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THE MORAL OBLIGATION TO INCLUDE PREGNANT WOMEN IN CLINICAL TRIALS

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of MSc (Med) in Bioethics and Health Law

Supervisor:

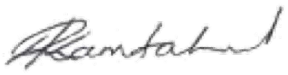
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Durban, 2024

DECLARATION

I, Kieara-Lee Ramtahal, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of MSc (Med) in Bioethics and Health Law at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(Signature of candidate)

10 day of June 2024 in Durban

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ABSTRACT

Many pregnancies are complicated by serious medical conditions that require treatment, and despite the need to use medication during pregnancy, the majority of clinical trials do not include the pregnant population, which leaves pregnant women with limited “robust” data regarding the safety and effectiveness of medications that they may require during pregnancy (Little & Wickremsinhe, 2017, p.1). In this report, I examine the reasons provided for the exclusion of pregnant women from clinical trials and the ethical reasons for their inclusion. I argue that, 1. the exclusion of pregnant women as participants in clinical trials could potentially expose future pregnant women to significant harms, 2. the benefits arising out of the inclusion of pregnant women in clinical trials far exceeds the possible harms to the pregnant women trial participants and their fetuses and 3. pregnant women deserve fair access to research trials where their participation will involve access to potential benefits. I also discuss objections to my arguments and provide a response. In conclusion, I contend that pregnant women should be included in clinical trials unless there are compelling reasons for exclusion.

CHAPTER 1: INTRODUCTION

1.1 Background

An essential component of any clinical trial is gathering of data on the performance of the investigational drug in the population that is likely to use it to guide “safe and evidence-based clinical decision-making” (Weld et al., 2021, p.7). However, it has been customary to exclude the pregnant population from clinical trials of new drugs (Weld et al., 2021). Many pregnancies are complicated by serious medical conditions that require treatment, and despite the need to use medication during pregnancy, the majority of clinical trials do not include this population, which leaves us with limited “robust” data regarding these medications' safety and effectiveness during pregnancy (Little & Wickremsinhe, 2017, p.1).

The limited research and data available on drugs in the pregnant population presents a challenge for clinicians when they must decide what drug to prescribe to pregnant women (Weld et al., 2021, p.11). This also poses a risk to pregnant women as they do not have access to adequate information to make informed decisions about their own treatment (Weld et al., 2021, p11). In view of the biological differences between pregnant women and other populations, it is vital to collect data regarding how drugs "behave in the pregnant body” (Little & Wickremsinhe, 2017, p.1).

Two strategies have been presented in the literature for effectively including pregnant women in research. The first proposed method is to run Phase I safety trials in pregnant women concurrently with Phase III efficacy trials in non-pregnant women and men, with this method an investigational drug that is proven unsuccessful in Phase I and II studies will not proceed to be tested on the pregnant population. The second approach is for pregnant women to participate in Phase III

studies once the Phase I and II studies have been completed successfully, this method would require greater safety monitoring (Baylis & Halperin, 2012, p.40).

While there may be adverse effects associated with clinical trials, excluding pregnant women completely from participating in clinical research trials ultimately hinders advancing maternal and fetal health. Many have argued that the inclusion of pregnant women in research is in fact a moral imperative (Goldkind et al., 2010, p.2242). I will similarly argue that pregnant women should be included in clinical trials unless there are reasons for exclusion.

1.2 Research Question

Is there a moral obligation for pregnant women to be included in clinical trials?

1.3 Rationale for the Study

The current pregnant population have limited information available to them for many drugs that they must take during pregnancy; this lack of available information could result in potential harm to the pregnant women and the fetus. While others have made some individual arguments for inclusion of pregnant women in clinical trials, I hope to have developed one comprehensive and robust argument for inclusion, with the hope of raising the awareness of the potential harms associated with their exclusion.

1.4 Thesis statement

I argue that pregnant women should be included in clinical trials unless there are compelling reasons for exclusion.

Clarification of thesis statement: Compelling reasons for exclusion of pregnant women from clinical trials may include an investigational drug that is known to be harmful to the pregnant women or fetus (e.g., a known teratogen), a drug that is of

no benefit to the pregnant population, when there is no or inadequate preliminary evidence from a variety of sources (e.g. from pregnant animals or non-pregnant women) that could inform an assessment of potential risk or, when there is such preliminary evidence, but it suggests pregnant women/foetuses might be exposed to an unacceptable level of risk given the potential benefit.

1.5 Research Aim

To critically defend the claim that pregnant women should be included in clinical trials unless there are compelling reasons for exclusion.

1.6 Research Objectives

1. To provide a thematic overview of the literature focusing on differing positions taken on the inclusion of pregnant women in clinical trials.
2. To critically defend the claim that pregnant women should be included in clinical trials unless there are compelling reasons for exclusion.
3. To describe and respond to objections to my argument.

1.7 Research Design and Methods

This was a type 1 normative study that used purely desktop and library-based research. This research report has reviewed the key literature relating to the inclusion and exclusion of pregnant women from clinical trials and the relevant bioethical references. This study did not collect or analyse new data. There was no human participation. This study adhered to the research methods and standards as used in philosophical research.

The sources of literature for this study included, but were not limited to, research databases such as Springer Link, PubMed and Google Scholar, bioethical textbooks and research articles from accredited journals.

1.8 Research Outcomes

To contribute to the awareness of the moral obligation to include pregnant women in clinical trials which will hopefully facilitate therapeutic development to address unfulfilled medical needs in the pregnant population.

1.9 Limitations

There is limited literature on the reasons for exclusion of pregnant women in clinical trials. The research question is limited pregnant women and does not include lactating women and their nursing infants.

CHAPTER 2: CONSIDERATIONS OF THE JUSTIFICATIONS PROFFERED FOR THE INCLUSION AND EXCLUSION OF PREGNANT WOMEN IN CLINICAL TRIAL RESEARCH

2.1 Introduction

In chapter 2 I outline the justifications proffered in the literature for and against the inclusion of pregnant women in clinical research. This chapter will be divided into two parts, in Section 2.2 I will outline the arguments presented in the literature in favour of including pregnant women in clinical research trials and Section 2.3 I will outline the arguments presented in the literature for the exclusion of pregnant women in clinical research trials.

2.2 Arguments presented for the inclusion of pregnant women in clinical trial research

I now turn to section 2.2; in this section I will outline the arguments that are presented in the literature for the inclusion of pregnant women in clinical research trials. Clinical research seeks to identify highly regulated, carefully controlled, ethically acceptable methods to gather information on how to effectively and safely treat individuals who are ill or to prevent illness (Kaye, 2019, p.1). In order for a drug to be prescribed safely and effectively, clinical research trials must be created to test it on all users who are anticipated to take the drug, not just a small population (Noah, 2014, p.355). Therefore, it is vital that all relevant populations are included in clinical research, when it is suitable, since different populations can present various patterns of response or adverse reactions related to the study drug (Noah, 2014, 353).

Although there has been great progress in integrating women in clinical research, it has been routine to exclude the pregnant population from clinical trials of new drugs (Weld et al., 2021). According to Macklin, while protecting pregnant women and their fetus from preventable harms that might be caused by experimental drugs is always important, there are a number of reasons why pregnant women should be included in more clinical research trials than is currently the case (Macklin, 2010, p.632). In sections 2.2.1 to 2.2.3 of this literature review, I will briefly discuss the three primary justifications offered in the literature for inclusion of pregnant women in clinical research.

2.2.1 Effective medical treatment for women during pregnancy

One of the justifications given in the literature for the inclusion of pregnant women in clinical research is the requirement for effective treatment during pregnancy (Lyerly et al., 2008, p.3). Since there are so few studies particularly created to address health issues and problems related to pregnant women, there isn't much information available to guide healthcare and treatment choices throughout pregnancy (Foulkes et al., 201, p.1429).

According to Lyerly et al., inclusion of pregnant women in research is essential in order to provide women and their fetuses with safe and effective treatment and reduce suboptimal care that may result from physicians prescribing medications that have not been researched in the pregnant population (2008, p.3). In an article by Little she explains that when it comes to how drugs are metabolized, the "pregnant body might behave as a ‘wild card’—during pregnancy, certain drugs dosed for people who aren't pregnant may leave the pregnant body too rapidly to have a

therapeutic effect" (2020). Other drugs might harm the developing fetus while ignoring the pregnant woman's condition entirely (Little & Wickremsinhe, 2017, p.1).

Baylis & Halperin argue that "physiological changes during pregnancy, such as increased plasma volume, body weight, body fat, metabolism and hormone levels preclude the extrapolation of data about dosing and safety (from men and nonpregnant women) to pregnant women" (Baylis & Halperin, 2012, p.141). Baylis and Halperin go on to state that it is difficult for clinicians who are treating pregnant women to effectively care for these women due to the limited information on drug "safety, toxicity, dosage, side effects, and contraindications" (Baylis & Halperin, 2012, p.141). The authors conclude their argument by asserting that pregnant women with pre-existing or prenatal conditions should be included in clinical trials except in cases where there are reasons why they should not be included (for instance if the study involves a known teratogen) (Baylis & Halperin, 2012, p.141). Similar to this, Foulkes et al. contend that pregnant women need to get safe, effective therapy with sufficient pharmacokinetic data to determine the right therapeutic dosage during each trimester of pregnancy and to evaluate the harms to the fetus (Foulkes et al., 2011, p.1429).

In addition to drugs for treatment of illnesses, Baylis & Halperin also contend that it is common for women to take preventative products during pregnancy (such as vaccines) (2012, p.141). Public health relies heavily on vaccines to prevent infectious diseases, but the pregnant population have routinely been excluded from vaccine research and development (Jaffe et al., 2020, p.6922). An important example of exclusion of pregnant women from vaccine research is the early Ebola vaccine trials

(Beigi et al., 2021) and more recently most COVID-19 vaccine trials (Jaffe et al., 2020).

Researchers must thus plan and carry out clinical trials and other sorts of data gathering methods for both new and currently approved medicines, treatments, and preventives in order to discover how safe these drugs, therapies, and preventives are to use during pregnancy (Noah, 2014).

2.2.2 Fetal safety

The second justification found in the literature for including pregnant women in clinical research is identical to the one sometimes offered for excluding them: fetal safety. Pregnant women take medication during pregnancy for pre-existing conditions and for illnesses that develop during pregnancy. However, practically all drugs used to treat disorders in women who are pregnant today including those for serious long-term ailments like diabetes, hypertension, and cancer are taken in an unapproved manner (Noah, 2014, p.353). The obvious with this manner of taking medication, which is represented in the literature is that several of the drugs routinely administered to pregnant women may be harmful to the fetus (Lyerly et al., 2008, p.4). Lyerly et al. use the example of ACE inhibitors, a drug that is frequently recommended to treat hypertension (Lyerly et al., 2008, p.4). ACE inhibitors were previously recognized to be contraindicated in the second and third trimesters, but it was unclear how risky they were in the first trimester until 2006 when new research was published. According to this study, using antihypertensive medication slightly but significantly raised the risk of cardiovascular and neurological problems in fetuses (Lyerly et al., 2008, p.4). However, the congenital defects brought on by the three

decades of usage since the medication's introduction may have been avoided if researchers had researched the medicine during pregnancy earlier (Lyerly et al., 2008, p.4). It is therefore crucial to include pregnant women in clinical research in order to protect the fetus from harms that could be caused by drugs that have not been studied in the pregnant population and which are currently being used without adequate research and data to support the safety of the drug during pregnancy.

2.2.3 Unfair denial of the benefits associated with participation in clinical research trials

The third justification often proffered for including pregnant women in clinical research is that doing so will prevent them from being unfairly denied the benefits of clinical research. Baylis & Halperin argue that by excluding pregnant women from research based on pregnancy alone, we deny these women the benefits that arise from the data collected from the research and the health benefits that arise from participation in research (2012, p.140).

There are several Phase II and III studies designed to determine if a particular medicine is effective for a certain medical condition (Lyerly et al., 2008, p.6). Participants in the active arm of these trials may see a significant improvement in their medical condition, therefore benefiting from trial participation (Lyerly et al., 2008, p.6). This means that by only allowing non-pregnant individuals to enrol in clinical trials, the pregnant population are unfairly disadvantaged in terms of “health and wellbeing” (Lyerly et al., 2008, p.6).

According to Foulkes et al., as a matter of social justice, that is seeing others as honourable beings deserving of the same level of moral consideration and seeing them as autonomous sources of moral value and dignity, clinical research that

excludes pregnant women can be seen as unfair discrimination against pregnant women (Foulkes et al. 2011, p.1430). Pregnant women's health concerns and treatment options should be taken into account, thoroughly researched, and given the same chance to enhance health status as any other population group (Foulkes et al., 2011).

In summary, this section has outlined the three main arguments represented in the literature for the inclusion of pregnant women in clinical research: Effective medical treatment for women during pregnancy, fetal safety and unfair denial of the benefits associated with participation in clinical research trials.

2.3 Arguments presented in the literature for the exclusion of pregnant women in clinical research trials

I'll now briefly summarize the primary justifications cited in the literature for excluding pregnant women from clinical research. Several types of arguments are made to support the claim that including pregnant women in clinical research may be ethically unsound. These arguments are discussed in sections 2.2.1 through 2.2.5 and include harm to the fetus, pregnant women's vulnerability as a group, the physiological complexity of pregnancy, drug manufacturers' reticence, and finally Institutional Review Board (IRB) reticence[1].

2.3.1 Harm to the fetus

One of the main reasons often proffered for exclusion of pregnant women from clinical research is the possibility of the investigational drug causing harm to the fetus. This is founded in the two historical cases of thalidomide and diethylstilbestrol

[1] Institutional Review Board (RB) is equivalent to a Research Ethics Committee (REC) in South Africa and other countries.

(DES) which are the two most prominent historical cases discussed in the literature as a reason for exclusion of pregnant women in clinical trials due to harm to the fetus.

The thalidomide tragedy which occurred during the late 1950s resulted in approximately 10 000 babies being born all over the world with severely deformed limbs (van der Graaf et al., 2018, p.378). Although it hadn't been tested on pregnant women, the drug was readily made available to treat morning sickness when it entered the market (van der Graaf et al., 2018, p.377). This case set a precedent for excluding pregnant women from clinical trials due to the potential risk of harm to the fetus.

The second historical case was the use of DES to prevent miscarriage for over 30 years, where between 1.5 - 3 million women were prescribed the drug during pregnancy (van der Graaf et al., 2018, p.377). It was later discovered that the drug caused cancer in the daughters of the those that took the drug and that the drug did not in fact prevent miscarriages (van der Graaf et al., 2018, p.377). Both these cases laid the foundation for the routine exclusion of pregnant women from clinical trials due to potential harm to the fetus and are still used in defence of the practice.

2.3.2 Pregnant women being classified as a vulnerable population

The second main reason advanced in the literature for the exclusion of pregnant women from clinical trials is the vulnerability of pregnant women, who could potentially be harmed or exploited as a vulnerable population (Kaye, 2019, p.2). Pregnant women, in the opinion of some, are included in the category of "vulnerable," which is often used to describe people whose ability to make decisions about participating in research is in some way impaired, such as children and

individuals with low cognitive ability (Krubiner and Faden, 2017, p.644). Many have also said that pregnant women as a group are seen as vulnerable because of the presence of a fetus, a third person with a special and inseparable connection to the mother, who may be impacted by the research but who is unable to provide informed consent which contributes to the vulnerability of a pregnant women's situation when deciding to participate in research (Noah, 2014, p.379).

2.3.3 Physiological complexity in pregnancy

The third concern is that pregnant women are physiologically complex. Pregnancy causes a number of major physiological changes that may affect the metabolism and efficacy of medications (Biggio, 2020, p.40). According to Biggio, the growth of plasma volume which is defined as the "volume of plasma in the blood vessels" (Oxford University Press, n.d.), which is normally between 50% and 60% during pregnancy, has a major influence on the effective volume of distribution of pharmacologic drugs (2020, p.40). As gestation progresses, the majority of pregnant women have some degree of hypoproteinaemia which is the, "medical term for lower-than-normal levels of protein in your body" (Watson, 2022), this changes the concentration of free drugs and the potential treatment window. (Biggio, 2020, p.40). Additionally, changes are made to the pharmacologic drugs' absorption and clearance properties (Biggio, 2020, p.40).

These factors collectively have the potential to modify the pharmacokinetics and pharmacodynamics of medications during pregnancy, in addition to the fact that these physiologic changes shift over the course of pregnancy (Biggio, 2020, p.40). Due to these reasons, researching therapeutics during pregnancy is not only more expensive but also more complex, which is why many pharmaceutical companies

and researchers exclude the participation of pregnant women in their studies (Biggio, 2020, p.40).

2.3.4 Drug manufacturers' reticence

The next reason provided in the literature for the exclusion of pregnant women from clinical trials is the reticence from the drug manufacturers, which is founded in the two historical tragedies of Thalidomide and DES as described in section 2.3.1. In response to the financial fallout due to the many lawsuits from the thalidomide and DES cases, several pharmaceutical companies have historically been resistant to including pregnant women in their clinical trials (Allesee and Gallagher, 2011, p.3). Because clinical trials are complicated and require as few variables as possible to ensure drug safety, manufacturers also do not include pregnant women in clinical trials (Bhat 2021, n.p). Researching medications in non-pregnant, healthy individuals lowers the likelihood of observing a high number of incident health occurrences such as stillbirths or miscarriages which may not be related to the study drug (Bhat 2021, n.p). It may also be more difficult to recruit pregnant women in clinical trials as they may be less interested in participating than non-pregnant individuals. Additionally there are ethical concerns with performing research on two people – the mother and the fetus (Bhat 2021, n.p). All of these reasons contribute towards drug manufacturers reticence to inclusion of pregnant women in clinical trials.

2.3.5 Institutional review board reticence

Finally, the last reason for exclusion is the reticence from Institutional Review Boards (IRBs). IRBs take liability into account because they are expected to access the risk-benefit ratio and make sure that clinical trial participants are fully informed of the

risks involved and because they are tasked with the responsibility of protecting the rights and welfare of human subjects participating in clinical trials (Allesee and Gallagher, 2011, p.4). Although they are rare, there have been instances where unborn children have suffered harm, and the inadequate informed consent was a key component of the complaint against the IRB (Allesee and Gallagher, 2011, p.4). The inherent and unknown risk to the fetus is the main concern to IRB members, thereby making the IRBs decision to approve protocols that include the pregnant population a difficult one (Allesee and Gallagher, 2011, p.4).

In summary, this section of the literature review has outlined the main justifications offered in the literature for the exclusion of pregnant women from clinical research, including the potential risk to the fetus, the fact that pregnant women are considered a vulnerable population, the physiological complexity of pregnancy, the reticence of drug manufacturers, and IRB reticence.

2.4 Conclusion

In conclusion, this chapter has provided an overview of the justifications offered in the literature for including pregnant women in clinical research as well as the justifications given for excluding pregnant women from clinical research. The exclusionary arguments provided—harm to the fetus, pregnant women being categorized as a vulnerable population, the physiological complexity of pregnancy, drug manufacturers' reticence, and IRB's reticence—are all valid reasons for concern, but as I will argue in the following chapters, these obstacles must be overcome in order to provide pregnant women with safe and effective treatment

during pregnancy, to ensure fetal safety, and to make it possible for pregnant women to gain from any potential advantages of taking part in research.

CHAPTER 3: NON-MALEFICENCE AND ETHICS OF CARE IN SUPPORT OF THE MORAL CLAIM THAT THE EXCLUSION OF PREGNANT WOMEN FROM CLINICAL TRIALS COULD EXPOSE FUTURE PREGNANT WOMEN TO SIGNIFICANT HARM

3.1 Introduction

In this chapter I will defend the claim that the exclusion of pregnant women as participants in clinical trials could potentially expose future pregnant women to significant harms. My strategy here will entail significant use of empirical evidence and the work of others who have argued similarly. I will also rely on the principle of non-maleficence, the ethics of care and other normative notions to defend the position that a failure to act to prevent foreseeable harm constitutes a serious moral wrong.

To defend my claim that the exclusion of pregnant women as participants in clinical trials could potentially expose future pregnant women to significant harms. I will centre my case on two sub-claims, sub-claim 1) The widespread use of medication during pregnancy makes pregnant women vulnerable to harm and sub-claim 2) The physiological changes experienced during pregnancy make pregnant women who take medications not tested in the pregnant population susceptible to harm. Each sub-claim will be intertwined with a moral theory that will demonstrate the immorality associated with excluding pregnant women from clinical trials and how this could potentially expose future pregnant women to significant harms.

3.2 The widespread use of medication during pregnancy and the associated harm

I now turn to my first sub-claim, the widespread use of medication during pregnancy makes pregnant women vulnerable to harm. This sub-claim will be divided into two parts: part 1: I will first discuss the empirical claim that many pregnant women use medication during pregnancy which has not been tested in the pregnant population and part 2: I will discuss the normative claim that the use of medication during pregnancy that has not been tested in the pregnant population makes pregnant women susceptible to harm and is therefore ethically unsound.

I will now turn to part 1 of sub-claim 1, which will provide empirical evidence to support the claim that many pregnant women use medication during pregnancy which has not been tested in the pregnant population. It has been reported that between 44% and 99% of pregnant women use some sort of drug during pregnancy (Obadeji et al., 2020 p.1207), this could be for a condition developed during pregnancy or a pre-existing condition. Given that pregnancy lasts nine months, it is not surprising that pregnant women take a range of medications, from over-the-counter (OTC) medications to prescription medications, to treat the numerous pregnancy symptoms they experience, including back pain, headaches, heartburn, nausea, vomiting, and haemorrhoids' (Obadeji et al., 2020, p.1207). The use of prescription medication is very common these days (Waitt, 2022), this could be because many women today decide to start families later in life which results in a higher prevalence of pre-existing conditions and pregnancy related medical conditions, as this becomes more prevalent as people get older (Mathews and Hamilton, 2009). Some of the common medical conditions experienced during

pregnancy are diabetes, mental health disorders, autoimmune diseases, and hypertension (Biggio, 2020, p.39), all of which require treatment.

However, most of the drugs (prescription and OTC) used to treat the medical conditions experienced during pregnancy, have not been specifically tested for pregnancy. As a result, doctors are left with no choice but to treat their pregnant patients for the many medical conditions they experience based on observational studies which are, “studies in which researchers collect information from participants or look at data that was already collected” (National Cancer Institute, 2023) orpregnancy registries which are “prospective observational studies specifically designed to collect clinically relevant data and provide information for treating” pregnant women (National Institutes of Health, n.d.) rather than accurate data obtained through clinical research (Thomas and Yate, 2012). In some cases, patients go untreated because their doctors are reluctant to give them medication because of a potential risk associated with it, or because pregnant women are afraid to take medications because there is no solid information available to make an informed decision, both of which could have negative consequences. An illustration of pregnant women being left untreated for medical conditions is the case of untreated asthma during pregnancy, which has been linked to “preeclampsia, premature birth, low birth weight, and haemorrhage” (Lyerly & Faden, 2013, p.776).

I will now discuss part 2 of sub-claim 1, which is the normative claim that the use of medication during pregnancy that has not been tested in the pregnant population makes pregnant women susceptible to harm which is ethically unsound. To support this part of my argument I will rely on the principle of non-maleficence which asserts that it is the obligation of a doctor not to harm the patient (Varkey, 2020, p.17). To fulfil this obligation, doctors require the safety, efficacy, and dosage information on

drugs to be readily available to them in order to weigh the risks and benefits and provide the best course of treatment for their patient. Without this information available on an entire population group, “the pregnant population”, doctors are unable to make the best medical decisions for their pregnant patients. This lack of information puts the pregnant population at risk of harm by failing to manage the many medical conditions experienced during pregnancy appropriately or by using a drug where safety, efficacy and dosage information is unknown. This is ethically unsound and completely disregards the principle of non-maleficence which should be the forefront when treating any human being; the pregnant population should not be an exception to this rule.

To practice non-maleficence and to respect autonomy which implies, “acknowledging that autonomous agents are entitled to hold their own viewpoints, are free to make choices, and act voluntarily according to their values, beliefs and preferences” (Motloba & Makwakwa, 2018), data on new drugs or already approved drugs needs to be collected in pregnant women in a clinical trial setting. This will result in future pregnant woman having the valuable information and medical care that they deserve and the ability to practice autonomy when making medical decisions during pregnancy which will ultimately prevent foreseeable harm.

To summarize the first sub-claim, in part one of this sub-claim I have provided empirical evidence to show that the majority of pregnant women use some sort of drug during pregnancy and that most of these drugs have not been researched in a clinical trial setting in the pregnant population. Then in part 2, I argued that as a result, doctors and their pregnant patients are left with little to no information on the safety and effectiveness of these drugs during pregnancy which could result in possible harm to the pregnant women and/or her fetus which is ethically unsound; it

is therefore only right to contend that the exclusion of pregnant women from clinical research ‘now’ could potentially expose every future pregnant woman that requires medical care to significant harm.

3.3 The effect of physiological changes experienced during pregnancy on medication use and the associated harm

I now turn to my second sub-claim, the physiological changes experienced during pregnancy also make pregnant women who take medications not properly tested in the pregnant population susceptible to harm. I will divide this sub-claim into two parts, part 1) I will first discuss the empirical fact that there are physiological changes experienced during pregnancy and that these changes have an impact on both safety and efficacy of medicines and part 2) I will discuss the normative claim that the physiological changes experienced during pregnancy alter the safety and efficacy of drugs taken during pregnancy and therefore expose pregnant women and/or their fetuses to harm which is ethically unsound.

To begin I will provide empirical evidence that there are physiological changes experienced during pregnancy and that these changes have an impact on both safety and efficacy of medicine. As discussed in sub-claim 1, medication use in pregnancy is extremely common, it is therefore important to understand the physiological changes experienced during pregnancy and the affect this has on the pharmacodynamic and pharmacokinetic (absorption, distribution, metabolism, and elimination) properties of certain medications in the pregnant body (Kepley et al., 2023, n.p). Several significant physiologic changes that influence the metabolism and action of medications occur during pregnancy, including for example, “the growth of plasma volume, which normally ranges from 50% to 60% during pregnancy” which has a significant impact on the volume of effective pharmacologic

drug delivery. (Biggio, 2020, p.40). Additionally, the majority of pregnant women have some degree of hypoproteinemia during pregnancy which “alters the concentration of free drug and the potential therapy window” (Kepley et al., 2023, n.p). It is also common for pregnant women to experience changes in their cardiovascular, pulmonary, gastrointestinal, urinary, and other organ systems in reaction to the developing fetus. (Kepley et al., 2023, n.p). Changes in hormone levels, the size of the fetus, and the “physiologic requirements” of the pregnant woman and the fetus are just a few of the factors that affect various organ systems (Kepley et al., 2023, n.p).

The physiological changes mentioned above are just a few of the many that are experienced by women during pregnancy. All these changes influence how a drug works in the body; the changes experienced may result in a drug being completely ineffective at the dosage prescribed or the prescribed dosage may even cause harm to the pregnant women and/or her fetus. As a result, failure to understand the physiologic changes during pregnancy by exclusion of pregnant women from clinical research can lead to “maternal morbidity and mortality” due to over or under-treating the pregnant patient (Kepley et al., 2023, n.p). For instance, as rates of morbidity and mortality among pregnant women during the H1N1 pandemic were greater than those of the overall population, researchers examined the pharmacokinetics of the medication oseltmavir phosphate (Tamiflu) in this demographic. According to their findings, the normal adult dose that was advised for expecting mothers during the pandemic may not have been sufficient for the treatment or prevention of influenza during pregnancy (Lyerly & Faden, 2013, 775). Another example of a drug that was not properly studied in the pregnant population is angiotensin-converting enzyme (ACE) inhibitors. These are drugs which is used to treat hypertension. The risk of

"increased risk of fetal cardiovascular and neurological abnormalities" was unknown until a 2006 study published these results (Lyerly et al., 2008, p.4). According to Lyerly et al., this drug has been used by pregnant women for decades and if the drug had been studied earlier on this could have prevented many congenital abnormalities over the years (Lyerly et al., 2008, p.4).

Now I will discuss the normative claim that this exposes pregnant women and/or their fetuses to harm and is therefore ethically unsound. To support this claim, I will rely on the ethics of care, which strongly emphasize the moral requirement of attending to and meeting the needs of the others (Virginia Held, 2006, p.10). The only way doctors can meet the needs of their pregnant patients and care for them appropriately is by having well researched data available to them on the safety, efficacy, and dosage of drugs in pregnancy. This is also true for a pregnant patient (with a medical condition) and her fetus; the only way a pregnant women can meet the needs of her growing fetus is by her doctor or the medication package insert providing valuable information on the safety, efficacy and correct dosage of a drug in pregnancy. With this knowledge, pregnant women together with a healthcare provider will be better equipped to manage medical issues that, if not properly managed, could endanger the fetus and/or the pregnant women. With access to knowledge generated through clinical research, aimed at testing drugs in the pregnant population, a pregnant woman would be able to take care and protect both herself and her unborn child from any potential harm brought on by incorrect drug usage.

Therefore, in line with the ethics of care and also relying on the principle of justice, it is only fair that all current and future pregnant women have access to proper care, are not denied access to safe medications at the correct dosages and are not

exposed to unsafe dosages of a drug because there is a lack of information available. Ultimately, the only way to achieve this is to conduct clinical research in the pregnant population aimed at understanding how the many physiological changes experienced during pregnancy affects the pharmacodynamics and pharmacokinetics of a drug.

3.4 Conclusion

To conclude, in this chapter I have used two sub-claims namely, 1) The widespread use of medication during pregnancy makes women vulnerable to harm and 2) the physiological changes experienced during pregnancy also make women who take medications not properly tested for pregnancy susceptible to harm. I have used these sub-claims to argue for the claim that the exclusion of pregnant women from clinical trials could potentially expose future pregnant women to significant harms. I have argued that most women use some type of medication during pregnancy for pregnancy related medical conditions and/or pre-existing medical conditions; and that there is limited data available on the safety, efficacy and correct dosage of most drugs that are being used by pregnant women, because of their exclusion from clinical trials. It is therefore critical to recognize that excluding pregnant women from clinical research entirely can lead to significant harm, it is only through research, which is appropriately timed and based on preliminary evidence, in this population group that the best treatments for medical conditions experienced during pregnancy can be established and possibly protect future pregnancies from foreseeable harm.

CHAPTER 4: RULE UTILITARIANISM IN SUPPORT OF THE CLAIM THAT BENEFITS ARISING OUT OF THE INCLUSION OF PREGNANT WOMEN IN CLINICAL TRIALS FAR EXCEED THE POSSIBLE HARMS

4.1 Introduction

In this chapter, I will defend the claim that benefits arising out of the inclusion of pregnant women in clinical trials far exceed the possible harms to the pregnant women trial participants and their fetuses. By utilising a rule utilitarianism approach, I will argue that the benefits of inclusion of pregnant women in research will far outweigh the harms. In the first part of my argument, I will outline the main harms associated with the inclusion of pregnant women in clinical trials such as fetal harm and maternal health risks. In the second part of my argument, I will outline the multiple benefits that will arise from the inclusion of pregnant women in clinical trials such as improved maternal and fetal health, reduction of harms associated with the use of off-label drugs, informed decision making and public health preparedness. I will then show, from a utilitarian standpoint, how the benefits that will arise out of the inclusion of pregnant women in clinical trials will far exceed the harms and therefore inclusion of pregnant women in clinical trials will result will in the greatest good for all concerned.

4.2 Predominant harms associated with the inclusion of pregnant women in clinical trials

To begin, I will discuss the two predominant purported harms associated with the inclusion of pregnant women in clinical trials which are fetal harm and maternal health risk. First, I will discuss fetal harm which is the harm the study drug could

cause to the developing fetus. A major concern associated with the inclusion of pregnant women in clinical trials is that the study drug will cross the placenta and potentially cause birth defects or developmental issues, this is because almost all drugs taken during pregnancy eventually cross the placenta and therefore will reach the developing fetus (Griffiths and Campbell, 2014, p.84). Drugs that may cause harm to the fetus are commonly known as teratogens, “a teratogen is any agent that causes an abnormality following fetal exposure during pregnancy” (District of Columbia Department of Health/Genetic Alliance , 2010, p.84). Teratogens are usually found after an increase in a specific birth defect is noticed (Genetic Alliance, 2009, p.82). There are some instances where a drug’s negative effect is not immediately noticed and the harm that results could have long-lasting negative consequences (Genetic Alliance, 2009, p.82). For instance, as mentioned in Chapter 3, a drug known as Thalidomide was used to alleviate morning sickness in the early 1960’s, and because morning sickness is usually associated with the first trimester which is the early stage of development for the fetus, the drug caused harm and resulted in cases of phocomelia, “a congenital malformation in which the hands and feet are attached to abbreviated arms and legs” (District of Columbia Department of Health/Genetic Alliance, 2010, p.84). Since drugs that are used in clinical trials are still in the experimental phase there is a great possibility that similar tragedies as the Thalidomide tragedy as well as other harms to the fetus could result from the inclusion of pregnant women in clinical trials. Therefore, in order to avoid any possible harm to the fetus, the inclusion of pregnant women in most clinical trials is usually avoided.

The second main purported harm associated with the inclusion of pregnant women in clinical trials is maternal health risk or the harm that the study drug could cause to the pregnant women. In all clinical trials there is a possibility for adverse reactions to the study drug, however a pregnant woman may be adversely affected by the study drug to a more severe extent than a participant who is not pregnant due to the physiological changes experienced during pregnancy. These physiological changes can impact how a drug is metabolized, distributed, and eliminated in a pregnant women's body and therefore may not be as well tolerated as it is in a non-pregnant woman (Frederiksen, 2001, n.p). As a result, the study drug could potentially have a greater negative effect on the pregnant participant because of her physiological state at the time of participation in the trial (Kaye, 2019). Therefore, if a pregnant woman is harmed in a clinical trial, it ultimately also harms her growing fetus which is a great concern when considering the possibility of including the pregnant population in clinical trials.

Now that I have discussed the two main harms associated with including pregnant women in clinical trials, namely fetal harm and maternal health risk, I will move on to discuss the second part of my argument which are the multiple benefits that will arise from the inclusion of pregnant women in clinical trials such as improved maternal and fetal health, reduction of harms associated with the use of off-label drugs, informed decision making and public health preparedness.

4.3 The benefits associated with inclusion of pregnant women in clinical trials

The first benefit I will discuss that is associated with the inclusion of pregnant women in clinical trials is improved maternal and fetal health. As discussed in detail in

chapter 3, there is currently limited data available on the safety and effectiveness of most drugs used in the pregnant population due the exclusion of this population group from clinical trials. As a result, pregnant women are prescribed off-label drugs for most of the medical conditions they experience, and the prescription is based on data registries or the experience of the prescribing doctor (Dathe and Schaefer, 2019). In some instances, medical conditions are left untreated due to the fear of harm that could result from taking the drug during pregnancy, since there is limited data available to make an informed decision (Dathe and Schaefer, 2019, p.785). In both these cases the pregnant women and the fetus could be harmed (Dathe and Schaefer, 2019, p.785). Therefore, one of the main benefits of the inclusion of pregnant women in clinical trials is that their inclusion will allow for the collection of accurate data on the safety and efficacy of drugs in the pregnant population, which in turn allows for safer and more effective treatment of medical conditions experienced by pregnant woman. This will have an overall benefit to current and future pregnant women and their fetuses as the data collected in clinical trials can be used to update medical guidelines and inform healthcare providers which in turn contributes towards the wellbeing of the current and future pregnant population and their fetuses.

The second benefit associated with the inclusion of pregnant women in clinical trials is the reduction of possible harms associated with the use of off-label drugs. The thalidomide tragedy which resulted in babies being born with major deformities, clearly shows how harmful a drug could be if prescribed to a pregnant woman without proper data on the safety and efficacy of the drug being collected in a clinical trial setting (Sachdeva, 2009, p.1). This case demonstrates the importance of researching a drug in a well-controlled environment such as clinical trial, where the participants in the trial are carefully monitored for adverse reactions and have

medical care easily accessible to them as opposed to using a drug off-label in the general pregnant population where adverse reactions may be left untreated because they are unnoticed and only picked up at a later stage when it is too late to intervene. In a clinical trial setting adverse events in response to a study drug are generally picked up during routine safety checks at scheduled study visits (e.g., by taking safety sample collections and performing physical exams etc.) which if picked up in a few pregnant women in a clinical trial is far better than exposing thousands of women to the same drug in the general population (outside of a clinical trial setting) and causing thousands of harmful reactions to that drug. Therefore, by including pregnant women in clinical trials, the risk of harm that is associated with treating patients with off-label drugs is reduced as the drug will first be tested in a clinical trial setting on a few pregnant woman before being available to the entire pregnant population, the pregnant women participants in a clinical trial will be closely monitored and any adverse reactions will be treated, or the study drugged will be stopped completely if the drug is found to be harmful to the pregnant women and/or her fetus. This will protect current and future pregnant women and their fetuses from being exposed to the possible harmful effects of off-label drugs.

The next benefit that I will discuss is the benefit of informed decision making. Currently due the lack of information available on drugs in the pregnant population, pregnant women cannot be provided with the information they require to make a well-informed decision about taking a specific drug during pregnancy. However, this can change with the inclusion of pregnant women in clinical trials, as their inclusion will ultimately result in the generation of data on the safety and effectiveness of a drug in pregnancy. This information will allow pregnant women to make informed decisions about their healthcare based on scientific evidence rather than taking a

drug ‘blindly’ without knowing the possible harmful effects to themselves of their unborn child. This respects their autonomy and allows the pregnant women to weigh the risks and benefits before making an informed decision for herself and the fetus.

The last benefit I will discuss is that of public health preparedness. Public health preparedness can be defined as “the knowledge, capacity and organizational systems that governments, response and recovery organizations, communities and individuals develop to anticipate, respond to, or recover from emergencies” (Lee et al., 2023, p.2). The need for public health preparedness can be demonstrated by the recent COVID-19 pandemic which showed the risks and profound health impacts that result from infectious disease emergencies. However, in the COVID-19 pandemic the pregnant population was mainly excluded from majority of clinical trials aimed at providing a safe an effective vaccine against COVID-19 (Bianchi et al., 2021, p.2). Pregnant women were therefore again left with no information on the safety and effectiveness of the available vaccines once they were offered to the public, resulting in many pregnant women not being vaccinated due to fear of possible harm to the fetus. According to Bianchi et al., “Pregnant people with laboratory confirmed severe or critical COVID-19 disease have higher adjusted relative risks of caesarean delivery, postpartum haemorrhage, hypertensive disorders of pregnancy, and preterm birth” (Bianchi et al., 2021, p.1). This is also true for the Ebola Virus epidemic of 2013-2016, in which the pregnant population were routinely excluded from vaccine development trials, even though data from previous outbreaks of Ebola “showed 89–93% maternal and 100% fetal/neonatal mortality” (Gomes et al., 2017, p.47). According to an article by Schwartz on the Ebola epidemic of 2013-2016, “the exact maternal mortality rate will likely never be

known; it has been estimated to be at least 80 percent during this epidemic" (2018, p.7).

Including pregnant women in clinical trials is therefore critical for emerging health threats such as pandemics. The development of vaccines and treatments for pregnant women in these instances can be lifesaving and mitigate the spread and the impact of the disease at hand which is the main purpose of public health preparedness.

4.4 Rule utilitarianism in support of the claim that the benefits of inclusion of pregnant women in clinical trial research far outweighs the harms

Finally, now that I have outlined the main harms and benefits associated with the inclusion of pregnant women in clinical trials, I will show, from a rule utilitarian perspective, how the benefits that arise from the inclusion of pregnant women in clinical trials far outweigh the harms and that their inclusion in clinical trials will result in the greatest good for the greatest number. Utilitarianism states that, "the right action is the action that is expected to produce the greatest good" (Savulescu et al., 2020, p.620). Therefore, in order for the action of 'including pregnant women in clinical trials' to be deemed the 'right action' the benefits that arise out of their inclusion in clinical trials should far outweigh the harms as this will result in the greatest good for the greatest number. More specifically, according to the Encyclopaedia of philosophy, "rule utilitarians apply the utilitarian principle directly to the evaluation of rules and then evaluate individual actions by seeing if they obey or disobey those rules whose acceptance will produce the most utility" (Nathanson, n.d.). Therefore, if the current practice or regulations of excluding of pregnant women in clinical trials is changed to be more inclusive of pregnant women in clinical trials, this will result in greater good for all pregnant women concerned.

As I have already outlined in this chapter there are multiple benefits associated with the inclusion of pregnant women in clinical trials, these benefits could improve the well-being of an entire population group and their fetuses and although the possible harms outlined are valid and a cause for serious concern, they do not override the need for clinical trials in the pregnant population. The harms associated with the inclusion of pregnant women in clinical trials can be addressed by having well established guidelines and monitoring in place when conducting a clinical trial that includes pregnant women as well as protocols which consider the inclusion of pregnant women in the clinical trial at the appropriate phases Therefore, possible harm should not be an excuse for the exclusion of an entire population group from clinical research. The CIOMs guidelines from 2016 outline considerations for inclusion of pregnant women in clinical trials and should be considered when writing up protocols which include pregnant women.

Consequently, the harms are outweighed by the good that will result from the inclusion of pregnant women in clinical trials and so from a rule utilitarianism perspective in order for all current and future pregnant women to reap the benefits of clinical trials and in order to improve the wellbeing of all current and future pregnant women and their fetuses, the general practice should be to consider the inclusion of pregnant women in protocol design from the start of protocol development.

4.5 Conclusion

In conclusion, I have discussed the main harms associated with the inclusion of pregnant women in clinical trials, namely fetal harm and maternal health risks as well

as the multiple benefits that will arise from the inclusion of pregnant women in clinical trials such as improved maternal and fetal health, reduction of harms associated with the use of off-label drugs, informed decision making and public health preparedness. I then explained, from a rule utilitarian perspective, how the benefits that arise out of the inclusion of pregnant women in clinical trials far exceeds the harms and claimed that ultimately the inclusion of pregnant women in clinical trials is essential in order to achieve the greatest good for the greatest number. Thus, although careful consideration of potential harms is essential, the overall well-being of the pregnant population and society (which include all current and future offspring) as a whole can be maximised through the modification of rules and regulations which govern clinical trials to be more inclusive of pregnant women.

CHAPTER 5: RIGHTS BASED THEORY AND JUSTICE IN SUPPORT OF THE MORAL CLAIM THAT PREGNANT WOMEN DESERVE FAIR ACCESS TO BENEFITS ARISING FROM CLINICAL TRIAL PARTICIPATION

5.1 Introduction

In this chapter, I will defend the claim that pregnant women deserve fair access to research trials where their participation will involve access to potential benefits. My approach here will involve the use of the rights-based theory and the principle of justice to support the argument that the exclusion of pregnant women from research will result in the violation of basic human rights which is ultimately unjust. First, I will discuss three key benefits associated with participation in a clinical trial, 1) the benefit of having access to an experimental drug that is not yet available to the general population 2) the benefit of the participants' health being closely monitored by the research team and 3) the benefit of potential post-trial access to an effective study drug. Then, I will discuss how the exclusion of pregnant women from clinical trials denies them access to these three benefits which is a violation of their basic human rights and is ultimately unjust.

5.2 The three key benefits that arise from participation in a clinical trial

To begin I will focus on the first benefit associated with participation in a clinical trial which is the benefit of having access to an experimental drug that is not yet available to the general population. Participants that enrol in a clinical trial may have access to a study drug that is still under investigation and therefore not yet available to the general population which can be beneficial if the drug has any possibility of improving the medical condition of the participant (National Institutes of Health, 2023). The study drug in a clinical trial is "tailored" to the specific medical condition

and patient population being studied and this could potentially “open doors” for people with serious medical conditions where there aren’t many alternative treatment options available or all options have been exhausted (Vial, 2023, n.p). Although it is important for trial participants to be informed that access to an experimental drug does not necessarily mean access to a drug that is going to provide effective treatment for their medical condition, participation in a clinical trial still allows for access to a drug that could potentially be lifesaving, improve the medical condition of the participant or even prevent a medical condition from developing such as in prevention clinical trials.

Now, I will discuss the second benefit of participation in a clinical trial, which is the benefit of the participants’ health being closely monitored by the research team. Sponsors and clinical trial study teams no longer see participants as “mere subjects” who generate data, – but as informed collaborators whose participation is “core” to the overall success” of the trials (Sharma, 2015, p.134) and therefore the participants in a clinical trial usually benefit from the “extra layer of care” they receive while participating in the clinical trial (National Institutes of Health, 2023). The conduct of a clinical trial is achieved through a multidisciplinary team of doctors, nurses, pharmacists and other professionals, all of whom provide specialised care to the participants as well as close observation to each participant (Johns Hopkins Medicine, n.d.). The team monitors safety concerns or adverse events that the participant may experience while participating in the study, this could be as a result of the study drug or any other safety event unrelated to the study drug (Johns Hopkins Medicine, n.d.). The specialized care participants receive in a clinical trial can include more frequent medical assessments, access to experimental treatments and other treatments and close communication with a dedicated study team.

Participants may also receive educational resources about their condition and the trial (Sharma, 2015, p.136). This type of approach to clinical trials is also referred to as a ‘patient-centric approach’ and ensures that participants receive comprehensive medical support while still contributing to scientific knowledge (Sharma, 2015, p.136).

The last benefit that I will discuss that occurs from participation in a clinical trial is the possibility of post-trial access to the study drug if the study drug is proven to be effective. According to the Declaration of Helsinki, “At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits” (Usharani, P. and Naqvi, S.M., 2013, p.58). Today this is known as Post-trial Access (PTA) and refers to the provision of an effective drug to trial participants after the study has ended (SAHPRA, 2021). According to the South African Health Products Regulatory Authority (SAHPRA) guidelines on post-trial access, “All research proposals that involve unproven or unregistered medicines should consider making provision for Post-Trial Access (PTA) or Continued Access (CA) to the investigational product, where appropriate. In advance of a clinical trial, sponsors / applicants as well as clinical researchers should make provisions for PTA / CA for all participants who still need an intervention identified as beneficial in the trial” (SAHPRA, 2021). Although PTA is not guaranteed in clinical trials, as per the defined guidance from SAHPRA, sponsors and clinical research teams should make every effort to ensure participants who benefitted from the study drug still have access to it after trial participation. It is therefore imperative to allow all population groups access

to clinical trial participation, as even the slightest possibility of receiving access to an effective experimental drug after trial participation is still a benefit only provided by actually participating in a clinical trial.

5.3 Unfair denial of the benefits associated with clinical trial participation- supported by the rights-based theory and principle of justice

Now that I have discussed the three main benefits associated with participation in clinical trials, namely, 1) the benefit of having access to an experimental drug that is not yet available to the general population 2) the benefit of the participants health being closely monitored by the research team and 3) the benefit of post-trial access to effective study drug, I will argue that excluding pregnant women from clinical trials denies them access to these benefits which are associated only with trial participation. I will utilise a rights-based approach and explore the principle of justice to argue that the exclusion of pregnant women from clinical trials denies them access to trial participation benefits which violates their basic human rights, and this is ultimately unjust.

To begin I will use a rights-based approach to argue that pregnant women deserve access to clinical trials that involves a potential for benefits, this approach will emphasize the importance of respecting and fulfilling the rights of pregnant women. The word ‘right’ can be defined as "a justified claim that individuals and groups can make upon other individuals or upon society" (White, 2021, n.p) “Rights-based ethics means that ethical behaviour must uphold the rights of people” (White, 2021, n.p). Rights can be categorised into legal rights and moral rights. The legal right of ‘equality’ is a basic human right, the South African constitution provides for the right to equality and states that “the state may not unfairly discriminate directly or

indirectly against anyone on one or more grounds, including race, gender, sex, pregnancy, marital status, ethnic or social origin, colour, sexual orientation, age, disability, religion, conscience, belief, culture, language and birth" (Republic of South Africa, 1996). Equality can also be looked at from a moral perspective, moral equality as described by Kilmister is, "the idea that 'we' all have equal moral worth, our interests ought to count for the same, and we possess the same bundle of basic rights" (2022). Therefore, to fulfil this standard moral and legal right, the pregnant population should not automatically be excluded from clinical trials solely on the purpose of pregnancy as this is discrimination, evokes injustice and deprives them of their right to equality.

The constitution also provides for a right to 'human dignity' which states that, "everyone has inherent dignity and the right to have their dignity respected and protected" (Republic of South Africa, 1996). Discrimination and unfair treatment of any population group deprives them of their "inherent dignity" and could therefore be considered immoral. In addition, the principle of autonomy dictates that those who are pregnant should be able to make their own decisions about participation in clinical research. Human rights are fundamentally based on dignity and autonomy, which are closely connected to the ideas of equality and non-discrimination. So, to promote equality, dignity and autonomy, research organisations need to recognize the autonomy of pregnant women and their need to equitable access to medical advancements and other benefits associated with trial participation. The pregnant population should be provided with a fair opportunity for participation in clinical research trials and research teams involved in protocol development should aim at the inclusivity of pregnant women in clinical trials from the very beginning, specifically for trials that may benefit the pregnant women or her fetus. Of course,

fair inclusion has limitations, for example when a drug is known to be a teratogen then exclusion is scientifically valid (van der Graaf et al., 2018, p.7). Therefore, exclusion of pregnant women from clinical trials is ultimately depriving them of the benefits associated with trial participation and is therefore violating their rights of equality, dignity and autonomy which is unjust. This leads me to the next part of my argument which will rely on the principle of justice.

Now, I will explore the principle of justice. According to Beauchamp and Childress, “the term fairness, desert (what is deserved), and entitlement have all been used by philosophers as a basis on which to explicate the term justice. These accounts interpret justice as fair, equitable and appropriate treatment in light of what is due or owed to persons” (2013). In order to balance justice in research, all population groups should be equally represented to ensure each population group shares the risks and benefits associated with trial participation. By the exclusion of pregnant women from clinical trials, this population group is inevitably excluded from any potential benefit that may arise from study participation such as access to effective experimental drugs. To further describe the meaning of justice, I will focus on distributive justice as this definition of justice is most relevant to clinical research. “Distributive justice refers to the fair, equitable, and appropriate distribution of healthcare resources determined by justified norms that structure the terms of social cooperation” (Varkey, 2020, p.20). Beauchamp and Childress state that, “determination of a fair distribution involves an evaluation of the following factors: to each person an equal share, to each person according to need, to each person according to effort, to each person according to contribution, to each person according to merit, or to each person according to free-market exchanges” (Allesee

and Gallagher, 2011, p.7). When using the factors represented in the definitions of distributive justice, the terms “appropriate distribution of healthcare resources” and “to each person an equal share” extracted from the quote above by Allesee and Gallager stand out specifically in my argument, as in order to distribute healthcare resources, which in this case will be the study drug, fairly and equally we first require safety and efficacy data on the drug in the target population group. However this data cannot be obtained by the exclusion of a population group from clinical trials. When pregnant women are excluded from clinical trials, this results in the pregnant population not receiving “an equal share” of any of the benefits associated with trial participation. Therefore, for the pregnant population to have access to medical advancements and benefits that may arise from a clinical trial, the automatic exclusion of this population group from clinical trials needs to be addressed, this will reinstate their basic human rights and restore justice by providing the pregnant population with fair and equal treatment when it comes to clinical trial participation. It is therefore imperative that the pregnant population have access to the benefits from a clinical trial that are derived only by participation, in order for pregnant women to combat the many medical conditions they face during pregnancy, whether pre-existing conditions such as cancer or conditions developed during pregnancy such as gestational diabetes, there should be an option to participate in a clinical trial where there is the possibility of benefits.

5.4 Conclusion

In conclusion, I have outlined the three key benefits associated with clinical trial participation, 1) the benefit of having access to an experimental drug that is not yet available to the general population 2) the benefit of the participants’ health being

closely monitored by the research team and 3) the benefit of post-trial access to an effective study drug. I then discussed the immorality of excluding pregnant women from such benefits and defended this claim by utilising a rights-based approach and the principle of justice. Thus, by automatically excluding the pregnant population from clinical trials on the basis of pregnancy alone denies them access to benefits that are only associated with trial participation which disregards their rights and is ultimately unjust. Denying any population group from these fundamental rights constitutes an injustice and therefore poses a serious moral wrong.

CHAPTER 6: A RESPONSE TO OBJECTIONS PROVIDED FOR THE INCLUSION OF PREGNANT WOMEN IN CLINICAL TRIAL RESEARCH

6.1 Introduction

In this chapter I will outline possible objections to my thesis and provide a response to each objection. I will focus on the three main objections prevalent in the literature. The first objection is the inclusion of pregnant women in clinical trials could potentially harm the fetus; in response I will argue that although there is a possibility of harm it is more harmful to exclude pregnant women from clinical trials, as the use of drugs that have not been researched in a clinical trial setting could potentially result in harm to a greater number of women and their fetuses. The second objection is that pregnant women are vulnerable and therefore informed consent is inadequate, in response I will argue that pregnant women are not vulnerable and should rather be classified as 'scientifically complex', and these complexities should be considered during protocol design to allow for inclusion of pregnant women in clinical trials. The last objection is that current regulations encourage Institutional Review Board (IRB) reticence which hinders research involving pregnant women and in response I will argue that existing regulations need to be clarified and there should be a greater focus on IRBs as they enable or hinder clinical trial conduct.

6.2 Objections and Reponses

To begin, I will discuss the first objection to my thesis which is that inclusion of pregnant women in clinical trials could potentially harm the fetus. Clinical trials involve testing new drugs and interventions which may carry potential risks and unknown side effects to the fetus. The fear which most sponsors, researchers, IRBs and expectant mothers face is that the experimental drugs in clinical trials could

affect the development of the fetus, result in deformities or even be fatal. Historical occurrences such as the thalidomide disaster in the 1960s and the transgenic effects linked to the use of diethylstilboestrol (DES) have impacted the debate regarding the use of drugs during pregnancy (Sachdeva, 2009, p.1). Because of these incidents, the United States Food and Drug Administration implemented stringent guidelines for drug labelling, the use of drugs during pregnancy, and the need for all drugs to undergo efficacious and safety testing before going on sale (Sachdeva, 2009, p.1). According to Sachdeva et al., medication that a pregnant woman may take during pregnancy can affect the fetus in many ways, “they can act directly on the fetus causing damage or abnormal development leading to birth defects or death. They can also alter the function of the placenta usually by constricting blood vessels and reducing the blood supply of oxygen and nutrients to the fetus from the mother and thus resulting in a baby that is underweight and underdeveloped” (Sachdeva, 2009, p.4). In addition, certain drugs, “can cause the muscles of the uterus to contract forcefully; indirectly injuring the fetus by reducing the blood supply or triggering pre-term labour and delivery” (Sachdeva, 2009, p.4). For these reasons, currently there is a major reluctance to include pregnant women in clinical trials.

In response to this objection, I assert that although there is a possibility of harm to the fetus, it is more harmful to exclude pregnant women from clinical trials, as the use of drugs that have not been researched in a clinical trial setting could potentially result in harm to a greater number of women and their fetuses. Although including pregnant women in clinical trials requires very careful and in-depth consideration and specific measures being implemented within the protocol design, it is still imperative that the pregnant population are enrolled in clinical trials in order to gather data on the safety and efficacy of drugs in this population group. Without safety and efficacy

data researched in the pregnant population, it results in pregnant women taking medication off-label with limited information on the safety and effectiveness. By taking medication in this way, this could potentially cause harm to the pregnant women and/or her fetus, since little is known about how the drug will react in the pregnant body.

Therefore, without proper information on study drugs generated through clinical trials, it will result in the general pregnant population self-medicating or being prescribed medication during pregnancy with no solid data available on the safety and efficacy of the drug on pregnant women. This will potentially result in greater numbers of pregnant women and/or their fetuses being harmed. This could be prevented by researching a drug in a controlled clinical trial environment in which only a few pregnant women are enrolled in the study to test the safety and efficacy of the experimental drug, and in which they are closely monitored by the research team for any adverse events that may occur due to the study drug.

To support my argument, I rely on the moral theory of utilitarianism which stresses that actions are “morally right or wrong” depending “on their effects” (Nathanson, n.d.). More specifically I make use of practice utilitarianism which dictates that “we can maximize utility only by setting up a moral code that contains rules. The correct moral rules are those whose inclusion in our moral code will produce better results (more well-being) than other possible rules” (Nathanson, n.d.). Therefore, if clear rules and regulations are implemented within clinical trial design for the inclusion of pregnant women and the inclusion of pregnant women in clinical trials is standard practice, this will aid research involving pregnant women. This will allow pregnant women and their fetuses access to safe and effective drugs which have been researched in a clinical trial setting within the pregnant population and will “produce

better results" for all current and future pregnant women and their fetuses as opposed to the possible harm that could result from the exclusion of pregnant women from clinical trials (Nathanson, n.d.). Therefore, it is more harmful to exclude pregnant women from clinical trials as the use of drugs that have not been researched in a clinical trial setting being used off-label in the general population could potentially result in harm to a greater number of women and their fetuses which all things considered is not the best outcome for all current and future generations of pregnant women and their fetuses.

The second objection to the inclusion of pregnant women in clinical trials that I will discuss is that pregnant women are "vulnerable" and therefore unable to provide adequate informed consent to participate in clinical trials. A vulnerable population may be defined as "one that has a compromised ability to protect its interest and provide informed consent" (American College of Obstetricians and Gynaecologists, 2015, p.3). Impaired decision-making is one of the characteristics linked to voluntary informed consent that is used to warrant particular protection for certain groups or populations, according to the Declaration of Helsinki and U.S guidelines (Wild, 2012, p.88). Impaired decision making is a strong argument used to support categorising pregnant women as vulnerable (Wild, 2012, p.88). This could be because the fetus has no capacity to make an informed decision or because of the impaired capacity of the pregnant women to make an informed decision due the physical and emotional changes experienced during pregnancy (Wild, 2012, p.88).

In response to this I argue that pregnant women should rather be defined as "scientifically complex" instead of "vulnerable" as pregnant women have the capacity to make autonomous decisions just as unpregnant women and therefore are able to make an informed decision on whether to participate in clinical research trials

(American College of Obstetricians and Gynaecologists, 2015, p.3). There have been studies that have researched the decision-making capacity of pregnant women and the results from these studies show that there are only certain situations which may impede the decision-making capacity of a pregnant women such as feeling intensive pain during childbirth, impairment due to “psychiatric conditions, drug abuse, or medical conditions like coma” (Wild, 2012, p.91). However, I contend that these conditions may impede anyone’s decision making capacity and therefore is not significant to pregnant women, therefore there is no reasonable argument that confirms that pregnancy itself results in impaired decision-making capacity of a woman. According to Wild pregnant women often feel that they have a” double responsibility” for themselves and their fetus which may actually sometimes lead to even more “reflective and prudential decision making” (Wild 2012). Classifying pregnant women as vulnerable must therefore be rejected.

I agree with the ‘Ethical considerations for including women as research participants’ developed by the Committee on Ethics of the American College of Obstetricians and Gynaecologists from 2015, and assert that pregnant women are “scientifically complex, which includes a combination of physiological and ethical complexities” (American College of Obstetricians and Gynaecologists, 2015, p.3). The first complexity is physiological complexity; during pregnancy, almost every organ system undergoes changes that appear to have a major effect on the pharmacokinetics of drugs administered during pregnancy, affecting the “absorption, distribution, metabolism, and excretion of therapeutic agents” (Sheffield et al., 2014, p.438). Due to the physiological changes experienced through each trimester in pregnancy, protocol design and conduct of the clinical trial becomes more complicated. As a

result, this makes it more complex for sponsors and researchers to include pregnant women in clinical trials.

The second complexity is the ethical challenge of balancing the interests of a pregnant woman and the interest of the fetus. There are many arguments for and against classifying the fetus as a 'person' and therefore makes balancing the fetuses' interests in clinical trials difficult. According to Symons, "In one view, the fetus is a person and has the same special moral status as an adult human being. In the alternative view, a fetus is not a person and, while it may have some sort of moral status, does not have the same rights and privileges as a fully developed human being" (2018). The different views around the 'personhood' of the fetus make inclusion of pregnant women in clinical trials ethically challenging and complex. However, I, contend that if these complexities are taken into consideration when designing clinical trials then there will be a greater probability to enrol pregnant women in clinical trials as the complexities faced will be addressed by research protocols that are designed in line with data taken from preclinical studies and clinical studies in non-pregnant women. As stated by Sheffield et al., "both preclinical studies and clinical studies in nonpregnant adults provide information pertinent to designing clinical trials in pregnancy. Dosing selection, inclusion and exclusion criteria, and dose–exposure effects with regard to safety and efficacy can be assessed and these parameters used to guide the development of drug studies involving pregnant women" (Sheffield et al., 2014).

One of the protocol designs described by Baylis and Halperin is for pregnant women to "join late Phase II or Phase III trials once the investigational product had passed safely through Phase I and at least early Phase II in men and nonpregnant women. The participation of pregnant women in these trials would be identical to that of men

and nonpregnant women, except for the enhanced monitoring of pregnant women, similar to that done in Phase I trials" (Baylis and Halperin, 2012, p.140). In addition, the Council for International Organizations of Medical Sciences (CIOMS) ethical guidelines also provides guidance on the criteria in which pregnant women should be included in clinical trials, some of the criteria mentioned are for inclusion of pregnant women in clinical trials which have the potential to benefit the pregnant/breastfeeding women or her fetus/infant is that " risks must be minimized and outweighed by the prospect of potential individual benefit" (CIOMS, 2016). For clinical research that has no potential benefit to the pregnant/breastfeeding women or her fetus/infant, "the risks must be minimized and no more than minimal; and the purpose of the research must be to obtain knowledge relevant to the particular health needs of pregnant or breastfeeding women or their fetuses or infants" (CIOMS, 2016). The guidelines also state that, "when the social value of the research for pregnant or breastfeeding women or their fetus or infant is compelling, and the research cannot be conducted in non-pregnant or non-breastfeeding women, a research ethics committee may permit a minor increase above minimal risk" (CIOMS, 2016).

Therefore, in summary I argue that pregnant women should not be assumed to be vulnerable based on pregnancy alone and are perfectly capable of providing adequate informed consent, the scientific complexities presented in pregnancy should not be mistaken for vulnerability and should rather be addressed by developing protocols and guidelines which address the physiological and ethical complexities presented during pregnancy.

The last objection I will consider is that current regulations encourage IRB reticence to the inclusion of pregnant women in clinical trials. Due to IRB reticence, clinical research sponsors and researchers could continue to avoid including pregnant

women in trials because of the potential risk that IRBs will be reticent to approve protocols they are presented with for ethical approval that include pregnant women. The current regulations in place assign IRBs the duty of protecting research participants who take part in clinical trials (Noah 2014, p.366). Using their collective knowledge, IRBs must evaluate the clinical trial they will approve or not approve in order to successfully protect human research participants (Blehar et al., 2013). The regulations that currently govern this review leave open some of the most challenging scientific problems, and they defer significant ethical issues to the judgement of the IRBs, who may interpret and apply the regulations differently (Blehar et al., 2013). Current regulations have also established safeguards which offer further protections to protect vulnerable populations in clinical research, which presently includes pregnant women, this is in recognition of historical episodes of clinical trial abuse (Noah 2014, p.366). These regulations result in IRB reticence which impedes clinical research in pregnant women and therefore may be seen as an objection by sponsors and researchers for the inclusion of pregnant women in clinical trials.

In response to this objection, I will argue that existing regulations need to be clarified in order to amend any ambiguous guidelines and that there should be more focus on IRBs as they enable or hinder clinical trial conduct. This will allow IRBs to make more informative decisions when considering the enrolment of pregnant women in clinical trials and may result in more trials being approved which include pregnant women (Blehar et al., 2013). In addition to the fundamental standards for clinical research, IRBs and principal investigators must fulfil the regulations governing research involving pregnant women, human fetuses and neonates in order to perform studies in these populations (Noah 2014, p.372). The current regulatory

framework for including pregnant women in clinical trials is “somewhat ambiguous” which is a major obstacle to implementation of clinical trials which include pregnant women (Blehar et al., 2013, p.5). For example, wording in 45 CRF 46 Subpart B states that, “pregnant women or fetuses may be involved in research if all of ten enumerated conditions are met. Condition (a) specifies that research may be conducted where scientifically appropriate, preclinical and clinical studies on non-Pregnant women provide an adequate basis for assessing potential risks to pregnant women and fetuses. IRBs are left to interpret how much prior research is sufficient and they typically interpret this directive conservatively” (Blehar et al., 2012).

In addition, IRBs find it difficult to define “minimal risk” when deciding if a proposed study poses risk to the fetus that is not greater than minimal (Blehar et al., 2013, p.5). Therefore, important research for pregnant women may be rendered unfeasible due to the extremely conservative safety stance of the current regulations. In a study done by White et al., which looked at the interpretation of “minimal risk” by IRB members as well as the factors that are considered to approve or disapprove research in pregnant women, the results showed that, “guidance is needed to assist IRB members in characterizing risk, applying federal regulations, and appropriately ensuring the inclusion or justified exclusion of pregnant women in research” (White et al., 2021). The differences in interpretation of regulatory requirements and ethical concerns by each IRB results in inconsistency which may impede research in pregnant women (Blehar et al., 2013, p.6). The inconsistencies among IRBs may also derive from the “lack of necessary expertise regarding research ethics and regulations for research with special populations such as pregnant women” (Blehar et al., 2013, p.6). The clinical trial community need to focus on the development of “specialized committees as well as training of IRB members in the specific

requirements of regulations for such populations may be helpful" (Blehar et al., 2013, p.6). Thus, I argue that to improve uniformity amongst IRBs in their decision-making processes, the current regulations which govern the inclusion of pregnant women in clinical trials need to be clarified to amend ambiguous guidelines In addition, there needs to be more "transparency" in the IRB decision-making process when it comes to pregnancy research (Blehar et al., 2013, p.6). Pregnant women's exclusion from clinical trials should be justified and the current legislation should take this into account as well as implementing an inclusive policy. This will ensure that pregnant women have a fair chance of trial participation and automatic exclusion of pregnant women from clinical trials solely due to unclear regulations and IRB reticence will be avoided.

6.3 Conclusion

In summary, I have presented three objections to my thesis for the inclusion of pregnant women in clinical trials and provided a response to each objection, namely objection 1: The inclusion of pregnant women in clinical trials could potentially harm the fetus; in response I argued that although there is a possibility of harm it is more harmful to exclude pregnant women from clinical trials, as the use of drugs that have not been researched in a clinical trial setting could potentially result in harm to a greater number of women and their fetuses; objection 2: Pregnant women are vulnerable and therefore informed consent is inadequate, in response I argued that pregnant women are not vulnerable and should rather be classified as 'scientifically complex', and these complexities should be considered during protocol design to allow for inclusion of pregnant women in clinical trials and objection 3: Current regulations encourage IRB reticence which hinders research involving pregnant women and in response I argued that existing regulations need to be clarified to

amend ambiguous guidelines and there should be a greater focus on IRBs as they enable or hinder clinical trial conduct. Therefore, although every objection should be reflected upon when considering the enrolment of pregnant women in clinical trials, these objections should not be seen as reasons for exclusion of an entire population group from clinical research but rather as obstacles that need to be addressed and overcome in order to allow for research which include the pregnant population and for the pregnant population to have access to safe and effective treatments.

CHAPTER 7: CONCLUSION

In this chapter I will summarize the main arguments I have presented in this report in defence of my thesis. I have provided three arguments in defence of my thesis, namely 1) I argued that the exclusion of pregnant women as participants in clinical trials could potentially expose future pregnant women to significant harms; 2) I argued that the benefits arising out of the inclusion of pregnant women in clinical trials far exceeds the possible harms to the pregnant women trial participants and their fetuses and 3) I argued that that pregnant women deserve fair access to research trials where their participation will involve access to potential benefits. I then described the possible objections to my thesis and provided a response to each objection.

To begin the argument for my thesis, I argued, in chapter 3, that the exclusion of pregnant women as participants' in clinical trials could potentially expose future pregnant women to significant harms. My strategy in this chapter entailed significant use of empirical evidence and the work of others who have argued similarly. I defended my claim by using two sub-claims; sub-claim 1) The widespread use of medication during pregnancy makes pregnant women vulnerable to harm and sub-claim 2) The physiological changes experienced during pregnancy makes pregnant women who take medications not tested in the pregnant population susceptible to harm. I also relied on the principle of non-maleficence, the ethics of care and other normative notions to defend the position that a failure to act to prevent foreseeable harm constitutes a serious moral wrong.

Next, in chapter 4 I argued that that the benefits arising out of the inclusion of pregnant women in clinical trials far exceeds the possible harms to the pregnant

women trial participants and their fetuses. By utilising a rule utilitarianism approach, I argued that the benefits of inclusion of pregnant women in research far outweighs the harms. In the first part my argument, I outlined the main harms associated with the inclusion of pregnant women in clinical trials such as fetal harm and maternal health risks. In the second part of my argument, I outlined the multiple benefits that arise from the inclusion of pregnant women in clinical trials such as improved maternal and fetal health, reduction of harms associated with the use of off-label drugs, informed decision making and public health preparedness. I then showed from a rule utilitarian position, how the benefits that arise out of the inclusion of pregnant women in clinical trials far exceeds the harms and therefore inclusion of pregnant women in clinical trials will result in the greatest good for the greatest number.

I concluded my arguments in chapter 5 by defending the claim that pregnant women deserve fair access to research trials where their participation will involve access to potential benefits. My approach in this chapter involved the use of the rights-based theory and the principle of justice to support the argument that the exclusion of pregnant women from research will result in the violation of their basic human rights which is ultimately unjust. First, I discussed three benefits associated with participation in clinical trials; 1) the benefit of having access to an experimental drug that is not yet available to the general population 2) the benefit of the participants' health being closely monitored by the research team and 3) the benefit of potential post-trial access to an effective study drug. Then, I discussed how the exclusion of pregnant women from clinical trials denies them access to these three benefits which is a violation of their basic human rights and is ultimately unjust.

Lastly, I presented possible objections to my thesis and provided a response to each objection. I focused on the three main objections prevalent in the literature, these objections are; objection 1: The inclusion of pregnant women in clinical trials could potentially harm the fetus; in response I argued that although there is a possibility of harm it is more harmful to exclude pregnant women from clinical trials, as the use of drugs that have not been researched in a clinical trial setting could potentially result in harm to a greater number of women and their fetuses; objection 2: Pregnant women are vulnerable and therefore informed consent is inadequate, in response I argued that pregnant women are not vulnerable and should rather be classified as 'scientifically complex', and these complexities should be considered during protocol design to allow for inclusion of pregnant women in clinical trials and objection 3: Current regulations encourage IRB reticence which hinders research involving pregnant women which encourages the exclusion of pregnant women in clinical trials and ultimately poses a harm to pregnant women and their fetuses and in response I argued that existing regulations need to be clarified and there should be a greater focus on IRBs as they enable or hinder clinical trial conduct in pregnant women.

In summary, I have provided three arguments in defence of my thesis, 1) I argued that the exclusion of pregnant women as participants in clinical trials could potentially expose future pregnant women to significant harms, 2) I argued that the benefits arising out of the inclusion of pregnant women in clinical trials far exceeds the possible harms to the pregnant women trial participants and their fetuses and lastly 3) I argued that pregnant women deserve fair access to research trials where their participation will involve access to potential benefits. Therefore, all things considered, I contend that pregnant women should be included in clinical trials unless there are compelling reasons for exclusion. To conclude I hope to have

provided a comprehensive and robust argument for the inclusion of pregnant women in clinical trials with the hope of raising the awareness of the potential harms associated with their exclusion.

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