UNETHICAL MANIPULATION OF PARTICIPANTS IN CLINICAL TRIALS
Masters Thesis – Leanne Woodward; McMaster University - Philosophy

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unethical manipulation of participants in clinical trials
Leanne Maye Woodward, Bachelor of Arts
Claudia Emerson, PhD
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Lay Abstract

This thesis will examine the need to include the term “manipulation” into current ethical guidelines for Western bioethics because manipulation is a concept that is separate from concepts such as “coercion,” “force,” “exploitation,” or “undue influence” which appear in current Western bioethical guidelines. Manipulation is an unethical influence of another’s decision-making that undermines their autonomy, whereas autonomy is a key feature of Western bioethics and must be fostered rather than undermined or hindered. This thesis will discuss a clinical case in which pregnant women with HIV were enrolled in a clinical trial and I will discuss how illness, gender, pregnancy, and HIV status can cause one’s ego to be depleted so that they are more vulnerable to manipulation than other clinical participants. Finally, I will recommend that states, ethics boards, and researchers are the primary actors responsible for ensuring that participants are not manipulated in clinical research settings.
Abstract

I will argue that the relationship between the clinician scientist and the participant in the ACTG 076 trials involved unethically manipulative elements. My question of unethical manipulation examines the relationship between the clinician scientist and the participant. My first chapter establishes manipulation as follows, ‘A manipulates B if and only if A motivates B to make a decision or perform an action that bypasses B’s rational capacities by means of deception, emotional pressure, or exploitation of B’s ego depleted state.’ I argue that manipulation is prima facie unethical because it violates one’s autonomy. In the second chapter I examine the concerns of illness, gender roles, pregnancy, and HIV status, which can cause ego depletion and increase the participants’ vulnerability to manipulation. After analysis, I conclude that, although none of these elements can be eliminated as concerns for the clinician scientist, if they are not adequately accounted for, the clinician scientist has unethically manipulated the participant to enter and remain a part of the trial. I suggest that an adequate account would involve special consideration of how these vulnerabilities interact within the specific context of the trial. My third and final chapter will relate my conclusions to the current and upcoming research that is actively incorporating pregnant women as participants.
Acknowledgements

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Abbreviations and Symbols

ACTG 076 – AIDS Clinical Trial Group 076
AIDS – Acquired immunodeficiency syndrome
CIOMS – The Council for International Organizations of Medical Sciences
HIV – Human immunodeficiency virus
iff – “if and only if”
REB – Research Ethics Board
TCPS2 – The Tri-Council Policy Statement
ZDV – Zidovudine
Declaration of Academic Achievement

This thesis was written entirely of my own efforts and revised through the assistance of my supervisory committee: Dr. Claudia Emerson, and Dr. Elisabeth Gedge. Every piece of work in this thesis that is not my own has been properly indicated through MLA citation. I have no other contributors to declare.
Introduction

In this thesis I will argue that the concept of manipulation is an under-examined one in the field of bioethics and that it is important to be studied because manipulation is distinct from the concepts of force, coercion, and exploitation. Force, coercion, and exploitation are concepts that are important to understand because they can violate the principles of autonomy, beneficence, and justice in clinical research. However, manipulation can also violate autonomy in clinical research and should be examined for its distinct nature that cannot be understood by use of the concepts of force, coercion, or exploitation alone.

To illustrate my point, I will examine the case of AIDS Clinical Trial Group (ACTG) 076 which involved participants who were pregnant women infected with HIV. This is a unique group of participants that do not often appear in other clinical trials due to fears of perceived vulnerability. My claim in this thesis is that, because the participants in these clinical trials were pregnant women infected with HIV, and because being a pregnant woman infected with HIV participating in a clinical trial makes one more situationally vulnerable to manipulation than other common clinical trial participants, the trial should be designed, and clinician scientists should act, in a way that reflects these vulnerabilities and promotes participant autonomy, rather than contributes to participant oppression and situational vulnerability. Due to the unique position of these participants in comparison to more common research participants, the design and conduct that is generally followed by clinician scientists in other clinical research is not enough to promote the autonomy of these particular participants and more should be done, such as state changes to diminish social oppression of women, and the addition of the concept of manipulation to ethical guidelines.

The scope of my thesis remains within the discussion of autonomy in Western bioethics. I
have chosen to work within the framework of Western bioethics because the trials that I will be examining were designed for Western medical practice and because the concern about autonomy and consent holds different weight in different systems of bioethics. I do not intend to compare Western bioethics to Eastern, Indigenous, African or other systems of bioethics, nor do I intend to claim that Western bioethics holds some sort of priority above other systems. For the purposes of my thesis, I have accepted autonomy, justice, beneficence and non-maleficence as the four key principles of western bioethics within my framework and accept that they hold relatively equal weight when in conflict with one another. I have further chosen to narrow the scope of my thesis to discuss autonomy because manipulation could be a threat to autonomy more strongly than it could be a threat to justice, beneficence or non-maleficence. Again, I do not intend to make the claim that autonomy is of more importance than the other pillars of Western bioethics, or that manipulation is not a threat to the other pillars, but rather I have chosen to limit my analysis to autonomy in the context of the ACTG 076 trial. Any challenges to my thesis that might arise in relation to the concerns about other systems of bioethics and about the importance of factors other than autonomy will not be addressed here, but I acknowledge that they are valid concerns if the scope of my argument were to be expanded.

In my first chapter, I will identify common terms that might be used interchangeably in other contexts: manipulation, coercion, force, persuasion, and exploitation. I will give my definitions of each of these terms based on the philosophical understanding of them and how they are applied to bioethics more broadly. Manipulation, coercion and force can be seen as a threat to autonomy and consent. I will also provide examples that fit the description of coercion and force to show how they are different from that of manipulation. Persuasion is a legitimate use of reason or argumentation to influence another’s beliefs or decisions by engaging their rational capacities.
and allowing them to autonomously change their perspective. Manipulation involves bypassing one’s rational capacities so that they act or decide upon something without the full use of their autonomy. Coercion involves a threat or violence or harm that causes someone to act or decide in favour of the coercer while maintaining full use of their rational capacities, and force is the use of violence to remove or reduce one’s ability to act or decide based on their rational capacities. Exploitation can be defined as the use of someone else’s lack of dignity to gain control of an ability or resource that they possess (Wood 43) and is present when one stands to gain something from the detriment of another, regardless of whether that person was manipulated, coerced, or forced.

I will use my own definition of manipulation “A manipulates B iff A motivates B to make a decision or perform an action that bypasses B’s rational capacities by means of deception, emotional pressure, or exploitation of B’s ego depleted state,” which I have developed by synthesizing the various philosophical definitions of manipulation and how they differ from the concepts of force, coercion, and exploitation. I have taken most of what they have in common and chosen to focus on the element of ego depletion, which appears in various forms throughout many definitions, but only appears by name in one. I will also discuss what makes manipulation unethical and the importance of identifying vulnerability to manipulation.

Manipulation is prima facie unethical. Eric M. Cave posits that motive manipulation always violates one’s ‘modest autonomy’ and that violating modest autonomy is prima facie unethical, therefore, manipulation is prima facie unethical. J.S. Blumenthal-Barby provides a list of non-virtuous elements that would make manipulation unethical. For example, manipulation that is done out of arrogance or laziness is non-virtuous and, therefore, unethical. This says that if one has the option of persuading someone else by presenting evidence, listening to the others’ view and responding thoughtfully, but they opt to manipulate the other person to save time, then they
are unethically manipulating the person. However, if it were an emergency, and influencing the person quickly via manipulation is done out of necessity or safety, this is not laziness and does not necessarily constitute unethical manipulation.

In my second chapter, I will identify the important elements within the case study of ACTG 076 that are relevant to the determination of manipulation: illness, pregnancy, gender, and HIV status. I will provide an in-depth explanation showing how each of these four factors could cause one to be ego depleted, and how this ego depletion allows vulnerability to manipulation. My analysis will suggest that the four factors are also related to situational vulnerability and social oppression and can be exacerbated by the power dynamics that exist in society.

For the case of pregnancy, one’s ego might be depleted by daily struggles that pregnant women face in their community, or by physical strain that is caused by pregnancy. Ego depletion reduces one’s tendency to engage in their rational capacities and, therefore, if one is ego depleted due to pregnancy, they might be more prone to make unideal choices than if their ego were intact. The same concern exists for gender when one is a part of an oppressed gender group in a society, illness in general, and HIV specifically when one is faced with decisions pertaining to health and treatment. These factors are also compounded for the participants of ACTG 076. For example, the overlap of being HIV positive and pregnant, while worried that your fetus could contract HIV as well, places stress on the potential participant while they decide whether to consent to the clinical trial.

In my third chapter, I will outline some recommendations for states, trial designers, research ethics boards, and clinician scientists surrounding their responsibilities toward participants to determine the relevant features of manipulation and how to counteract or mitigate its effects where possible. I contend that asking questions such as: is the power imbalance
significant? and is the power imbalance structural? is a start to piecing together which types of power imbalances in the social and cultural context can contribute to ego depletion that would cause a participant to be vulnerable to manipulation.

I will recommend that it is necessary to discuss the concept of manipulation, have clear definitions in ethics guidelines as well as fact-sheets for research ethics boards, and discuss how the vulnerability to manipulation can be prevented or counteracted. This includes understanding the social circumstances and cultural norms of the location of the trial and how there could be power imbalances between individuals in the society.

This thesis will conclude that there is currently a gap in Western bioethical guidelines that does not account for the participants’ vulnerability to manipulation in many cases. The Council for International Organizations of Medical Sciences (CIOMS) guidelines, the Tri-Council Policy Statement 2 (TCPS2) and others account for power imbalances between clinician scientist and participant that can threaten a participant’s autonomy. They account for the harm of overt threats such as coercion, and undue influence, such as an offer of excessive incentives that could convince a participant to accept very high, or unnecessary risks. The manipulation of a participant or a potential participant due to social circumstances that oppress certain groups of people such as pregnant women infected with HIV cannot easily be prevented or counteracted by current bioethical guidelines as they are written.
Chapter One- Theory of Manipulation

In this chapter I will defend the need to focus on the possibility of manipulation in clinical research and present the concept of manipulation and examples of manipulation in everyday life. To analyze the existence of unethical manipulation in the clinical case that I will present, I will first need to define manipulation, and outline what constitutes unethical manipulation. I will also explain the relevant difference between inherent vulnerability and situational vulnerability and explain why I have chosen to focus on the concept of situational vulnerability in relation to the participants of ACTG 076. First, I will define a few terms that become confused with manipulation in everyday English, or in other fields of academia. I will be providing common philosophical definitions for the terms ‘coercion,’ ‘force,’ and ‘exploitation.’ Next, I will give my definition of manipulation, which constitutes a combination of the similar definitions presented by many philosophers, and separate it from ‘persuasion,’ which is considered to generally be a legitimate influence on one’s autonomy. I will defend the use of a non-moralized definition before finally explaining why manipulation is prima facie unethical, using a common example of power dynamics in the workplace.

The concept of manipulation is not as thoroughly explored in bioethical literature as the concepts of coercion or exploitation. All three of these concepts pose a potential threat to the autonomy pillar of bioethics. As you will see when I go through the respective definitions, manipulation is distinct from concerns over force, coercion, and exploitation, and is also distinct from the more acceptable act of persuasion. It is necessary to understand and analyse the act of manipulation, or acts that can be described as manipulative, because they outline unethical behaviour for which one cannot account through the analysis of other concerns. Manipulation is related to the concepts of force, coercion, exploitation, and persuasion and it is possible that the
terms could be confused or used interchangeably in certain contexts, but it is important to distinguish manipulation because it points to an under-examined concern about power dynamics in social contexts and more a covert undermining of autonomy than similar, more examined terms.

The concern over manipulation in clinical research is not often found in bioethical literature. In some cases, there is a nominal mention of manipulation, but no clear definition of the term. Norman M. Goldfarb has a guide for clinician scientists and ethicists to determine if a study is exploitative. In this guide he outlines the difference between exploitation and undue influence. He examines the concept of vulnerability and answers questions about the presence of harm, the ability to consent to exploitation, and even the potential duty for governments to approve exploitative studies that might have positive results (3). Goldfarb mentions that ethical studies contain “no coercion, deceit, fraud or manipulation,” but he does not offer a definition or explanation for the term ‘manipulation’ (3). This points to a general concern for the existence of something unethical that is not coercive, but it is not enough to examine the nature of manipulation.

Outside of philosophical literature and ethical criticism, various ethical guidelines do not have much to say about manipulation. The Declaration of Helsinki states that consent given “under duress” is improper consent but does not mention manipulation (World Medical Association Declaration of Helsinki A.8). The CIOMS guidelines require medical research to “refrain from unjustified deception or withholding of relevant information, undue influence, or coercion” (International Ethical Guidelines for Health-related Research Involving Humans 33) and mention that, in order to maintain a just balance of benefits and burdens, that participant groups should not be chosen based on “their compromised social or economic position or their ease of manipulation,” but does not mention manipulation in relation to autonomy (7). The Tri-Council Policy Statement (2014) requires that “REBs and researchers should be cognizant of situations where undue
influence, coercion or the offer of incentives may undermine the voluntariness of a participant’s consent to participant in research” and later defines coercion (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, & Social Sciences and Humanities Research Council of Canada 26). However, when it mentions manipulation, there is no definition of manipulation given in the document and it references a concern of undue influence, which does not fully cover my definition of manipulation (Canadian Institutes of Health Research et al. 26).

Non-Moralized Definitions

The definition of manipulation that I will defend is a non-moralized definition based on multiple philosophical definitions of the term and what they have in common. Many philosophers who offer a definition of manipulation also contend that a non-moralized definition is the most defensible. Jan-Willem Van der Rijt argues that moralized definitions of terms like manipulation can lead to circular reasoning in ethical analysis (12). Once something is determined to be manipulative, we then cannot ask if it is unethical, and for the same reason we cannot recognize actions as manipulative if we have determined the action to be ethical (12).

A moralized definition of manipulation would have many difficulties when applied to cases, the first of which being determining a moral basis. To have a definition of manipulation that is moralized, it is necessary to establish moral rules relevant to the definition. This will evidently lead to multiple definitions of manipulation, one for each moral theory. This leads to the second concern, that identifying a case of manipulation will be a simultaneous act of applying the definition and analyzing the morality of the situation.

Similarly, a moralized definition of manipulation could also include a broad qualifier of immorality. For example, it could be stated that A manipulates B iff A unethically motivates B to
make a decision or perform an action that bypasses B’s rational capacities by means of deception, emotional pressure, or exploitation of B’s ego depleted state. This definition includes the element of immorality, but does not include criteria for a moral basis, thus leaving the definition open to multiple interpretations depending on the applied moral theory. Instead of having multiple, clearly separate definitions of manipulation which each point to a separate ethical theory, the single definition of manipulation would lead to multiple, contradictory conclusions depending on how it is applied and by whom. Whether the definition includes a clear ethical theory or not, it is best to have a non-moralized definition of manipulation to maintain consistency and ease in application.

What is important for a definition is similarity of kind. For example, two cases may be exactly alike in particular interactions between manipulating agent and manipulated victim. Defining these two cases as manipulation does not tell us whether they were moral acts. To determine morality, we would need to look at other contexts surrounding the situation and how this might apply to a chosen or relevant ethical theory. Calling the act manipulation in both cases, clarifies that we are speaking about a particular type of interaction that can be identified through a clear philosophical definition. Determining the ethical status of that interaction can be done more accurately by separating the analysis into steps. First, we determine if the interaction involved manipulation, second, we analyse the act of manipulation through a particular ethical theory. Trying to combine these steps adds unnecessary confusion and extra work, which is why I have opted for a non-moralized definition of manipulation.

Definition of Manipulation

First, let us distinguish manipulation from similar terms that may be used interchangeably in other contexts. Manipulation is not coercion, force, or persuasion. The relevant difference between coercion and manipulation in kind is that coercion will influence the actions of another
by engaging their rationality, whereas manipulation will bypass it entirely (Coons and Weber 15).

On the surface, it can be said that one main difference between most cases of coercion and manipulation is that victims are usually aware that they are being coerced (Van der Rijt 40). The TCPS2 defines coercion in medical research as, “involving a threat of harm or punishment for failure to participate” (Canadian Institutes of Health Research et al. 27), which is consistent with the philosophical definitions of coercion that I will use in this thesis.

My definition of manipulation is as follows: A manipulates B iff A motivates B to make a decision or perform an action that bypasses B’s rational capacities by means of deception, emotional pressure, or exploitation of B’s ego depleted state. This definition takes into consideration major elements of agreement between the various definitions and theories of manipulation from various philosophers. I will briefly explain the relevance of some below.

Anne Barnhill states that “manipulation is directly influencing someone’s beliefs, desires, or emotions such that she falls short of ideals for belief, desire or emotion in ways typically not in her self-interest or likely not in her self-interest in the present context” (52). J.S. Blumenthal-Barby describes manipulation, in part, as “non-argumentative influence” (126), which separates it from argumentative influence such as persuasion. Eric M. Cave suggests that manipulation can be achieved through deception, mild threats that cannot be considered coercive, or by “artificially constraining [the] other’s options,” (129). He also states that manipulation can be unintentional but chooses to focus on intentional manipulation when discussing morality (129).

Michael Cholbi claims that the common philosophical understanding of manipulation is a modification of one’s choice through the modification of their psychology (201). Because manipulation is a psychological modification, one’s vulnerability to manipulation increases when they have been ego depleted (202). This concept of ego depletion is what I have relied on for my
chosen definition of manipulation.

Moti Gorin’s definition of manipulation puts an emphasis on the use of deception. Gorin explains that manipulation is unethical due to its relationship to deception and the harm it causes against the manipulated’s autonomy (74). Gorin does concede that deception is not a necessary feature of manipulation, but claims that deception is an important concept to examine to understand manipulation because deception speaks to the ability for manipulation to interfere with one’s ability to self-govern (76). Like others, Gorin describes the effect of manipulation as bypassing one’s rationality (90). The concepts of deception and bypassing rationality are key to my definition and explanation of manipulation.

Joel Rudinow defines manipulation in the following way “A attempts to manipulate S iff A attempts the complex motivation of S’s behaviour by means of deception or by playing on a supposed weakness of S” (346). This coincides with others’ concepts of manipulation being defined by playing upon emotion or weakness, which is not the same as an overt threat of harm.

Allen W. Wood states that “‘manipulation’ refers to a way of interfering with or usurping someone’s free agency that does not limit or destroy free choice but, rather, influences it in certain ways that promote the outcome sought by the manipulator” (31). This definition separates manipulation from coercion or force because the latter two would “limit or destroy free choice” through the use of a threat or violence respectively. The similarities of these definitions are that manipulation does not limit one’s free choice through a threat of harm, or a change of the circumstances. Rather, manipulation functions to influence one’s mental state so that they might believe that their choices are limited, or that they might defer to someone else to make their choice.

In application of these philosophical theories, I find that the Tri-Council Policy Statement’s definition of ‘undue influence’ best fits my definition of manipulation, although not fully. The
TCPS 2 states that “undue influence and manipulation may arise when prospective participants are recruited by individuals in a position of authority” (Canadian Institutes of Health Research et al. 26) and that undue influence is “the impact of unequal power relationships on the voluntariness of consent” (210). The concern about power imbalances will be discussed later in this chapter. I have chosen to not use the term ‘undue influence’ nor to compare it to manipulation because in other contexts undue influence in clinical research refers specifically to an offer of excessive or inappropriate incentives, which is not relevant to the ACTG 076 trials that I will analyse, and the CIOMS guidelines do not have a clear definition of undue influence to analyse.

Throughout this thesis, I will focus mostly on the latter parts of my definition: emotional pressure and exploitation of B’s ego depleted state. I find that the concept of deception in clinical research is already well examined and considered unethical. If a clinician scientist manipulates by means of deception, that would be unethical under current Western guidelines and render the concern over manipulation moot.

Theory of Coercion

What the above-mentioned theories on manipulation have mostly in common, is the separation of manipulation from other, similar terms, such as coercion. The distinct nature of manipulation can also be seen in the given definition of coercion by Jan-Willem Van der Rijt. If one coerces another into acting, the coercer has caused the coerced to decide between two or more options that all result in a poor situation for the coerced. In most cases of coercion, the coerced is aware that they do not have control over the situation. They may be aware that both options put the coercer at an advantage, but the coercer has changed the circumstances so that the most rational choice available to the coerced is to comply. Finally, there is no option the coerced can take that will maintain their current state of well-being, they will always be worse off (Van der Rijt 20).
The example of a bank robbery involves coercion. The robber is the coercer in this case. Let us assume that the robber has entered the bank with the intention of leaving with the money, and not needing to use any violence. The robber has brought with them a gun, not because they intend to shoot it, but because they intend to coerce the teller and patrons to comply with their wishes. If I am the teller, and the robber points the gun at me and tells me to lie down, they have set up a situation where all options are undesirable. If I stay standing, or try to run, I risk being shot. If I lie down, I risk the robber leaving with large sums of money. Either way, the robber is at an advantage and I will be worse off.

Another important element to coercion is the engagement of rational capacities. When the coercer sets up a situation so that all options available to the coerced are unideal, they are still depending on the belief that the intended target will in fact be coerced to choose the best option. For the example of the bank robbery, it is better for me to lie down and risk the robber leaving with cash than it is for me to risk being shot. The robber relies on the assumption that I will use my rationality to determine that complying is the better outcome for me. Despite that I am aware of my own disadvantage, and I am aware that the coercer wants me to lie on the ground rather than to shoot me, I still think it is best for me to choose to comply. This can be described as having the coercer’s will imposed upon me via coercion (Van der Rijt 33). I am doing what someone else wishes that I should, not because they have persuaded me to do it and not because I have simply chosen to do it out of my own free will, but because they have used my rationality to impose their will upon me. They are also doing this in an overt manner. As I have mentioned, I am aware of what is happening, and my awareness does not affect the coercer’s power over me. We will later see that manipulation is commonly a covert act, and often relies on this covertness for its success.

Engaging in rationality and choosing to comply also separates coercion from manipulation or
force through the act of autonomy. I have been given my options, I have been allowed time and freedom to consider what is best, and I have used my rational capacities to make the autonomous decision to comply. The coercer has control over the circumstances I am in by pointing a gun at me, but they do not have control over my actions or decisions because I am physically and psychologically free to choose my action. One key factor in coercion is the *agency* of both me and the coercer (Van der Rijt 14).

In the case of medical research, the concern about coercion is understandable. However, in Western bioethics, coercion is already seen as a case to be aware of and to avoid because it is unethical to use coercion on participants or potential participants. An example of coercion in clinical trials would be if local physicians and health care professionals in a local clinic refused to see patients who were not enrolled in the study; patients that they would otherwise have accepted. This action made by the physicians would cause the patients to rationally decide that the best option for themselves is to enroll in the study. This is an example of coercion because the patients of the clinic who do not want to participate in the study are presented with two undesirable options: become participants in the study, or to stop receiving medical care. When faced with these two options, many patients would determine that it was rationally in their best interest to enroll in the study. By making this decision based on the circumstance that they were placed in by the clinic, the patients are coerced into participating in the study.

The above scenario of refusing to treat patients who are not study participants is unlikely to unfold because ethical guidelines prevent studies from being designed in this way, research ethics boards would likely catch this error of unethical conduct, and the personal morals of the health care professionals involved in the clinic and the study might cause them to report such a case if it ever happened. If we are to analyse all clinical research cases simply based on a concern for
coercion, it may be difficult to find scenarios that fit this type of description, and we may be
inclined to declare that a lack of coercion points in the direction of ethical conduct. However,
without analysing the possibility of manipulation, we would be missing a much larger picture.

Theory of Force

Force is a term separate from both coercion and manipulation. The concept of force implies
that one, or both, parties lack agency in the action being performed. In the case of the bank robbery,
I have previously stated that by choosing to lie on the ground, I have exercised my autonomy. This
exercise is what makes me a moral agent. If the robber were to come in and physically hold me to
the ground instead of pointing a gun at me, I could not say that I was coerced into lying down. By
being physically held down, I was not given a choice between options, regardless of their appeal.
The robber, using their agency, has taken away my agency or my ability to exercise my autonomy
as it pertains to the action of lying down. In this case I would say the robber has forced me to lie
down. Whereas coercion can be identified by a threat of violence, force is a use of violence.

The term force also applies in cases where I do have agency, but my actions are influenced or
restricted by a non-agent. An example of this could be a fallen tree. If I am walking down the street
and I come across a fallen tree in my path, I have no choice but to navigate around the tree in some
way. I cannot keep walking as I had previously planned. Perhaps I can step or climb over the tree,
but maybe I must find a way to walk around it. In this case I can exercise my autonomy to a limited
extent and have a limited agency. I can choose how I will navigate around the tree, limited by my
physical capacities, or I can choose to turn around and not continue down the path at all. One may
say that the options available to me are all unideal, like in the case of coercion, but because the
tree is not a moral agent, I would not be correct in saying that I have been coerced into my decision
(Baron 105).
So far, we have seen definitions and examples of coercion and force, the main difference between them being the element of agency, and the involvement of harm or violence. Coercion often involves a threat of violence or harm, whereas force can involve the use of violence. In the case of coercion, both the coercer and the coerced have agency and exercise this agency. The coercer limits the options of the coerced so that every option is non-ideal to the coerced and the most rational option is to comply with what the coercer prefers, but the coerced still can exercise their autonomy. In the case of force, an agent may have their agency removed by someone else with agency, or they may have their agency limited by a non-agent. In either case, only one player is exercising their agency at a time, regardless of their position as the forcer or the forced.

If we were to look for cases of force in medical research, these scenarios may be even harder to find than coercive ones. An example of forcing a participant to be in a clinical trial would be the act of holding individuals against their will to participate in medical experimentation, or not informing individuals that they are part of experimentation. Cases of force in Western clinical research would be effectively impossible to find now due to the focus on autonomy of participants and the requirement that consent be voluntary, informed, and ongoing.

Theory of Manipulation

Manipulation is distinct from both concepts of coercion and force. My definition captures this distinction with the factor of ‘bypassing rational capacities,’ which can be seen in the work of J.S. Blumenthal-Barby (123). This points to a lack of agency, separating manipulation from coercion, but also from force. The distinction between manipulation’s ‘bypass’ of rational capacities or autonomy, and force’s removal of agency is an important one. Allen W. Wood outlined a few ways in which manipulation can bypass one’s autonomy. First is use of deception. Although deception is not inherent to manipulation, it is quite frequently a feature of it (Coons and Weber 10). Joel
Rudinow describes deception as being “crucially involved” in many cases of manipulation (340). When one lies, makes false promises, or provides misleading information, they are not giving the other person an opportunity to make autonomous decisions (Wood 31). Moti Gorin agrees with this analysis of deception. One is expected to be truthful in their interactions; knowing this, the manipulator exploits the trust of the manipulated and influences their decision-making process (77). This influence interferes with their ability for accurate self-governance (76). Wood describes this as steering a moving automotive, separating it from coercion, which causes the automotive to move (34). This is an indicator of the covert and insidious nature of manipulation because it is arguably more difficult to notice when someone is being guided in their actions than when someone is being pushed.

The second factor to bypassing autonomy according to Wood is “pressure to acquiesce” (32). This ties in to the concept of ego depletion that will be discussed later. Acts such as wearing down one’s hold on their position, demeaning them, embarrassing them, or offering inducements contribute to this pressure (32). Instead of a bank robber, perhaps I have been asked by a friend to lend them $1000, but I refuse. My friend does not like that I have refused and berates me. Perhaps my friend tells me that I am not being reasonable, that I should be more kind, and follows me home as I try to walk away. Instead of telling my friend to leave me alone and going inside my house, I agree to lend her the money. This is a case of overt manipulation because I am aware that they are taking advantage of my situation. What separates this from coercion is that they have not completely limited my options. I can still refuse to give them the money and maintain my current state of well-being. I could even continue to argue back or threaten to call the police and accuse my friend of harassment. There is no reason to believe that handing over the money is the most rational decision available. I have only done so because I have been pressured to in some form,
and in this case the pressure has worn down my autonomy, causing me to make the decision to hand over the money.

The final connection between manipulation and autonomy per Wood is “playing upon emotions or weaknesses” (32). This can overlap with pressure to acquiesce in some ways, but the emotions being elicited do not necessarily involve pressure. Wood cites emotions such as fear, sympathy, gratitude, guilt, and greed (32). These emotions are then used to influence behaviour, drawing one away from rationality. For example, the fear of losing a loved one is virtually universal. A person who wishes to manipulate me may try to invoke that feeling of fear within me before requesting that I perform an action. Perhaps this person is trying to sell me hurricane insurance. I know that I live in an area where hurricanes are rare, if not impossible, but the sales associate has focused the conversation towards protecting my family. With this fear in mind, my rationality has less of an influence over my decision-making process and I am more likely to purchase the unnecessary insurance.

Wood’s concept of playing upon emotions relates to Anne Barnhill’s mention of targeting emotions and beliefs (55). Barnhill suggests that overloading someone with information causes an emotional response that makes a person vulnerable. When one feels too overwhelmed to process the information that they are being given, they are more likely to trust someone else to interpret it for them (55). In relation to the hurricane insurance, perhaps instead of focusing on my love for my family, because I live alone, the sale associate starts handing me pamphlets that they claim are important for me to read while simultaneously speaking quite quickly about the dangers of hurricanes. Maybe they speak in statistics about hurricanes, start comparing their insurance to other companies, and point out the fact that there is a heavy storm forecasted for tomorrow. If I were given a moment to read the information in the package I would realize that I do not live in the
hurricane danger zone that it outlines, but I am now feeling like I need to make my decision before tomorrow’s storm and I see the sales associate as an expert in the field. I trust them to give me advice because I am overwhelmed and less able to access my own rational thought.

The three cases of deception, pressure to acquiesce, and playing upon emotions are all examples of how manipulation bypasses rational capacities and autonomy in ways that are covert or overt to the individual being manipulated. Ego depletion also allows for an individual’s rational capacities to be bypassed so that they may be manipulated into performing an action or making a decision that the manipulator wants them to make. I have chosen to focus on the concept of ego depletion because I believe that the exploitation of one’s depleted ego is a factor in manipulation partially due to power dynamics, where the one in power might not fully intend to manipulate the one with less power, but they can still reasonably be aware of the circumstances, including ego depletion, that might cause the other to have diminished autonomy and to be manipulated.

The concept of ego depletion appears in only one theory of manipulation, but I have chosen to use it in my definition to represent similar concepts that appear in other definitions. Michael Cholbi explains ego depletion in the context of self-control and willpower, stating that “[these] are resources that, within a given context, become depleted as they are exercised” (202). He later uses the example of a person who is on a diet needing to use their willpower to suppress their desire for a hamburger. Cholbi claims that the energy used to suppress the desire to eat a hamburger early in the day drains one’s ability to suppress the desire to do something else harmful, such as drink alcohol, later in the day (206). Individuals who are in a constant state of desire suppression for one reason or another are more likely to “make choices that favor immediate gains over long-term benefit,” or “devolve choice to an authority” (206). These are important factors for manipulation vulnerability because the manipulator may depend on the victim’s lack of rational thought, or their
trust. Cholbi later makes the claim that vulnerability to manipulation is more likely to be due to an individual’s ego depletion than their character (213). In the next chapter, we will see how Cholbi supports the idea that those who are impoverished are ego depleted due to their poverty and, therefore, more vulnerable to manipulation.

Specific to Eric M. Cave is the term “motive manipulation” (132), which is more precise and more accurate to my usage of the term. My definition of manipulation of one agent by another is specific to psychological cases, rather than a more literal definition of manual control. For the purposes of this essay, I have chosen to use the term ‘manipulation’ instead of ‘motive manipulation,’ but my definition is exclusive to the latter. Other definitions of manipulation, whether they be philosophically relevant or linguistically descriptive, will not be applied.

Another important element to manipulation is that the manipulator need not know that what they are doing is manipulative. Marcia Baron relates this to the concept of insults. It is possible to insult someone without intending to and without realizing what you are saying is an insult, but that does not change the fact that it is insulting (102). Baron goes on to say that one must, however, have the intent to influence someone for the case to count as manipulation. Perhaps they intended to legitimately persuade the other person but did not realize that their execution of that persuasion was reckless and resulted in manipulation (103). The possibility of unintentional manipulation is important for my analysis.

This is important to note for the case of clinical research. Western bioethics has changed the way many people view clinical research, whether it be the overall goal, or the status of a participant. Due to the ongoing development of ethical research, it becomes less likely to see intentional or malicious actions that are unethical. The examples of manipulation that I have given above suggest that the manipulator is fully aware of, and intent on manipulating their victim. Cases
like these are not as likely to be found in clinical research. It is the unintentional manipulation, like the accidental insult, that we are more likely to see. An example of unintentional manipulation is something like that of the boss manipulating the employee. Instead of an insurance agent using special tactics to sell me insurance, perhaps my boss comes to work at a typical office with some of her daughter’s chocolate and vanilla girl guide cookies in hopes that her employees will want to buy some. This could still lead to her placing pressure to acquiesce on her employees.

Let’s say that first, my boss puts up a sign in the breakroom advertising the fact that the girl guide cookies are available. If an employee approaches the boss to purchase a box of cookies, it may be difficult to say that the boss’s sign pressured this employee to purchase the cookies because the employee has autonomous control over a series of decisions and actions in between seeing the sign and purchasing the cookies. Perhaps then, after a few days of only one or two sales, the boss walks around to all her employees to ask them if they saw the sign in the breakroom. The boss is doing this because she wants to help her child sell cookies, and because she genuinely believes that the sign must have not been well-placed if she only sold two boxes. In reality, the problem is that everyone loves the fall mint thins, but this is spring, and no one wants the inferior girl guide cookies.

The boss continues to pressure her employees through constant reminders, and the employees also feel a bit of pressure because she is their professional superior. However, the boss genuinely believes that she is doing the right thing by helping her daughter sell cookies and by making the cookies more accessible to her employees. Finally, after a week or so, my boss comes by to my office at lunch time because she knows that I use cash to pay for my lunch out. She is holding a box of cookies and she says that I should buy one now because I have the cash with me. Again, my boss believes that she is actually helping me by delivering the cookies and making sure I had
the cash to pay for them because she believes that I do want to buy a box. In this situation, my boss has placed immense pressure on me, and, since she has brought me the cookies, I need to decide quickly. To clarify the example, we can imagine that I do not have a very good relationship with the boss, and that less than a month ago she threatened to fire me for ‘not being a team player.’ Because of all this, I buy the cookies.

In this example, the boss has not intended to manipulate me into buying cookies. She is trying to help her daughter and the Girl Guide organization by making sure that everyone has been given a chance to buy the cookies and she believes that her actions are helping her employees have this chance. However, this could easily be a case of manipulation because of the pressure to acquiesce and the time frame I have been given to make a decision which diminish my ability to engage with my rational capacities. I have quickly decided to buy the cookies because of pressure by my boss and fear of being fired. She did not tell me that I would be fired for not buying the cookies, so this is not a case of coercion because coercion requires an explicit threat of harm. She has not stolen my money, so this is not a case of force. She also has not intentionally deceived me in any way, but she still has unknowingly taken advantage of her position as a superior and she has unknowingly placed a great amount of pressure on me to buy the cookies because of her behaviour in the last few weeks. The significance of my boss’ manipulation is not relevant here. I am not trying to prove that she has unethically manipulated me, but she has unknowingly manipulated me.

Theory of Persuasion

It is also important to separate manipulation from cases that are often seen as a legitimate change of mind. I have previously mentioned the act of persuasion. Persuasion cannot be described as one’s will being imposed upon another, or by bypassing the autonomy of an agent. Persuasion refers to cases where the agent’s rational capacities are engaged by the other, and they have
legitimate choice in the matter. Anne Barnhill describes persuasion as an act that improves one’s understanding of the relevant facts to decide or act (61). In a similar example to the bank robbery, perhaps my friend is short on cash and needs money. They choose then to come talk to me and ask for money. As opposed to the bank robber, my friend simply reasons with me in a way that engages my rationality and does not threaten my life. I have the option to not give my friend money and I will maintain my current baseline well-being. I also have time to think rationally about the proposal they are giving, and I am not emotionally pressured into complying, nor are they trying to exploit my weaknesses. If I choose to give my friend my money, it is because I reasonably believe that their genuine arguments are compelling enough to comply. They have persuaded me.

Manipulation and Exploitation

The term exploitation is often used in relationships involving apparent power imbalances. Exploitation can be defined as the use of someone else’s lack of dignity to gain control of an ability or resource that they possess, when one should instead be remedying their lack of dignity (Wood 43). An example of exploitation can be seen in market transactions. If one individual needs a stock of corn to survive, they lack the dignity of sustenance. They attend the market, expecting corn to be a reasonable price such as $1 per stock, the common price in the area. When they arrive at the market there is only one booth open selling corn, the price is $10 per stock. The individual selling the corn is exploiting the person in need of corn. The seller knows that other people need corn to survive and so they will likely buy corn at any cost. The seller is using the buyer’s lack of dignity to gain access to their resources; in this case, money. This is an act of exploitation.

As you can see, this example of exploitation does not fit neatly into the definitions of coercion or manipulation. The buyer is very aware that they are being exploited and that they are given a poor option, but they do maintain the reasonable option of not buying the corn and finding
something else. The seller has not put them in a position where both options are controlled to make the buyer worse off. The awareness and engagement of rationality means this case is not manipulation, the option to walk away and maintain the same level of well-being is not coercion. Of course, cases of exploitation can overlap with cases of manipulation, coercion, or force. In the case of the bank robbery, the robber might not be exploiting me because they do not stand to gain access to my abilities or resources, but if I had the key to the vault or if they intended to rob me and not the bank, they would be in a position of both coercing and exploiting me. In fact, they would be coercing me in order to exploit me more easily.

We have examined definitions and examples of the following terms: manipulation, coercion, force, persuasion, and exploitation. Each definition has some form of overlap with at least one other term. Manipulation, coercion, force, and persuasion all involve some aspect of influencing the decisions or behaviours of an individual. Exploitation is set apart because it refers to the benefit that one yields from an interaction, rather than the influence that has been placed over the interaction. There can be cases of exploitation, where one stands to gain from another’s lack of dignity, that do not involve any sort of motive influence like manipulation, coercion, or force. There may also be cases of manipulation which do not involve exploitation such as the case of paternalism where A is manipulating B because B is not acting rationally, and A wishes to save them from harm, not to gain anything personally.

In the case of paternalistic manipulation, A is most likely not exploiting B because paternalism often involves cases where A has B’s best interest in mind. This is not consistent with the concerns of exploitative manipulation (Barnhill 56). Exploitation explains what A stands to gain from the relationship, and, as Barnhill describes, it can be assumed that if A is acting in B’s best interest, that A has nothing to gain from manipulating B. In definitions given of these terms,
exploitation can be seen as mutually exclusive to paternalism. We could problematize this case by questioning the act versus the relationship, or the encounter. For example, A may be acting paternalistically towards B, and A manipulates B to act in B’s own best interest, but overall, preserving the best interest of B is done so that A may gain something from it. This would be a question of intentions behind A’s paternalism, which I will not consider here.

Norman M. Goldfarb has written a guide for determining whether a clinical study in a low-resource setting is exploitative. In order to analyse whether a study is exploitative, he sets out a few assumptions about the example case being used. One of these assumptions is that “there is a strong inducement to participate, but there is not coercion, deceit, fraud or manipulation” (3). Unfortunately, as I have demonstrated, there is no clear agreed upon definition, or even a small set of agreed upon definitions of ‘manipulation’ that Goldfarb could reasonably be assumed to refer. He goes on to expand upon the definition of exploitation, but not before a brief explanation that separates exploitation from the concept of undue influence. Goldfarb makes the claim that undue influence is defined by a study offering its participants advantages “that cause him or her to enroll in the study against his or her best interests” (2). This also applies to cases where the study simply appears to offer these advantages. He gives the example of a clinician scientist who is the participant’s physician (2). In this case, the therapeutic misconception that occurs when a patient believes that the study is offering therapeutic benefit because it was suggested by the physician, is undue influence.

Goldfarb suggests that attempts to relieve exploitation concerns can result in undue influence (2). Offering a participant money for the trial may be a good way to ensure that they are compensated for their time, but, offering them too much money may cause someone to participate in a study that they may find too risky otherwise. His solution to this concern is to find a “three
bears” balance to the compensation given for trials; something that will ensure participants are not exploited, but that will not create undue influence (3). The rest of the article focuses on explaining Goldfarb’s own definition of exploitation. Goldfarb’s article shows that some bioethicists are concerned with manipulation in relation to consent and enrollment, but that the definitions of manipulation and how the terms relate to concerns of exploitation or coercion are not substantive.

**Ethics of Manipulation**

Now that a non-moralized definition of manipulation has been established, and separated from terms such as coercion, force, exploitation, and persuasion, it is necessary to determine which factors would make manipulation ethical and which would make it unethical. Eric M. Cave posits that manipulation (what he refers to as “motive manipulation”) is prima facie unethical. He defends this notion by establishing the concept of “modest autonomy” (138). One’s modest autonomy is satisfied if they are free to act upon their own will without interference, meaning that an individual has the negative duty to “refrain from activities that threaten to undermine the capacities of others to manage their concerns” (138). Modest autonomy in this case can only ethically be violated under extenuating circumstances. Cave insists that violating modest autonomy is prima facie unethical (139). He also contends that manipulation always violates modest autonomy and, therefore, manipulation is prima facie unethical (140). His views are consistent with my concern that manipulation violates a participants’ autonomy in consenting to a clinical trial.

Persuasion, however, is not prima facie unethical (Cave 142). Persuasion is a case where one engages with another’s rational capacities in order to convince them to change their mind or perform an action. Because it engages with one’s rational capacities, persuasion may even improve one’s understanding of their situation (Barnhill 61). For example, if my brother plans to interrupt his ex-wife’s wedding ceremony to prevent her from getting married, I may think that this is a bad
idea. Perhaps he came up with this plan quite suddenly, so I believe that he has not spent a lot of time considering his options. I may reason with him, telling him how everyone involved would be affected by his actions, and he may agree with me that it is better to stay away, taking the utilitarian approach to his decision. Barnhill might say that I have improved my brother’s understanding of the consequences of his actions. I have not forced, coerced, or manipulated him into doing anything, and I have added to his rational decision-making with my philosophical arguments. He remains capable of exercising his autonomy, even if he is persuaded by my arguments. For this reason, persuasion is prima facie ethical.

J.S. Blumenthal-Barby makes the claim that the ethics of manipulation are tied to virtue, among elements of promoting autonomy, and fulfilling duties. She gives a list of non-virtuous elements that appear in unethical manipulation: “dishonesty or violation of trust, disrespect, arrogance, predatoriness, and laziness” (128). Blumenthal-Barby claims that ethical forms of manipulation are cases where person A manipulates person B for virtuous causes. An example she gives is of a person manipulating their roommate into exercising more and improving their health. The example includes the person placing fitness magazines and running shoes around the apartment as subtle encouragement. Blumenthal-Barby argues that the concern for the health of a friend does not constitute a violation of trust, or elements of disrespect. She claims that the subtle work that went in to manipulating the friend is not arrogant or predatory, and the fact that the person has put time and effort into the manipulation, cannot be seen as lazy (130). Although one may disagree about the analysis of the actions, we can see how the virtues and vices apply to a situation that would fit my definition of manipulation. Other theories explaining the ethical status of manipulation have similar outcomes in their analysis of actions.

Exploitation is prima facie unethical. If you recall, exploitation can appear in cases of force,
coercion, and manipulation so long as there is a gain at the victim’s expense. Above, I have given an example of manipulation that Blumenthal-Barby contends is ethical, and it is also not exploitative because the manipulator is not gaining anything from the manipulated roommate. Perhaps there is some personal satisfaction in helping a friend, but that satisfaction can occur without detriment to the manipulated. Blumenthal-Barby’s element of “predatoriness” is similar to the case of exploitation.

The vice of dishonesty is related to the concept of deception, which I have considered a factor of manipulation in my definition. As I mentioned above, I have chosen not to expand on the concern for deception or dishonesty because it is already considered unethical for clinician scientists to be deceptive or dishonest.

Based on the above claims, manipulation can be considered unethical in a variety of circumstances, and it is prima facie unethical. This means that manipulation should be avoided in most circumstances. For the particular case of clinician scientists, if manipulation of a participant occurs, the onus is on the clinician scientist to prove that their act of manipulation was ethical. For clinical research, a major relevant aspect of manipulation is the violation of autonomy. Vices such as arrogance or laziness as described by Blumenthal-Barby are less important than concerns over dishonesty, disrespect, or predatoriness because they are likely to threaten one’s autonomy.

Summarizing Unethical Manipulation

There are a few questions that need to be addressed for me to properly argue my point. The first is: *how can someone unknowingly manipulate someone else?* The second is: *if the manipulation is unknown and unintentional, why is it still the manipulator’s responsibility?* I can answer these questions through the lens of manipulated consent in sexual relationships. My definition of manipulation includes the use of deception and emotional pressure as factors that
cause manipulation, but I have not been focussing on them in this thesis. I have chosen to exclude
the discussion of deception altogether and provide a limited explanation of the relationship
between emotional pressure, power dynamics, and manipulation as I did above with the example
of the boss and the Girl Guide cookies. I have chosen here to focus on the concept of ego depletion
because it applies to the element of power relationships that causes manipulation and is relevant
to the case of clinician scientists.

If I am in an abusive relationship where my partner has slowly instilled in me the idea that I
am not good enough for them, that my ideas are not worthy, and that I might work to prove my
dedication to the relationship, then I might be more inclined to act in a way that pleases my partner
instead of myself. In this case, when my partner asks me to perform a sexual act that they know I
do not like, they might not need to apply pressure on me because they know that, even though I do
not want to do what they have asked, the abuse might make me feel like I have no choice in the
matter. They are bypassing my rational capacities, which would have told me that the relationship
is abusive. My rationality would have allowed for me to exercise my agency by firmly saying “no”
and maintaining that stance with my partner. If I choose to perform a sexual act on my partner, I
am doing it not because I want to, not because my rationality has chosen to, but because I have
been manipulated into thinking that this is a good idea, or that it is my only option. In this instance,
I have not consented, but rather I have been manipulated into consenting.

The above scenario can be drawn out in many ways. Firstly, what I have presented as-is would
be a case of intentional and known manipulation. My partner is explicitly using my ego depletion
to undermine my rationality, so they get what they want without having to wait or use legitimate
persuasive measures that engage my rationality. If my partner spoke to me as a rational human
being, perhaps they would learn that I had a fear about the act that they wished for me to perform.
They could take the time to discuss this fear with me and maybe dispel my worries, causing me to genuinely consent to the act in the end. However, my partner could also manipulate me while trying to use persuasive tactics.

If we analyze this using Blumenthal-Barby’s criteria, there are a couple of non-virtuous acts that may have taken place here. The emotional abuse by my partner trying to convince me that I have not properly proved my love can be seen as dishonest, or a violation of trust depending on the actual beliefs of my partner and their intentions. Secondly, one could argue that my partner is being disrespectful by constantly belittling me and my contribution to the relationship. There is also an element of predatoriness because my partner is benefiting from this manipulation. According to Blumenthal-Barby, this is an unethical act of manipulation.

You can imagine a scenario where perhaps my choice to comply with requests does not come from an abusive relationship or ego depletion, but rather from pressure that I might feel due to an imbalanced power relationship. If I am young and my partner is older and more experienced, I may feel pressure to please them. This is not an attempt by my partner to manipulate me, but it could unknowingly contribute to my manipulation through the pressure that comes from a significant power imbalance.

The concern over inadvertent or unknown manipulation explains why sexual relationships between superiors and subordinates in the workplace are unethical. There may not be any explicit act of coercion, force, threat, or anything of the like, but the power dynamics alone allow for an atmosphere that could manipulate the subordinate into making choices without the use of their autonomous, rational capacities. Furthermore, it is commonly accepted that the superior must recognize these manipulating factors and act in a way that will avoid them. It is not enough for a superior to say that they did not intend to manipulate their subordinate or that the subordinate fully
consented, we still place responsibility on the superior to ensure these relationships do not come about. Not for fear of nepotism, but for the recognition that power dynamics can contribute to a manipulative environment in which it is difficult, if not impossible, to ensure that the relationship is truly consensual.

I may not say in the ordinary relationship example that my partner has a duty to recognize and remove instances of ego depletion, so they can avoid manipulating me, because it is assumed that we are equal partners and there is no reasonable expectation of manipulation due to power dynamics. However, I can say this in the case of the workplace relationship. The concerns over these power dynamics are commonly known and the superior has a certain responsibility to their subordinates so as not to abuse that power. The same can be said for clinician scientists and other researchers in cases of manipulation into consenting to enter or remain in the trial. Alongside the duty to gain knowledge and help the community, the clinician scientist has a duty to protect the autonomy of the participant. Manipulation subverts autonomy and if it can be avoided by clinician-scientists, then it should be avoided to preserve that autonomy.

What is different is that I would bring these responsibilities one step further for the clinician scientist than for the superior in the workplace. Not only must the clinician scientist be aware of the known power dynamics that cause manipulating circumstances, but they must also place due care to recognize social dynamics that cause ego depletion and take these into consideration to the same degree of concern. This is consistent with Blumenthal-Barby’s claim that influencers may bypass one’s autonomy through the use of knowledge about their psychology, or facts about human psychology in general (127). Blumenthal-Barby’s claim demonstrates the ability one may have to unethically manipulate a person who has been ego depleted by their social conditions.

The clinician scientist is in a place of power over the participant because of the trial, their
expertise, and their social status among other factors relating to their position, but might also be in a place of power over the participant because of their respective identities. For example, it is common among cultures for men to be regarded as generally more knowledgeable, skilled, or to have more authority over decisions. In this case, it would be the responsibility of the man as a clinician-scientist to recognize that fact in the culture in which they work and ensure that they are not taking advantage of women participants who may feel pressure to acquiesce to the suggestions of a man, or might be ego depleted by their existence as a member of a socially oppressed group in society. The application of this concern will be addressed further in Chapter Two.

Defining Vulnerability

The definition of vulnerability that I will use in this thesis is Catriona Mackenzie’s. She uses Martha Albertson Fineman’s definition of vulnerability, which describes it as “a universal, inevitable, condition of our embodied humanity,” (Mackenzie 36). Mackenzie also accepts Fineman’s contention that vulnerability is a constant for humans and describes a constant possibility of harm that is contextual and experienced subjectively (Mackenzie 36). However, Mackenzie rejects Fineman’s description of vulnerability as oppositional to autonomy (Mackenzie 33). Mackenzie’s definition allows me to make claims about the vulnerability of research participants and the duties that one might have to participants because of this vulnerability, while maintaining that participants are still autonomous, capable of deciding for themselves, and responsible for their own actions.

Although vulnerability is a universal condition of humanity, Mackenzie outlines different types of vulnerabilities that one might have, based on Robert Goodin’s distinctions: inherent, situational, and pathogenic. Inherent vulnerabilities are ones that exist because of the fallibility of the human body and a social dependency on other humans (38). Situational vulnerability is
“context specific and is caused or exacerbated by social, political, economic, or environmental factors” (39). Finally, pathogenic vulnerability is a morally loaded term, which refers to situational vulnerabilities that should not exist in a just society, such as gender discrimination (39). Mackenzie also incorporates Goodin’s claim that vulnerability is not wholly natural and is created, affected, maintained, or exacerbated by social circumstances (Mackenzie 38). This includes vulnerability due to lack of social support for individuals who might need them (38).

Inherent and situational vulnerabilities can also be categorized as dispositional or occurrent, which describe the potential for harm and the experience of harm respectively (Mackenzie 40). For example, if a woman is being manipulated into consenting to participate in a clinical trial, then her vulnerability to manipulation is occurrent. In this thesis, I will be concerned with the dispositional vulnerability to manipulation of the potential and actual research participants in the ACTG 076 trials that took place in the United States.

Mackenzie’s definition of vulnerability aids in my analysis of manipulation by allowing me to identify those who might be more vulnerable to manipulation than others and make a claim about the duties that might be owed to them because of their vulnerability to manipulation. I contend that a vulnerability to manipulation is situational. I could make the stronger claim that the vulnerability to manipulation is pathogenic, since I will be making the claim that the circumstances that make one vulnerable to manipulation are often ones that should be remedied, such as gender discrimination, but I do not believe that all vulnerabilities to manipulation are pathogenic.

The Vulnerability of Pregnant Women

I mentioned that I will be using Mackenzie’s definition of vulnerability to aid my analysis of manipulation by discussing one’s vulnerability to manipulation. I also have chosen to examine the topic of vulnerability because of the historical use of the term in research ethics. Concerns
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about ‘vulnerable populations’ have led to the exclusion of different groups from medical research in the West. This exclusion, in an attempt to protect these populations, has resulted in severe negative consequences in clinical practice for those deemed ‘too vulnerable’ for research. It has been argued that medical research on children, despite their vulnerable nature, provides an extremely valuable contribution to the health and well-being of children due to the different reactions that a child’s growing body has to medical therapies. For example, the 1940s case of children being permanently blinded by a treatment of pure oxygen to aid their development when born premature (Munson 16). Without medical testing on children, there would be a lot more guess work in the clinical treatment setting and more children would have been harmed by the treatment (16). Mackenzie outlines how her definition of vulnerability impacts the duties society has towards vulnerable persons, or vulnerable populations. She clearly states that previous definitions of vulnerability often lead to “objectionably paternalistic” outcomes such as the exclusion of groups deemed to be vulnerable from participation in parts of society (Mackenzie 47). She maintains that an action is objectionably paternalistic if it selectively restricts a vulnerable group, because the duty that one has to vulnerable individuals is “fostering agency” where possible, and meeting needs, or “providing appropriate care” when fostering agency is not possible (46). Therefore, if we accept Mackenzie’s definition of vulnerability and we allow certain groups, such as pregnant women, to be considered vulnerable to manipulation in clinical research, the previously chosen action of excluding those women from clinical research is not an acceptable approach.

Mackenzie outlines different types of vulnerability. In the case of pregnant women, many past analyses might fit more closely to the description of inherent vulnerabilities. Bioethical guidelines that excluded pregnant women from clinical research presented the pregnant woman as inherently vulnerable qua pregnancy. As well as describing the inherent vulnerability of their
fetuses as something in need of protection. However, in this thesis, I will be using the concept of situational vulnerability to describe the vulnerability of pregnant women in the United States which arises due to social circumstances that I describe in-depth in chapter two. I do not discuss the vulnerability of the pregnant woman’s fetus, nor do I consider the fetus a participant in the clinical trial.

Adults infected with HIV are inherently and situationally vulnerable. Again, as you will see in my second chapter, I describe the social circumstances in the United States that contribute to the situational vulnerability of adults who are HIV positive. Mackenzie’s distinction between inherent and situational vulnerability allows her to make separate claims about what is owed to the vulnerable person and how their vulnerability might affect their lives. I am inclined to say that the history of considering pregnant women inherently vulnerable and excluding pregnant women from clinical research, has contributed to their situational vulnerability, much like Mackenzie posits that “social policy discourses of vulnerability and protection can be used to justify paternalistic and coercive forms of state intervention that generate pathogenic forms of vulnerability” (15). I will remind you that her use of the term “pathogenic vulnerability” means that the situational vulnerability created is unjust and in need of rectification (39). My claim is that, when pregnant women were first being included in clinical research more regularly, they were pathogenically vulnerable due to their previous exclusion, which impeded the understanding of effects of pharmaceuticals on pregnant women.

Baylis and Ballantyne point to the case of the “precautionary principle” used with pregnant women in medical research and in medical care. The precautionary principle is based on the theory that a lack of evidence to prove harm is not enough to presume safety (1). In the United States, pregnant women are deemed as vulnerable, resulting in the precautionary principle being used in
the methodology towards their treatment and inclusion in clinical trials, resulting in a policy of automatic exclusion from clinical trials, or a refusal of medical treatment due to lack of evidence proving safety (6). Baylis and Ballantyne also argue that the use of the precautionary principle to exclude women from clinical trials is harmful, unfair, and unreasonable. Labelling pregnant women as situationally vulnerable allows us to consider their vulnerability as being caused by their environment and circumstances and not merely by their pregnancy.

The connection between the concepts of manipulation, ego depletion, situational vulnerability, and power imbalances might be unclear. I have included a flow chart in Appendix A to help clarify the connections that I am making in this thesis. Firstly, manipulation can be caused by three main factors: deception, emotional pressure or ego depletion. For the purposes of this thesis, I will only discuss the relationship that pressure and ego depletion have with manipulation (connections 2 and 3). This is because in clinical research, it is very unlikely that researchers will use deceptive tactics in order to gain their consent to participate. It is also unlikely that researchers will apply pressure to acquiesce, but it is important to understand how power imbalances can cause unintentional pressure, which I will explain later.

Ego depletion can cause one to be vulnerable to manipulation because some of the effects of ego depletion include deferring one’s decision-making to a person of authority, or a person of perceived authority, making decisions based on short-term benefits rather than long-term, and making decisions that do not fully engage one’s own rational capacities. For example, if Person A is ego depleted, they might decide to enter into a clinical trial because of the possibility of short-term relief from their chronic headaches, without fully considering the potential for long-term negative side effects such as liver damage, whereas Person B, who is not ego depleted might decide that the potential for liver damage is not worth the short-term relief of their headaches and would
choose to not enter the study. If the researcher knows that Person A is ego depleted and chooses to accept their consent to participate in the study, then the researcher has taken advantage of Person A’s ego depleted state and has manipulated them into entering into the study.

Next is to develop the connection between ego depletion and situational vulnerability. This connection is very close because both situational vulnerability and ego depletion can be caused by the same factors. In the case of ACTG 076, the factors of illness, pregnancy, gender, and HIV status can cause one to be situationally vulnerable to many negative outcomes such as long term harm to one’s physical health. Illness in general, and HIV specifically can cause irreversible harm to one’s body which might lead to early death. Pregnancy causes one to be more vulnerable than non-pregnant people to some medical conditions that could lead to irreversible harm to one’s physical health. Finally, one’s gender, depending on the social context in which they live, can cause them to be more vulnerable to violence than people of another gender, which can lead to irreversible harm to their physical health. Illness, pregnancy, gender, and HIV status can also lead to ego depletion due to external constraints placed on one’s will. For example, those with communicable illnesses, including HIV, might be ego depleted by being constrained in their ability to interact with other people. Perhaps their illness has caused them to be put into isolation in a hospital, constraining their ability to exercise their will. A pregnant person might face external constraints to their will if they live in a society where the public views the perceived health of a fetus to be superior to the autonomy of the pregnant woman. In this case, pregnant women would face constraints such as being refused service at a coffee shop or bar because the server believes the woman is harming the fetus with her consumption of caffeine or alcohol. Finally, gender might cause one to be ego depleted if one is part of an oppressed gender group where their will is limited in their ability to apply for a job, to drive or purchase a car, or other daily tasks that they might be
Finally, I will explain how power imbalances are connected to all these concepts. Power imbalance is connected to these concepts through its connection to ego depletion and pressure. One of the effects of ego depletion is the deference of one’s decision-making to an authority, real or perceived (3c). That means that in a situation where Person A is ego depleted and in an imbalanced power relationship with the clinician scientist, Person A might defer their decision-making to the authority of the clinician scientist and might consent to entering the clinical trial because they believe that the clinician scientist is saying it is a good thing to do so. Therefore, the deference to authority is a deference to the person of power in the imbalanced power relationship (3ci). This connection means that, when there is a power imbalance between the clinician scientist and the potential participant, beyond the inherent imbalance that exists in that relationship, the potential participant might be more vulnerable to manipulation than if the power imbalance did not exist.

Power imbalances can also be present in the case of emotional pressure (connection 2a). The example I gave with the boss selling cookies demonstrates this connection. The pressure placed on me by my boss might not be intentional and overt, but might exist simply because she has power over me in a very meaningful way, namely that she could fire me, so I feel pressured by her repeated requests to buy the cookies and make the decision to buy them based off of this pressure, rather than based off of my rational capacities or desires.

In this chapter I have defined manipulation in clinical research and separated it from coercion, force, exploitation, and persuasion. I provided my definition of manipulation as “A
manipulates B iff A motivates B to make a decision or perform an action that bypasses B’s rational capacities by means of deception, emotional pressure, or exploitation of B’s ego depleted state” and explained that one can be vulnerable to manipulation due to their identity or circumstances creating situational vulnerabilities. In the following chapter, I will analyze the case of ACTG 076 in reference to ego depletion of the participants to demonstrate their vulnerability to manipulation. I will focus on the four elements of their identity that could cause situational vulnerability and are pertinent to manipulation and necessary for participation in the trial: pregnancy, gender, HIV status, and illness. I will show how these four elements contribute to one’s ego depletion due to social context and examine how this ego depletion was maintained or exacerbated by the trial design.
Chapter Two - Applying Manipulation

In this chapter I will use my definition of manipulation, “A manipulates B iff A motivates B to make a decision or perform an action that bypasses B’s rational capacities by means of deception, emotional pressure, or exploitation of B’s ego depleted state,” to analyse a case study and show one example of the potential for manipulation in clinical research. My analysis will demonstrate the ways in which a participant might be ego depleted due to social and cultural factors. I will also be relying on Catriona Mackenzie’s definition of vulnerability and her distinction between inherent vulnerability and situational vulnerability to indicate that situational vulnerability to manipulation can occur due to these social factors and it does not indicate that certain groups of people are inherently more vulnerable than others. It is important to outline the potential for the participants to be ego depleted because one part of my definition of manipulation is “exploitation of B’s ego depleted state,” and I will demonstrate the potential ego depletion of these participants for the purposes of showing their vulnerability to be manipulated by clinician scientists.

I have chosen to focus on the aspect of ego depletion causing a vulnerability to manipulation rather than cases such as deception or emotional pressure, which also appear in my definition of manipulation, because I believe that ego depletion is the most relevant aspect to clinical research. It is very unlikely that researchers will use means of deception or emotional pressure to manipulate potential participants into consenting to join or remain in the clinical trial, but I believe that it is very possible for researchers to take advantage of a potential participant’s ego depleted state, likely unknowingly, as means to manipulate them into consenting to join or remain in the clinical trial.

The case study that I will analyse is the AIDS Clinical Trial Group 076 (ACTG 076) trials
that occurred in the early 1990s. These trials were designed to test the efficacy of a medication called Zidovudine, which is supposed to prevent transmission of HIV from mother to child during pregnancy, childbirth, and breastfeeding. These trials took place in The United States of America and France. My analysis will focus on the trials in the US. The International Maternal Pediatric Adolescent AIDS Clinical Trial Group (IMPAACT) currently hold the ACTG data and have provided me with a copy of consent forms that were used in the US trials and I will be referencing these consent forms later in my thesis. I have chosen to analyze the ACTG 076 trials in the United States because of the particular situation of their being forefront in bioethical criticism, but instead of being criticized, they were used as the measuring stick to determine that trials that followed them were unethical (Lurie and Wolfe 534).

The ACTG 076 trials established a new regime for preventing mother-to-child transmission of HIV in the Western world. After the establishment of this regime as the new standard of care, it was determined that the regime would be ineffective in low resource settings where pregnant mothers do not often present to the clinic early enough in their pregnancy to receive treatment in this way (Benatar 200). It was also a concern that the newly established standard of care would be too expensive to be largely available in low resource settings, where HIV had a high incidence rate and prevalence (Benatar 200; Lurie and Wolfe 533). Due to the concerns over the effectiveness of the 076 regimen, many new trials were conducted in low-and-middle income countries (LMIC) using a placebo control and the experimental treatment was of a lower dosage than in the ACTG 076 trials (Benatar 200). For clarity, I will call the new trials in the LMIC “B trials”. The B trials were heavily criticized for their choice to not use the current standard of care as a control, something that would have been required of trials completed in countries such as the US (Lurie and Wolfe 534). While much concern was spent criticizing the B trials, the original ACTG 076
trials were used as a comparison point with bioethicists requesting that the B trials be performed in the same way as the 076 US trials were. There has been less of a concern, however, over the ethics of the original ACTG 076 trials in the US, and the focus of the criticisms has been mainly about standard of care, and not about manipulation, consent, or autonomy (Lurie and Wolfe 536). By focusing on the original ACTG 076 trials I aim to show that manipulation as a concern is quite easily overlooked, even when the trial in question is part of much controversy.

I will begin chapter two by explaining relational autonomy and why it is the most relevant definition of autonomy for my thesis, as well as how autonomy differs from agency. Next, I will provide a more in-depth explanation for ego depletion than I have done thus far. Michael Cholbi’s definition of ego depletion focuses on internal factors that constrict one’s autonomy, but also leaves room for external factors and I will explain why the external factors are my focus in this thesis. Following the definition of ego depletion, I will relate the concept to vulnerability to manipulation, as well as power imbalances in relationships. Next, I will describe the role of social oppression in the United States and how oppression can lead to ego depletion. Finally, I will examine the four elements in the trial that I believe could present a concern for ego depletion in participants and how they each pose a risk to ego depletion. The elements are: illness, gender, pregnancy, and HIV status.

Illness can lead to ego depletion through drained mental strength due to coping with external constraints that override responses. The concern for ego depletion in issues of gender is dependent on social context. For ACTG 076, the context is the United States in the 1990s, which indicates that ego depletion could occur in women due to social oppression of women that can contribute to an external restriction of choices such as women being less likely to be promoted to managerial positions at work (Lebowitz “A new study”). Pregnancy could also lead to ego
depletion due to social pressure to put the health of one’s fetus over their own, leading to the effect of making decisions that have short-term benefits rather than long-term benefits. Finally, HIV stigma can cause ego depletion due to a lack of social resources or medical support for those who are HIV positive, coupled with the potential for internalizing the belief that those with HIV deserve the illness. These causes of ego depletion are all due to social oppression. Ego depletion, like situational vulnerability, can cause one’s vulnerability to manipulation.

Relational Autonomy and Agency

Throughout this thesis I have made claims about the importance of respecting autonomy in Western bioethics. I have granted autonomy as a main pillar of Western bioethics and I do not intend to argue against the system, but rather to work within what already exists. However, I have yet to outline a comprehensive definition of autonomy, taking for granted that all possible definitions are similar enough to maintain my previous argument that manipulation is a violation of one’s autonomy and, therefore, prima facie unethical in Western bioethics. Moving forward, however, I will need to define autonomy more specifically to show how it fits with my concern about vulnerability, ego depletion, oppression, and to make claims about how to foster one’s autonomy in clinical research. The theory of autonomy that best fits my claims surrounding vulnerability, ego depletion, and oppression is that of relational autonomy.

In the previous chapter I defined vulnerability as a constant possibility of harm that is contextual and experienced subjectively (Mackenzie 36) and explained that vulnerability can manifest itself in a few different ways. One of the ways that vulnerability can manifest itself that I will focus on in this thesis is that of situational vulnerability. Situational vulnerability is the vulnerability of a person that can occur due to the circumstances in which they are and can be remedied by changing the circumstances (7). This explanation of multiple types of vulnerabilities
and the definition of situational vulnerability that I am using belong to Catriona Mackenzie, who insists that her definitions of vulnerability rely on an understanding of autonomy as relational autonomy.

**Autonomy and Agency**

Autonomy and agency are separate terms that I need to distinguish before going forward. My concern in this thesis is about manipulation undermining the autonomy of participants in clinical research and I have chosen to focus on the specific case of pregnant women infected with HIV with the case study of ACTG 076, but there are many other scenarios where one’s autonomy could be undermined or diminished. Since it is possible for all types of people’s autonomy to be diminished in many different scenarios, the next concern would be the consequences of declaring such large scores of people as having diminished autonomy. The solution to this concern is to understand that diminished autonomy does not mean that a person does not have agency, or that they are not responsible for themselves.

Relational autonomy is a theory of self-governance that depicts selfhood as “an ongoing process” that is shaped by personal and public relationships with others (Sherwin 23-24). Since relational selfhood is defined in a way that considers the interdependence of humans and autonomy is a theory of self-governance, relational autonomy considers the interdependence of humans in the same way and does not insist that one is only fully autonomous when their self-governance is wholly independent as other theories of autonomy tend to do (17).

Agency, in comparison to autonomy, accounts for one’s ability to make a choice (Sherwin 22). If one’s autonomy is diminished, for example, by external constraints such as physical location, that does not indicate that the agent is incapable of making a rational or reasonable choice based on the position in which they currently are. Moving forward with the example of ego
I will make the case that ego depletion diminishes one’s autonomy by constraining their ability for self-governance, but that this diminished autonomy does not equate to a removal of the person’s agency. People who are ego depleted are still rational agents even if their autonomy is not fully intact. As agents, ego depleted people still hold responsibility for their actions and should not be excused from the consequences or culpability of their choices, but perhaps more importantly, ego depleted agents do not need to be treated paternalistically.

**Ego Depletion**

The concept of ego depletion is important to establish for my analysis of manipulation because I contend that one can be manipulated through an exploitation of their ego depleted state. Although some may argue that the phenomenon of ego depletion is not real, I have chosen to grant its existence for the purpose of my thesis, and I will not spend time attempting to prove that ego depletion is real. In psychology, ego depletion refers to the concept of self-regulation as being a limited resource that one has. Self-regulation involves a psychic action such as active choice or overriding temptation and motivated responses (Baumeister et al. 1253). This psychological explanation identifies ego depletion as the state that occurs when the limited resource of self-regulation is diminished by an overburden of its use (1253). Michael Cholbi cites Baumeister’s experiments in his article on manipulation. Cholbi defines ego depletion in a similar way as Baumeister through the lens of philosophy and links the effects of ego depletion with the action of manipulation by explaining that one who is ego depleted might be more easily manipulated than one who is not.

**Cholbi’s Definition**

Michael Cholbi defines ego depletion as “the result of an inability to regulate executive function and self-control” (Cholbi 206). When one suppresses a desire, they become less likely to
be able to suppress another desire that occurs soon after. When these desires are suppressed in close sequence, one becomes less likely to be able to control themselves and make rational decisions in their own best interest (206). This is significant because, when one has been ego depleted by something like desire suppression, it causes one to “devolve to choice strategies that simplify choice” such as preferencing short-term satisfaction, and deferring to an authority as decision-maker (206). Desire suppression might come from within, such as suppressing a desire to eat a hamburger, but it might also come from external sources called “choice environments” (217). For the purposes of this thesis, I will be focusing on the external suppression.

Cholbi states that those who are put in undesirable situations such as poverty are more likely to make irrational decisions that may maintain their poverty (217). Many like to claim that this means those who are impoverished got there because of their character as irrational decision makers (217). Cholbi suggests, rather, that those who are impoverished make these decisions because of ego depletion caused by their poverty (217). Specifically, he says that “those with fewer resources must exert greater willpower or self-control precisely because their lesser resources necessitate their deliberating about trade-offs among a wider range of options” (214). For example, a person with low income who struggles to pay their bills unless they are capable of working every scheduled shift at their job might be more likely to purchase a lottery ticket than someone who makes enough money that they can feel secure in their ability to continue to pay their bills even if they need to take a day or week off work, or if they run into a large unexpected expense. It might seem irrational for someone with such little money to spend some of that money on a lottery ticket that is very unlikely to provide them with more income, rather than to place that money into a savings account. However, having a depleted ego means that the energy needed to make these decisions has been drained from them by previous restricted choices and they are more likely to
make decisions for the short-term benefit or they are more likely to trust someone else to make the decisions for them (206). This demonstrates that poverty will possibly, though not necessarily, lead to ego depletion. Not everyone who faces these restrictions will be affected the same way by them. I contend that the tendency to make irrational decisions is a strong element in the identification of manipulation. Ego depletion is affected by more than just poverty and it is important to recognize how these factors interact with each other to make certain groups of people situationally more vulnerable to manipulation.

*Causes of Ego Depletion*

Cholbi’s concept of ego depletion focuses mostly on one’s inability to maintain their willpower while consistently suppressing it, such as when one might choose to drink alcohol after having a hard day at work although they know that alcohol is not healthy and they have other, healthier, beverage options (206). However, both Cholbi and psychologists like Baumeister give examples of ego depletion that are caused by a suppression of wills or options from the outside world. Cholbi mentions the case of poverty, while the psychological experiments refer to cases where one has been instructed to suppress their thoughts of white bears. In the psychological experiments, the external factor is the researcher who has instructed the participants to suppress their will, whereas in everyday life, external factors could be situations such as poverty, where one’s will is being suppressed not by their active choices, but by the constraints that their poverty, or a comparable condition, has placed on their ability to perform daily functions such as shopping, riding the bus, or socializing with friends.

One cause of ego depletion is external constraints such as a lack of resources. I have mentioned above that Cholbi attributes a lack of resources to financial resources and explains that poverty might cause ego depletion in an individual, whereas I see the lack of social resources to
be a plausible factor in causing ego depletion. In the psychological experiments, the resource that was drained to elicit the effect of ego depletion was the internal resource of self-regulation (Tice et al. 380). In one version, the constraint on the internal resource was externally imposed by the experimenters who provoked thoughts of white bears, then asked participants to suppress these thoughts as much as possible (380). When a participant was asked to perform a second draining act after having an already depleted ego, their ability to continue was diminished (381).

*Effects of Ego Depletion*

Through the definitions above and examples of their application, I have determined a set of effects that I will be using throughout the rest of this chapter to indicate the possible presence of ego depletion due to power imbalances or social oppression. These effects are i) drained mental strength due to coping with external constraints that override responses, ii) making decisions to benefit the short term rather than long term, and iii) deferring decision-making to others.

Effect i) of ego depletion is drained mental strength due to coping with external constraints that override responses. Since it will be difficult to determine the existence of drained mental strength in the case study, or how it might affect one’s decision-making, I have chosen to focus on the latter two of making decisions for the short-term benefit, and deferring decision-making to authority.

Effect ii) of ego depletion is that individuals who are ego depleted are more likely than their intact ego counterparts to make decisions that benefit themselves in the short-term, rather than to make decisions that benefit them in the long-term. As it pertains to becoming a participant of clinical research an example of this might be a tendency for ego depleted individuals to join a clinical trial because they will feel better in the moment about taking action to treat their illness, but not fully considering the risks that have been explained to them about entering the trial.
Effect iii) of ego depletion is that individuals who are ego depleted are more likely than their intact ego counterparts to defer their decision making to someone they view as an authority figure. As it pertains to becoming a participant of clinical research, an example of this might be a higher tendency for ego depleted individuals to trust the researchers of the trial and to agree to join the trial without making many careful considerations about the risks and benefits to themselves.

**Vulnerability to Manipulation**

Ego depletion can be seen as a situational vulnerability to manipulation. I say situational vulnerability instead of inherent vulnerability because the nature of ego depletion is situational. If an individual is in an ego depleted state, they are vulnerable to manipulation. The example above of poverty does not apply to the case of ACTG 076 that I am analysing because the women may have come from various socioeconomic backgrounds. However, the example is analogous to other situations, such as HIV stigma causing a lack of available treatment. I believe the example of poverty is analogous because Cholbi’s claim about ego depletion refers to people with lower resources needing to exert more willpower due to their situation. It is my claim that ‘lower resources’ can refer to other circumstances such as fewer medical resources. Again, we must note that having lower resources which restrict one’s choices only demonstrates a possibility of ego depletion and not a definite existence of it.

**Illness**

Illness can cause one to be vulnerable to manipulation. In respect to ego depletion one’s ego might be depleted by their illness suppressing their will. For example, if my illness causes me to tire easily and I cannot do the same tasks that I once did when I was not ill, I must choose between certain tasks based on what is necessary and what might tire me the least. My will is being suppressed because my options are limited, and if this leads to ego depletion, it might have the
effect of causing me to defer my decision-making to someone else, especially someone I see as an authority. If that authority knows that I am likely ego depleted and that I will defer my decision-making to them and choose to exploit this ego depletion by gaining something from me, then the authority has manipulated me; this is why there is a concern that illness can cause one to be vulnerable to manipulation.

Next, I will discuss the influence that power imbalances in relationships can have on one’s vulnerability to manipulation. I will examine the relationship between a researcher and a participant particularly in the case of Phase III clinical trials where participants are ill. Because the relationship examines power dynamics when one is ill, that analysis can be seen in part as an extension of this one where I will further explain how illness can cause one’s vulnerability to manipulation. I will discuss the other three elements of gender, pregnancy, and HIV status a bit later on, in the section examining social oppression.

Power Imbalances in Relationships

As discussed in the section concerning the unethical nature of manipulation in my first chapter, power imbalances in a relationship can cause situational vulnerability of the subordinate to manipulation, regardless of the possibility for ego depletion. If you recall, I provided the example of a workplace romantic relationship between a superior and a subordinate. The subordinate may feel pressured to comply with the wishes of their superior, but, more importantly, the superior should be aware that they do not have a clear way of knowing if the consent is legitimate and, therefore, should not accept it. If the superior has chosen to accept the perceived consent of the subordinate, and they have not taken steps to promote the subordinate’s autonomy, they could be unknowingly manipulating them.

The issue of the emotional pressure to acquiesce to a superior is raised in Mandava and
Millum’s article about enrollment manipulation where they give the case of a doctor suggesting to their colleague that they recruit people for the study by simply wearing a white coat and presenting their authority (1). Responding to the atmosphere is called situationism (Cholbi 213). The high tendency for individuals to comply with requests by doctors or scientists was demonstrated in the Milgram experiments where participants were asked to administer painful electric shocks to whom they believed to be other participants in the study (Wood 32). At least one of those who continued to administer the shocks (which were not real anyway), cited an uneasiness about complying with the command, but a declaration that he, as the participant, was not responsible for his actions (Kaposi 390). I will not attempt to defend the claim that the participants in the Milgram experiments were manipulated or had diminished autonomy. I am simply using this example to illustrate a documented effect that authority figures might have on the actions of those with whom they interact. Baumeister et al. suggest a similar phenomenon of individuals who choose to relinquish their control to others’ in some circumstances, and even more those who do not generally wish to have control over most of their decision-making in most circumstances (1263).

Definition of Power

In this section I will describe vulnerabilities to manipulation due to power imbalances in relationships and to ego depletion that may be caused by oppressive cultural norms. I will be using a feminist account of power as presented by Amy Allen, which separates concepts such as power-over, power-to, and power-with. Power-over refers to one’s ability to constrain the choices of another “in a nontrivial way” (33). Power-over can refer to instances of abuse, or to acceptable situations such as the power of a basketball coach to constrain the choices of the players in order to improve the team (34). It is this concept of power-over that I will be focusing on in my descriptions of power dynamics between doctor and patient. I wish to describe the extent to which
a doctor has power over a patient to constrain their choices such as their choice of treatment for a particular illness. This also describes the power that men might have over women in the United States where men have power to constrain women’s choices about their own body, such as men in political positions choosing to what medical services a woman is allowed access. The social dynamics can also be a description of power-to, where power-to refers to an agent’s ability to accomplish some sort of end (34). A description of unequal power dynamics could also be in reference to a dominant group’s power to serve their own ends more often, or in larger numbers than an oppressed group. The first of these power imbalances that I will describe is that of the researcher-participant relationship, which is descriptive of a researcher’s power over a participant or potential participant.

**Researcher-Participant Relationship**

One reason why I have chosen to emphasize power imbalances in relationships is that the concept of power imbalances is important for Western bioethics. The power imbalance between researcher and participant during a clinical trial has already been seen as a potential threat to autonomy and there are regulations that aim to mitigate the negative effects of the power imbalance. For example, The Declaration of Helsinki insists that a patient who is in a “dependent relationship” with a physician cannot legitimately consent to research that is presented by that physician, and that another physician, on whom the patient is not dependent, must be the one to obtain the informed consent from the patient to be a participant (B.23). The TCPS 2 cites the imbalance of power between researcher and participant as a potential threat to justice in clinical experiments and recognizes that the power imbalance has historically been used in a way that harms participants (Canadian Institutes of Health Research et al.9). The dynamic between doctors and patients in health-care settings is recognized as a power imbalance (McLeod and Sherwin
In the case of ACTG 076, we are specifically looking at the dynamics between researchers and participants. Researchers have more knowledge and application skills about the subject in question than participants. This can cause some participants to choose to trust the researchers, rather than attempt to come to their own rational conclusions about the information available to them. Participants are always vulnerable to manipulation because of this potential for trust in researchers such as clinician scientists. This does not mean that all participants trust clinician scientists or that trust alone will cause a participant to be manipulated. A vulnerability to manipulation indicates a potential for a harm to occur due to the circumstances.

For the case of ACTG 076, the research is a Phase III trial. When I discuss here the importance of the power imbalance between clinician scientist and participant, I am referring specifically to a situation where participants are ill and have an opportunity to be treated for their illness by the experimental treatment in question. There are other situations of clinical research where early stage research is conducted on healthy patients to determine effects of the compounds being used in the medical treatment, or effects of experimental therapy whatever it may be, that are not medically beneficial. These participants are not in the same position as ill participants because they are healthy and are less likely to be seeking medical treatment when joining the trial. There are also early phase trials that are tested on ill patients who are terminal. For example, the effects of a new chemotherapy treatment might be tested on terminally ill cancer patients. The researchers know that it is virtually impossible for the terminally ill patients to benefit medically from the early phase trial and that the goal of the trial is to look for effects like toxicity in the experimental treatment rather than to look for a therapeutic outcome, but it might be more difficult for a terminally ill participant to fully comprehend that they are taking part in a medical experiment that does not have in its aim the ability to improve their medical condition (Munson 42). The cases
above of healthy participants and terminally ill participants in early stage trials have a different set
of concerns in the power imbalance between researcher and participant due to the difference in
illness and I do not intend my claims here to apply to those types of medical trials. I wish only to
speak to Phase III trials where the participants are ill and have reasonable expectation of the
possibility of direct medical benefit from the experimental treatment.

The vulnerability to manipulation applies outside of research as well, to any doctor who
has a duty to keep the patient’s best interest in mind. If a doctor tells their patient about medical
research and suggests that the patient participate in the research, the patient might believe that the
treatment is therapeutic and not experimental because the suggestion was made by their regular
doctor whom they trust (Mandava and Millum 38). The belief of participants that the experimental
treatment is approved as a therapeutic treatment is called therapeutic misconception. Therapy in
clinical practice has a goal of improving the life or managing the symptoms of a single patient and
the health care professional has the best interest of the individual patient as a goal when they are
prescribing therapy for a patient. However, research has an overall goal of improving the
community through increased medical knowledge, which means the best interest of the individual
participant is not a priority for clinician scientists. It is also important to note that prescriptions of
therapy often come from a sense of confidence in the certainty of an outcome, whereas clinical
research is performed when there is a genuine uncertainty about the therapy in question. These
differences in objectives and knowledge contribute to the importance of understanding therapeutic
misconception and ensuring participants in medical research are aware of the differences between
therapy and research.

The concern for therapeutic misconception also appears in the case of ACTG 076. Dr.
Maria Kreszentia Sheppard defines therapeutic misconception as “the situation where research
subjects who have legal capacity do not understand the distinction between clinical care and clinical research and misinterpret the nature of clinical research and the intentions of the researchers” (128). When a participant enters into a relationship with a clinician scientist, it is necessary that the patient understand this distinction between a physician and a clinician scientist, in order to decrease the likelihood that they will have therapeutic misconception about the research. The latest Tri-Council Policy Statement (TCPS2) guidelines advise that “researchers should take all necessary measures to separate their role as researcher from their role as physician,” in order to minimize the risk of therapeutic misconception (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, & Social Sciences and Humanities Research Council of Canada 153). This duty to minimize the risk of therapeutic misconception also aids in minimizing the participant’s vulnerability to manipulation, because manipulation can occur when a participant’s autonomy is undermined by therapeutic misconception and a confusion about the roles of the clinician scientist.

Sheppard suggests that, in order to remedy the issue of therapeutic misconception, consent forms and verbal communication with participants should use specific vocabulary to clarify the intentions of the experiment. She recommends that words such as “experiment” be used over words like “treatment,” so as not to lead a participant to associate the research with clinical practice (129). It is necessary that, when participants are giving consent to join a clinical trial, they do not believe that they are giving consent for a medical treatment. If participants believe that they are giving consent for a treatment, that is not genuine consent for a clinical trial (129).

What is novel about my concern for therapeutic misconception is the explanation of its inappropriate nature through the concept of unethical manipulation. In Western bioethics, if a participant has not given voluntary, informed consent to take part in the trial, then their consent is
not valid. However, stating that a participant’s consent is not valid does not point to any specific wrongdoing. It is possible that the consent is invalid based on reasons beyond the clinician scientist’s control, such as a participant being pressured by family members, which would mean their consent is not truly voluntary. The clinician scientist might not be aware of this fact when accepting the participant’s consent, and they may believe that the consent is voluntary. If a clinician scientist is aware that a potential participant is under duress from a third party to consent to the trial, the clinician scientist has a duty to view that as involuntary, and to not accept the participant’s consent (Declaration of Helsinki A.8). Regardless of who has caused the participant’s consent to be involuntary, the clinician scientist is responsible for safeguarding the participant’s autonomy. This also applies for concerns surrounding manipulation of the participant.

A participant might be manipulated into consenting to a trial due to an exploitation of their vulnerability. Concerns regarding the power imbalance between health care professional and participant in clinical trial settings, due to the health care professional being an expert, and being perceivably healthy, whereas the participant is not, can be explained through the lens of manipulation. There is already a general concern for this type of manipulation between clinician scientist and participant in Western bioethical guidelines. My claim is that this concern needs to take an explicit step forward and consider other social and cultural aspects that cause imbalances of power that could lead to a similar outcome of participants being manipulated by clinician scientists due to their personal identities.

If there is a goal in Western bioethics of maintaining a form of consistency across guidelines and regulations, it is important that the concern about power imbalances in relationships be extended beyond the relationship between researcher and participant by virtue of their statuses as researcher and participant, but also to include power imbalances that might occur due to social
factors, such as the power imbalance between men and women in social situations where one
gender is given more social power or privilege than another.

Oppression, Autonomy and Self-Trust

Carolyn McLeod and Susan Sherwin write about the effect of oppression on one’s ability
to exercise their autonomy, which relates to the concept of ego depletion. They claim that “many
have diminished ability to exercise autonomy as a consequence of their experiences as members
of oppressed groups,” while also placing the caveat that “not every person who belongs to one or
more groups that is subject to oppression is incapable of exercising autonomy” (260). McLeod and
Sherwin focus on the oppression of women and how oppression undermines a woman’s ability to
make certain medical decisions completely autonomously in the case of substance abuse. Instead
of using ego depletion, McLeod and Sherwin explain this diminished autonomy through the lens
of self-trust, stating that self-trust is needed for a full exercise of autonomy and oppression can
cause self-distrust (263). I relate this to the concern for ego depletion because McLeod and Sherwin
state that oppression can cause a type of social deprivation (262), which relates to Cholbi’s concept
that lower resources can cause ego depletion. Earlier in this chapter I gave an account of relational
autonomy in contrast to agency where autonomy accounts for one’s capacity to self-govern and
agency refers to the exertion of this will. Later in this chapter, I will expand upon McLeod and
Sherwin’s work surrounding oppression and self-distrust in relation to gender dynamics and how
this relates to my use of ego depletion. What I will take from these claims is that a diminished
autonomy requires some care from those who are meant to promote autonomy in order to restore
full autonomy. A diminished autonomy does not indicate an inability to be autonomous or a
requirement of paternalism.
Vulnerability to Manipulation

McLeod and Sherwin’s concept of self-distrust diminishing autonomy, especially as I have related it to ego depletion, points again to a vulnerability to manipulation of those who have been oppressed and have a diminished level of self-trust. If ego depletion can cause a vulnerability to manipulation as Cholbi describes, and social oppression causes self-distrust that acts similarly to ego depletion, social oppression can cause a vulnerability to manipulation that is situational for those who are socially oppressed. In the following section I will outline the social situation of the United States during the ACTG 076 trials and point to a few areas of social oppression that could have affected participants of the ACTG 076 trials. My goal in this next section is to demonstrate that the social oppression that occurred in the US at the time of the trials might have caused participants’ vulnerability to manipulation.

Oppression in the United States during the ACTG 076 trials

In this section I have outlined the definition of ego depletion and how it manifests in people who are faced with external oppression. The case study of ACTG 076 that I have chosen to analyze in this thesis was conducted in the United States from 1991-1993. For that reason, I will be outlining the relevant factors of oppression in the United States during those years. ACTG 076 was designed to study the effects of zidovudine in presenting mother-to-child-transmission of HIV, requiring that participants in this study be pregnant women infected with HIV. For this reason, I will outline the nature of oppression against women in general, pregnant women, and people with HIV within the United States in the 1990s. After describing the nature of this oppression, I will explain how oppression against these identities contributes to the potential for ego depletion in these individuals and how that can make them vulnerable to manipulation.
Gender Oppression

One of the situational oppressive elements in the United States in the early 1990s was that of gender oppression. As I had noted above with the power imbalance between researcher and participant, the element of gender might add to an imbalance that was already existent due to the researcher being more knowledgeable, healthier, and socially respected than a participant. If women live in a society where medical decisions are not commonly their own, they might be inclined to agree to a clinical trial without considering all the necessary factors first. Depending on the social convention, the women might want to defer the decision to enter the trial to their family members. This deference might be culturally appropriate in many non-Western contexts, but for Western bioethics, it is necessary that the potential participant as an individual gives voluntary informed consent without pressure from others. In the first part of this section, I will give a brief description of the written consent forms that were presented to the potential participants prior to their enrollment in the ACTG 076 trial in the United States. After the description, I will give my analysis about the potential for ego depletion in the participants due to their being women in the United States in the 1990s and give an analysis about the participants’ vulnerability to manipulation based on their potential ego depletion. For the purposes of this thesis, I will be considering gender oppression in the case of cisgender women and I will not examine the differences in gender oppression against transwomen or other genders.

The consent process of the ACTG 076 trials required the father of the fetus to also consent to the enrollment, if he was readily available. In the US trials, there were two versions of written consent forms given to the patients. The first was a set of two separate consent forms, one subtitled “mother’s consent form” and the other subtitled “father’s consent form.”. In the second set of consent forms, these two have been combined into one document to be signed by both mother and
father of the unborn child. First, I will give a brief description of these consent forms and include some analysis about therapeutic misconception before moving on to demonstrate why I assert that the wording in the consent forms perpetuates gender oppression of the culture in which the trials take place, in this case, the United States.

The “mother’s consent form” first explains the purpose of the consent forms, then the nature of the study, which includes information about the illness such as “your baby may become HIV-infected during pregnancy, at delivery, or shortly after he/she is born,” and information about the treatment zidovudine (ZDV) such as, “ZDV has been shown to prevent the growth of HIV in adults and children infected with the virus.” Next, it describes study procedures, which includes information about randomization and placebos. In this section, there is a statement that says, “neither you nor your doctor will know which treatment you are assigned,” and later “If your baby is unable to tolerate fluids at 12 hours, the medication will be given intravenously.” This wording of “doctor,” “treatment,” and “medication” is language that Sheppard suggests can increase the likelihood of therapeutic misconception, leading the potential participant to consent to the trial because they believe that they are receiving treatment, even if they receive the placebo, by referring to both the active ZDV and the placebo as “treatment” or “medication.” Following this, are descriptions of the risks to the participant, risks to the fetus, risks to the baby, benefits to the participant and the baby, among smaller details such as confidentiality.

The “father’s consent form” is virtually identical to the mother’s, with relevant changes in wording like “your partner and your baby” in place of “you and your baby.” This means it contains statements such as “you may withdraw your permission to allow your baby to participate at any time,” to indicate that the father is providing consent for his baby. Upon my first reading of these forms, I interpreted the term “baby” on the father’s consent form to indicate a child that has been
born. This would mean that the father does not have the ability to remove the consent of the participant while the child is still a fetus in utero. There is also mention of “risks to the fetus” and “your unborn baby,” which strengthened my interpretation that “baby” is being used in contrast to “unborn baby.” However, when the consent forms were combined into one, there were additions. One of these additions reads “the father of your baby may refuse to give his consent, and this would prevent you from participating in the study.” The combined consent forms clearly show that the father has veto power over the mother’s participation in the trial. I find that the combination of these consent forms, indicating that the father can withdraw consent for the mother of his child is a reflection of the social atmosphere of the United States at the time of the trial, which held some tolerance of gender oppression of women, where men have power over women’s bodies, or at least the ability to gain power over a woman’s body.

At the time of the trials, in the United States of America, women were at a social and political disadvantage to men, including the oppression of women’s bodily autonomy. The year 1993, when the US trials finished, also marked the year that all US states criminalized ‘marital rape’ (Paquette 1), meaning that the women participating in the trials became pregnant during a time in which it would be legal in some parts of their country for men to rape their wives, potentially causing pregnancy. The culture of tolerance of violence against women perpetuated by men, and the historical ability for violence to be perpetuated legally, contributes to the gender dynamics of the culture in which the study was taking place. The fact that the combined consent forms gave fathers the ability to withdraw the mother’s consent, not just their own child’s, shows, in part, a lack of sensitivity to the cultural gender dynamics of the country at the time. Because the consent forms were created by US organizations, the control given to the man over the woman’s body was perhaps more than a lack of sensitivity to the culture, but rather a reflection of the culture
itself. Due to these laws and customs that allow for violence against women to be perpetuated by men, there is a clear power imbalance as it pertains to gender, contributing to the vulnerability for manipulation of some women who live in the culture.

The year 1993 was also eventful in the way of anti-abortion activism. Two prominent OBGYNs were shot, one fatally, for their practice of performing abortions. Dr. David Gunn was fatally shot in March 1993 by an anti-abortion activist (Lithwick “The Murderer”). Later that year, Dr. George Tiller was also shot by an anti-abortion activist (Stumpe and Davey “Abortion Doctor Shot”). This was not Dr. Tiller’s first time being a target of anti-abortion violence, as his clinic was the target of one of the series of bombings that occurred in the 1980s (Stumpe and Davey “Abortion Doctor Shot”). Years later, Dr. Tiller would be fatally shot by yet another anti-abortion activist for the abortion services that he performed and defended (Stumpe and Davey “Abortion Doctor Shot”). The atmosphere within the United States during the time of the trials was not one that promoted the reproductive rights of women, or their bodily autonomy, and demonstrated a real, physical risk for women seeking abortions and for those who try to promote women’s autonomy. McLeod and Sherwin explain that this limitation of options, placing women in a “double bind” is a demonstration of their oppression (261). In this case, the double bind is between choosing to carry a pregnancy to term and risk health issues, or to seek an abortion and risk physical threat or verbal abuse. Furthermore, this oppression “may shape agents’ values and desires in ways that undermine their capacity for autonomous choice in certain matters” (261). Oppression can contribute to a woman’s ego depletion, especially in a case where her bodily autonomy is pitted against the ability of a man to revoke that autonomy. As with the other examples, the ego depletion of the women in the society is not universal or a necessary outcome of oppression. It is possible that the self-distrust that comes from oppression can apply only to
specific situations and not to all situations (McLeod and Sherwin 264), or that some women are not affected by these instances of oppression.

Gender oppression can cause ego depletion because the social oppression of women in the United States places an external constraint that limits social resources available to women in the society. For example, if a woman infected with HIV wishes to avoid infecting her fetus, she might consider terminating the pregnancy as one of her options. However, if she lives in the United States in the early 1990s when abortions are legal but can be difficult to obtain due to violence against doctors who perform abortions, or even dangerous to obtain due to violence against abortion clinics en whole, the woman might consider abortion to be a less reasonable option than if it were safe and easy to obtain. The woman is now attempting to make an autonomous decision about the best way to act while being HIV positive and pregnant, but her resources are limited, and she is working within the external constraints of the socially oppressive society. This fits the criterion for ego depletion of drained mental strength due to acting within external constraints. Again, it is important to note that not all women who face these types of decisions will be constrained in the same ways, not all women who are constrained will be ego depleted, and not all women with ego depletion will be manipulated into making their next decision. However, I think that it is important to focus on social oppression and individuals who belong to oppressed groups when examining the potential for ego depletion, rather than trying to determine if an individual is ego depleted due to factors other than social oppression.

**Pregnancy**

Pregnancy can be its own cause of ego depletion. Considering the factors of power dynamics and gender, pregnancy compounds the vulnerability of participants in a way that would not be experienced for the same women had they not been pregnant. This compounded oppression
provides further support for the case of considering the women in the ACTG 076 trials as situationally vulnerable to manipulation.

In the Western medical field, pregnant women have been intentionally excluded from participating in clinical trials that are not about pregnancy itself (Welch et al. 4). This points to the possibility that clinician scientists and those designing the trial would not have a lot of experience considering the unique needs of pregnant women in clinical research. It also demonstrates social oppression of pregnant women manifesting in the medical field. One main reason that pregnant women have been excluded for so long is a fear for the safety of fetuses (Lyerly et al. 8). This common rhetoric of protecting the fetus from the decisions made by the mother could shape how many people view the ability of a pregnant woman to make informed decisions for herself, another example of social oppression. The medication being tested in the ACTG 076 trials that I have chosen to analyse does not directly benefit the pregnant woman, although it needs to be administered to her until her child is born. Benefits from preventing transmission of HIV would be the decreased likelihood of medical concerns for the child, avoidance of continuing stigma, and a psychological ease that one’s child is born as healthy as possible. I illustrate the focus on the fetus to further emphasize that the exclusion of pregnant women from medical research could hinder the discourse around supporting a pregnant woman’s autonomy. With a focus on the health of the fetus and a belief that the pregnant woman is a threat to her own fetus, a pregnant woman’s autonomy might be deprioritized.

Maria Kreszentia Sheppard cites findings from British and German studies that interviewed pregnant women about their decision to enroll in a fetus-regarding trial, on their opinion about enrolling in a trial. These studies found that, in the German interview, “almost all women would participate in a trial if it was for the benefit of the fetus. Even if there was a risk to themselves,”
and in the British interview, “most women believed” that they were not at risk while participating, despite being informed of the risks before consenting (Sheppard 128). In the trials I have analysed above, the women benefited from the outcome in a less direct way. The goal of the intervention was not to suppress their HIV so that they can live healthy lives, but rather to suppress it long enough that their children would not be infected from birth. The women benefit from these trials by the potential for giving birth to an HIV negative baby, which means fewer health issues and expenses that may go along with an HIV positive child, and less psychological strain that would come from having an unhealthy baby. Not all clinical trials involving pregnant women are designed with this focus in mind.

The tendency for pregnant women in the Western world to overestimate the benefit of clinical trials for their fetus and underestimate the risks to themselves indicates a potential for ego depletion. I have previously characterized ego depletion as having an effect of drained mental strength due to coping with external constraints that override responses, making decisions to benefit the short term rather than long term, and deferring decision-making to others. In this case, we can see that women in the US might have drained mental strength due to coping with external constraints such as lessened social support for pregnant women and their autonomous choices, as well as external constraints that come from the social oppression of women. The worry is that the women in British and German medical trials who perceived the risk to themselves as minimal could have been making decisions based on short-term benefits or deferring their decision-making to an authority such as the medical professional who told them about the trial. The potential for ego depletion of pregnant women due to social oppression is where I place the concern that pregnant women could be vulnerable to manipulation, that they might make decisions about entering into medical research without fully engaging in their own rational capacities.
HIV Status

Being HIV positive carries with it a lot of stigma. Social stigma is contingent on the community in which one lives as it can manifest itself quite differently in different places. Overall, having an incurable disease with attached stigma can contribute to one’s potential for ego depletion. Included in the common bioethical concerns over the power imbalance between researcher and participant is the compounding of the power imbalance because one is ill and vulnerable to the researcher. A researcher might be in a position of power over a participant because the researcher is a medical expert and the participant wants to defer to that expertise, but also because the researcher is well, and the participant is ill and looking for answers. This imbalance is compounded further by different types of illnesses, due to their ability to be treated easily, and the stigma that they carry.

It is important to note that HIV is not a curable disease because the incurability means that it could make people more desperate for help than they would be if they had various treatment options and cures available. Sheppard cites particular vulnerabilities of trial participants that could relate to their situations. If a participant is medically vulnerable, it is because their condition is serious and not currently treatable. Patients may have ego depletion caused by their experience with medical professionals because they do not have the ease and comfort that would be given to participants who have other options (Sheppard 128). The type of vulnerability that the HIV positive participant has is partially inherent because it is a vulnerability that exists by virtue of a condition that the participant has that cannot be cured, but it is also situational because HIV might one day have a cure, and the stigma associated with HIV is also not permanent.

A 2009 Public Agenda report stated that many US citizens still believe that the contraction of HIV is related to personal behaviour and responsibility (18). The report states that there is more
sympathy among the focus group participants for people who contract HIV in a way that could not possibly be their fault, such as being born with it, than there is sympathy for those who contract HIV as a consequence of some sort of action that they took such as recreational intravenous drugs. The participants did show a general unhappiness about the existing stigma surrounding HIV, however, there was still a strong belief that demographics who were more likely to contract HIV were that way because they participate in more risky behaviour (18). The stigma surrounding HIV has changed over the years in the United States and has been shaped differently in other cultures and countries. It is important for the clinician scientist to recognize the common beliefs around HIV in the culture in which they are conducting the trial in order to better understand the possible social situation of the participant.

I had mentioned earlier that Western bioethics has taken great care in considering the power dynamic that is developed between a healthy researcher and a sick participant, but that does not mean the consideration of the power imbalance can account for the amount of stigma attached to HIV. It is one thing to be vulnerable to a clinician scientist because you have cancer, a disease that many find to be worthy of special attention and a cure. It is another to be vulnerable to a clinician scientist because you have HIV, a disease that many may believe you contracted because you made bad decisions, and that you are less worthy of being healed or cured because the illness was a fault of your own. If we wish to be consistent with present standards of Western bioethics, factors that cause vulnerability to manipulation such as social stigma around illness should be considered relevant to the consent process just as the power dynamic between clinician scientist and participant is carefully minded.

HIV stigma demonstrates ego depletion because the stigma can place a constraint on the individual’s ability to respond to their situation, similar to the psychological experiment that
required individuals to suppress their thoughts of a white bear. If an individual must override their natural responses in a way that drains their mental energy, causing ego depletion, then they might be more prone to make decisions based on the short-term rather than the long-term, or defer their decision-making to others, which devalues their autonomy. HIV stigma can contribute to or cause an individual to be ego depleted because of this drained mental energy.

In this chapter I have defined relational autonomy, separated the concept of relational autonomy from agency, defined ego depletion, explained how ego depletion can cause one to be vulnerable to manipulation, defined power and power relationships, explained the concepts of oppression and self-trust, and analyzed the case of ACTG 076 through the lens of oppression and ego depletion causing a vulnerability to manipulation. My analysis examined the elements of illness, gender, pregnancy, and HIV status of the participants in the ACTG 076 trials in the United States and I have explained how the oppression of women in general, pregnant women in particular, and people who are HIV positive within the United States at the time of the trial has lead me to believe that participants of ACTG 076 were likely at risk for ego depletion and vulnerable to manipulation by the clinician scientists. This does not indicate that the participates were manipulated by the clinician scientists, but the existence of this vulnerability indicates a need for action on the part of the clinician scientists to prevent the likelihood of manipulation of the participants from occurring. I have also indicated that there is at least one flaw in the written consent forms that were presented to the participants of ACTG 076 that might not have occurred if the trial designers, research ethics board, and researchers were actively aware of the concern over manipulation and were trying to take steps to avoid manipulation of the participants by fostering autonomy instead.

There are many other important factors to consider outside of the four I have examined
above. I did not analyse concerns about socioeconomic status, race, gender identity, sexuality, disability, language, marital status, or others, because these elements were not core to the case at hand. All of the participants in the US trial were pregnant women infected with HIV. It was not necessarily the case that clinician scientists were of a different race than participants as there were clinician scientists from multiple backgrounds involved in the trials. It was also not necessary that the participants were transgender, gay, disabled, or had other socially oppressed identities. Although individual participants may have had other factors of concern, this analysis was meant to focus on the factors that were known and necessary for the trial participants and the design of the trial.

I do not intend my claim to be that all the participants of the ACTG 076 trials are always being manipulated and that they are incapable of engaging with their rational capacities to make decisions about their own lives. I do not intend to say that a vulnerability to manipulation always results in manipulation, or even that it is easy to spot a case of manipulation in clinical research. The oppression and vulnerability of the participants of ACTG 076 is compounded on top of their illness due to the other factors of, gender, pregnancy and HIV being present at the same time, whereas other individuals might only face oppression in one aspect of their life, such as gender. My claim in this thesis is that, because all of the participants in these clinical trials were pregnant women infected with HIV, and because being a pregnant woman infected with HIV participating in a clinical trial makes one more vulnerable to manipulation than other common clinical trial participants, the trial should be designed, and clinician scientists should act, in a way that reflects these vulnerabilities and promotes participant autonomy, rather than contributes to participant oppression and vulnerability.

In the next chapter I will make suggestions for research ethics boards about how to spot
potential vulnerability to manipulation in a clinical trial design and elaborate more on what the responsibilities of the people in power are to lessen the negative effect of the power imbalance. Some of my suggestions will come from suggestions made by Catriona Mackenzie in relation to situational and inherent vulnerabilities, as well as suggestions made by McLeod and Sherwin in relation to the promotion of autonomy in oppressed groups. I will also draw on suggestions made by Baumeister and others who give psychological explanations of ways to counteract ego depletion in an individual.
Chapter 3- Applying Analysis to Future Research

This is my third and final chapter. In this chapter I will make recommendations about the changes in ethical guidelines and research practices that need to occur to avoid the manipulation of clinical research participants. In the first two chapters I defined the term manipulation, situated it in relation to the similar terms of coercion, force, exploitation, and persuasion, and the importance of examining manipulation instead of these other terms. I focused on the concept of ego depletion within the definition of manipulation to show how social oppression and power imbalances in social and medical contexts can lead to the manipulation of participants in clinical research.

I have chosen to focus my concern of unethical manipulation on the case of pregnant women infected with HIV because only recently in Western medical literature has the discussion of including pregnant women in clinical trials become available. The ACTG 076 was a useful case study for a starting point because it has been heavily criticized from different angles, but I have yet to see a focus on the concern for manipulation, so this case points to a gap in bioethical discussions. From there, I can extrapolate to other case studies involving pregnant women and the recommendations can be adjusted based on the particularities of the illness being treated or the prophylactic. In this chapter, I will use Catriona Mackenzie’s definition of vulnerability and her recommendations about the duties that society has to vulnerable individuals as a starting point for my recommendations about the proper treatment of clinical research participants who are vulnerable to manipulation because of their social disadvantages.

Current Guidelines and Literature

As I have demonstrated in previous chapters, the current guidelines and literature surrounding Western bioethics in clinical research cannot properly account for the concerns that I
have raised about manipulation. In the latest Tri-Council Policy Statement (TCPS 2) and the Council for International Organizations of Medical Sciences (CIOMS) research guidelines, the term “manipulation” is mentioned, but not defined, and mentioned so infrequently that one cannot easily extrapolate an implied definition that is clear and distinct from similar terms. The guidelines instead touch on issues such as vulnerable participants, which I believe takes the focus away from the actions of wrongdoing against a participant and places the focus on the characteristics of the participants alone. It is not enough to say that a participant is vulnerable, we must also place focus on what actions of wrongdoing might occur against the participant in part due to that vulnerability. Throughout this thesis I have argued that manipulating a participant undermines their autonomy in a way that is prima facie unethical and inconsistent with the duties of a clinician scientist in Western bioethics. Specifically, the duties of the clinician scientist to uphold or promote the autonomy of the participants in clinical trials. For that reason, I have chosen to focus on the threat that manipulation has to one’s autonomy in clinical research and shed a light on the harm that manipulation might allow.

In addition to Western medical research guidelines, Western bioethical literature also has a blind spot in the area of examining manipulation. For the case of ACTG 076, most of the criticism came against trials that took place years after and in low-and-middle income communities across the world (what I called “B trials”). The criticisms that were widely known, focused on the fact that the ACTG 076 trials had already developed a treatment regimen to decrease the transmission of HIV from mother to child by two-thirds, creating a standard of care, but the B trials were conducted with placebo controls, rather than a control group using the standard of care. As I pointed out in previous chapters, this literature did not mention concerns over manipulation, but rather issues of double standards, exploitation, or even coercion.
Guidelines and literature that focus on concerns such as coercion cannot account for the subtleties of manipulation because coercion is defined by an explicit threat of harm to one’s baseline wellbeing such as a general practitioner threatening to terminate the individual as a patient if they do not agree to participate in medical research. Cases of coercion are very uncommon in Western clinical research and not the only concern for compromising autonomy, that is why I have chosen to focus on the concern of manipulation.

Who is Responsible?

My analysis of the ACTG 076 case brought up concerns of ego depletion, power imbalance, and vulnerability to manipulation. As it pertains to illness causing situational vulnerability, this concern has been addressed previously in medical literature and there have been guidelines and recommendations created that reflect an attempt to promote a patient’s autonomy when it might be diminished by the situational vulnerability that is caused by their illness. My concern about perpetuating gender oppression in ACTG 076 was based on the consent forms allowing the father of the fetus control over the mother’s ability to consent to the trial while pregnant. The concern about HIV status was based on social stigma in the United States surrounding HIV. My next step is to determine the party or parties responsible for counteracting ego depletion and reducing vulnerability to manipulation of potential trial participants similar to those in ACTG 076. Catriona Mackenzie suggests that vulnerability of certain kinds requires action on the part of society (or the state) to remedy the circumstances that make one vulnerable (34). This is especially true if the state contributes to vulnerability of the individual. Mackenzie attributes this to Robert Goodin who “proposes that the duty to protect the vulnerable falls on anyone who is in a position to assist but most especially on those to whom a person is most vulnerable,” meaning that an authority like the political state holds “special responsibilities toward
those over whom they have power or who are particularly dependent on them” (Mackenzie 14). Placing some responsibility at the state level can have the effect of counteracting the social oppression that can lead to ego depletion or vulnerability to manipulation in the first place.

Throughout this thesis I have also referenced the need for trial designers, research ethics boards, and clinician scientists to be aware of the concept of manipulation, how it affects clinical research, why it is important, and to perform reasonable action to prevent a situation in which a participant might reasonably be manipulated into consenting to or remaining within the trial. Although it might be intuitive to some why I have chosen these individuals as the ones who have the duty to prevent manipulation in clinical research, it is important to spend at least a brief mention of why this is the case. In this section, I will give a brief explanation for why I chose the actors of the state, the trial designers, the REBs and the clinician scientists as those who are responsible, and in a later section I will explain what they should do with their responsibility.

State

The state, in the case of the United States of America, holds some responsibility to prevent or counteract the situational or pathogenic vulnerability of the citizens that might be caused by social oppression such as gender oppression, or HIV stigma. I had mentioned that 1993 marked the end of the ACTG 076 trials and also the year that ‘marital rape’ became illegal in all 50 US states. This is an example of a state action that took place to reduce the vulnerability of women in the US by allowing them to take legal action against their potential abusive husbands. Unfortunately, this legal change was not likely to have benefited all of the early participants of ACTG 076, which is why I cited it as a factor contributing to the potential vulnerability of the participants, but it is a change that could benefit women as future potential trial participants and reduce their potential for vulnerability to manipulation. This is only a first step in decreasing the
possibility of manipulation of participants in clinical research as it simply addresses the issue of vulnerability, but not the actions of the clinician scientists.

**Trial Designers**

The researchers responsible for designing the trial currently have the duty to ensure to the best of their ability that trials hold scientific validity and respect the pillars of Western bioethics, among other factors. The Declaration of Helsinki states that “the research protocol should always contain a statement of the ethical considerations involved,” (B.14) suggesting that the concern about ethics begins when the study is being designed, and it is the responsibility of the researchers who submit the study to the research ethics board to have already considered how the study can be conducted ethically.

**Research Ethics Boards (REBs)**

Research ethics boards unsurprisingly have a strong interest in determining the potential for ethics violations based on a study design. This includes ethical considerations of justice and beneficence in relation to the scientific validity of the trial and the target group of participants in the trial overall. The REB also reviews the proposed consent forms and considers the autonomy of the individual participants. In this process, they look for facets of the trial that might seem coercive or unethical for other reasons. It is, therefore, their responsibility to also consider the potential for manipulation based on the study’s design and to advise the researchers of any aspects that might seem concerning.

**Clinician Scientists**

The clinician scientists are responsible for maintaining the well-being of the participants during the study. This includes protecting the physical health of the participant as well as their autonomy. I do not expect clinician scientists to be personally responsible for analysing the
vulnerability to manipulation of each individual participant or potential participant, but rather, added on to their expectation of assessing the participant’s ability to consent to the trial, they should follow an established protocol that reflects the needs of the target participant group. For example, Phase I clinical trials generally do not involve experimental medications being tested on participants with the illness that is meant to be treated. In this case, it would not be necessary for the clinician scientist to be informed of the vulnerability of a potential participant with HIV if the participants are expected to all be relatively healthy. Perhaps it is still possible that one or two participants have HIV because that is not a condition that will exclude them from participating, but their status is not relevant to their participation in the trial and the clinician scientist can not be faulted for not considering this a factor in their vulnerability to manipulation, but should be aware of the factors that are relevant to their participation, like a case where all participants are women.

Analysing Power Dynamics

A difficult step in the process of determining what responsibilities a clinician scientist has towards participants is first to determine what exactly the nature of the relationship is in terms of power. For example, *is the power imbalance significant? Is the power imbalance structural?*

*Is the Power Imbalance Significant?*

This question seeks to analyse the degree of difference in power. You can imagine a ranking system from one to ten, where ranks that are closer together are virtually the same, but the difference between one and ten is very noticeable and provides significant outcomes. The significance of the power imbalance is important for the analysis of one’s vulnerability to manipulation. I have previously stated that power imbalances can make one vulnerable to manipulation due to ego depletion and that ego depletion can diminish one’s ability to engage their rational capacities, making them prone to manipulation. We can imagine a scenario in which a
power imbalance is not significant enough to diminish one’s rational capacities, so the power imbalance does not make them more vulnerable to manipulation.

For example, if I work as an employee in an office where there is one managerial boss and ten employees, and each employee has a different set of responsibilities, but the managerial boss has the final say over all work-related decisions, then the power imbalance between me and my co-worker might not be significant enough to influence my rational capacities. I might be consciously aware that my co-worker has the ability to overrule my decision to paint my office green, but if she is unable to change the hours that I work, and she is unable to fire me or reprimand me for performing improper work, then the power imbalance that exists between our work interactions is not very significant.

Is the Power Imbalance Structural?

This question takes into consideration concrete institutionalized differences such as the imbalance between a citizen being legally capable of voting in a democratic government and a non-citizen who is not legally able to influence government in that way. It also considers social differences such as the difficulty a single mom may face when looking for a job because there are few resources for her to ensure her children are looked after while she is at work. This power imbalance may not be clearly written into legislation or policies, but it is a real struggle that she may face in certain societies.

Power imbalances that are not structural are ones that are more context-based. Like the power I may hold in my family setting. Being the youngest child in Canadian society does not meaningfully determine how much power I may hold in a family, but perhaps my family believes that the youngest child must always be given first choice in family decisions, and their decision must be respected. In this way, I could be said to hold power over my older siblings due to a social
belief, but because the belief is only shared by my family, it is not structural.

Structural power imbalances hold more weight because they reflect the instability or injustices that might exist within a whole society. For example, the power imbalances between Indigenous Peoples and non-Indigenous Peoples in Canada exist because of a history of unjust political practices by European-Canadians that forcibly places Indigenous Peoples at a disadvantage. Structural imbalances affect many aspects of a person’s life and shape their interactions with the rest of society. It can also be noted that non-structural imbalances are likely more difficult for outsiders to determine, making it unreasonable for us to expect them to be sensitive to these issues.

Including Pregnant Women

There have been recommendations about the inclusion of pregnant women in clinical research recently such as: amending research ethics guidelines that do not yet require the inclusion of pregnant women to reflect the importance of their inclusion (Baylis and Halperin 142), increasing funding of studies on pregnant women who already take medication not previously tested on other pregnant women (Lyerly et al. 8), and treating pregnant woman as complex, rather than vulnerable (Foulkes et al. 1429). These recommendations point not only to the marked lack of inclusion of pregnant women in clinical research, but also to the gap in guidelines between the ethical treatment of non-pregnant adults and the ethical treatment of pregnant adults based on their different needs.

The inclusion of pregnant women in clinical research cannot be done without taking precautions not to manipulate pregnant women. Many Western bioethical guidelines have been created based on the needs of non-pregnant adults and children, meaning they might not be able to reflect the needs of pregnant women. As you might recall, I mentioned in chapter two that children
were once excluded from clinical research. You can imagine that when children were excluded, bioethical guidelines did not need to reflect the particularities of the inclusion of children such as proxy consent by a parent, or how to communicate with a child. When children began to be included in medical research there would have been a much clearer gap in the guidelines and literature about how to ethically treat their inclusion than the gap that exist now for pregnant women, but the gap does still exist. In order to respect all populations, we need to be aware of their particular needs.

Going forward with the inclusion of pregnant woman in clinical research, it is important to ensure that their inclusion comes with a recognition that pregnant women could be situationally vulnerable to manipulation or ego depleted due to the social oppression of women in general and pregnant women in particular in the United States. In the next section “What Should be Done?” I will mention some changes that could take place in guidelines and protocols that are an attempt to address the issue of including more pregnant women needing to come with a larger push for ethical guidelines that include the particular needs of pregnant women.

What Should be Done?

In the previous sections I identified the state, trial designers, REBs, and clinician scientists as being in part responsible for ensuring that there is a reduction in the vulnerability to manipulation of participants in clinical trials. I have also given some suggestions about how to identify power imbalances that might be between clinician scientist and participant in the trials, as well as looking at how to include pregnant women in clinical trials in a responsible manner. In this section, I will make suggestions about what each of those responsible groups should do in the future because of their responsibilities and based on the suggestions about power imbalance and the proper inclusion of pregnant women.
State

The state is responsible for preventing or counteracting one’s vulnerability by ensuring social and political justice such as demonstrated above with the case of the United States completely criminalizing the rape of women by their husbands. The state also has responsibilities more directly related to bioethical guidelines for clinical research by signing international guidelines and creating laws that enforce these guidelines. In the case of avoiding the manipulation of participants in clinical research, the state could be responsible for a diverse range of things. Firstly, the United States arguably does not have equal rights for all genders, or equal protections of these rights. In order to decrease the social inequality between men and women in particular, the United States government, or at least individual state governments, could place a larger focus on protecting women who report sexual harassment at school or work, allowing women a better chance to feel comfortable in professional environments and giving them a better chance to succeed in their work. If the social inequality between men and women in the United States diminishes, women’s vulnerability to manipulation is reduced by a few factors. Those factors are a reduction in ego depletion that can be caused by the external constraints on one’s will when they are part of an oppressed class in society, and a narrowing of the power imbalance between men and women in a public setting. Starting at the basics with the state, we can see how changes to structural concerns that cause oppression and power imbalances can begin to protect potential research participants from vulnerability to manipulation.

One thing that states could do that would address issues of ego depletion for women in clinical trials is to mandate that there will be childcare provided for participants of clinical research. This step would allow participants, women in particular, to freely participate in clinical research and focus on the trial rather than needing to worry about finding alternative care, making decisions
under time constraints due to day-care pick up times, or other concerns about their child.

Another possibility is a state protection for those who work while participating in clinical research. If one knows that they cannot be fired or given poor performance reviews for the time that they must take off to participate in clinical research, they are also less likely to feel constrained by the circumstances and are less likely to be ego depleted when attempting to participate in clinical research. This affects all participants with jobs, but is particularly important for low-income people, or pregnant women who might face stress in relation to deciding how much time to take off of work for childbirth and care, depending on what their state and job allows.

*Trial Designers*

It is important for trial designers to be aware of the potential for manipulation in the clinical research that they propose. Currently, trial designers must include an ethics statement indicating that the research complies with the Declaration of Helsinki (B.14). Since the Declaration of Helsinki does not mention concerns of manipulation, the ethics statement provided by the designers would not need to contain any mention of consideration for manipulation of participants. It is my suggestion that the trial designers need to include a mention of manipulation in this ethics statement to prevent the manipulation of participants. This statement could include a mention of the factors of participants that might lead to ego depletion or situational vulnerability. For example, if the trial plans to enroll pregnant women to test the effects of anti-depressants on pregnant women, then the trial designers’ ethics statement should mention the potential for ego depletion of pregnant women who live in a society that restricts their freedom, and how the trial intends to take that potential for ego depletion into consideration so as not to manipulate the participants.
Research Ethics Boards

Just like the trial designers, REBs need to be aware of the potential for manipulation and the reason it is a serious issue in clinical research. REBs are responsible for ensuring that a trial is designed in a way that is ethical and follows the current ethical guidelines. That means that they are not looking out for concerns of manipulation. A possible step forward for REBs is to use a fact sheet that lists key elements in the concern for vulnerability and manipulation. For example, if an REB comes across a clinical research proposal that would usually raise concern about vulnerability such as participants who are exclusively pregnant women, the members could refer to a fact sheet that prompts them to consider the power dynamics between the clinician scientists and the potential participants due to the social atmosphere of the location of the trial. If the REB agrees that there is concern for manipulation due to a significant power imbalance, the fact sheet would prompt them to check the research proposal for considerations about this power imbalance and what safeguards, if any, are put in place to reduce the potential for manipulation.

Clinician Scientists

In chapter two I stated that therapeutic misconception might be greater for pregnant women in fetus-regarding trials such as ACTG 076 because of social pressure that might encourage pregnant women to place the health and safety of their fetus above their own. One might be manipulated into consenting to a trial if they believe that the trial holds more promises than it truly does. Dr Sheppard suggests that, specifically for fetus-regarding trials that exist as the only viable option for a woman to potentially treat her fetus’ health concern, “an extended discussion between the researcher and the research participant is much more likely to improve understanding than any improvement to the consent form” when women are under stress and worried about the health of their fetus (129). Sheppard’s concern is specific to therapeutic misconception being a threat to
autonomy, but I believe that it can be applied to concern of manipulation. Sheppard insists that pregnant women are vulnerable, but her description of this vulnerability matches what I have previously distinguished as situationally vulnerable. She claims that pregnant women in fetus-regarding clinical trials, when no other treatment is available, are vulnerable due to their worry of their fetus’ ill health, which makes them vulnerable to therapeutic misconception in a way that other participants might not be, and diminishes their ability to exercise their autonomy (129). This claim is similar to mine about pregnant women, due to social norms, being more situationally vulnerable to manipulation in a way that non-pregnant people would not be, making pregnant women less likely to engage in their rational capacities and exercise their autonomy than others in similar situations. If our analyses of the situations involve similar concerns and if exploiting therapeutic misconception can be seen as an act of manipulation, then Dr. Sheppard’s solution of extended discussions with potential participants who are situationally vulnerable can apply as a way to counteract many cases of vulnerability to manipulation.

As a counter argument to Dr Sheppard’s suggestion, one might be concerned that an extended discussion with potential participants might instead cause the potential participant to trust the clinician scientist as an authority and defer their decision-making to that authority. For example, if the potential participant does not fully understand the difference between treatment and experiment, an extended discussion could have the goal benefit of providing that explanation as Dr. Sheppard suggests, but could also simply increase the potential participant’s confidence that the clinician scientist is trying to help them. If one is worried about this negative possibility, a patient advocate might be necessary.

Counteracting Ego Depletion

In chapter two I focused on the ego depletion of participants causing their vulnerability to
I outlined the effects of ego depletion such as drained mental strength due to coping with external constraints that override responses, rational decisions taking great willpower, making decisions to benefit the short term rather than long term, and deferring decision-making to others. I demonstrated how social oppression can cause ego depletion and outlined how the factors of illness, gender, pregnancy, and HIV status can contribute to one’s ego depletion. Because ego depletion can cause a vulnerability to manipulation, one way to reduce a participant’s vulnerability to manipulation is to counteract their ego depletion. Tice et al. performed multiple scientific experiments testing the level of one’s ego and how it can be replenished. Their study suggests that, when one’s ego is depleted by actively suppressing their thoughts, mood, or desires it can be replenished by positive affect caused by receiving a surprise gift, or watching a stand-up comedy clip (Tice et al. 383). Although this experiment cannot give us specific direction for how to replete the egos of clinical trial participants when their ego depletion is caused by systemic social oppression, Tice et al. have shown that the effects of ego depletion can be counteracted by the actions of others, at least in some cases.

In this chapter I have given a few suggestions for the state, trial designers, REBs and clinician scientists to begin engaging with the concept of manipulation and understanding how a participant’s vulnerability to manipulation can be prevented or counteracted. I have also suggested that Western bioethical guidelines should include definitions of manipulation and provide some context about power imbalances that might cause a potential participant to be vulnerable to manipulation. I do not claim these suggestions to be undeniable or complete and I welcome the input that others might have to this thesis.
Conclusion

By examining the concept of manipulation as well as the concepts of force, coercion, and exploitation, research trial designers, research ethics boards, and clinician scientists can better understand the actions that potentially make a clinical trial unethical by undermining participant autonomy. The examination of manipulation is important because it clearly points to a feature about power imbalances that is generally considered unethical in Western institutions that does not constitute coercion or force. The failure to counteract a participant’s vulnerability to manipulation can be seen in clinical trials that have already taken place; regardless of whether these studies were previously put under scrutiny. When beginning this project, I first set out to examine the actions in the clinical trials that came about subsequent to the ACTG 076 because they have been heavily criticized in various ways and for various aspects that philosophers and bioethicists consider unethical, but through the research of this project I came to realize that there were concerns with the original ACTG 076 trials themselves, despite a notably smaller amount of attention given to them. This shows that a concern about manipulation can lead us to find flaws in clinical research that we might have missed in the past, or we will continue to miss if we do not begin to consider manipulation an important issue going forward.

The TCPS 2 has a definition of “undue influence” which closely resembles the heart of my definition of manipulation and, therefore, is close to properly considering the factors of vulnerability to manipulation that I have presented in this thesis (Canadian Institutes of Health Research et al. 26). Undue influence in other contexts refers to a case where potential participants are offered excessive incentives in order to entice them to disregard the risks of the clinical trial and consent to participate. To avoid confusion, I believe that the TCPS 2 should opt for the word “manipulation” where it uses the term “undue influence.” This will allow the guidelines to
maintain consistency with other Western guidelines and emphasize the importance of understanding the influence that power imbalances have over potential participants and their vulnerability to manipulation.

Manipulation is also about a concern for ego depletion. One who has a depleted ego due to factors such as gender oppression or social stigma of HIV. Ego depletion can be caused by many different factors and affects different people differently. Effects of ego depletion such as: rational decisions taking great willpower, making decisions to benefit the short term rather than long term, and deferring decision-making to others explain in part why ego depletion can threaten one’s autonomy.

I began this thesis by defining manipulation as “A manipulates B iff A motivates B to make a decision or perform an action that bypasses B’s rational capacities by means of deception, emotional pressure, or exploitation of B’s ego depleted state,” which is a definition I developed after examining multiple philosophical definitions of manipulation and how they differ from similar concepts such as coercion, force, and exploitation. I have defended the need to focus on manipulation based on its distinction from these other concepts and how defining manipulation can point to an ethical wrongness that still exists beyond what can be seen from analysing the existence of coercion, force, or exploitation.
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Masters Thesis – Leanne Woodward; McMaster University - Philosophy


World Medical Association Declaration of Helsinki, June 1964, WMA General Assembly [Declaration of Helsinki].
Appendix A

Manipulation

Deception  Pressure  Ego Depletion

1  2  3

Situational Vulnerability

- Illness
- Gender
- Pregnancy
- HIV status
  (ACTG 076)

3a  →  Short-term Benefits
3b  →  Drained Mental Energy
3c  →  Deference to Authority
  3ci

Power Imbalance
Appendix B

APPENDIX XIII

CONSENT TO BE A RESEARCH SUBJECT

A MULTICENTER PHASE III RANDOMIZED PLACEBO-CONTROLLED TRIAL TO EVALUATE THE
EFFICACY, SAFETY AND TOLERANCE OF ORAL ZIDOVUDINE (ZDV) IN HIV
INFECTED WOMEN AND THEIR INFANTS

(MOTHER’S CONSENT FORM)

You and your baby are being asked to participate in a research study entitled,
"A Phase III Randomized Placebo-Controlled Trial to Evaluate the Efficacy,
Safety and Tolerance of Oral Zidovudine (ZDV) in Pregnant HIV Infected Women
and their Infants." To decide whether or not you wish to participate in this
study, you should understand enough about its risks and benefits to make an
informed decision. This process is called informed consent.

This consent form provides detailed information about the research study which
your doctor will discuss with you. Once you understand the study and if you
agree to participate, you will be asked to sign this consent form and you will
be given a copy to keep. The father will also be asked for consent if he is
reasonably available.

It is important that you understand the following: a) your participation is
entirely voluntary; b) you may decline to participate in or withdraw from the
study at any time without penalty or loss of benefits to which you are
otherwise entitled; c) your decision to withdraw from the study will not
jeopardize your future medical care or possible participation in future
research studies.

Nature of the Study:

You are pregnant and infected with the Human Immunodeficiency Virus (HIV or
AIDS). It is estimated that out of 100 babies born to HIV-infected mothers,
16 to 40 will become infected and, if infected, are at risk of dying from AIDS
within the first two years of life. Your baby may become HIV-infected during
pregnancy, at delivery, or shortly after birth. It is not known exactly when the virus can infect an unborn baby or why some babies are
infected and others are not.

Zidovudine, or ZDV, (previously called AZT) is an antiretroviral (a drug that
slows or prevents the HIV virus from multiplying). ZDV has been shown to
prevent the growth of HIV in adults and children infected with the virus. ZDV
given to mice and kittens in controlled studies suggests its safety. For the
newborn baby at risk of developing the HIV infection, the best time to begin
treatment with ZDV may be as soon as possible after birth. You and your baby
are being asked to participate in a research study to determine if ZDV given
to an HIV-infected pregnant woman as early as the first three months of
pregnancy, and continued in her infant from birth to six weeks of age, will
protect the baby from becoming infected with HIV. To make this determination,
ZDV will be compared to an inactive substance called a placebo.
Study Procedures

Prior to entry into the study, you will undergo some routine tests to see if you qualify for the study and to determine that your participation is safe for you and your baby. These tests include a history and physical examination and blood and urine tests. A sonogram will be performed to determine your baby's age and to rule out any abnormalities that may place him/her at risk for participation. A non-stress test (a recording of your baby's heart activity) will also be performed to rule out any fetal heart rate abnormalities.

If participation in this study is safe for you and your baby and you agree to participate, you will be randomly assigned (by equal chance) to receive oral (by mouth) ZDV or placebo. This means that you will have a 50% chance of receiving either a drug (ZDV) that may prevent the HIV virus from infecting your baby or an inactive substance (placebo) that has no actual effect and is used only to compare it with the active drug. Treatment will continue throughout your pregnancy. Neither you nor your doctor will know which treatment you are assigned.

You will receive oral medication five times a day before delivery. During labor, the drug will be administered continuously by an intravenous infusion (through a vein in the arm) until the umbilical cord is clamped. The intravenous drug will be discontinued after the baby is delivered.

You will undergo routine laboratory and clinical evaluations to include blood, urine, sonogram, and non-stress tests, to monitor the condition of your baby and any apparent side effects of drug therapy. The total amount of blood drawn at each visit will not exceed 1-3 teaspoons.

After delivery, your baby will be evaluated in the newborn nursery to determine his/her medical condition. If your baby is found eligible to continue the study, your baby will receive the same study drug you received. This means your baby will be given either ZDV or placebo and neither you nor your doctor will know which drug your baby is getting. The study drug will be administered as a strawberry flavored syrup soon as your baby can tolerate fluids and within 8-12 hours. If your baby is unable to tolerate fluids at 12 hours, the medication will be given intravenously (through a vein in the arm). The syrup will be taken every 6 hours for a total of six weeks. Your baby will be evaluated in the clinic for evidence of HIV infection at 1 week, 2 (or 3) weeks, 6 weeks and 12 weeks of age and every 3 months until he/she is 18 months old. Blood will be drawn at birth (approximately 1-2 teaspoon) and routinely throughout the study (1-2 teaspoon) to check for any side effects of the medication or evidence of HIV infection.
APPENDIX XIII (Cont.)

At several hospitals participating in this study, and depending on the baby’s
age, weight and whether or not he/she is taking medication for drug
withdrawal, special blood tests to study how much drug is taken into the
baby’s body will be performed. Only babies receiving active drug will
participate in these special studies. If your baby is enrolled at one of
these hospitals, the investigator will check to see if your baby is on active
study drug treatment. If your baby has been taking active drug, approximately
0.3 ml (1/4 teaspoon) of blood will be withdrawn from your baby’s vein.

This test will be repeated several times while your baby is taking medication.
The total amount of blood to be withdrawn for this test will not exceed 0.9 ml
(3/4 teaspoon). If your baby has been taking placebo (inactive drug), he/she
will be withdrawn from this medication but will continue to be evaluated and
followed.

Risks to You

The major side effect seen in adult patients taking ZDV is anemia (a decrease
in the number of red blood cells in your blood) that may cause premature
labor. A decrease in hemoglobin (the part of the red blood cell that carries
oxygen from the lungs to the tissues) and a decrease in the number of white
blood cells which could reduce your body’s ability to fight infection may
occur. Minor side effects that you may experience include nausea, vomiting
and dizziness. Blood drawing may cause some discomfort, bleeding or bruising
at the site of entry of the needle, and rarely, fainting. A small blood clot
may form or swelling of the surrounding skin may occur. There is a small risk
of infection from the blood drawing procedure.

Risks to the Fetus

Although your unborn baby is at risk of developing anemia and a low white
blood cell count, data from earlier studies suggest that the development of
maternal anemia from ZDV therapy occurs infrequently and does not harm the
newborn. The long term effect ZDV may have on your unborn baby is not known.

Risks to Your Baby

The major side effect noted in children is anemia but this usually occurs when
the drug is taken for more than 6 weeks. Blood drawing may cause some
discomfort, bleeding or bruising at the site of entry of the needle. A small
blood clot, swelling of the skin or infection may occur.
Benefits to You/Your Baby

The use of ZDV in pregnant women and knowledge about its effect on an unborn baby is limited. You may benefit from participation in the study because ZDV has been shown to prevent the growth of HIV in HIV-infected adults. The ACTG OB-GYN working group recommends that pregnant women with CD4+ cell counts less than 200 and those with AIDS take ZDV. It is felt women who have very low CD4+ cell counts or AIDS should take ZDV. The CD4+ cell count is often used as an indication of your health status. The benefits of initiating or continuing ZDV therapy during pregnancy for women with CD4+ cell counts between 200 and 500 are unclear. It is not known whether participation in this study will reduce the risk of your baby becoming infected with the HIV virus. You and your baby may not benefit directly from this study but the information gained may be useful in finding a treatment to prevent the transmission of HIV from mothers to infants.

Confidentiality of Records

Research records of your and your baby's participation in the study will be kept confidential to the extent permitted by law and will not be released without your written permission. Information about you and your baby, including your baby's test results, will not be shared with anyone else without your written permission. You and your baby will be identified by a code number known only to you and study personnel, and all information about you and your baby will be identified by this number. The code will be stored in a secure location with access only to study personnel and the Food and Drug Administration (FDA). Medical records which identify you and your baby by name may be inspected by the FDA, the National Institute of Allergy and Infectious Diseases Division of AIDS, and the manufacturer of ZDV, but confidentiality will be maintained to the extent permitted by law. You and your baby will not be identified by name in any publication or presentation resulting from this study.

Circumstances for Withdrawal from the Study Without Your Consent

Your and your baby's participation in this study may end without your consent for the following reasons: a) deteriorating health or other conditions that might make continued participation harmful to you or your baby; b) decision to breastfeed your baby; c) failure to keep appointments or take medications as instructed; d) a serious adverse reaction to drug therapy; e) termination or cancellation of the study by the study sponsor.

Safeguards

You and your baby (before and after birth) will undergo careful checkups throughout the study. An ultrasound will be performed at scheduled intervals throughout the study. If any abnormalities are noted suggesting anemia in the fetus, the study drug will be discontinued. If you develop an AIDS defining illness or your CD4 counts drop below 200, you will be offered active drug. Your baby will continue to receive his/her randomized treatment.
APPENDIX XIII (Cont.)  ACTG 076 (01/28/91)
Version 1.0
Page 5 of 12

Costs to You for Participation
There is no cost to you or your baby for the medication, clinic visits or laboratory tests associated with this study. All other medical costs outside of this study will be paid by you or your insurance carrier. These costs include your delivery and the time your baby spends in the newborn nursery. You will receive no money for your or your baby's participation in the study.

Alternatives to Participation
There is no treatment that can guarantee that you will deliver a baby that is not HIV infected.

Policy Regarding Research Related Injuries
Immediate necessary care is available if you or your baby become injured due to participation in this study. However, no financial compensation will be provided by the (name of ACTU), the Burroughs Wellcome Company, or the National Institute of Allergy and Infectious Diseases. Treatment will be at your expense or the expense of your insurance carrier.

Significant New Findings
Any significant new findings that develop during the study which could affect your willingness to continue participation will be made available to you.

Study Drug
This study involves the use of a drug called zidovudine (ZDV) which is approved for use in adults infected with the virus who are not pregnant. ZDV has not been approved for general use in pregnant women but has been approved for use in this study to determine the safety and effectiveness of preventing an unborn baby from becoming infected with HIV.

Problems or Questions
If you have any questions about this study or your rights as a participant, you should contact Dr. __________ (telephone __________), the principal investigator responsible for safeguarding your welfare and the welfare of your baby, or __________ (name and title of IRB member).
The purpose of the study, procedures to be followed and risks and benefits have been fully explained to me. I understand that I may withdraw my participation or my baby's participation at any time without affecting my rights or those of my baby to receive the best medical care.

Volunteer's Name
(typed or printed) or Volunteer's Signature
Volunteer's Legal Representative or Guardian, as appropriate Date

Witness' Name
(typed or printed)
Witness' Signature Date

I have explained the purpose of this study to the patient. To the best of my knowledge, she understands the purpose, procedures, risks and benefits to her and her baby.

Investigator's Name
Investigator's Signature Date
A MULTICENTER PHASE III RANDOMIZED PLACEBO-CONTROLLED TRIAL TO EVALUATE THE
EFFICACY, SAFETY AND TOLERANCE OF ORAL ZIDOVUDINE (ZDV) IN HIV
INFECTED WOMEN AND THEIR INFANTS

(FATHER’S CONSENT FORM)

Your partner and your baby are being asked to participate in a research study
titled, "A Phase III Randomized Placebo-Controlled Trial to Evaluate the
Efficacy, Safety and Tolerance of Oral Zidovudine (ZDV) in Pregnant HIV
Infected Women and their Infants."

This consent form provides detailed information about the research study. Once
you understand the study and if you agree to allow your baby to participate,
you will be asked to sign this consent form and you will be given a copy to
keep.

It is important that you understand the following: a) your permission to
allow your baby to participate is entirely voluntary; b) you may withdraw your
permission to allow your baby to participate at any time without penalty or
loss of benefits to which your baby is otherwise entitled; c) your decision to
withdraw your baby's participation from the study will not jeopardize your
baby's future medical care or possible participation in future research
studies.

Nature of the Study:

Your partner is pregnant and infected with the Human Immunodeficiency Virus
(HIV or AIDS virus). It is estimated that out of 100 babies born to HIV-
infected mothers, 16 to 40 will become infected and, if infected, are at risk
of dying from AIDS within the first two years of life. Your baby may become
HIV-infected during pregnancy, at delivery, or shortly after he/she is born.
It is not known exactly when the virus can infect an unborn baby or why some
babies are infected and others are not.

Zidovudine, or ZDV, (previously called AZT) is an antiviral drug (a drug that
slows or prevents the HIV virus from multiplying). ZDV has been shown to
prevent the growth of HIV in adults and children infected with the virus. ZDV
given to mice and kittens in controlled studies suggests its safety. For the
newborn baby at risk of developing the HIV infection, the best time to begin
treatment with ZDV may be as soon as possible after birth. Your partner and
your baby are being asked to participate in a research study to determine if
ZDV given to an HIV-infected pregnant woman as early as the first three months
of pregnancy and continued in her infant from birth to six weeks of age will
protect the baby from becoming infected with the HIV virus. To make this
determination, ZDV will be compared to an inactive substance called a placebo.
Study Procedures

Prior to entry into the study, your partner will undergo some routine tests to see if she qualifies for the study and to determine that her participation is safe for her and your baby. These tests include a history and physical examination and blood and urine tests. A sonogram will be performed to determine your baby’s age and to rule out any abnormalities that may place your baby at risk for participation. A non-stress test (a recording of your baby’s heart activity) will also be performed to rule out any fetal heart rate abnormalities.

If participation in this study is safe for your partner and your baby and you consent to have your baby participate, your partner will be randomly assigned (by equal chance) to receive either oral (by mouth) ZDV or placebo. This means that your partner will have a 50% chance of receiving either a drug (ZDV) that may prevent the HIV virus from infecting your baby or an inactive substance (placebo) that has no actual effect and is used only to compare it with the active drug. Treatment will continue throughout your partner’s pregnancy. Neither your partner nor her doctor will know which treatment she is assigned.

Your partner will receive oral medication five times a day before delivery. During labor, the drug will be administered continuously by an intravenous infusion (through a vein in the arm) until the umbilical cord is clamped. The intravenous drug will be discontinued after the baby is delivered.

Your partner will undergo routine laboratory and clinical evaluations to include blood, urine, sonogram, and non-stress tests, to monitor the condition of your baby and any apparent side effects of drug therapy. The total amount of blood drawn at each visit will not exceed 1-3 teaspoons.

After delivery, your baby will be evaluated in the newborn nursery to determine his/her medical condition. If your baby is found eligible to continue the study, your baby will receive the same study drug your partner received. This means your baby will be given either ZDV or placebo and neither you, your partner nor your partner’s doctor will know which drug your baby is getting. The study drug will be administered as a strawberry flavored syrup as soon as your baby can tolerate fluids and within 6-12 hours. If your baby is unable to tolerate fluids at 12 hours, the medication will be given intravenously (through a vein in the arm). The syrup will be taken every 6 hours for a total of six weeks. Your baby will be evaluated in the clinic for evidence of HIV infection at 1 week, 2 (or 3) weeks, 6 weeks and 12 weeks of age and every 3 months until he/she is 18 months old. Blood will be drawn at birth (approximately 1-2 teaspoon) and routinely throughout the study (1-2 teaspoon) to check for any side effects of the medication or evidence of HIV infection.
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At several hospitals participating in this study, and depending on the baby’s age, weight and whether or not he/she is taking medication for drug withdrawal, special blood tests to study how much drug is taken into the baby’s body will be performed. Only babies receiving active drug will participate in these special studies. If your baby is enrolled at one of these hospitals, the investigator will check to see if your baby is on active study drug treatment. If your baby has been taking active drug, approximately 0.3 ml (1/4 teaspoon) of blood will be withdrawn from your baby’s vein. This test will be repeated several times while your baby is taking medication. The total amount of blood to be withdrawn for this test will not exceed 0.9 ml (3/4 teaspoon). If your baby has been taking placebo (inactive drug), he/she will be withdrawn from this medication but will continue to be evaluated and followed.

Risks to Your Partner

The major side effect seen in adult patients taking ZDV is anemia (a decrease in the number of red blood cells in your blood) that may cause premature labor. A decrease in hemoglobin (the part of the red blood cell that carries oxygen from the lungs to the tissues) and a decrease in the number of white blood cells which could reduce your partner’s ability to fight infection may occur. Minor side effects that your partner may experience include nausea, vomiting and dizziness. Blood drawing may cause some discomfort, bleeding or bruising at the site of entry of the needle, and rarely, fainting. A small blood clot may form or swelling of the surrounding skin may occur. There is a small risk of infection from the blood drawing procedure.

Risks to the Fetus

Although your unborn baby is at risk of developing anemia and a low white blood cell count neutropenia, data from earlier studies suggests that the development of maternal anemia from ZDV therapy occurs infrequently and does not harm the newborn. The long term effect ZDV may have on your unborn baby is not known.

Risks to Your Baby

The major side effect noted in children is anemia but this usually occurs when the drug is taken for more than 6 weeks. Blood drawing may cause some discomfort, bleeding or bruising at the site of entry of the needle. A small blood clot, swelling of the skin or infection may occur.

Benefits to Your Partner/Your Baby

The use of ZDV in pregnant women and knowledge about its effect on an unborn baby is limited. Since ZDV has been shown to prevent the growth of HIV in HIV-infected adults, your partner may benefit from participation in the study. However, it is not known whether participation in this study will reduce the risk of your baby becoming infected with the HIV virus. Your partner and your baby may not benefit directly from this study but the information gained may be useful in finding a treatment to prevent the transmission of HIV from mother to infant.
Confidentiality of Records

Research records of your partner’s and your baby’s participation in the study will be kept confidential to the extent permitted by law and will not be released without your written permission. Information about your partner and your baby, including your baby’s test results, will not be shared with anyone else without your written permission. Your partner and your baby will be identified by a code number known only to you and study personnel and all information about your partner and your baby will be identified by this number. The code will be stored in a secure location with access limited to study personnel and the Food and Drug Administration (FDA). Medical records which identify your partner and your baby by name may be inspected by the FDA, the National Institute of Allergy and Infectious Diseases Division of AIDS and the manufacturer of ZDV, but confidentiality will be maintained to the extent permitted by law. Your partner and your baby will not be identified by name in any publication or presentation resulting from this study.

Circumstances for Withdrawal from the Study Without Your Consent

Your partner’s and your baby’s participation in this study may end without your consent for the following reasons: a) deteriorating health or other conditions that might make continued participation harmful to your partner or your baby; b) your partner’s decision to breastfeed your baby; c) failure to keep appointments or take medications as instructed; d) a serious adverse reaction to drug therapy; e) termination or cancellation of the study by the study sponsor; f) your partner’s choice to withdraw from the study.

Safeguards

Your partner and your baby (before and after birth) will undergo careful checkups throughout the study. A sonogram will be performed at scheduled intervals throughout the study. If any abnormalities are noted suggesting anemia in the fetus, the study drug will be discontinued. If your partner develop an AIDS defining illness or her CD4 counts drop below 200, she will be offered active drug. Your baby will continue to receive his/her randomized treatment.

Costs to Your Partner/Your Baby for Participation

There is no cost to you, your partner or your baby for the medication, clinic visits or laboratory tests associated with this study. All other medical costs outside of this study will be paid by you, your partner or your insurance carrier. These costs include your partner’s delivery and the time your baby spends in the newborn nursery. You or your partner will receive no money for your partner’s or your baby’s participation in the study.
Alternatives to Participation

There is no treatment that can guarantee that your partner will deliver a baby that is not HIV infected.

Policy Regarding Research Related Injuries:

Immediate necessary care is available if your partner or your baby become injured due to participation in this study. However, no financial compensation will be provided by the (name of ACTU), the Burroughs Wellcome Company, or the National Institute of Allergy and Infectious Diseases. Treatment will be at your partner’s expense or the expense of your partner’s insurance carrier.

Significant New Findings

Any significant new findings that develop during the study which could affect your willingness to continue to allow your baby to participate will be made available to you.

Study Drug

This study involves the use of a drug called zidovudine (ZDV) which is approved for use in adults infected with the virus who are not pregnant. ZDV has not been approved for general use in pregnant women but has been approved for use in this study to determine the safety and effectiveness of preventing an unborn baby from becoming infected with HIV.
Problems or Questions

If you have any questions about this study or your baby’s rights as a participant, you should contact Dr. (telephone ___________), the principal investigator responsible for safeguarding your baby’s welfare, or ___________ (name and title of IRB member).

The purpose of the study, procedures to be followed and risks and benefits have been fully explained to me. I understand that I may withdraw my consent for my baby’s participation at any time without affecting my baby’s rights to receive the best medical care.

Father’s Name
(typed or printed)

Volunteer’s Signature

Date

Witness’ Name
(typed or printed)

Witness’ Signature

Date

I have explained the purpose of this study to the baby’s father. To the best of my knowledge, he understands the purpose, procedures, risks and benefits to his partner and his baby.

Investigator’s Name

Investigator’s Signature

Date
66. **APPENDIX XV (Sample Informed Consent)**

The mother's and father's consent forms have been **COMBINED** into one consent form.

3rd para

**ADDED:**

The father of your baby may refuse to give his consent and this would prevent you from participating in the study.

**Nature of Study, 1st para**

**ADDED:**

HIV can be passed to your baby during pregnancy, during birth, or after birth through breast milk.

**Study Procedures, 3rd para**

**ADDED:**

You will be evaluated at six months after your baby is born. If you develop AIDS or your CD4+ count drops below 200 during your pregnancy, you will be offered active drug (ZDV) throughout your pregnancy and for six weeks after your baby is born.

**Study Procedures, last para, last sentence**

**READ:**

If your baby has been taking placebo (inactive drug), he/she will be withdrawn from this medication but will continue to be evaluated and followed.

**CHANGED TO READ:**

If your baby has been taking inactive drug (placebo), he/she will be discontinued from taking placebo but will continue to be evaluated and followed on study until he/she is 18 months old.

**Risks to the Fetus**

**ADDED:**

There is a 1% to 2% risk of intrauterine fetal demise (death of the fetus in utero).
Benefits to You and Your Baby

ADDED:

If you develop AIDS or your CD4+ count falls below 200 during your pregnancy, you will be allowed to discontinue study drug. You will be offered ZDV throughout your pregnancy and for six weeks after your baby is born while appropriate medical follow-up is being arranged.

Circumstances for Withdrawal from Study Without Your Consent

ADDED:

If the father of the baby withdraws consent for your baby’s participation in the study.

Safeguards, 4th sentence

READ:

If you develop and AIDS-defining illness or your CD4 count drops below 200, you will be offered active drug.

CHANGED TO READ:

If you develop AIDS or your CD4+ count drops below 200, you will be offered ZDV for six weeks after your baby is born while appropriate medical follow-up is being arranged.

Statement of Consent

ADDED:

Father’s signature line.
APPENDIX XV

SAMPLE INFORMED CONSENT

A PHASE III RANDOMIZED PLACEBO-CONTROLLED TRIAL
TO EVALUATE THE EFFICACY, SAFETY AND TOLERANCE OF ZIDOVUDINE
FOR THE PREVENTION OF MATERNAL-FETAL HIV TRANSMISSION

You and your baby are being asked to participate in a research study entitled, “A Phase III Randomized Placebo-Controlled Trial to Evaluate the Efficacy, Safety and Tolerance of Zidovudine for the Prevention of Maternal-Fetal HIV Transmission.” To decide whether or not you wish to participate in this study, you should understand enough about its risks and benefits to make an informed decision. This process is called informed consent.

This consent form provides detailed information about the research study which your doctor will discuss with you. Once you understand the study and if you agree to participate, you will be asked to sign this consent form and you will be given a copy to keep. The father of your baby will also be asked to sign a consent form if he is reasonably available.

It is important that you understand the following: a) your participation is entirely voluntary; b) you may decline to participate in or withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled; c) a decision to withdraw from the study will not jeopardize your future medical care or possible participation in future research studies; d) the father of your baby may refuse to give his consent and this would prevent you from participating in the study.

Nature of the Study:
You are pregnant and infected with the Human Immunodeficiency Virus (HIV or AIDS). HIV can be passed to your baby during your pregnancy, during birth, or after birth through breast milk. It is estimated that out of 100 babies born to HIV-infected mothers, 16 to 40 will become infected with the HIV virus. If infected, babies are at risk of dying from AIDS during the first years of life. It is not known exactly when the virus can infect an unborn baby or why some babies are infected and others are not.

Zidovudine (ZDV or AZT) is an antiretroviral (a drug that slows or prevents the HIV virus from multiplying). ZDV has been shown to prevent the growth of HIV in adults and children infected with the virus. ZDV given to mice and kittens in controlled studies suggests its safety. For the newborn baby at risk of developing HIV, the best time to begin treatment with ZDV may be as soon as possible after birth. You and your baby are being asked to participate in a research study to determine if ZDV given to an HIV-infected pregnant woman as early as the first three months of pregnancy, and continued in her infant from birth to six weeks of age, will protect the baby from becoming infected with HIV. To make this determination, ZDV will be compared to an inactive substance called a placebo.

*Note: The informed consent is provided as a "sample" and should be modified to meet the requirements of site Institutional Review Boards.
Study Procedures

Prior to entry into the study, you will undergo routine tests to see if you qualify for the study and to determine that your participation is safe for you and your baby. These tests include a history and physical examination and blood and urine tests. A sonogram will be performed to determine your baby’s age and to rule out any abnormalities that may place him/her at risk for participation. A non-stress test (a recording of your baby’s heart activity) will also be performed to rule out any fetal heart rate abnormalities.

If participation in this study is safe for you and your baby and you agree to participate, you will be randomly assigned (by equal chance) to receive oral (by mouth) ZDV or placebo. This means that you will have a 50% chance of receiving either a drug (ZDV) that may prevent the HIV virus from infecting your baby or an inactive substance (placebo) that has no actual effect and is used only to compare it with the active drug. Treatment will continue throughout your pregnancy. Neither you nor your doctor will know which treatment you are assigned.

You will receive oral drug five times a day before delivery. During labor, the drug will be administered continuously by intravenous infusion (through a vein in the arm) until the umbilical cord is clamped. The intravenous drug will be discontinued after the baby is delivered. You will be evaluated at six months after your baby is born. If you develop AIDS or your CD4+ count drops below 200 during your pregnancy, you will be offered active drug (ZDV) throughout your pregnancy and for six weeks after your baby is born.

You will undergo routine laboratory and clinical evaluations to include blood, urine, sonogram, and non-stress tests, to monitor the condition of your baby and any apparent side effects of the drug. The total amount of blood drawn at each visit will not exceed 1 to 3 teaspoons.

After delivery, your baby will be evaluated in the newborn nursery to determine his/her medical condition. If your baby is found eligible to continue the study, your baby will receive the same drug you received. This means your baby will be given either ZDV or placebo and neither you nor your doctor will know which drug your baby is getting. Drug will be given as a strawberry flavored syrup as soon as your baby can tolerate fluids and within 8-12 hours. If your baby is unable to tolerate fluids at 12 hours, drug will be given intravenously (through a vein). The syrup will be taken every 6 hours for a total of six weeks. Your baby will be evaluated in the clinic for evidence of HIV infection at weeks 1, 2 (or 3), 6, 12 and 3 months thereafter until he/she is 18 months old. Blood will be drawn at birth (approximately 1 to 2 teaspoons) and routinely throughout the study (1 to 2 teaspoons) to check for any side effects of the medication or evidence of HIV infection.
APPENDIX XV (cont.)

At several hospitals participating in this study, and depending on the baby's age and whether or not he/she is taking medication for drug withdrawal, repeat blood tests to measure how much drug is taken into the baby's body will be performed. Only babies receiving active drug (ZDV) will be asked to participate in these repeat blood tests. If your baby qualifies for these tests, your baby's doctor will check to see if your baby is taking ZDV. If your baby is taking ZDV, a small needle will be placed in a vein from which blood will be drawn. These blood tests will be repeated several times while your baby is taking ZDV. Each blood test will require about 0.3 ml (less than 1/4 teaspoon) of blood. If your baby has been taking inactive drug (placebo), he/she will be discontinued from taking placebo but will continue to be evaluated and followed on study until he/she is 18 months old.

Risks to You

The major side effect seen in adult patients taking ZDV is anemia (a decrease in the number of red blood cells in the blood) that may cause premature labor. A decrease in hemoglobin (the part of the red blood cell that carries oxygen from the lungs to the tissues) and a decrease in the number of white blood cells which could reduce your body's ability to fight infection may occur. Minor side effects that you may experience include nausea, vomiting and dizziness. Blood drawing may cause some discomfort, bleeding or bruising at the site of entry of the needle, and rarely, fainting. A small blood clot may form or swelling of the surrounding skin may occur. There is a small risk of infection from the blood drawing procedure.

Risks to the Fetus

Although your unborn baby is at risk of developing anemia and a decrease in white blood cells, data from earlier studies suggest that the development of maternal anemia from ZDV therapy occurs infrequently and does not harm the newborn. There is a 1% to 2% risk of intrauterine fetal demise (death of the fetus in utero). The long-term effect ZDV may have on your unborn baby is not known.

Risks to Your Baby

The major side effect noted in children is anemia but this usually occurs when the drug is taken for more than six weeks. Blood drawing may cause some discomfort, bleeding or bruising at the site of entry of the needle. A small blood clot, swelling of the skin or infection may occur.
**Benefits to You and Your Baby**

The use of ZDV in pregnant women and knowledge about its effect on the unborn is limited. If you receive ZDV in this study, you may benefit from participation because ZDV has been shown to prevent the growth of HIV in HIV-infected adults. It is recommended that women who develop AIDS or whose CD4+ cell count falls below 200 take ZDV. The benefits of initiating or continuing ZDV during pregnancy for women with CD4+ cell counts between 200 and 500 are unclear. If you develop AIDS or your CD4+ count falls below 200 during your pregnancy, you will be allowed to discontinue study drug. You will be offered ZDV throughout your pregnancy and for six weeks after your baby is born while appropriate medical follow-up is being arranged. It is not known whether participation in this study will reduce the risk of your baby becoming infected with HIV. You and your baby may not benefit directly from this study but the information gained may be useful in finding a treatment to prevent the transmission of HIV from mother to infant.

**Confidentiality of Records**

Research records of your and your baby’s participation in the study will be kept confidential to the extent permitted by law and will not be released without your written permission. Information about you and your baby, including your baby’s test results, will not be shared with anyone else without your written permission. You and your baby will be identified by a code number known only to you and study personnel, and all information about you and your baby will be identified by this number. The code will be stored in a secure location with access only to study personnel and the Food and Drug Administration (FDA). Medical records which identify you and your baby by name may be inspected by the FDA, the National Institute of Allergy and Infectious Diseases Division of AIDS, and Burroughs Wellcome, the manufacturer of ZDV, but confidentiality will be maintained to the extent permitted by law. You and your baby will not be identified by name in any publication or presentation resulting from this study.

**Circumstances for Withdrawal from the Study Without Your Consent**

Your and your baby’s participation in this study may end without your consent for the following reasons: a) deteriorating health or other conditions that might make continued participation harmful to you or your baby; b) failure to keep appointments or take medications as instructed; c) a serious reaction to study drug; d) termination or cancellation of the study by the study sponsor; e) if the father of the baby withdraws consent for your baby’s participation in the study.
Safeguards

You and your baby (before and after birth) will be carefully evaluated during the study. A sonogram will be performed at scheduled intervals throughout the study to check for any abnormalities in the fetus. If anemia is noted in the fetus, treatment will be discontinued. If you develop AIDS or your CD4+ count drops below 200 during your pregnancy, you will be offered ZDV throughout your pregnancy and for six weeks after your baby is born while appropriate medical follow-up is being arranged.

Costs to You for Participation

There is no cost to you or your baby for the study drug, clinic visits or laboratory tests associated with this study. All other medical costs outside of this study will be paid by you or your insurance carrier. These costs include your delivery and the time your baby spends in the newborn nursery. You will receive no money for your or your baby’s participation in the study.

Alternatives to Participation

There is no known treatment available at this time that can guarantee that you will deliver a baby that is not infected with HIV.

Policy Regarding Research Related Injuries

Immediate necessary care is available if you or your baby become injured due to participation in this study. However, no financial compensation will be given to you by (name of institution), the drug manufacturer, Burroughs Wellcome Company, or the National Institute of Allergy and Infectious Diseases. Treatment will be at your expense or the expense of your insurance carrier.

Significant New Findings

Any significant new findings that develop during the study which could affect your willingness to continue participation will be made available to you.

Study Drug

This study involves the use of a drug called zidovudine (ZDV or AZT) which is approved for use in adults infected with the virus who are NOT pregnant. ZDV has not been approved for general use in pregnant women but has been approved for use in this study to determine the safety and effectiveness of preventing an unborn baby from becoming infected with HIV.
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