIFE and MISO (i.e., gestational age, maternal age, and the number of past deliveries)?

$H_0$2: There is no statistically significant relationship between the MA protocol time gap (i.e., 6 hours vs. 24to 36 hours vs. simultaneous) and the efficacy of the procedure as measured by the percentage of women who required a second intervention to complete the expulsion after controlling for factors that impact the effectiveness of MIFE and MISO (i.e., gestational age, maternal age, and the number of past deliveries).

H_A2: There is a statistically significant difference between the MA protocol time gap (6 hour vs. 24 to 36 hours vs. simultaneous) and the efficacy of the procedure as measured by the percentage of women who required a second intervention to complete the expulsion after controlling for factors that impact the effectiveness of MIFE and MISO (i.e., gestational age, maternal age, and the number of past deliveries).

Theoretical Foundation

The framework of this quantitative study was formed by postpositivism and empiricism (Theory of Knowledge, 2015). The linear, uni-directional nature of my study design aligns with positivism; however, the relative complexity of postpositivism when compared to positivism (see Tashakkori & Teddlie, 1998) was a better fit, especially when interpreting and generalizing the findings. Postpositivism is not limited to the observable (Clark, 1998) and holds that objectivity is an ideal but requires critical interpreters (Fischer, 1998). Postpositivism takes a realist perspective of science and

demands that science requires precision, logical reasoning, and attention to evidence (Theory of Knowledge, 2015). If, at the end of my study, I found that the two shorter protocols (or one of them) had efficacy and safety values that were acceptable (albeit lower in comparison to the conventional protocol), the postpositivist approach would allow me to recommend such a protocol for wide use given the benefits (both subjective and objective) that it would bring to women across nations. Tashakkori and Teddlie (1998) showed that studies grounded in a postpositivist framework allow subjectivity as well as allow researchers to take the realities of life at the point in time into account while interpreting their results. Postpositivism is well aligned with the ability of a simpler MA protocol to possibly improve women's subjective MA experience by shortening the time needed and removing the need for an overnight experience. Grounding my study in a postpositivist theoretical framework allowed me to follow an objective path and set aside my views of abortion and my opinion of MA. The postpositivist approach allowed me to remain objective, for observers with varying stances on abortion can set them aside and focus on the tangible, quantitative, observation-based findings.

Empiricism stresses that observation and measurement form the core of scientific study (Trochim, 2006). Baird and Kaufmann (2008) showed how researchers who design studies grounded through empiricism recognize empirical evidence and the knowledge received through observation and experimentation in the formation of ideas. In my study, I derived results and conclusions using a quantitative, scientific approach and measured the efficacy and the safety of the MA protocols by scientific analysis of observed, retrospective, patient data. The empirical approach I used in this study was reductionist,

reducing research ideas into a small, discrete set of variables that comprise hypotheses and research questions (see Creswell, 2013). Empiricism was aligned with this study by assessing the effectiveness of the outcomes of those receiving a new intervention compared with outcomes of the group who received the conventional regimen (see Davies & Nutley, 1999).

Olsen (2004) claimed empiricism is behind a mathematics-fetishism that promotes quantitative study and puts off qualitative research. While meant as a criticism, the claim showed that empiricism was a good fit for this study where objective, quantitative analyses of independent, dependent, and control variables were conducted with the aim of quantifying the efficacy and safety of different MA protocols. I developed the hypotheses of this study to focus on objective efficacy and safety outcomes of three MA protocols. A postpositivist and empiricist approach supported measuring the efficacy and the safety of MA protocols using objective, measurable, independent, dependent, and control variables as well as the interpretation of the findings without discarding subjective benefits for women.

Nature of the Study

In this study, I conducted a retrospective analysis of a large secondary data set from one of the largest abortion care providers in the United Kingdom. Authors who discussed research study designs (i.e., Creswell, 2013; Frankfort-Nachmias & Nachmias, 2008) as well as authors of past quantitative studies that explored abortion outcomes and abortion safety (Li et al. 2011; Tendler et al., 2015; Verma et al., 2017) provided rationale for my study design choice. Secondary data use and retrospective designs allow

large sample sizes to be studied with much lower burdens in terms of resources, logistics, and time (Creswell, 2013; Frankfort-Nachmias & Nachmias, 2008). A retrospective cohort analysis of a large secondary data set allowed me to include large sample sizes under each of the three protocols without infringing on women seeking a MA being able to choose their preferred protocol. The data set includes the medical records of over 25,000 women who underwent MA services within 1 calendar year from the abortion provider. I was able to find adequate sample sizes for each of the three MA protocols from within this large data set, allowing me to conduct this study with good power and confidence intervals.

Past authors of quantitative studies who compared or measured the efficacy and the safety of various MA protocols have commonly used quantitative designs. In their systematic review on the effectiveness, safety, and acceptability of MA protocols, Sjöström et al. (2017) focused on six studies that assessed these parameters; all six had quantitative, cohort analysis designs. In their systematic review of the clinical outcomes and adverse effects of MA regimens, Chen and Creinin (2015) included 20 studies that included a total of 33,846 women. All the studies in their review had quantitative designs, with four using retrospective cohort analyses and 16 using prospective cohort analyses. In their systematic review of the efficacy of different MA protocols, Shaw, Topp, Shaw, and Blumenthal (2013) included 29 studies; all were quantitative designs, with nine being observational designs.

In this study, I had one independent variable (i.e., MA protocol, decided by the dosing interval) with three levels (i.e., dosing interval of 24 to 36-hours, dosing interval

of 6- to 8-hours, and simultaneous dosing). I had two dependent variables, each with two levels and three control variables. All three (i.e., gestational age, maternal age, and parity) were controlled for when exploring the relationship between the MA protocol and the efficacy of the procedure. Only gestational age and maternal age were controlled for when exploring the relationship between the protocol and the safety of the procedure.

Using a retrospective cohort design, I conducted a retrospective analysis of a large secondary data set obtained from one of the two largest abortion care providers in the United Kingdom. The data from MA clients are captured at multiple centers that are operated by one organization across the United Kingdom. All clinics use the same health information system. All client data are housed in a common database, which was the source of my data set. The database captures over 100 data points for each client, from among which, I obtained the data on the independent, dependent, and the control variables for any client. If the record of a client was incomplete due to human error in entering client information into the health information system, those clients were excluded from the study. I analyzed the relationship between the independent variable and the dependent variables using regression analysis, which allowed me to control for the relevant control variables when analyzing the relationship of the MA protocol to each dependent variable. The organization provided me with a de-identified data set with all data points that could potentially be used to identify a client removed. This de-identification was done by the organization, and I did not have access to data with identifiers at any point in the process. The de-identification was carried out at the point

when the data were transferred from the master database to the Excel format in which I received it.

Definitions

The following definitions for the safety and efficacy of MAMA is limited to this study. While several authors have used these or similar definitions in MA-related research (e.g., Gatter et al., 2015; Smith et al., 2014), others have differed in the definitions used. As stated by Whitehouse et al. (2017), the process of developing universal definitions for these terms is ongoing.

Abortion: A procedure for terminating a pregnancy (Ganatra et al., 2014).

Dosing interval: The time gap between the MIFE dose and the first/only MISO dose when performing a MA given in hours (Shaw et al., 2013).

Medical abortion: The induction of abortion using medication alone (Gopal et al., 2017).

Medical abortion complication: Receiving an abortion-related diagnosis or treatment at any source of care within 6 weeks after an abortion (Upadhyay et al., 2015)

Medical abortion efficacy: The percentage of women who took a single MIFE dose followed, after a dosing interval, by a single MISO dose for a MA that did not require a second MISO dose or a vacuum aspiration to complete expulsion (Guest et al., 2007).

Medical abortion safety: The percentage of women who took a single MIFE dose followed, after a dosing interval, by a single MISO dose for a MA that did not encounter complications or side effects that required a clinical consultation (Raymond et al., 2013).

Parity: The number of past pregnancies that a woman undergoing a MA has carried to term (Ota et al., 2014).

Unsafe abortion: A procedure for terminating a pregnancy performed by persons lacking the necessary skills or in an environment not in conformity with minimal medical standards, or both (Ganatra et al., 2014).

Assumptions

In my study, I assumed that women who seek first trimester MAs at the clinics managed by the organization who provided my data set were representative of all women who seek first trimester MAs in the United Kingdom (except for Northern Ireland) in terms of their age, their gestational age at seeking an abortion, and their parity. This assumption was based on MA being allowed across the United Kingdom (except for Northern Ireland) up to 10 weeks and only using MIFE and MISO (see Francome, 2017). It was also based on the large size of my data set, increasing the likelihood of women representative of those seeking MA in the United Kingdom being captured and the fact that the clinics where the data come from being spread widely across the United Kingdom (except for Northern Ireland). In interpreting my findings and generalizing them to the rest of the world, I assumed that women who seek first trimester MAs in the United Kingdom are comparable to such women in other settings in term of their biology. I was aware that women seeking MAs in the United Kingdom may differ from those in other settings in terms of their age, their gestational age, and their parity; however, these variables are controlled for in my analyses.

Another assumption was that women in general would find MA protocols that are shorter and simpler more attractive if they have acceptable levels of safety and efficacy. Levine and Cameron (2009) and Cameron et al. (2010) showed that MA where expulsion occurs at home is acceptable to most women, including to women in resource-poor settings. Both shorter MA protocols included in my study allow women to complete the expulsion at their homes with greater privacy, giving women greater control over the timing of abortion and allowing family or friends to provide emotional support. Ho (2006), Clark et al. (2007), and Iyengar et al. (2016) showed that women who seek abortions find these options attractive.

The final assumption was that women who receive MIFE and MISO at a clinic where my data set comes from and return home contact the abortion provider in the case of incomplete expulsion or side effects or complications that require further medical care. This assumption was based on the facts that the organization maintains a 24-hour toll-free hotline, women who receive an abortion from them receive a unique identifier number that allows them to be easily recaptured into the medical information system if they were to seek follow-up care, and that any such care is provided free of charge. These facts make it highly unlikely that a woman who has significant side-effects, complications, or has an incomplete expulsion would contact another provider. All women who seek abortion care at the said organization receive pre procedure as well as pre discharge counselling. The signs and symptoms of incomplete expulsion as well as of side effects and complications that necessitate further care are clearly given to all women. The

robustness of these counselling sessions makes it highly likely that women would fail to recognize a situation where they must contact the provider again.

The above three assumptions were critical to this study. The first was critical because it allowed the safety and efficacy rates found in the study to be generalized across the United Kingdom as well as across settings outside the United Kingdom within the maternal age, gestational age, and parity restrictions. The second assumption was critical because it allowed MA protocols that have acceptable safety and efficacy levels to be interpreted as protocols that women would prefer, allowing the safety and efficacy of a given medical protocol to be proxy measures of its attractiveness and acceptance to women in all settings. The final assumption was critical because the organization whose data I used do not conduct active follow-up appointments with women who return home following the MISO dose, assuming instead that the robustness of counselling, the ease with which such women can contact them, and the fact that any woman who experiences serious side-effects or complications or who need extra procedures to complete expulsion receive free care would lead to them contacting the organization in those circumstances.

Beyond these assumptions, I also assumed the accuracy and reliability of the secondary data that my study was based on. Upon receiving the anonymized data set, I manually screened the data points relevant to the analyses of each patient, and patients whose records were missing one or more data points required for the analyses were excluded. However, this process did not capture any inaccuracies in entered data. I assumed that key data points, such as the age and parity of each woman, the gestational age at their presentation to the clinic, and the information given on the MA protocol

received, are accurate. Furthermore, if an identifier number of a given MA recipient did not appear among the identifiers of women who had a second contact with the clinic network due to a complication, adverse event, or due to incomplete expulsion, I assumed that they had a safe and efficacious procedure according to the variable definitions.

Scope and Delimitations

In my study, I compared the efficacy and the safety of MAs in women with gestational ages below 10 weeks. The length of the MA procedure was used as the single independent variable of the study. Cost, level of pain, and the length of bleeding were other factors that have been studied in past abortion research (Bracken et al., 2014; Fiala et al., 2014; Lo & Ho, 2015). I chose the topics of efficacy and safety for this study because they are the two parameters that regulatory bodies mostly consider when approving new abortion procedures (see Ganatra et al., 2014). Other factors such as cost, pain, and bleeding period relate more to the acceptability of an abortion procedure by women (Louie, et al., 2014; Swica et al., 2013). While important, these factors were left out due to my focus on comparing the efficacy and the safety of the different MA protocols in this study.

This study has a high generalizability to women seeking MAs using the protocols studied prior to completing the 10th week of gestation. The generalizability is limited to women seeking a MA at one of the United Kingdom's largest abortion providers. The subjects are likely to be British (while any woman who walks into a clinic can obtain a procedure) and likely to be registered with the National Health Service (i.e., most of the British population) because a procedure costs a nonregistered woman approximately

U$500. Nonregistered women who paid for the procedure fee were included in the sample frame. Despite being limited to (mostly) British women who are (mostly) registered with the National Health Service, the specific gestational age limits and the specific MA protocols support generalizing the findings to MAs below 10 weeks using these exact protocols in settings outside of the United Kingdom. The professional standards of UK abortion providers (Chamberlain, 2017; Rubin, 2014) is unlikely to limit generalizability to settings where a MA is carried out by lower level providers because MAs carried out by them have been shown to be safe (Løkeland et al., 2014; WHO, 2015).

I considered positivism and empiricism as standalone theories for this study. Positivism was a suitable framework for the linear, uni-directional, flow of my study design (see Theory of Knowledge, 2015). Manjikian (2013) demonstrated that positivism suits studies where observations are analyzed, hypotheses tested, and conclusions reached. Hjørland (2005) and Theory of Knowledge (2015) showed positivism to be suitable for quantitative study models; however, the room afforded by postpositivism to introduce subjective interpretation of analyses was critical to summarizing the findings of this study, allowing me to focus not simply on how the efficacy and safety of the three MA protocols compare to one another but also consider the benefits given to women by the shorted protocols. I also considered empiricism as a standalone framework. Hjørland (2005) demonstrated similarities between empiricism and today's positivism and showed how theoreticians see experienced or observed data as the only way of acquiring knowledge. My ultimate choice of theoretical framework was a postpositivist approach

that places empirical studies in a broader framework based on a contextual understanding of social inquiry (see Fischer, 1998).

Limitations

Cohort designs are suitable when describing subgroups within a population with respect to an outcome and a set of risk factors (Levin, 2006). Past studies have showed the likelihood of MA failure and MA complications to be very low with MIFE and MISO combinations (WHO, 2015). This made a cross-sectional design with a large sample size a practical choice. A retrospective design allows larger sample sizes for each protocol, thereby increasing power and narrowing the confidence intervals. Cohort designs suit studies that describe patterns of relationships between variables (Frankfort-Nachmias & Nachmias, 2008). Such a design was appropriate for this study because I developed the research questions to address the correlation between MA protocols and the safety and the efficacy of the resulting procedures instead of proving a causality. The other benefits of using a retrospective cohort are the low financial and temporal cost, the ability for the analysis to include multiple control variables, and having no risk of loss to follow up (Levin, 2006; Sedgwick, 2014).

Using an observational study design instead of an experimental design with randomization was a major limitation of my study. Observational studies are less rigorous than true experiments with randomization (Creswell, 2013). The design used in this study does not allow an experimental approach where the independent variable(s) can be manipulated to observe the effect(s) of such manipulation on the dependent variables (see Frankfort-Nachmias & Nachmias, 2008). The design does not exclude the likelihood of

either MA failure or complications arising due to factors other than the protocol used, although this was minimized by controlling for several control variables. My use of real-life data, not data collected for research under research rigor was another limitation. The accuracy of the records included in the analyses was maximized, however, by my review of each client record to check for completeness. The large sample size that represents the UK population included in my study improves the generalizability despite the design used (see Levin, 2006).

I considered both experimental and quasi-experimental, prospective, quantitative designs for this study. Prospective designs (either experimental or quasi-experimental) that could answer the two research questions with an adequate sample size were rejected due to logistical, financial, and time constraints (see Creswell, 2013). Given that the failure of MAs is lower than 5% when MIFE and MISO combinations are used (WHO, 2015), capturing a significant number of failures in the three MA protocol groups would require a long prospective, follow-up period (see Creswell, 2013). A full experimental design was also unfeasible due to randomizing women into one of the three MA protocols without giving consideration to the choice of the individuals raising significant ethical challenges. While a prospective design could lead to more robust data being gathered (Frankfort-Nachmias & Nachmias, 2008), it would have required dedicated data gatherers and training of the clinical staff that enters patient data into the information system to achieve that higher data quality. An experimental design would be more resource intensive compared to a quasi-experimental design (Creswell, 2013; Frankfort-Nachmias

& Nachmias, 2008), and the selected retrospective cohort analysis design is less resource intensive than both of the previously mentioned designs.

Significance of the Study

The body of literature on MA is wrought with gaps. My exhaustive literature review discovered 13 published studies that included short-protocol studies. None of those studies simultaneously compared more than two protocols, and none compared the 6- to 8-hour dosing interval with simultaneous dosing. Both the 6- to 8-hour dosing interval and the simultaneous MIFE and MISO dosing have the potential to shorten the MA process, potentially allowing women to complete their MA at home. Homebased MAs could improve women's acceptability by allowing greater privacy, giving women greater control over the timing of the process, and allowing family or friends to provide emotional support (Clark et al., 2007; Ho, 2006). Taking MISO at home has also been shown to be acceptable to women in resource-poor settings (Iyengar et al., 2016; Louie, et al., 2014). Past MA literature also lacks studies that undertook secondary analyses of real MA patient data of any short MA protocol. No researcher studying a MA protocol with a dosing interval less than a day has analyzed a retrospective data set. Each of the 13 short MA protocol studies that have been published so far were prospective. Efficacy and safety analyses using a large, retrospective data set where the women underwent a MA outside of a research setting could uncover efficacy differences between these protocols administered in a research setting versus in day-to-day clinical practice.

The results of this study could also fill a gap in the literature concerning 6- to 8-hour and simultaneous dosing conducted in the United Kingdom. Only one study that

explored the 6-to 8-hour dosing interval (Guest et al., 2007) and one that explored the simultaneous dosing protocol (Lohr et al., 2007) has been published in the United Kingdom. Both studies had small sample sizes, with Guest et al. (2007) having 215 women and Lohr et al. (2007) having 120 women in total. The United Kingdom differs from many countries with liberal abortion legislature in not allowing home administration of MISO (Francome, 2017). Demonstrating that the 6-to 8-hour dosing interval protocol or the simultaneous dosing protocol has acceptable safety and efficacy would be of great value to women and healthcare providers in the United Kingdom. Such findings could potentially lead to a MA protocol change or expansion in the United Kingdom. Such a change in the United Kingdom could potentially have a cascading effect on the MA protocols used in other commonwealth countries and bring these protocols to the notice of organizations such as the WHO, United Nations Population Fund, International Federation of Gynecology and Obstetrics, and the Royal College of Obstetrics and Gynecology.

These organizations guide reproductive health practices across the globe. Hence, policy and guideline changes in these institutions would lead to a change in the way MA is practiced across the world. If they become the global norm, these shortened MA protocols could bring safe, first trimester MAs that are completed at home within the reach of millions of women across the globe. The public health and social implications that these changes could lead to further augment the significance of my study.

Half of the approximately 50 million annual abortions in the world are unsafe (Sedgh et al., 2014; Vrachnis et al., 2016). These unsafe abortions produce an estimated

4.7% to 15% of the approximately 300,000 global annual maternal deaths (Filippi et al., 2016). MA is safer, cheaper, and less medicalized compared to surgical abortion (Simmonds et al., 2017; Zane et al., 2015). The shorter MA protocols that I might demonstrate to be alternatives to the current lengthy protocols can persuade more women to choose MA instead of surgical abortion. MA becoming a 1-day process could also entice more clinics, hospitals, and practitioners to offer it. Both of these changes can increase access to safer abortions for women across the world, and in turn, reducing the morbidity and mortality that is seen today due to unsafe abortions. Healthcare systems and governments could save resources that are currently spent both for providing more expensive surgical abortions as well as for managing complications from unsafe abortions due to MAs becoming commoner and more acceptable to women. With MIFE registered in 57 countries (Dunn & Cook, 2014) and MISO registered in over 100 countries (Medication Abortion, 2016), a 1-day MA protocol that uses these two drugs could give millions of women access to safer abortions and prevent many surgical abortions due to women opting for the (now) fast and efficient MA option.

Summary and Transition

MA is rapidly growing in popularity among the approximately 40 million women who seek an abortion each year (Gopal, Ganamurali, & Kumari, 2017; Grossman & Goldstone, 2015). A growing percentage of those 40 million women who might have resorted to unsafe surgical abortion are now turning to safer medical options for their termination (Sedgh et al., 2014; Vrachnis et al., 2016). The length of the MA procedure, which is predominantly dictated by the dosing interval between MIFE and MISO,

remains a key barrier to MA becoming a shorter and simpler process that women could complete at home in relative comfort. The literature on MA has notable gaps with regards to explorations of protocols that are shorter and simpler than the present norm. In this study, I compared the efficacy and the safety of two MA protocols with dosing intervals shorter than a day to the conventional protocol and to each other. If one or both shorter MA protocols was shown to have acceptable efficacy and safety, they could potentially replace the lengthier conventional protocol, making MA a shorter and simpler procedure that many more millions of women find acceptable.

In Chapter 1, I highlighted the public health importance of shorter, simpler, MA protocols and outlined the gap that I aimed to fill in the field of MA research. In the chapter, I presented a brief background, the problem statement, and its purpose. Chapter 1 also included a presentation of the research questions and the hypotheses along with the variables of the study. The theories used to guide this study and form its theoretical foundation were outlined. Definitions of the different terms related to MA that I used in the study were also presented. Additionally, the nature of the study was presented, along with its assumptions and limitations and its significance from the perspectives of public health and social change.

In Chapter 2, I will provide a broader background on MA and the drive to simplify and shorten MA. In the chapter, I will present the literature review and the analysis done on existing research to find the gap that I attempted to fill with this study. I will also outline the research question, hypotheses, the problem statement, and the objectives of my study. I will also compare MA literature in the chapter, giving specific

focus to studies conducted on MA protocols with a dosing interval of less than 12 hours. Chapter 2 will also include a broader account of the theoretical framework of my study and a presentation of the relationships among the key variables of the study based on past literature.

Chapter 2: Literature Review

Restating the Problem

Devereux (1954, p. 98) stated that "Abortion is an absolutely universal phenomenon, and it is impossible to imagine a social system in which no woman would ever feel at least compelled to abort". Despite centuries of debate over the morality, legality, and the ethics of abortion and irrespective of whether abortion was outlawed where they lived, women have terminated undesired pregnancies (Dellapenna, 2006). Hippocrates instructed women who wished an abortion to jump repeatedly, touching their buttocks with their heels (Fant & Lefkowitz, 1992). *The New York Times* estimated that 200 abortionists were active in New York in the 1870s (Gordon, 1976). Women have used primitive practices, such as weightlifting, strenuous labor, fasting, irritant leaves, and bloodletting, to induce abortions (Devereux, 1967). Thyme, worm fern roots, and other infusions have been used to induce abortions since the time of Nero (Gordon, 1976). More recently, the ingestion of turpentine, ammonia, mustard, and other substances have been used to induce abortions (Devereux, 1967; Gordon, 1976).

The WHO (1992) defined a maternal death as "the death of a woman whilst pregnant or within 42 days of delivery or termination of pregnancy, from any cause related to, or aggravated by pregnancy or its management, but excluding deaths from incidental or accidental causes" (section 15). Unsafe abortion is a "procedure for terminating an unintended pregnancy either by people lacking the necessary professional skills or in an environment lacking the minimal medical standards, or both" (WHO, 2011, p. 5). In 2012, there were 213 million pregnancies in world, with 85 million being

unintended and over 40 million of the unintended pregnancies being aborted (CITE). Over half of the 40 million abortions were carried out in an unsafe manner (Sedgh et al., 2014; Vrachnis et al., 2016). In 2015, there were 303,000 maternal deaths in the world, with unsafe abortion causing an estimated 4.7% to 15% of them (Filippi et al., 2016; Kassebaum et al., 2014).

The induction methods used for abortion in the last 3 decades can be classified as either surgical or medical. Curettage, invented in 1844, was the first widely used surgical method despite its high complication risks (Wu & Wu, 1958). Wu and Wu (1958) designed the first electric vacuum aspiration in 1958 (Coombes, 2008), and this was the primary method of inducing abortion in the 1960s (Li, Lee, & Wang, 2017). In the 1970s, manual vacuum aspiration was developed by Karman with the aim of replacing the risky curettage in low resource settings (Potts, 2010). With prostaglandins, such as MISO, becoming available in the early 1970s and anti-progesterones, such as MIFE in the 1980s, MA, the induction of abortion using medication alone (Gopal, et al., 2017), became an alternative to vacuum aspiration (Kulier et al., 2004). MIFE in conjunction with a prostaglandin is effective for early pregnancy termination (Urquhart et al., 1997), and MA quickly became a popular alternative to surgical abortion (Gatter et al.; Ngo et al., 2011)

Clinically, first trimester, legal abortion carries much less risk compared to childbirth; Raymond and Grimes (2012) showed that the mortality risk associated with childbirth is approximately 14 times higher than that with legal, first trimester abortion. The authors also showed that the overall morbidity associated with childbirth greatly

exceeds that with legal, first trimester abortion. Berer (2017) showed that abortion is safer when it is available on request, is affordable, and accessible. Hence, any woman who carries an unintended pregnancy to term due to her inability to access a safe abortion is being forced to putting her health and safety at risk. Even in contexts where abortion is legally allowed, requiring high-level clinicians or surgeons to provide the service and limiting abortion provision to high-level care facilities blocks women's access to safe abortion services (WHO, 2012). These facts demonstrate the need for addressing what developments could make abortion cheaper, simpler, and remove provider type related barriers that limit access to safe abortion.

Study Purpose

In this study, I compared the efficacy and the safety of three MA protocols. The first uses the conventional 24- to 36-hour dosing interval between the drugs. The second uses a 6-hour dosing interval between the drugs, while in the third, the two drugs are administered simultaneously. I used a retrospective cohort analysis of a large secondary data set of MA patients in this comparison. Efficacy of a protocol was measured by the percentage of women who had a MA using the said protocol that required either an additional abortifacient dose or a vacuum aspiration to complete the procedure. Safety of a given MA protocol was measured by the percentage of women who had a MA using the said protocol that experienced a complication that required clinical care.

Concise Synopsis of the Literature Review Findings

Current, safe, abortion induction is carried out using several surgical and medical protocols (Gaudineau, Agostini, & Vayssière, 2016; Morris et al., 2017). WHO (2012)

and Gaudineau et al. (2016) recommended manual and electric vacuum aspiration for surgical abortion up to 14 weeks and combinations of MIFE and MISO (exact protocols varying with gestational age) for MA. MA allows safe, cheaper, abortion services in de-medicalized settings (Raymond et al., 2013; Simmonds et al., 2017; Zane, et al., 2015). Women can complete a MA at home without follow up at a health facility (Mählck & Bäckström, 2017). Women who wish to avoid surgery or anaesthesia value having a choice of abortion method (Hamoda & Templeton, 2010). MA should be routinely available to women, and it is the best option for improving safe abortion access for women (Hamoda & Templeton, 2010; Orrantia & Armand, 2017).

Although prostaglandins other than MISO can be used with MIFE, due to lower incidences and severity of side effects and lower costs, MISO is the preferred prostaglandin option (Sang, 1999; WHO, 2010). While MISO alone in different dosages can be used to induce abortion at different gestational ages, it is always inferior to MIFE and MISO combinations (WHO, 2012). Regimens of MIFE followed by a dosing interval by MISO is the norm for MA (Gatter et al., 2015; Raymond, et al., 2013). This time gap has remained at 24 hours or more over the last 2 decades (Creinin et al., 2004; WHO, 2015), making MA a much longer process than surgical abortion. Furthermore, many countries do not allow the self-use of either drug (Gatter et al., 2015). Due to these reasons, women who want to have a MA are forced to stay in a health facility for over a day, make two or more visits, or take one or both drugs and complete the expulsion with no clinical supervision (Aiken et al., 2017).

Starting with studies of MIFE in combination with varying prostaglandin analogues (Baulieu, 1985; Yan, 1983), many aspects of different MA protocols at various gestational ages have been studied over the past 3 decades. MA research has sought the best prostaglandin analogue to be coupled with MIFE (Avrech et al., 1991; Swahn & Bygdeman, 1989), the most efficacious dosages of MIFE and MISO (Creinin, 2000; McKinley, Thong, & Baird, 1993), and the best routes of MISO administration (Aubeny & Chatellier, 2000; Newhall & Winikoff, 2000). The most efficacious doses being broadly established as 200mg of MIFE with 800 µg of MISO (Raymond et al., 2013), MA research has also assessed the feasibility of MA completed or fully conducted at home (Constant et al., 2017; Purcell et al., 2017) and lighter-touch approaches of following-up with women who had MA (Anger, et al., 2017; Chen et al., 2016) and expanded into shortening the length of the MA process by shortening the dosing interval. However, only 13 studies have been conducted with researchers exploring MA protocols with dosing intervals below 12 hours. The first (i.e., Pymar et al., 2001) as well as others (i.e., Creinin et al., 2004) have showed comparable efficacy between MIFE 200 mg, followed 6 to 8 hours later by MISO 800 µg vaginally and the conventional protocol (i.e., 24- to 36-hour dosing interval) at gestational ages below 49 days. Fox et al. (2002) and Guest et al. (2007) showed that the 6- to 8-hour dosing interval for MA up to 63 days of gestation provides acceptable efficacy. Creinin et al. (2004), authors of the first randomized trial, also showed comparable efficacy between the 6- to 8-hour dosing interval and the conventional protocol. Protocols with simultaneous dosing at gestational ages up to 49 days (Li et al., 2006; Li et al., 2011; Murthy et al., 2005), 56 days (Kapp et

al., 2006), and 63 days (Creinin et al., 2007; Schreiber et al.; Verma, et al., 2017) have been shown to have expulsion rates of approximately 90%. Only Lohr et al. (2007) showed simultaneous dosing to have expulsion rates below 80% at all gestational ages (below 49 days, 50–56 days, and 57–63 days).

Outline of the Chapter

In this chapter, I will outline the literature review conducted related to the clinical areas related to the study as well as to the theoretical frameworks that underpins it. Literature findings on multiple aspects of abortion provision will be presented with a strong focus on MA. The evolution of current abortion will be reviewed, focusing briefly on the evolution of current surgical methods and the inception of MA. How the introduction of MA affected the abortion care landscape with regards to women's preference of method, women having a choice between two approaches (i.e., medical versus surgical), and how access to safe abortion increased will be outlined. I will review past research into the ideal dosing of MIFE and MISO as well as research into the best route of MISO administration. Research in to reducing the length of the MA process by reducing the dosing interval between the MIFE and MISO will be exhaustively reviewed. Through this, I will outline the journey from a 36- to 48-hour dosing interval to the 6- to 8-hour dosing interval and to complete removal of the dosing interval (i.e., simultaneous MIFE and MISO dosing). I will present the key research gaps found in studies of shorter, simpler MA protocols. In this chapter, I will also present past findings on abortion, including an exhaustive review of past studies conducted in attempts to reduce the dosing interval between MIFE and MISO in early MA. A review of the literature around the key

variables and a summary will also be provided. Finally, an account of postpositivism and empiricism, the theoretical frameworks that underpinned this study will be presented. Brief accounts of the evolution of postpositivism and empiricism and the links between is the two will be provided. The use of postpositivism and empiricism in studies like mine in the past and the suitability of these theories as the theoretical frameworks for this study will be demonstrated.

Literature Search Strategy

I conducted the literature review for this study through searching multiple, peer-reviewed, scholarly articles from reputable databases. The databases searched were PubMed, Cumulative Index to Nursing and Allied Health Literature (CINHAL), Medline with Full Text, Health and Medical Complete (ProQuest), and the Cochrane Database of Literature reviews. The search terms used were *medical abortion, pregnancy termination, mifepristone + abortion, mifepristone + termination, misoprostol + abortion,* and *misoprostol + termination*. I limited the search to these databases because adding more databases resulted in search result overlap rather than new findings. Articles going back to 30 years were screened to capture important knowledge on the inception of MA; however, my review of evidence related to the simplification and shortening the MA process focused on evidence from the last 15 years, with a heavy focus on evidence published in the last 5 years. I reviewed 813 articles, with 260 published in or after 2012.

Literature was searched for multiple aspects of abortion, with a stronger focus on MA. The evolution of current abortion was reviewed, focusing briefly on the evolution of current surgical methods and the inception of MA were explored. The effect of MA with

regards to women's preference of method, women having a choice between two approaches (medical versus surgical), and how access to safe abortion increased due to MA was explored. Research into finding the ideal dosing of the two abortifacient medications MIFE and MISO were explored, as well as research into the best route of MISO administration. The greatest focus of the literature review was focused on research that explored ways to reduce the length of the MA process by reducing the dosing interval between the MIFE and MISO. Through the review of literature on reducing the dosing interval, the journey from a 36- to 48- hour to the 6- to 8- hour dosing interval and to complete removal of the dosing interval (simultaneous dosing) was outlined

Variations in Global MA Practice

With MISO becoming available since the early 1970s and MIFE being available since the 1980s, various MA protocols that use these in conjunction have been used for early pregnancy termination (Urquhart et al., 1997). Currently, MIFE is registered in 57 countries (Dunn & Cook, 2014) and MISO in over 100 (Medication Abortion, 2016). MA using MIFE and MISO combinations is allowed in all countries where MIFE is registered. This includes most European countries with a few exceptions such as Malta, Ireland, Poland, Czech Republic, and Slovakia (Medication Abortion, 2016). The list of countries where MA using MIFE and MISO combinations is allowed also includes low and middle-income countries such as India, Nepal, Bangladesh, Ethiopia, Vietnam, and Ghana (Medication Abortion, 2016). However, the indications for which an abortion is allowed, and the intricacies of what is allowed and prohibited when providing a MA differs greatly among these 57 countries.

For example, England and Wales does not allow either MIFE or MISO to be taken outside of a health facility, while in Scotland, prescribed MISO can be taken by women at home (Regan & Glasier, 2017). India and Nepal have laws that are less restrictive than many European countries, allowing both MIFE and MISO to be obtained from pharmacies with a prescription (Powell-Jackson et al., 2015). This is also the case in Australia (Grossman & Goldstone, 2015). Bangladesh, a colourful example of the variety seen in legal MA, allows on demand termination of pregnancies using MIFE and MISO up to 10 weeks of gestation but under the medical term menstrual regulation (Singh, et al., 2017). In countries with MIFE and MISO allowed but have restrictions on home use and use of either drug without direct medical supervision, those restrictions are based on a lack of confidence in the safety and efficacy of MAs carried out using the combination (Regan & Glasier, 2017).

Key Variables

The Efficacy and Safety of Medical Abortion

Reaching a consensus regarding how MA safety and efficacy should be measured has been challenging (Whitehouse et al., 2017). This difficulty extends into measures of abortion outcomes in clinical trials, with selecting and reporting on outcomes across trials showing a large variation (Creinin & Chen, 2016). Under the Core Outcome Measures in Effectiveness Trials (COMET) Initiative (2017), doctors Whitehouse and Gulmezogluthe of the WHO are in the process of developing a core outcome set for induced abortion. Until those are published, The MA Reporting of Efficacy (MARE) guidelines (Creinin & Chen, 2016) represents the only guidance available to streamline abortion outcomes for

efficacy. The authors recommended that MA failure must be clearly defined (e.g., ongoing pregnancy, incomplete abortion, and participant symptoms).

Routine follow-up visits are not needed for women who undergo MA using MIFE and MISO (Mählck & Bäckström, 2017; WHO, 2012). Less than 5% of them require surgical intervention to resolve incomplete abortions, continuing pregnancies, or bleeding (Gopal et. Al., 2017). Pain is the main side effect, and in most cases, simple analgesics easily manage the pain of MA (Cavet, Fiala, Scemama, & Partouche, 2017). Other side effects (diarrhoea, fever, and abdominal pain) rarely reach a severity that require facility care (Lo & Ho, 2015; Nijman et al, 2017). In defining MA efficacy, my study considered both an ongoing pregnancy and an incomplete abortion as failures (Gatter et al., 2015; Gopal et al., 2017). Complications and severe adverse events defined MA safety, with the percentage of women who had a MA using a given protocol and did not experience symptoms that needed further health facility care being used as the indicator of the protocol's safety (Gatter, et al., 2015; Sanhueza, et al., 2014).

Abortifacient Dosing Interval and the Route of MISO Administration

The recent Medical Abortion Reporting Efficacy (MARE) guidelines (Creinin & Chen, 2016) and Standardizing Abortion Research Outcomes (STAR) initiatives (Whitehouse et al., 2017) outlined how abortifacient exposure should be presented in abortion research. Both dictated that the drugs used, their dosage(s), the dosing interval in hours, and route(s) of administration must be given. Many researchers have explored varying dosages and routes of administering MIFE and MISO (Meena, 2016; Tsereteli et al., 2016; Sheldon et al., 2017). The dosages of both have varied continuously, with

researchers seeking the dosages of both drugs that provide the best balance between efficacy of the MA procedure and not exposing women to unnecessary dosages, and hence to more side effects. Many countries' standard dosage for MIFE in first trimester abortion was initially set at 600mg (Raymond et al., 2013). However, recent study findings have resulted in the standard MIFE dose to be reduced to 200mg (Faundes, 2011; RCOG, 2011; WHO, 2012).

Irrespective of gestational age, MIFE is always administered orally (WHO, 2012). The best route of MISO administration however, has been the focus of many researchers. WHO (2012) recommended four routes of MISO administration (vaginal, buccal, sublingual or oral) for pregnancies less than 9 weeks (63 days). The MISO dosages recommended are 800 µg for vaginal, buccal, and sublingual routes and 400 µg for the oral route. Oral MISO has lower MA efficacy compared to the vaginal, buccal, and sublingual routes (Raymond et al., 2013) and is therefore not recommended for gestational ages over 7 weeks (WHO, 2012). All patients included in my study received MISO through the buccal route. The evidence on MA efficacy based on the route of MISO played a critical role when analyzing the efficacy of the different MA protocols in my study and when assessing the suitability of those protocols to be considered as viable alternatives to existing protocols.

Apart from the dose and the route of MISO, the key variable in MA protocols is the gap (dosing interval) between the MIFE and the MISO. From the decade-old U.S. Food and Drug Administration approved dosing interval of 48 hours (Pyeron, et al., 1993; Spitz, et al, 1998) to the WHO (2012) recommended 24- to 36- hour dosing interval, and

to the more recently studied dosing intervals of 6- to 8- hours (Creinin, et al., 2004; Guest et al., 2007), 2 hours (Tendlar et al., 2015), and zero hours (Creinin et al., 2007; Li et al., 2011; Verma et al., 2017), many authors have shown the efficacy of MA to vary with the dosing interval. This is outlined in detail below and forms the foundation of the relationships that I explored in my study.

The Inter-Relationships of the Study Variables

Both dependent variables of this study (efficacy and safety) are affected by service providers' competency (Pawde, Ambadkar, & Chauhan, 2016). The United Kingdom is one of the world's most regulated clinical systems. Considering the regulations that govern service providers' licensure and routine competency (Chamberlain, 2017; Rubin, 2014), it can safely be assumed that the MAs of the study subjects were conducted by competent providers (Care Quality Commission, 2012). The standards were further elevated by the Care Quality Commission (2016), introducing stringent standards specific to abortion services and abortion providers. The independent variable of this study is the MA protocol. Any protocol used in MA has three contributors. They are the dosage of MIFE or MISO; the dosing interval between MIFE and MISO; and the route of MISO (oral, vaginal, buccal/sublingual). Up to 63 days' gestation, the relationships among the variables of this study is as follows. Changing the dosage of MIFE or MISO or both changes the efficacy of MA (Soon, Costescu, & Guilbert, 2016). Changing the dosing interval between MIFE and MISO also affects the efficacy of MA (Tendler et al., 2015). MIFE is always given orally. Changing the route

of MISO also affects the efficacy of MA (Bhattacharjee et al., 2008; Shannon et al., 2006; Tang, Danielsson, & Ho, 2007).

Due to variations in how studies define the efficacy of MA, it's important to keep in mind that the means used to verify the efficacy of treatment have a strong influence on the results (Haimov-Kochman et al., 2008). The efficacy and the safety of a given MA protocol is affected by certain variables. Efficacy is affected by the gestational age of the pregnancy, the parity of the mother, and the number of past abortions (Cotte, Monniez, & Norel, 2008; Lefebvre et al., 2008; Thiebaut et al., 2017; WHO, 2012). Safety is affected by the gestational age (Lefebvre et al., 2008; Raymond et al., 2013; Thiebaut et al., 2017; Zane et al., 2015).

Figure 1. Relationships among key variables.

Evidence suggest that MA safety is not affected by the number of past pregnancies or the number of past abortions (Ashok et al., 2002; Lefebvre et al., 2008). It is important to keep in mind the obvious, strong, relationship between maternal age and parity. As most of the authors did not assess the effect of parity and maternal age on MA safety separately, it is difficult to determine if both affect its safety. The relationships among the independent, dependent, and the covariables of the study are portrayed in Figure 1.

Evolution of the Reduced Dosing Interval

The dosing interval between MIFE and MISO has remained over 24 hours for several decades (WHO, 2015). Pymar et. Al. (2001) were the first to study a protocol with a dosing interval less than 12 hours, and where MA could be a 1-day process. The authors showed that the efficacy of MIFE 200 mg, followed 6- to 8- hours later by MISO 800 µg vaginally in women with gestational ages below 49 days was comparable to the convention protocol with a 36- to 48- hour dosing interval. Fox et. Al., (2002) showed that the same short protocol had comparable expulsion rates and side effect rates to the conventional protocol in women with gestational ages between 50 and 63 days. Guest et al. (2007) reproduced these results. Creinin et al. (2004) showed that the same protocol is comparable to a protocol where the dosing interval was 24 hours at gestational ages up to 63 days.

Murthy et. al., (2005) were the first to study a protocol where MIFE and MISO were given simultaneously. They showed that simultaneous oral MIFE 200 mg and 800 µg vaginal MISO produced expulsion rates of 90% (95% CI 80% - 99%) at 24h when the

gestational age was below 49 days. Schreiber et. al., (2005) showed that the same protocol has 24-hour expulsion rates of 88% (95% CI, 77% - 98%) at gestations between 50 and 56 days and expulsion rates of 83% (95% CI, 77% - 94%) at gestations between 57 and 63 days. Kapp et. al., (2006), studying the efficacy of a simultaneous protocol where the MIFE dosage was reduced to 100mg showed a similar expulsion rate to Schreiber, et al. (2005) in women with gestational ages below 56 days. Li et al. (2006), reproduced the results of Murthy et al. (2005a) and Creinin et al. (2007) reproduced the results of Schreiber et al. (2005b) in a randomized, noninferiority trial with a control group using a protocol with a dosing interval of 24 hours.

Studying a simultaneous dosing protocol of MIFE 200 mg and MISO 600 μg for gestational age limits up to 49 days, Li et al. (2011) showed the protocol to have complete expulsion rates of 92.6%. Verma et al. (2017) studied a simultaneous dosing protocol with the MISO dose reduced to 400 μg. Comparing its efficacy in women with gestational ages below 63 days to the efficacy of the conventional protocol (dosing interval of 36- to 48- hours), the authors showed the simultaneous protocol to have an expulsion rate of 96% (95% CI 95.1-98.2%) compared to 95% (95% CI 93.0-96.8%) for the conventional protocol. The only study where a simultaneous protocol had expulsion rates of below 80% in the first trimester was Lohr et al. (2007). However, in the simultaneous protocol used by the authors, the MISO 800 μg was administered using the buccal route (not the vaginal route as in all other studies of simultaneous protocols). The expulsion rates shown by the authors were 73% (95% CI 56% - 85%) at gestations below

49 days, 69% (95% CI 52% - 83%) at gestations between 50 and 56 days, and 73% (95% CI 56% -85%) at gestations between 57 and 63 days).

Multiple authors of pharmacokinetic studies of MISO that compared oral and vaginal administration have shown that vaginal misoprostol results in slower absorption, lower peak plasma levels, but slower clearance. This gives a result similar to an extended-release MISO preparation (Danielsson et al., 1999; Khan et al., 2004; Ziemann et al., 1997). MISO administered vaginally also results in a greater overall exposure to MISO, augmenting the drug's effects on the cervix and uterus (Danielsson et al., 1999). The superior results produced by vaginal MISO is the likely cause of Lohr et al. (2007) observing poor outcomes with their simultaneous dosing protocol that used buccal MISO compared to the other six sets of authors, all of whom used simultaneous protocols that administered MISO using the vaginal route. There is a case for trying to avoid administering MISO vaginally, as authors (Arvidsson, Hellborg, & Gemzell-Danielsson, 2005; Schaff, Fielding & Westhoff, 2001) have shown that women prefer oral, buccal, or sublingual routes to the vaginal route.

A closer exploration of studies that examined dosing intervals (and hence a shorter MA process) of less than 12 hours is of value. In doing so, attention should be paid to the dosages of MIFE and MISO and the routes of MISO used in these studies. The findings in this section show that the protocol with a 6- to 8- hour dosing interval and simultaneous dosing shows promise as alternatives to the conventional protocol. These two protocols could potentially make most MAs a single-day process. Both protocols have been shown to carry safety and efficacy levels that are either equal to, or near to

those of the conventional protocol. Seeking out and reducing gaps in literature on these two protocols could strengthen the case for healthcare systems and countries adopting these protocols as their first-line MA protocol or as viable alternatives to be offered alongside the conventional protocol. In my study, I analyzed a data set that is larger than any previous study. I also present efficacy and safety analyses based, for the first time, on a large, retrospective data set where the women underwent MA outside of a research setting.

Gaps in the Literature and Their Significance

Gaps are found in the large body of literature on MA. In my literature review, I could not discover any study that simultaneously compared more than two protocols. I also failed to discover any study that compared the 6- to 8- hour dosing interval with simultaneous dosing. None of the authors in the 13 short-protocol studies pointed out these areas as requiring further research. In many countries without restrictive abortion laws, MISO can be prescribed to be taken at home (Berer, 2017), meaning that women must visit a doctor only once for a MA prior to a gestational age of 63 days. Evidence suggests that women prefer the completion of MA at home. One in four women requesting abortions at the Royal Infirmary of Edinburgh preferred home MA if it was available (Levine & Cameron, 2009). Cameron, et al. (2010) showed 79% of women who had first trimester MAs at home would recommend it to a friend. Homebased MA may improve its acceptability by allowing greater privacy, giving women greater control over the timing of abortion, and allowing family or friends to provide emotional support (Clark et al., 2007; Ho, 2006). Women taking the MISO at home is less burdensome for

health care providers (Lie, Robson, & May, 2008) and acceptable to most women, including in resource poor settings (Iyengar et al., 2016; Louie et al., 2014). Whether MA where the second stage is completed at home is as effective as clinic-based protocols is unclear (Ngo et al., 2011).

The other significant gap is in secondary analyses of MA patient data of any short MA protocol in any setting. During my literature review, I did not find a single study that analyzed a retrospective data set. All thirteen published studies on such protocols are prospective studies, where the authors started gathering data with the intent of analyzing clients' outcomes for publication. In my study, I present the first efficacy and safety analyses based on a large, retrospective data set where the women underwent MA outside of a research setting. Such analyses of large patient data sets could uncover efficacy differences between these protocols administered in a research setting versus in day-to-day clinical practice. Another relevant gap in the literature exists around studies of 6- to 8- hour dosing interval and simultaneous dosing in the United Kingdom. Guest et al. (2007) represent the only published study that explored the protocol using the 6-8-hour dosing interval in the UNITED KINGDOM, while Lohr et al. (2007) is the only published UK based study that explored the simultaneous dosing protocol. Both these studies have relatively small sample sizes, with Guest et al. having 215 women on the 6- to 8- hour dosing interval and Lohr et al. having 120 women in total. United Kingdom differs from many countries with liberal abortion legislature in that home administration of any abortifacient is not allowed under criminal law (Francome, 2017). Analyzing the safety of the efficacy of both the 6- to 8- hour dosing interval and simultaneous dosing,

my study findings could offer information that is of great value to women and healthcare providers in the United Kingdom and should be studied further.

Theoretical Foundation

None of the published quantitative studies that explore MA (and quantitative studies of abortion in general) mention or use a clear theoretical foundation. Only qualitative studies of the emotional effects on and personal experiences of women who had abortions (Foster et al., 2015; Taylor, 1998) have used foundations rooted in philosophical theory. This is not to say that theoretical foundations have no role in quantitative studies of abortion. When designing research, theory provides a foundation to start from and helps determine the methods and direction for that research (McEachan et al., 2008). Rather aesthetically, Creswell (2013) equates theoretical foundations of a study to rainbows that bridges the independent and the dependent variables. In my study, I use theories to form its foundation in a manner that aligns with the Theory to Research or Theory Then Research strategy" (Reynolds, 1971), where a theory is made explicit through continuous, reiterative interactions between it and empirical inquiry.

The framework of my quantitative study is formed by postpositivism and empiricism (Theory of Knowledge, 2015). Postpositivist philosophy is a traditional approach that holds true for quantitative research (Creswell, 2013). The linear, uni-directional nature of the study aligns with positivism, which states that science should not deviate from the observable and the measurable, and that the goal of knowledge is to describe phenomena that we experience (Trochim, 2006). The relative complexity of postpositivism when compared to positivism (Tashakkori & Teddlie, 1998) is a better fit

for interpreting and generalizing my study findings. As the authors showed, postpositivism allows controlled values to exist beyond hard objectivity. However, postpositivism is not limited to the observable (Clark, 1998). It is grounded in the idea that reality exists but cannot be fully understood or explained due to the multiplicity of causes and effects and social meaning. According to postpositivism, objectivity is an ideal, but requires a critical community of interpreters (Fischer, 1998).

Postpositivism sees the goal of science as getting it right in reality (Trochim, 2006). It takes a realist perspective of science and demands science to have precision, logical reasoning, and attention to evidence (Theory of Knowledge, 2015). If I find that one or both shorter protocols have an efficacy and safety that are either comparable or within acceptable range (albeit being slightly lower than the conventional protocol), postpositivist approach would allow me to still recommend that protocol (or protocols) as acceptable alternatives for women who seek a faster and simpler MA given the benefits it would bring to women across nations. The postpositivist approach places empirical studies in a broader framework based on a contextual understanding of social inquiry (Fischer, 1998), and allow some subjectivity into interpreting objective results, allowing for reality in the process of interpreting the results (Tashakkori & Teddlie, 1998). The authors showed how postpositivism allows a valuable imperfection in research findings that allows researchers to take the realities of life at the point in time of interpreting their results.

This is aligned with the two simpler and shorter MA protocols included in my study being able to possibly improve women's MA experience by shortening the time

needed and removing the need for an overnight experience. Postpositivism holds reality as a social construction, shifts the focus of research findings to the situational context, and plays a critical role in interpreting the findings of the analysis with contextual aspects being taken into account (Fisher, 1998). Abortion has conventionally been surrounded by clashing of morals, controversies, and subjective viewpoints. In studying abortion, as I do in my study, remaining objective and grounding the findings on solid facts is important. Findings of postpositivist, quantitative studies and non-positivist qualitative studies tend to differ (Taylor, 1998). Referring to studies done on the effects of having an abortion on women's psyche, Taylor (1998) stated that postpositivist studies that deal with tangible, measurable outcomes show that the effects are negligible while non-positivist studies that deal with subjective, intangible outcomes show significant negative consequences. Grounding my study in a postpositivist theoretical framework allows me to follow an objective path and set aside my views of abortion and my opinion of MA. The postpositivist approach allows the study to remain objective, for observers with varying stances on abortion can set them aside and focus on the tangible, quantitative, observation-based findings.

Empiricism stresses that observation and measurement form the core of scientific study, (Trochim, 2006). Baird and Kaufmann (2008) showed how the theory recognizes the role of empirical evidence, the knowledge received through observation and experimentation in the formation of ideas. In my study, I derived results and conclusions using a quantitative, scientific approach, and I measured the efficacy and the safety of the MA protocols by scientific analysis of observed patient data. The empirical approach of

this study is reductionist, reducing research ideas into a small, discrete set of variables that comprise hypotheses and research questions (Creswell, 2013). Empiricism can be aligned with this research by assessing the effectiveness of the outcomes of those receiving a new intervention compared with outcomes of the group who received the conventional regimen (Davies & Nutley, 1999). Olsen (2004) claimed empiricism is behind a mathematics-fetishism that promotes quantitative study and puts off qualitative research. While meant as a criticism, it shows that empiricism is a good fit for studies where objective, quantitative analyses of independent, dependent, and control variables with the aim of quantifying the efficacy and safety of different MA protocols. The hypotheses of this study focus on objective efficacy and safety outcomes of two MA protocols. A postpositivist and empiricist approach supports measuring the efficacy and the safety of MA protocols using objective, measurable, dependent and control variables.

Summary, Conclusions, and Transition

Evidence shows abortion as a practice that has endured over millennia (Dellapenna, 2006; Devereux, 1967; Gordon, 1976). However, unsafe abortion persists, and causes between 5% and 15% of the annual global maternal deaths (Kassebaum et al., 2014; Filippi, et al., 2016). The safe abortion methods currently in use fall into surgical and medical categories (Gopal et al., 2017; Li et al., 2017; Morris et al., 2017). MA is fast becoming women's preferred option as it allows safe, cheaper, abortions in de-medicalized settings (Raymond et al., 2013; Simmonds et al., 2017; Zane et al., 2015). Protocols of MIFE and MISO are the norm for MA (Raymond, et al., 2013; Gatter, et al., 2015). The dosing interval between the drugs in current protocols makes MA a lengthy

procedure that takes multiple days (Aiken et al., 2017; Gatter et al., 2015). Over the last 3 decades, many aspects of MA have been studied. MISO has been identified as the best prostaglandin to accompany MIFE (Avrech et al., 1991; Swahn & Bygdeman, 1989;). The most efficacious routes of MISO administration, and the dosages of MIFE and MISO that provides the best balance between good efficacy and acceptable side-effects are known (Raymond et al., 2013). The feasibility of at-home MA (Constant et al., 2017; Purcell et al., 2017) and lighter follow-up of MA (Anger et al., 2017; Chen et al., 2016) are deemed possible. The next frontier in MA research is shortening the dosing intervals. Limited research has been done in this area, with only 13 studies with small sample sizes having been published. During the literature review, neither studies that compared more than two protocols, nor studies that included more than one short MA protocol were found. No retrospective analyses of large data sets of MA clients who had the procedure in a non research setting have been conducted.

In my study, I compared the efficacy and the safety of three MA protocols with varying dosing intervals between MIFE and MISO. The first uses a 24- to 36- hour dosing interval, the second a 6- hour dosing interval, and the third has the two drugs being administered simultaneously. The shorter protocols showing acceptable levels of safety and efficacy could make MA a shorter, simpler procedure, increasing access for many women. Chapter 3 outlines the retrospective cohort design that was used to analyze a large secondary data set of patients who had a MA using one of the three protocols being. Efficacy of a protocol was measured by the percentage of women who had a MA using the said protocol that required either additional abortifacients or a vacuum

aspiration to complete the procedure. Safety of a protocol was measured by the percentage of women who had a MA using the said protocol that experienced a complication that required clinical care. In addition, Chapter 3 explains in detail the specifics for the research design and approach, justification for this approach, selection criteria for setting and sample, instrumentation, and data analysis. Most importantly, Chapter 3 offers the associations between the assessed MA protocols and the safety and efficacy of the MA performed using those protocols.

Chapter 3: Research Method

Introduction

The purpose of this study was to compare the efficacy and the safety of three different MA protocols with varying dosing intervals between MIFE and MISO. The first protocol uses the conventional 24- to 36-hour dosing interval between the drugs and requires women to visit a health facility on two occasions on different days to complete it. The second protocol uses a 6-hour dosing interval between the drugs, with MIFE being taken in the morning and MISO during the afternoon of the same day. The third eliminates the dosing interval, with the two drugs being administered simultaneously. In this chapter, I will discuss the research design, methodology, and rationale for my study; the population under study; sample size; method and procedure for data collection; the instruments used for data collection; and how the data were analyzed.

Research Design and Rationale

Variables.

I explored the relationships between a single independent variable and two dependent variables. There were two control variables (i.e., covariates) in the relationship for one of the dependent variables, and three control variables for the other. The variables were:

Independent variable: I had a single independent variable, the MA protocol. This variable had three levels, the three protocols being different from each other according to the dosing interval length between the MIFE and the MISO. The first

protocol has a dosing interval of 24–36 hours, the second a dosing interval of 6–8 hours, and the third uses simultaneous dosing.

Dependent Variable 1: MA safety was the first dependent variable. A MA procedure received by a woman was deemed safe if the woman did not contact the clinic network within 1 week due to symptoms (i.e., either side effects or complications) that required her to be brought in for a follow-up consultation. This variable had two levels: safe and unsafe.

Dependent Variable 2: MA efficacy was the second dependent variable. A MA procedure received by a woman was deemed efficacious if she did not have to take additional abortifacient doses or undergo a vacuum aspiration after the MISO dose. This variable had two levels: effective and ineffective.

Control Variable (Covariate) 1: Gestational age, the advancement of the pregnancy at the time of the MA given in days, was a control variable when conducting analyses for both dependent variables (i.e., safety and efficacy).

Control Variable (Covariate) 2: Number of past pregnancies, the total past pregnancies carried to term by the woman prior to the pregnancy for which she is seeking a MA, was used as a control variable only when analyzing the efficacy of the dependent variable.

Control Variable (Covariate) 3: Maternal age, the age of the mother given in years, was a control variable when conducting analyses for both dependent variables.

Study Design.

My chosen approach for this study was quantitative. The rationale behind my choice lies in the fact that a quantitative methodology aligned perfectly with the purpose of the study as well as the two research questions. Quantitative research is a means for testing objective theories by examining the relationship among variables (Creswell, 2013). Choosing a retrospective cohort design followed the views of Creswell (2013) on quantitative designs in having assumptions, deductively testing theories, building in protections against bias, controlling for alternative explanations, and paying attention to being able to generalize and replicate study findings. Retrospective cohorts are observational designs and sometimes referred to as historic cohorts (Sedgwick, 2014). They are usually constructed from databases of healthcare records that have already been collected and the exposure to risk factors or to independent variables is usually recorded prior to the recording of the outcomes (Sedgwick, 2014).

In this study, I compared the efficacy and the safety of three different MA protocols with varying dosing intervals between MIFE and MISO. The key difference among the protocols lay in the dosing interval between the MIFE and the MISO tablet administration. Cohort designs are suitable when describing subgroups within a population with respect to an outcome and a set of risk factors (Levin, 2006). Choosing a retrospective analysis of a secondary data set allowed me to capture a large sample size for each of the three protocols without a large time and resource cost. The large sample coming from a large clinic network spread widely across the United Kingdom where

demographics of women seeking abortion remains uniform (see Francome, 2017) minimizes selection bias (see Sedgwick, 2014).

I used a retrospective cohort analysis and regression analyses to explore the relationships of the three protocols to the efficacy and safety of the protocols. In exploring the relationship between protocols and the safety of the procedures, I controlled for factors that impact the safety of MAs conducted using MIFE and MISO (i.e., gestational age and maternal age). In exploring the relationship between protocols and the efficacy of the procedures, I controlled for factors that impact the efficacy of MAs that use MIFE and MISO (i.e., gestational age, maternal age, and the number of past deliveries).

The data that I extracted from an anonymized patient database captured over 100 data points for each woman negates the risk of recall bias, which is a concern in retrospective cohort designs (see Sedgwick, 2014). Despite the database that captured patient data used in my study not having been initially constructed with the intention of identifying a cohort for future studies that explore relationships between the different MA protocols offered and the abortion outcomes, its use allowed me to conduct this retrospective study in a relatively cheap, quick, and easy manner. Creswell (2013) and Sedgwick (2014) stated these benefits of using pre collected, standardized, electronic records. The authors highlighted that retrospective cohort studies that use pre collected health data could miss the identification of some pertinent risk factors and not record them; however, the clinic network who produced my data set has a medical information

system that captures all patient characteristics that are known to affect the safety and the efficacy of MA procedures, which negated the said risk.

This comprehensive capture of patient data allowed me to use the independent, dependent, and control variables that I have previously outlined in this study. The comprehensive nature of the Medical Information System and the fact that each clinic staffer who enters patient data to the system are well trained in entering patient information with little interpersonal variations negated the risk for inconsistent data sets that is a risk carried by retrospective cohort designs (see Sedgwick, 2014). With all MA protocols, both the expulsion of the products of conception as well as complications captured under my dependent variable of safety, occur within 3–4 days of administering MIFE and MISO (see Cleland et al., 2013; WHO, 2015). Furthermore, the data set from which I extracted data spans multiple years, with each woman being allocated a unique identifier that would capture her if she were to contact any of the clinics in the network from which the data set is drawn. Together, these factors mitigate the risk that Sedgwick (2014) pointed out regarding retrospective cohort designs potentially not spanning a length of time sufficient to capture clinical outcomes of interest.

Methodology

Population

The population of a study refers to the complete set of relevant units of analysis, while the population sample of that study refers to a population subset that is used to generalize the study results back to the population (Frankfort-Nachmias & Nachmias, 2008). The target population for my study was all women who sought a MA for

pregnancies below 9 weeks of gestation at a facility where the counselling and prescription is provided by trained clinical staff. The population sample used in my study were women who sought a MA prior to the ninth week of gestational age at one of the largest abortion service networks in the United Kingdom. Estimating the size of my full population presented challenges. Of the 213 million pregnancies in world in 2012, over 40 million were aborted (Sedgh et al., 2014; Vrachnis et al., 2016), with over half being carried out in a safe manner. Sedgh et al. (2016) estimated that approximately 60% of safe abortions in the world use MAs and that most of those are conducted in the first trimester. These statistics put the estimated size of my study population around 12 million women globally (per year). There were 190,406 abortions carried out in England and Wales in 2016, with MA being the method used in 62% of the total, or approximately 120,000 (Department of Health, 2017). All MAs in the United Kingdom are carried out in the first trimester (Department of Health, 2017; Lancome, 2017). The medical organization from whose clinics I obtained my data set provides approximately 65,000 safe abortion services in the United Kingdom annually. Over the last 3 years, the percentage of these procedures provided using MA has approximately been 50%. This percentage implies that my sample frame would comprise of approximately 25,000 women who received a MA using one of the three MA protocols included in my study.

Sampling

I included all women who received a MA from the organization whose data were available in the 2017 data set except women whose anonymized records lacked data points that were critically related to the variables of the study in the analyses. I will

provide the sample size calculation in the next subsection. The information of all women who received a MA was in a single database and a specific data field allowed the identification of the MA protocol that a given woman opted for. Based on this data point, I separated women who had MAs using the three protocols into three distinct lists with serial numbers. The database records the discharge information of the women and allowed for the identification of women who did not complete the two drug protocols, who vomited or in other ways expelled the tablets. Only women who took both drugs in line with their chosen MA protocol and were discharged with the health providers' contact information were included in the analyses. The presence of a data point that allowed for the identification of the MA protocol that each woman received made the process of dividing the main sampling frame into three groups by the protocol relatively simple. I assumed that the demographic characteristics of women who sought a MA at any clinics of the healthcare provider from whom my data set was obtained are similar. The data set allowed for this assumption to be tested by tabulating key demographics such as age, parity, and past abortions by clinic. Hence, no stratification was needed or carried out based on the individual clinic where a given woman who qualified to be included in the analyses received her MA.

Power Analysis and Sample Size Determination

I had one nominal independent variable (MA protocol) with three levels (Protocol A, B, C). The protocols differed from each other by the dosing interval between MIFE and MISO, with protocol A having a 24- to 36- hour interval, B having a 6- to 8- hour interval, and C having a 0-hour interval (simultaneous dosing). I had two dependent

variables (both binary). The first was MA protocol efficacy (efficacious/not) and the second was be MA protocol safety (safe/unsafe). There were three control variables in the efficacy analysis: Gestational age given in days, past pregnancies given as 1, 2, 3, etc., and maternal age given in years. Based on past evidence, only gestational age and maternal age was controlled for in the safety analysis. I used binomial logistic regression for the analyses, running six separate models, one for each MA protocol and binary dependent variable with the applicable covariates.

Bivariate analyses were conducted prior to using the regression models. The first step was running separate bivariate analyses to study the relationships between my independent variable (MA protocol) and each dependent variable. This was followed by separate bivariate analyses between each of the two, dependent variable and each of the three control variables.

Given the large size of the data set, which makes normality highly likely, the bivariate analyses would be done using a relatively simple test such as the chi-square. Two sets of chi-square test would be conducted. Assuming the three MA protocols were labelled a, b, and c, the first set of chi-square tests was done to compare the safety of protocol a to the safety of b, the safety of a to the safety of c, and the safety of b to the safety of c. The second set of chi-square tests compared the efficacy of protocol a to the efficacy of b, the efficacy of a to the efficacy of c, and the efficacy of b to the efficacy of c. The second set of chi-square tests was done between the dependent variables and each of the control variables.

1. Chi-square gestational age with safety (all protocols combined)

2. Chi-square mothers' age with safety (all protocols combined)
3. Chi-square past pregnancies with safety (all protocols combined)
4. Chi-square gestational age with efficacy (all protocols combined)
5. Chi-square mothers' age with efficacy (all protocols combined)
6. Chi-square past pregnancies with efficacy (all protocols combined)

The results of these bivariate analyses helped determine the empirical relationship between the MA protocols and their safety and efficacy. They also allowed me to identify the control variables that would be meaningful to include. These in turn, informed my regression modelling. My independent variable, the two dependent variables, as well as one control variable (past pregnancies) are categorical variables that can be directly used in the bivariate analyses. The other two control variables (maternal age and gestational age), which are continuous, required conversion to categorical variables (using age groups and gestational age given in weeks) for the bivariate analyses.

Effect Sizes and Alpha Levels

Effect size allows us to move beyond the simplistic question; does it work or not? to the far more sophisticated question; how well does it work in a range of contexts? (Coe, 2002). I used an effect size of 5% when conducting analyses on the efficacy of the different MA protocols. When conducting analyses on the safety of the different MA protocols, a much smaller effect size of 1% was used. These effect size choices are justified as follows. Effect sizes calculated from a very large sample it is likely to be more accurate than one calculated from a small sample (Coe, 2002), allowing me to draw confidence from the large data set I was using. Currently, below the MIFE and MISO

combination, the next most commonly used MA protocol category is the use of MISO as a stand-alone drug. The (WHO, 2015), the International Federation of Obstetrics and Gynecology (Morris, et al., 2017), and other institutions have included MISO only MA protocols for terminating pregnancies, up to 24 weeks. The efficacy of MISO only protocols in pregnancies with gestational ages below 10 weeks (as are the pregnancies included in my study) are in the 85% to 90% range (WHO, 2012, 2015). A robust systematic review of efficacy and safety of MA where the expulsion occurred at home across multiple countries, Ngo et al. (2011) demonstrated failure rates between 3% and 14%. Compared to the approximately 95% efficacy of the conventional MIFE and MISO protocol (WHO, 2012, 2015), the MISO only protocols fall well behind. If the efficacy of either the MIFE and MISO protocol with a 6- to 8- hour dosing interval or the simultaneous dosing protocol (or both) is above 90%, they would be practical alternatives to the existing MA protocols. An effect size of 5% would enable me to detect if the efficacy of either protocol (6- to 8- hour dosing interval or simultaneous dosing) falls below 90%.

The 1% effect size for safety is due to the very low complication rates seen with early MA. I could not find a single study that demonstrated a MA protocol that used a MIFE and MISO combination that had an adverse event rate of over 1%. Cleland et al. (2013) stated that protocols used for early MA have a low probability of clinically significant adverse events. In a large study of MA adverse effects that involved 233,805 MAs provided in 2009 and 2010, the authors only recorded significant adverse events or outcomes in 1,530 women (0.65%). I assumed that 1% of women who opt for the

conventional (24- to 36- hour) protocol would face a significant safety event, while women who opt for one of the two shorter protocols would have a 2% likelihood of facing such a safety event.

In both the efficacy and the safety analysis, I set an alpha of 0.05. I consider being able to identify significant difference in the efficacy or the safety among the three MA protocols with a 95% confidence level to be adequate. The study power was set at 80%, allowing an 80% probability of detecting a 5% difference in the efficacy and a 30% difference in the safety among the three protocols. G*Power software version 3.1.9.2 (http://www.gpower.hhu.de/en.html) was used in all power and sample size estimations. The steps for the dependent variable efficacy (alpha 0.05, effect size 5%) for each MA protocol with the three covariates are as follows:

1. Select 'Z Tests' and 'Logistic Regression'
2. Select two tails.
3. Click 'Options' tab
4. select 'Two Probabilities'
5. The probability of an efficacious procedure with the conventional MA protocol is 0.95. For either of the shorter protocols, it is 0.90
6. Alpha is 0.05. Power is 80%.
7. All covariates, maternal age, past pregnancies, and gestational age (within the 4 to 10-week range) have a low association with both efficacy and safety. Hence R2 for these would be set at 0.04.

8. X- distribution is set for binomial, X-papram π would be set at 0.5 as the number of women in the sample who opted for a given protocol from among the three is expected to be roughly equal.

The steps for the dependent variable safety (alpha 0.05, effect size 30%) for each MA protocol with the two covariates are as follows:

1. Select 'Z Tests' and 'Logistic Regression'
2. Select two tails.
3. Click 'Options' tab
4. select 'Two Probabilities'
5. For safety, the probability of an efficacious procedure with the conventional MA protocol is 0.01. For the shorter protocols, it is 0.02
6. Alpha is 0.05. Power is 80%.
7. Both covariates, past pregnancies and gestational age (within the 4 to 10-week range) have a low association with both efficacy and safety. Hence R2 for these would be set at 0.04.
8. X- distribution is set for binomial, X-papram π would be set at 0.5 as the number of women in the sample who opted for a given protocol from among the three is expected to be roughly equal.

With the above approach, the sample size for efficacy for a given medical protocol is 917 and the sample size for safety for a given MA protocol is 4,883. The data set I used allows for sample sizes that easily exceeds the required sample sizes calculated above. Following each of the two analyses for the two dependent variables safety and

efficacy, a post hoc power analysis was carried out using G*Power. Post hoc power analyses done using the sample size and the effect size provided insights into the statistical validity of the results (specifically the likelihood of a Type-2 error).

Data Acquisition

All analyses in this dissertation are based on secondary data from women who opted for a MA from the reproductive health clinic network managed by the largest abortion providing agency in the United Kingdom. Experimental and quasi-experimental designs that could answer my research questions were decided against as such designs require much more intensive logistical, financial, and time resources (Creswell, 2013). With the less than 5% failure rate of early MA (WHO, 2015), capturing significant failure numbers in each protocol groups would require lengthy prospective follow up (Creswell, 2013). Full experimental designs were also rejected as randomizing women into one of the MA protocols would interfere with their choice and raise ethical questions. This cohort design based on secondary analyses is appropriate for describing relationships between variables (Frankfort-Nachmias & Nachmias, 2008). The secondary analysis-based design also has lower financial and temporal cost, allows the inclusion of multiple control variables, and removes risks of loss to follow-up (Levin, 2006; Sedgwick, 2014).

Following discussion with the Walden University Institution Review Board (IRB), a formal request was made to the abortion provider organization for an anonymized data set of all women who obtained MAs from their clinics within the United Kingdom (Appendix A). permission was obtained from the Caldicott Guardian of the organization on the 17th of May 2018. The proposal was approved by the IRB (Approval:

04-26-18-0389171). Additionally, I successfully completed the National Institute of Health Human Research Protection training. No data of women who opted for surgical abortions (either using manual vacuum aspiration or using dilatation and curettage) was requested. Anonymization was done by those who maintain the health information systems of the organization, and the data set was given to me only after removal of all surgical abortion clients and the full anonymization of all MA clients.

The data set included all non-identifier data points of all women who obtained a MA using one of the three protocols in question within 2017. The anonymization is in accordance with the Health Insurance Portability and Accountability Act of 1996. All women were identified by the unique personal identifier numbers generated by the health information system at the time of their initial registration. This number was used to follow each woman up through to the completion of their procedures and allowed a subsequent complaint or a visit to any of the organization's clinics to be linked to the same person. The data set given to me did not contain any data that would provide clues to the individuals linked to a given personal identifier number.

The health information system used by the medical organization is one developed specifically for the customized collection of their patient data. The data set was converted to an Excel database format following anonymization and delivered to me for the purpose of this study in said format. Information of each MA patient after anonymization included approximately 100 data points, giving the full Excel database approximately 3 million data points. Both to make the handling of the data set easier and to maximize the security of the patients' data (despite anonymization), the data points that are irrelevant to the

analyses were removed. The number of data points of a given woman that would be required for the analyses included the MA protocol chosen, the times of the administration of both MIFE and MISO (together indicating the protocol chosen), the route used for the administration of MISO, the actual protocol, the woman's age, gestational age at the time of the abortion, number of past pregnancies, and several data points that capture subsequent contacts, clinic visits, complaints, and follow up communications. A copy of the original anonymized data set was saved in a secure external hard drive with no online accessibility, while the simplified data set was used for all analyses from the point of its creation.

Medical as well as surgical options are offered to every woman who contacts the medical organization seeking abortion options in the first 10 weeks of gestation. Those who choose MA are offered all three protocols being compared in my study, with the protocol a given woman opts for being her independent choice following a counselling session during which the three protocols are explained to them. The efficacy rates presented for each protocol are the rates based on the smaller studies that were outlined in Chapter 2. All women are provided with the same follow up options and have access to the same complication management options. There are no grounds to suspect significant differences of the key variables among women who opt for the three different MA protocols.

Operationalization

The independent variable (MA protocol) is defined based on the time gap between the oral 200 mg MIFE tablet and the vaginally inserted four 200 μg MISO tablets. The

three protocols are labelled 1, 2, and 3. Protocol 1 is the conventional protocol, where the time gap between MIFE and MISO was 24- to 36- hours. The time gap of Protocol 2 is 6- to 8- hours. In Protocol 3, the time gap is zero (MIFE and MISO administered simultaneously). The data set indicates the protocol that each woman received following counselling. This was used to separate women into the three protocol groups. The data set also records the exact time of the administration of MIFE and MISO for each woman. These were used to cross-check the accuracy of including a given woman in the protocol group she was allocated to. Women who opted for Protocols 1 or 2, who did not proceed (did not return to the clinic for the MISO) with the MISO despite receiving MIFE were excluded from the sample. This possibility did not arise in Protocol 3 due to the simultaneous administration of the two drugs. Women in Protocol Groups 1 and 2 who vomited the MIFE tablet were given a second. But for the purpose of the study, these were excluded as the time gap between the second MIFE and the MISO did not always correspond to the time gap of the particular protocol.

The dependent variable MA efficacy was defined for a given woman based on whether she required either an additional dose of MISO or a vacuum aspiration to complete her uterine evacuation. This information for a given woman was available in the data set. The used MA protocol was considered to have been effective in women who did not require additional MISO dosing or vacuum aspiration for completing expulsion, with the protocol being deemed ineffective if either is required. The dependent variable MA safety was defined for a given woman based on whether she encounters symptoms (either side effects or complications) that require her to receive a follow up consultation at a

health facility within a week of her procedure (from the day/time when she received her MIFE dose). Due the unique patient identifier given to each woman who received care in the clinic network, any follow up medication, procedures, or referrals to other facilities for the management of conditions that cannot be managed in that particular clinic network she receives can be tracked. This allows the identification of women whose MA was non efficacious or 'non safe'. In terms of the variable efficacy, an efficacious MA was coded 1 and a non efficacious MA coded 2. Similarly, a safe MA was coded 1 and an unsafe MA coded 2.

The first control variable (Covariate 1) is gestational age. It is defined as the number of days the pregnancy has been in situ. For the initial bivariate analysis, gestational age was converted into a categorical variable by grouping women into ranges of days (e.g. gestational age days 36- to 42 coded as 1, 43- to 49 coded as 2, 50- to 56 coded as 3). These groups ranged from 36 days to 69 days, with each group being 7 days in length. In the main (logistic regression) analyses, gestational age was recoded as an ordinal variable with the advancement of the pregnancy given in weeks. The second control variable (Covariate 2) is the number of past pregnancies, defined as the total pregnancies carried to term by the woman prior to the pregnancy for which she is seeking a MA. This was coded in line with the number of past pregnancies, as 1, 2, 3, up to 9 and a last group for 10 or more. Being a ratio variable, past pregnancies did not require any changes for either the bivariate analysis or the regression analyses. The third control variable (Covariate 3) is maternal age, the age of the woman in years at the time of her seeking the MA. Similar to gestational age, this was converted to a categorical variable

for the bivariate analysis by grouping women in to age ranges. Each age group had a 5-year range. Those <15 years were coded as 1, the group 15- to 19 were coded 1, 20- to 24 coded 2, up to the group 35- to 39, which was coded 6. Those aged 40 or above were coded as 7. For the regression analyses, maternal age was used as an ordinal variable with the age of each woman given in years.

Data Analysis Plan

Once the data set is handed to me by the medical organization following organization approval and the full data set anonymization, the first step was the division of all women who received a MA in to three groups based on the MA protocol that they opted for and received. In each of the three groups, women whose records miss the data points critical for the analyses were excluded, with a clear record of all excluded women from each protocol group being maintained. The number of women in each of the three groups whose data records are complete with regards to all data points required for the analyses were compared against the sample size estimations conducted to ensure that each protocol group has adequate members for the study purpose. All analyses were conducted using Statistical Package for the Social Science (SPSS) version 25 (released June 2017), which allows stronger regression analyses, as well as more options for presenting data and results using graphs and charts.

Binomial logistic regression was used to answer the two research questions. The choice of binomial logistic regression is based on the fact that both my two dependent variables are binary (safe vs. unsafe, and efficacious vs, inefficacious).With the first question, I explored the relationship between the MA protocol (6- to 8- hours and

simultaneous vs. 24- to 36- hours) and the safety of the procedure measured by the percentage of women who experienced a complication that required facility care after controlling for factors that impact the safety of MAs conducted using MIFE and MISO (gestational age and the age of the pregnant woman). The null hypotheses was that there is no statistically significant relationship between the MA protocol time gap (6- to 8- hours and simultaneous vs. 24- to 36- hours) and the safety of the procedure as measured by the percentage of women who experienced a complication that required facility care after controlling for factors that impact the safety of MAs conducted using MIFE and MISO (gestational age and the age of the pregnant woman). The alternate hypothesis is that there is a statistically significant relationship between the MA protocol (6- to 8- hours and simultaneous vs. 24- to 36- hours) and the safety of the procedure as measured by the percentage of women who experienced a complication that required facility care after controlling for factors that impact the safety of MAs conducted using MIFE and MISO (gestational age and the number of past deliveries).

With the second research question, I explored the relationship between the MA protocol (6- to 8- hours and simultaneous vs. 24- to 36- hours) and the efficacy of the procedure as measured by the percentage of women who required a second intervention to complete the expulsion after controlling for factors that impact the effectiveness of MIFE and MISO (gestational age, maternal age, and the number of past deliveries). The null hypothesis is that there is no statistically significant relationship between the MA protocol time gap (6- to 8- hours and simultaneous vs. 24- to 36- hours) and the efficacy of the procedure was measured by the percentage of women who required a second

intervention to complete the expulsion after controlling for factors that impact the effectiveness of MIFE and MISO (gestational age, maternal age, and the number of past deliveries). The alternative hypotheses was that there is a statistically significant difference between the MA protocol (6- to 8- hours and simultaneous vs. 24- to 36- hours) and the efficacy of the procedure as measured by the percentage of women who required a second intervention to complete the expulsion after controlling for factors that impact the effectiveness of MIFE and MISO (gestational age, maternal age, and the number of past deliveries). In answering the first question, the relationship between the MA protocol (Protocol 1, 2, or 3) and the safety of the resulting MA was examined while controlling for gestational age (given in weeks) and maternal age (given in years). In answering the second question, the relationship between the MA protocol (Protocol 1, 2, or 3) and the efficacy of the resulting MA was examined while controlling for gestational age (given in days), maternal age (given in years), and past pregnancies given as 1, 2, 3, and 4 or more.

Data Interpretation

In line with the problem statement and the purpose of the study, I explored the relationships between the MA protocols and each protocol's efficacy and safety through my two research questions. From a practical perspective, the key practical consideration was whether the efficacy and the safety of the two shorter protocols are at levels that would make either or both of them suitable to be offered as an alternative to the conventional, lengthy protocol. If the efficacy or the safety of a shorter protocol exceeds that of the conventional (24- to 36- hour) protocol, that would be considered a positive

result. If the efficacy of a shorter protocol was lower than that of the conventional protocol, but if the efficacy difference is less than 5%, I considered the shorter protocol to be a likely alternative to the conventional protocol from an efficacy perspective. If the safety of a shorter protocol is lower than that of the conventional protocol, but the significant adverse event rate of the two protocols differ by less than 1% (e.g. 1% for the conventional protocol and <2% for the shorter protocol), I considered the shorter protocol to be a likely alternative to the conventional protocol from a safety perspective.

Threats to Validity

Multiple factors threaten the reliability and the validity of a study. Creswell (2013) showed subject selection, history, maturation, experimenter bias, mortality, compensatory demoralization, diffusion, regression towards the mean, and confounding as common threats to internal validity. Most of these do not threaten the internal validity of my study due to its design. From the threats named in Creswell, history, mortality, and maturation are not of concern due to the retrospective design and the rigorous data cleaning undertaken. Due to the retrospective nature, experimenter bias and Ambiguous temporal precedence also do not apply. With no instruments used, and having no Pre–Post test design, participant sensitization is also not a concern.

Compensatory demoralization is not a concern as the study is retrospective, and each woman received the MA protocol that she selected, rather than being allocated to a given protocol for study purposes. The selection of participants and confounding could hold potential threats to validity in my study, as the rationale behind a given woman's choice of MA protocol cannot be determined with certainty. There may be unforeseen

confounding variables that affect women's choice of a given protocol, although this likelihood is extremely unlikely. The likelihood of these threatening the internal validity is further lessened due to the data set including women who came for procedures in different parts of the United Kingdom (Zwarenstein, et al., 2008). Demographic analyses of the women who chose each of the three protocols were carried out to detect possible trends that suggest significant variations in variables that could affect the safety and the efficacy of a MA among women who chose each protocol.

The findings of my study could potentially lead to changes in MA protocols in many countries. Hence the generalizability of the results (external validity) is a major concern and demonstrating the generalizability of the study findings is of key importance. Metcalfe and Lynch (2002) differentiated between generalizability across situations and generalizability across peoples. Creswell (2013) and Trochim and Donnelly (2001) outlined the common factors that threaten the external validity of studies. Of these, pre and post test effects as well as reactivity, Hawthorne effect, and Rosenthal effect do not threaten my study due the retrospective nature of the design that I used. However, Aptitude-treatment Interaction (interaction effects of selection and experimental variables) was a potential concern, especially when considering the generalization of my results to settings outside of the United Kingdom. This arises due to the study sample being drawn from a group of women who were mostly British that visited the clinics of a specific abortion providing agency.

Based on demographic information on abortion seeking women in the United Kingdom and the United States (Francome, 2017), it can safely be assumed that this

concern is negligible for those countries. Negating concerns around interaction effects of selection and experimental variables for women in countries that vastly differs from the United Kingdom however is more challenging. Similarly, the reactive effects of experimental arrangements (situation under which MA is performed) could also a potential threat to external validity. In the study sample, in line with the United Kingdom law, all women have received both MIFE and MISO with close medical supervision and high-quality counselling. The safety and efficacy levels seen in such a setting are likely to exceed those seen with the same protocol but with the two abortifacients being administered under poor or absent supervision, and where the quality of the counselling received by women is questionable. In my opinion, this is the biggest threat when attempting to generalize the study findings to settings outside of the United Kingdom.

Considering the above arguments related to the internal and the external validity of my study, I have confidence in its ecological validity (Brewer & Crano, 2000; Schmuckler, 2001). According to these authors, ecological validity of my study refers to whether I can generalize my study observations to natural behavior in the world. If the safety and the efficacy of either of the shorted MA protocols (simultaneous dosing or the 6- to 8- hour dosing interval) are found to be within acceptable range of the safety and the efficacy of the conventional (24- to 36- hour dosing interval) protocol, the likelihood of that shorter protocol being used as an alternative to the conventional protocol in the United Kingdom would be very high. Considering the anatomical and physiological similarities of the female reproductive systems of women across our species, logic would

dictate that such findings would also make that shorter protocol a suitable alternative to the conventional protocol in other countries as well.

Ethical Procedures

The ethical requirements for the suggested study are expected to be relatively light considering what is proposed is the retrospective analyses of a secondary data set (Research Ethics Guidebook, n.d.). However, I have had my fair share of ethical pitfalls to avoid and ethical permissions to be obtained. Kaplan (2014) stated that electronic health records and secondary use of such, while enabling exciting opportunities for improving health and health care, exacerbate privacy concerns. The author specified such concerns around secondary health data, showing how intimacies are revealed in the interest of good health care and how clinicians' professional and fiduciary duties include a duty of confidentiality.

Discussions were had with both the IRB and the United Kingdom's relevant bodies regarding the requirements for ethical clearance. Guidance was sought regarding the United Kingdom ethical approvals needed from the Confidentiality Advisory Groups of the Health Research Authority (National Health Service, 2017). In line with their guidance, the second step was to discuss the study and the anonymization process with the Caldicot Guardian of the healthcare organization that provided the MAs included in the study and whose data set I used for this study. Once written approval is obtained by the Caldicot Guardian, that was submitted to IRB together with the full IRB application for obtaining ethical clearance to obtain the data set and proceed with the analyses.

Kaplan (2014) states that the European Union Data Protection Directive as well as almost every single privacy statute and regulation in the U.S. and Europe embraces the assumption that anonymization protects privacy and extends safe harbors to those who anonymize their data. Tripathy (2013), discussing ethical issues and challenges of secondary data analysis, also states that fully anonymized patient data is considered to protect individuals' privacy, and outlines what full anonymization entails. The data set was anonymized by the data guardian(s) of the healthcare organization providing the data. All direct identifiers were removed, and the data extracted from the organizations health information system on to an Excel database. The unique patient identifier numbers allocated by the health information system were replaced by other numbers (coded) in a manner that the same unique code replaced a given unique patient identifier in each instance that the said identifier appears. However, due to the coding, it was impossible for me to use the data set to identify any patient even if I gain access to the health information system of the organization. Furthermore, I was required to provide assurances to the Caldicot Guardian of the healthcare organization that I would not share the data set with any entity outside of the European Economic Area, even for future publication purposes.

Summary and Transition

In this chapter I outlined the purpose of my study with a special focus on the research design of my study, the methodology I used, and the rationale behind my study. I also explored the population used in the study, the details of my sample size and power calculations, as well as the rationale behind the effect sizes I chose for my two research

questions. I outlined the method and procedure I used for data collection, steps taken to protect the women whose medical data were used in my analyses, and how the data were analyzed. Finally, I presented the threats to the internal and external validity of my study and what steps were taken to minimize or negate those threats. In the fourth chapter, the results of the analyses used to test the two research questions and hypotheses generated for this study are presented.

Chapter 4: Results

Introduction

In this chapter, I will describe the analyses conducted to address the research questions. In this quantitative study, I used regression analyses to explore the relationships of three MA protocols to the efficacy and safety of the procedures resulting from those protocols. In exploring these relationships, factors that have been shown to impact the safety and efficacy of MAs conducted using MIFE and MISO (i.e., gestational age, maternal age, and the number of past deliveries) were controlled for.

The independent, dependent, and the control variables included in my study are outlined in Table 1. I had one independent variable (i.e., MA protocol, decided by the dosing interval) with three levels (i.e., dosing interval of 24- to 36-hours, dosing interval of 6- to 8-hours, and simultaneous dosing). There were two dependent variables: safety (decided based on whether a given client faced a complication that required healthcare or not) and efficacy (decided based on whether a given client required an intervention to complete evacuation due to MA failure).

Table 1

Key Variables

Variable name	Type of variable	Level of measurement
Medical abortion protocol	Independent variable	Nominal
Maternal age	Control variable	Ordinal
Gestational age	Control variable	Ordinal
Past pregnancies	Control variable	Ordinal
Medical abortion efficacy	Dependent variable	Nominal; dichotomous
Medical abortion safety	Dependent variable	Nominal; dichotomous

Each dependent variable had two levels (i.e., efficacious or not and safe or unsafe). I controlled for all three control variables (i.e., gestational age, maternal age, and past pregnancies) when exploring the relationship between the MA protocol and procedural efficacy. Only gestational age and maternal age were controlled for when exploring the relationship between the MA protocol and procedural safety. The two research questions and the corresponding hypotheses were as follows:

Research Question 1: What is the relationship between the MA protocol time gap (i.e., 6 hours vs. 24–36 hours vs. simultaneous) and the safety of the procedure as measured by the percentage of women who experienced a complication that required medical care after controlling for factors that impact the safety of MAs conducted using MIFE and MISO (i.e., gestational age and maternal age)?

$H_0$1: There is no statistically significant relationship between the MA protocol time gap (i.e., 6 hours vs. 24–36 hours vs. simultaneous) and the safety of the procedure as measured by the percentage of women who experienced a complication that required medical care after controlling for factors that impact the safety of MAs conducted using MIFE and MISO (i.e., gestational age and maternal age).

H_A1: There is a statistically significant relationship between the MA protocol time gap (i.e., 6 hours vs. 24–36 hours vs. simultaneous) and the safety of the procedure as measured by the percentage of women who experienced a complication that required medical care after controlling for

factors that impact the safety of MAs conducted using MIFE and MISO (i.e., gestational age and maternal age).

Research Question 2: What is the relationship between the MA protocol time gap (6 hours vs. 24–36 hours vs. simultaneous) and the efficacy of the procedure as measured by the percentage of women who required a second intervention to complete the expulsion after controlling for factors that impact the effectiveness of MIFE and MISO (i.e., gestational age, maternal age, and the number of past deliveries)?

$H_0$2: There is no statistically significant relationship between the MA protocol time gap (i.e., 6 hours vs. 24–36 hours vs. simultaneous) and the efficacy of the procedure as measured by the percentage of women who required a second intervention to complete the expulsion after controlling for factors that impact the effectiveness of MIFE and MISO (i.e., gestational age, maternal age, and the number of past deliveries).

H_A2: There is a statistically significant difference between the MA protocol time gap (i.e., 6 hours vs. 24–36 hours vs. simultaneous) and the efficacy of the procedure as measured by the percentage of women who required a second intervention to complete the expulsion after controlling for factors that impact the effectiveness of MIFE and MISO (i.e., gestational age, maternal age, and the number of past deliveries).

In this chapter, I will discuss the participant demographics and descriptive statistics, followed by details of the methods used to address each of the questions. This

will include the use of binomial logistic regression analyses to statistically analyze the safety and efficacy of the three MA protocols studied. The chapter will conclude with an overall summary of results.

The data used to formulate the results were retrospective and came from the patient database of one of the United Kingdom's largest providers of safe abortion care. The data captured all women who received MAs in the year 2017. The gestational age for MA was capped at 9 weeks. I obtained the data following receiving approvals from the medical provider organization as well as Walden IRB. The data were anonymized to meet the United Kingdom's stringent patient data protection requirements, and the anonymization process aligned with the European Union medical data protection requirements.

Data Collection

The data for this study came from one of the United Kingdom's largest safe abortion care providers. The data set captured all women who had a MA (capped at 10 weeks' gestation) between January 2017 and June 2018. Following approval from the Caldicott Guardian of the organization and receiving Walden's IRB approval, I received a fully anonymized data set that included all women who had a MA within the aforementioned period from the organization. The original Excel extract from the health information system did not contain details of patients referred for facility care for complications and severe adverse events. Records of 878 referrals were obtained separately from the organization's United Kingdom-wide call-center that provides information, makes patient bookings, and manages follow up and referrals. The center

maintains records of all referrals made for complications and adverse events. The two data sets were combined prior to anonymization using unique patient identifiers included in both data sets. All 878 referral records could be matched to corresponding clinical records. The data were transferred to me following anonymization.

The combined data set contained records of 58,672 women who received a MA between January 2017 and June 2018. Records of women who sought surgical abortion had been removed. I then cleaned the combined data set, removing data fields that were not applicable to the analyses and patient records that were incomplete or contained invalid figures. Of the 58,672 records in the data set, 1,555 were removed because the MA protocol used could not be clearly determined. I removed a further 638 because they were duplicated (i.e., multiple database entries made for a single procedure). Another 424 were removed because the gestational age was not entered (i.e., given as 0 weeks) and 63 removed because the past pregnancy number was inaccurate (i.e., negative values shown). Finally, 24 were removed due to invalid gestation age figures (see Figure 2).

The cleaned data set included records of 55,968 women who chose one of the three MA protocols. Each record included all required variables (i.e., protocol chosen, the patient's age, the gestational age at presentation, past pregnancy number, the abortion outcome, and if the patient was referred for medical care due to complications and severe adverse events). There were no major discrepancies in data collection when compared to the data collection plan outlined in Chapter 3. I had not envisioned the need to extract data from two (i.e., clinical and call center) data sources earlier. This was not a major discrepancy because the final anonymized data set handed over to me was in line with

that outlined in Chapter 3. Another unexpected finding was that the number of patients who opted for the 6- to 8-hour protocol was much smaller than the numbers that opted for the conventional and the simultaneous protocols.

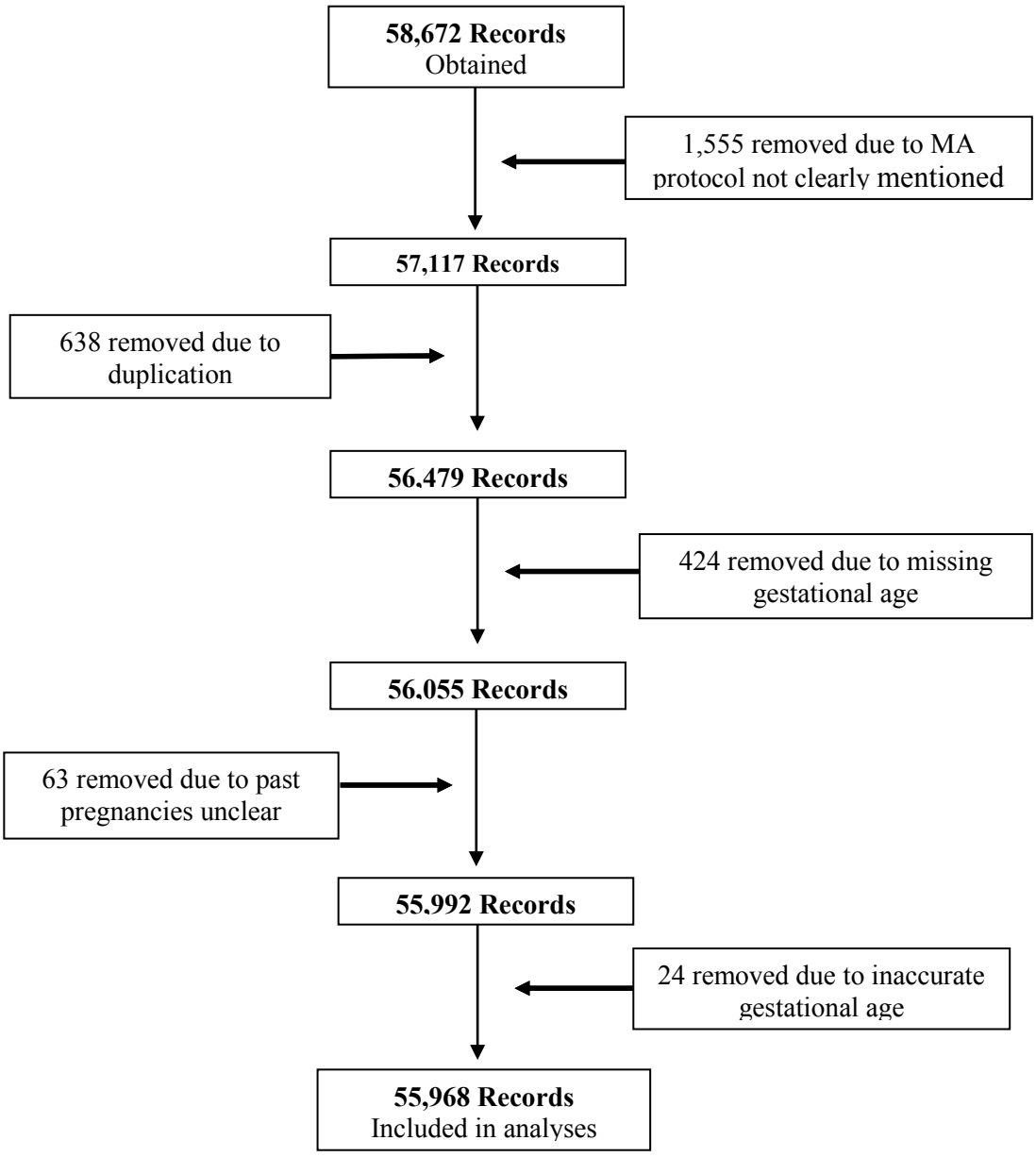

Figure 2. Data cleaning process.

Data Analysis

I imported the cleaned Excel data to SPSS for Windows (Version 25). The descriptive analysis for demographic data included the numbers of patients that chose each protocol and the percentages, means, and standard deviations for patient age, gestational age, and past pregnancies among patients who opted for each abortion protocol. Hypothesis testing was completed using binomial logistic regression. I conducted bivariate analyses prior to regression modelling. First, separate bivariate analyses were done to study the relationships between the independent variable (i.e., MA protocol) and each dependent variable. For this purpose, two sets of chi-square test were conducted. With the three MA protocols labelled 1, 2, and 3, the first set of chi-square tests compared the efficacy of the three protocols. The second set of chi-square tests compared the safety of the three protocols. I conducted another set of chi-square tests between the dependent variables and the control variables relevant to each dependent variable to help determine the empirical relationship between the MA protocols and their safety and efficacy as well as confirm the suitability of the control variables to be included in the regression analyses.

To answer the first question, I examined the relationship between the MA protocol (i.e., Protocol 1, 2, or 3) and the safety of the resulting MA while controlling for gestational age (given in days) and past pregnancies (given as 1, 2, 3, and 4 or more). To answer the second question, I examined the relationship between the MA protocol (i.e., Protocol 1, 2, or 3) and the efficacy of the resulting MA while controlling for gestational

age (given in days), maternal age (given in years), and past pregnancies (given as 1 to 9 and 10 or more).

Statistical Power Analyses

Post hoc power analyses were carried out using G*Power software Version 3.1.9.2 (http://www.gpower.hhu.de/en.html). Post-hoc power analyses were done for binary logistic regression analyses. The safety and the efficacy of the conventional protocol was compared to the safety and efficacy of the 6- to 8- hour protocol and those of the simultaneous protocol.

The efficacy of the conventional protocol was taken as 95% ($H_1 = 0.95$).

The efficacy of the other two protocols was taken as 90% ($H_0 = 0.90$).

The safety of the conventional protocol was taken as 99% ($H_1 = 0.99$).

The safety of the other two protocols was taken as 98% ($H_0 = 0.98$).

The alpha was set at 0.05 for all analyses.

For efficacy analyses, the odds ratio obtained when comparing the conventional protocol to the simultaneous protocol was 1.034. The odds ratio when comparing the conventional protocol and the 6- to 8- hour protocol, the odds ratio was 0.210. For the safety analyses, the odds ratio between the conventional protocol and the simultaneous protocol was 0.524. The odds ratio between the conventional protocol and the 6-8-hour protocol was 0.386. For both the efficacy and the safety analyses, the simultaneous protocol sample size was 27,616. For both the efficacy and the safety analyses, the 6- to 8- hour protocol sample size was 3,869.

The power values of the different analyses achieved according to the above are:

Efficacy comparison conventional vs. simultaneous protocol = 71.8%

Efficacy comparison conventional vs. 6- to 8- hour protocol = 100%

Safety comparison conventional vs. simultaneous protocol = 100%

Safety comparison conventional vs. 6- to 8- hour protocol = 100%

Three of these power estimates exceed the required sample size estimations that were predicted in Chapter 3. Due to the small difference in efficacy (OR = 1.034) between the conventional and the simultaneous protocols, the sample size of 27,616 was insufficient (a sample size of 34,572 is required) for the power of 80% to be reached.

Representativeness of The Sample to The Population of Interest

The data set includes patient records from clinical across the United Kingdom. The abortion provider organization has 42 clinics across England, Scotland, and Wales. I consider the data to be representative of UK women of reproductive age. The data set captured all women who sought a MA in all 42 clinics between January 2017 and June 2018. Only the records of 2,704 patients were removed from the data set. The removal was only based on the completeness of patient records and was not based on any patient characteristics. This removal of 4.6% of the original data set is insufficient to affect the representativeness of the data. I would also consider the sample to be globally representative of women who seek abortion before 10 weeks. The conventional protocol is what is recommended by the WHO for global use. That recommendation is based on multiple studies that showed the protocol to be effective irrespective of patients' nationality or other characteristics that might change based on patients' nationality. This

suggests that for the purpose of MA prior to 10 weeks of gestation, women across the globe shows homogeneity with regards to abortion protocol effectiveness and safety.

Intervention Fidelity

No deviations from the protocols explained in Chapter 3 were detected in patient records. All three protocols were in line with what was outlined in the first three chapters. While occasional deviations in practice (not captured in the patient records) cannot be ruled out, intervention fidelity is safe to assume. Serious adverse events and severe complications are captured in the analyzed data set and they are included in the analyses on protocol safety

Results

Descriptive Statistics

A total of 55,968 patients were included in the analyses. Of these patients, 24,483 accepted the conventional protocol, 3,869 accepted the 6- to 8- hour protocol, and 27,616 accepted the simultaneous protocol. Patients' age breakdown was; <15-years [*n* = 32 (0.06%)], 15-19-years [*n* = 5,803 (10.4%)], 20-24-years [*n* = 15,140 (27.1%)], 25-29-years [*n* = 14,589 (26.1%)], 30-34-years [*n* = 10,739 (19.2%)], 35-39-years [*n* = 7,174 (12.8%)], and ≥40-years [*n* = 2,491 (4.4%)]. The median age group was 25-29-years (Table 2). Gestational ages (Table 3) were; 4 weeks [*n* = 67 (0.12%)], 5 weeks [*n* = 7,194 (12.9%)], 6 weeks [*n* = 22,332 (39.9%)], 7 weeks [*n* = 14,052 (25.1%)], 8 weeks [*n* = 9,601 (17.2%)], and 9 weeks [*n* = 2,722 (4.9%)]. The mean of the gestational age was 6.6 weeks (SD = 1.07). The number of past pregnancies (Table 4) were; 0 [*n* = 17,763 (31.2%)], 1 [*n* = 10,685 (18.8%)], 2 [n = 9,215 (16.2%)], 3 [*n* = 7,632 (13.4%)], 4 [n =

4,890 (8.6%)], 5 [*n* = 2,771 (4.9%)], 6 [n = 1,492 (2.6%)], 7 [n = 737 (1.3%)], 8 [n = 339 (0.6%)], 9 [n = 206 (0.4%)], and ≥10 [*n* = 238 (0.4%)]. The mean of the past pregnancies was 1.91 (SD = 1.99).

Table 2

Age of Study Participants Stratified by Chosen Medical Abortion Protocol

Age	Total Population (*n = 55,968*)	Conventional Protocol (*n = 24,483*)	6-8-Hour Protocol (*n = 3,869*)	Simultaneous Protocol (*n = 27,616*)
< 15	0.1%	0. 1%	0.1%	0.1%
15-19	10.3%	9.0%	9.2%	11.8%
20-24	27.1%	26.8%	29.3%	27.0%
25-29	26.1%	26.7%	26.7%	25.4%
30-34	19.2%	19.8%	18.3%	18.8%
35-39	12.8%	13.2%	12.9%	12.4%
≥ 40	4.5%	4.5%	3.6%	4.5%

Table 3

Gestational Ages Stratified by Chosen Medical Abortion Protocol

Gestational Age (Weeks)	Total Population (*n = 55,968*)	Conventional Protocol (*n = 24,483*)	6-8-Hour Protocol (*n = 3,869*)	Simultaneous Protocol (*n = 27,616*)
4	0.1%	0.2%	0.1%	0.1%
5	12.9%	16.2%	8.1%	10.6%
6	39.9%	45.2%	35.7%	35.8%
7	25.1%	23.8%	28.3%	25.8%
8	17.2%	13.7%	21.0%	19.7%
9	4.9%	1.0%	6.8%	8.0%

Table 4

Past Pregnancies Stratified by Chosen Medical Abortion Protocol

Past Pregnancies	Total Population (*n = 55,968*)	Conventional Protocol (*n = 24,483*)	6-8-Hour Protocol (*n = 3,869*)	Simultaneous Protocol (*n = 27,616*)
0	31.2%	29.4%	32.1%	33.8%
1	18.8%	18.8%	20.2%	19.2%
2	16.2%	16.8%	17.7%	16.0%
3	13.4%	14.5%	13.4%	12.9%
4	8.6%	9.2%	8.0%	8.4%
5	4.9%	5.4%	3.9%	4.7%
6	2.6%	2.9%	2.5%	2.5%
7	1.3%	1.5%	1.0%	1.2%
8	0.6%	0.7%	0.6%	0.5%
9	0.4%	0.4%	0.2%	0.3%
≥10	0.4%	0.5%	0.4%	0.4%

The bivariate analyses for comparing the two outcomes of the protocols are given below. They include the *Pearson Chi-square* value as well as the *Cramér's V* value for each of the two analyses. Table 5 outlines the bivariate analyses for efficacy while Table 6 outlines the bivariate analyses for safety (no covariates included).

Table 5

Bivariate Analyses for The Efficacy of The Three Protocols

Outcome	Protocol 1	Protocol 2	Protocol 3
Failures	374	284	439
Expected failures	479.9	75.8	541.3
Total cases	24,483	3,869	27,616

	Value	*p value*
Pearson Chi-Square	626.384	0.000
Cramér's V	0.106	0.000

Table 6

Bivariate Analyses for the Safety of the Three Protocols

Outcome	Protocol 1	Protocol 2	Protocol 3
Complications	232	103	543
Expected complications	384.1	60.7	433.2
Total cases	24,483	3,869	27,616

	Value	*p value*
Pearson Chi-Square	119.391	0.000
Cramér's V	0.046	0.000

With no control variables factored in, there are weak/very weak associations (both *Cramér's V* values are below 0.15) among the efficacy and the safety of the different MA protocols. These weak/very weak associations are statistically significant (both *p* values are below 0.0001). Tables 7 and 8 show the results of the chi-square tests conducted between the dependent variables and the control variables relevant to each dependent variable. These two analyses help determine the suitability of the control variables to be included in the regression analyses that analyse the empirical relationships between the MA protocols and their safety and efficacy.

Table 7

Bivariate Analyses – Covariates for Efficacy

Covariate	*Pearson Chi-square*	*df*	*p value*
Maternal Age	57023.827	7	0.000
Gestational Age	72.716	5	0.000
Past Pregnancies	51.955	10	0.000

The analysis justified the inclusion of all three covariates (maternal age, gestational age, and past pregnancies) in the regression modelling for the dependent variable efficacy. Accordingly, the regression analysis for efficacy was done with all three covariates included. Protocol 1 (conventional) was taken as the baseline. Table 9 gives the regression analysis results for MA efficacy.

Table 8

Bivariate Analyses - Covariates for Safety

Covariate	*Pearson Chi-square*	*df*	*p value*
Maternal Age	56944.039	7	0.000
Gestational Age	72.196	5	0.000
Past Pregnancies	7.205	10	0.706

The analyses justify the inclusion of two covariates (maternal age and gestational age) in the regression modelling for the dependent variable safety. The inclusion of past pregnancies is not justified. Accordingly, the regression analysis for safety included two covariates. Protocol 1 (conventional) was taken as the baseline in the safety analysis as well. Table 10 gives the regression analysis results for MA safety.

Statistical Assumptions as Appropriate to the Study

The dependent variables were binary, the sample sizes are large, and the coding is done in a way that (Y=1) in the probability of as event occurring (MA failure, and severe complication or adverse event). A stepwise approach used ensures that the models fit correctly. A factor analysis prior to running the logistic regression analyses showed no significant multicollinearity, which is also assured because the abortion protocols are

independent of each other. Linearity of independent variables and log odds is assured by the independent variable being categorical.

Table 9

Binomial Logistic Regression Output – Protocol Efficacy

			95% CI For *OR*	
Variable	*OR*	Significance	Lower	Higher
Protocol 1				
Protocol 2	0.210	0.000	0.178	0.246
Protocol 3	1.034	0.647	0.897	1.191
Maternal Age	0.822	0.000	0.782	0.864
Past Pregnancies	0.977	0.175	0.945	1.010
Gestational Age	0.811	0.000	0.767	0.858

Regression results show a statistically significant difference ($p < 0.0001$) between the efficacy of the conventional protocol and the 6- to 8- hour protocol (Protocol 2). There is no such difference between the conventional (Protocol 1) and the simultaneous (Protocol 3) protocol. The odds-ratios suggest that the 6- to 8- hour protocol has a 79% higher likelihood of failure compared to the conventional protocol (*OR* = 0.210, 95% CI: 0.178 - 0.246). The simultaneous protocol has a 3.4% lower efficacy (*OR* = 1.034, 95% CI: 0.897-1.191) but this is not significant ($p = 0.647$). The null hypothesis is rejected due to the statistically significant difference between the conventional and the 6-8-hour protocol (Protocol 2).

The analysis shows that maternal age and gestational age affects the efficacy of MA protocols in a statistically significant manner ($p < 0.0001$). The number of past pregnancies does not. Each advance in maternal age along the 5-year age blocks used in the analysis increases the risk of MA failure by 17.8%. Each week's advance in

gestational age increases the risk of MA failure by 18.9%. While each past pregnancy increases the risk of MA failure by 2.3%, this effect is not statistically significant. This differs from the result of the bi-variate analysis, where past pregnancy (as a standalone) was shown to significantly affect MA efficacy. This suggests possible interaction(s) between the past pregnancy number and maternal age and/or gestational age.

Table 10

Binomial Logistic Regression Output – Protocol Safety

			95% CI For *OR*	
Variable	*OR*	Significance	Lower	Higher
Protocol 1				
Protocol 2	0.386	0.000	0.304	0.489
Protocol 3	0.524	0.000	0.447	0.613
Maternal Age	1.093	0.001	1.039	1.150
Gestational Age	0.825	0.000	0.776	0.877

The odds-ratios suggest that the 6- to 8- hour protocol (Protocol 2) and the simultaneous protocol (Protocol 3) have higher likelihoods of severe adverse events or complications compared to the conventional protocol. Both differences are statistically significant ($p < 0.0001$). The safety of the 6- to 8- hour protocol (Protocol 2) is 61% less (*OR* = 0.386, 95% CI: 0.304- 0.489) than the safety of the conventional protocol (protocol 1). The safety of the simultaneous protocol (Protocol 3) is 48% less (*OR* = 0.524, 95% CI: 0.447 - 0.613) than the safety of the conventional protocol. The null hypothesis is therefore rejected.

The analyses show that maternal age and gestational age affects MA protocol safety in a statistically significant manner ($p < 0.0001$). Each advance in maternal age

along the 5-year age blocks used in the analysis reduces the risk of severe complications (and/or adverse events) by 9.3%. Each week's advance in gestational age increases the risk of severe complications (and/or adverse events) by 17.5%.

Summary of Results

The descriptive results and the results of the bivariate analyses done to validate the covariables and the hypothesis testing was provided in this chapter. The assumptions of logistic regression were ensured. Both null hypotheses were rejected, with regression analyses showing significant differences in efficacy and the safety of the three MA protocols when the relevant covariates are controlled for. The efficacy of the conventional protocol is comparable to that of the simultaneous protocol while the 6- to 8- hour protocol has a significantly lower efficacy. Both the simultaneous and the 6- to 8-hour protocols showed significantly lower safety that that of the conventional protocol. The absolute risk of a severe adverse event or complication was very low for all protocols (0.98% for conventional protocol, 2.67% for the 6-to 8-hour, and 1.97% for the simultaneous.

Advancing maternal age as well as advancing gestational age were shown to reduce the efficacy of MA, while the effect of past pregnancies on MA efficacy went from being significant when considered as a standalone to non significant when considered with the other two covariables. Advancing gestational age was shown to reduce the safety of MA while advancing maternal age showed a small but significant protective effect.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this quantitative, retrospective study was to explore the relationships of different MA protocols with different dosing intervals to the efficacy and safety of the procedures resulting from those protocols. I measured the efficacy of a protocol by the percentage of women who had a MA using the said protocol that required either an additional abortifacient dose or a vacuum aspiration to complete the procedure. Safety of a given MA protocol was measured by the percentage of women who had a MA using the said protocol that experienced a complication that required clinical care. According to the results, both null hypotheses were rejected. The efficacy of the conventional and the simultaneous protocols were comparable while the 6- to 8-hour protocol showed a lower efficacy. Both the simultaneous and the 6- to 8-hour protocols showed lower safety rates when compared to the conventional protocol.

A growing proportion of induced abortions across the globe are MAs (Jones & Jerman, 2017; Kapp, Eckersberger, Lavelanet, & Rodriguez, 2018). MIFE is registered in 57 countries (Dunn & Cook, 2014) and MISO in over 100 (Medication Abortion, 2016). Regimens of MIFE followed by a dosing interval by MISO is the norm for MAs (Gatter et al., 2015; Raymond et al., 2013). This time gap has remained at 24 hours or more over the last 2 decades (Creinin et al., 2004; WHO, 2015), making MA a much longer process than surgical abortion. If one or both shorter MA protocols are shown to have acceptable efficacy and safety (albeit being significantly different from the conventional protocol),

they could potentially replace the lengthier conventional protocol, making MA a shorter and simpler procedure that many more millions of women find acceptable.

Interpretation of Findings

I found the efficacy of the conventional protocol to be comparable to that of the simultaneous protocol. The 6-to 8-hour protocol was found to have a significantly lower efficacy to that of the others. The safety of both the simultaneous and the 6- to 8-hour protocols was significantly lower than that of the conventional protocol. Despite their higher risk compared to the conventional protocol (when odds ratios are considered), the absolute risk of a severe adverse event or complication that required facility care was 0.98% for the conventional protocol (i.e., 232 referrals among 24,483 women), 2.67% for the 6-to 8-hour protocol (i.e., 103 referrals among 3,869 women), and 1.97% for the simultaneous protocol (i.e., 543 referrals among 27,616 women). The rates of severe adverse events and complications seen among simultaneous protocol recipients who experienced severe adverse events or complications are comparable to the 1.5% serious adverse event rate recorded by Creinin et. al. (2007) but higher than the 1.2% reported by Schreiber et al. (2005), the 0.2% rate reported by Lohr et. al. (2007), and the 0.1% rate reported by Li et al. (2011). Rates of severe adverse events and complications seen among the 6- to 8-hour protocol recipients were higher than the 0.6% reported by Creinin et. al. (2004). The high rates of clinical referrals observed might be due to substandard record keeping at the 24-hour call center of the abortion provision organization. The possibility of referrals made due to protocol failures (i.e., where clients are referred for additional MISO doses or surgical evacuation) being recorded as being due to

complications or severe adverse events cannot be ruled out. Within their study groups, some past researchers (i.e., Guest et al. 2007; Tendler et al., 2015) have recorded similar adverse event frequencies between the shorter and the conventional protocols. Fox et al., (2002), however, recorded higher adverse events among women opting for shorted medical protocols. These higher rates were acceptable, and the higher rates of adverse events were assumed to be due to the greater overlapping of MIFE and MISO plasma peaks.

In terms of efficacy, the analyses showed that the conventional protocol had a 1.53% failure rate, while the corresponding rate for the 6- to 8-hour protocol was 7.3% and the simultaneous protocol had a failure rate of 1.59%. These results are comparable to the efficacy rates shown for the 6- to 8-hour protocol in other studies (Fox et al., 2002; Guest et al., 2007; Pymar et al., 2001). However, the efficacy rates seen for the simultaneous protocol and the conventional protocols are superior to the 90% to 94% efficacy rates seen in past studies (Creinin et al., 2007; Li et al., 2006; Murthy et al., 2005; Verma et al., 2017). The superior rates could also be explained with the assumption that referrals due to protocol failures (where clients are referred for additional misoprostol doses or surgical evacuation) being recorded as being due to complications or severe adverse events. I addressed this in the limitations of the study and the recommendations for future research sections.

Advancing maternal age and advancing gestational age were shown to reduce MA efficacy. The effect of past pregnancies on MA efficacy went from being significant when considered as a standalone variable to nonsignificant when considered with

gestational age and maternal age as covariables. These findings are of great value because to the best of my knowledge, no past study of abortion efficacy had used any covariables in their analyses. No past researchers had explored the effect of maternal age or the number of past pregnancies on MA efficacy. The effect of gestational age on efficacy seen in this study corroborates the results of Fox et al. (2002) who found the efficacy of the 6- to 8-hour protocol at 50 to 56 days to be higher than its efficacy at 57 to 63 days of gestation. Similar findings were reported by Schreiber et al. (2005) and Verma et al. (2017) who found a gestational age over 56 days was a predictor for MA failure. The findings did not support Creinin et al.'s (2007) study though, where the authors did not find efficacy variations with gestational age up to the 10th week of gestation. Advancing gestational age was shown in my study to reduce the safety of MA while advancing maternal age showed a small but significant protective effect. No past studies had carried out analyses that assessed the effect of these variables on MA safety.

The study was grounded in postpositivism and empiricism. Empiricism recognizes that observation and measurement form the core of scientific study (Trochim, 2006) and recognizes the role of empirical evidence and the knowledge received through observation and experimentation in the formation of ideas (Baird & Kaufmann, 2008). The theoretical framework provided by postpositivism (see Tashakkori & Teddlie, 1998; Theory of Knowledge, 2015) provided me with valuable guidance in interpreting the results and when the results are consulted for the practical implications that they might have on MA care provision. Postpositivism ventures beyond the observable (Clark, 1998) and posits that objectivity is an ideal that requires critical interpretation (Fischer, 1998).

The results of this study show the simultaneous protocol to have comparable efficacy to the conventional protocol, while its safety is 58% less compared to the conventional protocol. In the data set (without covariates factored in), however, the conventional protocol users showed a 1.53% failure rate, while the simultaneous protocol users showed a failure rate of 1.59%. With all covariables factored in, the results indicated that if the conventional protocol has a 1.53% risk of failure, the risk of failure of the simultaneous protocol would be 1.58%. In day-to-day practice, women are very likely to accept this small absolute increase in failure in return for a shorter protocol. Postpositivist reasoning follows this logic by taking a realist perspective that allows researchers to take the realities of life into account when interpreting their results (Theory of Knowledge, 2015).

The results of this study show promise for recommending the simultaneous protocol as an option that can be offered to women seeking a MA prior to the 10th week of gestation. The higher failure rate of the 6- to 8-hour protocol combined with its higher likelihood of complications and/or severe adverse events does not make it an acceptable option. With many women seeking shorter protocols (Iyengar et al., 2016b), the ability to offer the simultaneous protocol would be of great importance, while the unsuitability of the 6- to 8-hour protocol as having less efficacy and safety would not have a significant negative impact. Evidence has demonstrated that women could leave health facility as soon as MISO was administered and handle the expulsion on their own (WHO, 2015). With the simultaneous protocol, this would mean that a MA prior to the 10th week of gestation could become a simple procedure that requires a clinical visit of approximately an hour including the time required for the pre- and post procedure counselling.

Study Limitations

This study had several imitations. The biggest was being a retrospective, observational study based on day-to-day clinical data. Observational studies are less rigorous than true experiments with randomization (Creswell, 2014). The data spanned 18 months and came from healthcare worker data entries rather than from robust data-entry in a research setting. Verifying referral data from the contact center was difficult with no source being available for triangulation. The reasons for some referrals might have been captured incorrectly by the contact center. Some women who experienced adverse events or complications might have sought care outside of the abortion provider organization, thereby not being captured in the data. Self-referrals to the National Health Service or those seeking care through their general practitioners or walk-in emergency centers cannot be ruled out.

The data related to MA protocols might have inaccuracies, which were impossible to rectify. Deviations from the exact administration of MISO (such as route, dosage, or timing) might have occurred but were impossible to capture if the documentation shows the administration was faultless. The study design did not allow for an experimental approach where the independent variable can be manipulated to observe the effects of manipulation on the dependent variables (see Frankfort-Nachmias & Nachmias, 2008). A women's choice of MA protocol is respected in abortion care, which ruled out any randomization. A true experimental design with random assignment and experimentally controlled treatments would be necessary to obtain more accurate estimates for efficacy and safety (Creswell, 2014).

Finally, the study design only controlled for three covariates that were known to impact the safety and the efficacy of MA from a clinical perspective. Gatter et al. (2015) showed that in settings where the quality of clinical care is well standardized, poverty and educational level does not impact early MA outcomes. However, in real-life settingsRamashwar (2013) and Gerdts et. al. (2015) have shown that covariates related to the socio-economic status of women, such as education, immigration status, and poverty, do impact abortion safety. Such covariates are not captured by the data system of the abortion provider, and hence, could not be considered in this study.

Recommendations for Future Studies

Future studies should aim to measure the efficacy and the safety of the simultaneous protocol with higher accuracy, including how its efficacy and safety compare across different gestational ages. Study designs that allow for experimental approaches where women who undergo MA are grouped by gestational age and are actively followed up with outcomes clearly tracked would allow us to gather more robust evidence on the protocols efficacy and safety and how those change with increasing gestational age. Such a study would also inform the gestational age up to which this protocol could be offered as an out-patient procedure. The complications and adverse events of the simultaneous protocol should be better understood. A study where women of different gestational ages who receive MAs using this protocol are actively followed up for up to 1- to 2- weeks would allow us to plot the different types of adverse events and complications as well as their frequencies.

Studies that alter the dosage of one or both drugs should be conducted. Groups of women who undergo early MA using different dosages could provide us with a study where the independent variable (dosages) is manipulated to observe the effects of manipulation on the dependent variables (Frankfort-Nachmias & Nachmias, 2008), in this case the safety and efficacy. Such a design could even involve randomizing women to the different dosage groups, as the potential difference between the different dosages is unlikely to lead to unacceptable risks for some groups. Such a true experimental design with randomization and experimentally controlled treatments would provide more accurate estimates (Creswell, 2014) for efficacy and safety.

Recommendations for clinical practice

The results suggest that the simultaneous protocol can be offered in all setting that currently offer the conventional protocol for MA up to the 10 weeks of gestation. The slightly higher absolute risk of complications and severe adverse events should be carefully incorporated into counselling. It should be presented in a manner that makes it easy for women to comprehend and compare. The efficacy rates of the conventional and the simultaneous protocols must be presented to women in a manner that makes it easy for them to understand and compare the slight difference in absolute risk between the protocols. All locations that offer the simultaneous protocol must have clear and reliable referral options available and all women should be provided with this referral information to be used in the case of complications or adverse events. Reliable follow-up mechanisms must be in place for women who have post–procedure concerns to seek advice from.

Implications for Positive Social Change

MA is becoming the norm is terminating early pregnancies across the globe, due to the process being safer, cheaper, and less medicalized compared to surgical options (Simmonds, Beal, & Eagen-Torkko, 2017; Zane et al., 2015). This is seen in the United States (Jones & Kooistra, 2011) as well as Europe. In several European countries, the proportion of early abortions carried out through medical methods exceeds 60% (Jones & Henshaw, 2002). With MIFE registered in 57 countries (Dunn & Cook, 2014) and MISO registered in over 100 countries (Medication Abortion, 2016), the findings of this study could pave the way for the simultaneous protocol to be offered to women as a viable alternative to the conventional 24- to 36- hour protocol. That will make MA a much shorter, simpler procedure. The simultaneous protocol with just one interaction with a care provider for its administration could turn MA in to a single day process and potentially replace the conventional protocol as the norm. That could make MA more enticing and accessible to millions of women worldwide. Even if the simultaneous protocol does not replace the conventional protocol, it might become an alternative to be offered side-by-side with the conventional protocol. In such a situation, the findings will help providers to accurately counsel women on the efficacy and the safety of these MA protocols on offer. They could also help women determine which method is the best for them, taking both clinical factors as well as factors related to convenience into account.

The findings could potentially lead to a MA protocol change in the United Kingdom. Such a change could have cascading effects on MA protocols used in many commonwealth countries. The study findings and a potential UK protocol change could

bring the simultaneous protocol to the notice of organizations such as the WHO, United Nations Population Fund, International Federation of Gynaecology and Obstetrics, and the Royal College of Obstetricians and Gynecologists. These organizations guide care practices across the globe. Policy and guideline changes in them can introduce the simultaneous protocol across the world, including in settings with restrictive abortion legislature. A simpler MA protocol could entice more clinics, hospitals, and practitioners to offer it. The simultaneous protocol could become popular among the various online platforms that inform women how to conduct early MAs at home, simplifying the process for millions of women across the globe. The shift of millions of women to simple, MA instead of the riskier, pricier, and harder to access surgical options could reduce serious complications. Healthcare systems and governments will be spared resources that are currently spent providing expensive surgical abortions as well as managing complications of unsafe abortions

Conclusion

This retrospective analysis of MA outcomes in women with gestational ages below ten weeks showed that the simultaneous protocol has comparable efficacy to the conventional MA protocol. The 6- to 8- hour protocol had a significantly lower efficacy. Both the simultaneous and the 6- to 8- hour protocols showed higher incidences of severe adverse events and complications when compared to the conventional protocol. The absolute rates of complications and severe adverse events however were very low. The simultaneous protocol is a viable alternative to the conventional protocol and should be offered as such to all women seeking MAs prior to the 10 weeks of gestation. Offering it

could give millions more women access to safe and effective single day MAs, cut the need for skilled clinicians, and reduce abortion costs for both women and for healthcare systems. These social changes could make abortion safer globally.

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