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A Pragmatic Analysis of Vulnerability in Clinical Research

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Abstract

Identifying which subjects are vulnerable, and implementing safeguards to protect them, is widely regarded as essential to clinical research. Commentators have endorsed a number of responses to these challenges and have thereby made significant progress on understanding vulnerability in clinical research. At the same time, this literature points to a central contradiction which calls into question its potential to protect vulnerable subjects in practice. Specifically, analysis suggests that all human subjects are vulnerable and vulnerability in clinical research is comparative and context dependent, in the sense that individuals are vulnerable relative to others and in some contexts only. If everyone is vulnerable, there seems to be no point in citing the vulnerability of some individuals. Moreover, the conclusion that everyone is vulnerable seems inconsistent with the claims that vulnerability is comparative and context dependent, raising concern over whether it will be impossible to develop a comprehensive account of vulnerability that is internally consistent. The solution to this dilemma lies in recognition of the fact that the practical significance of claims regarding vulnerability depends on the context in which they are used. The claims that appear to lead to the central contradiction are in fact accurate conclusions that follow from different uses of the term ‘vulnerability’. The present manuscript describes this ‘pragmatic’ approach to vulnerability in clinical research and considers its implications for ensuring that subjects receive appropriate protection.

Keywords

Vulnerability; Pragmatics; Harm; Clinical Research

INTRODUCTION

There is something of a crisis in discussions regarding vulnerability in clinical research.¹ Identifying which subjects are vulnerable, and implementing safeguards to protect them, is widely regarded as essential to ethically appropriate research. Yet, analyses of vulnerable subjects have become so diverse and inconsistent² and lists of which subjects are vulnerable have become so extensive, that the potential for this work to protect subjects in practice has been called into question: ‘The concept of vulnerability has been used so extensively, and so inconsistently, that it is tempting to conclude that it is incapable of providing any meaningful ethical guidance.’³ This concern is well illustrated by the CIOMS list of vulnerable subjects:

medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, members of armed forces, police, the elderly, patients with incurable, serious, potentially disabling or life-threatening diseases, nursing home residents, people receiving welfare benefits, people receiving social assistance, poor people, the unemployed, patients in emergency rooms, some ethnic and racial minority groups, homeless, nomads, refugees, displaced persons, prisoners, politically powerless, members of communities unfamiliar with modern medical concepts.⁴

This is just one list, and it is intended to provide only some examples, thus pointing to the extent of any final list, and the scope of the current problem. What are investigators, institutional review boards, ethics review committees and other stakeholders supposed to do in response to an ever expanding universe of vulnerable subjects? And if the answer to that question is unclear, how is attention to vulnerable subjects going to protect those who need protection?

In some sense, it seems undeniable that all human subjects, being human, are vulnerable. Yet, insisting on special protections for everyone seems tantamount to providing special protections for no one: 'If everyone is vulnerable, then the concept becomes too nebulous to be meaningful'.⁵ Attempting to ensure appropriate protections by creating extensive lists of vulnerable subjects also raises the potential for stigmatization, suggesting that many individuals are everywhere and always unable to look after themselves.⁶ Appearance on the CIOMS list of vulnerable subjects seems to imply that individuals who receive welfare benefits are uniformly incapable of making decisions for themselves.

Commentators have attempted to address these concerns by endorsing comparative or context dependent analyses of vulnerability. For example, New Zealand guidelines on observational studies note that vulnerability is a broad category that covers many groups, including people who speak a different language or have a different cultural background than the investigators.⁷ The guidelines go on to address the potential for over inclusiveness by pointing out that 'even if a group is identified as being likely to be vulnerable, the label may not apply to all individuals in such groups, and even where it does apply, it may do so only intermittently'.⁸ While this approach may help to address the potential to stigmatize individuals within the cited groups, it leaves investigators and review committees with the initial challenge that analyses of vulnerability are supposed to address: which individuals within the cited groups are vulnerable and when do they need additional protections? The present paper attempts to identify the sources of this persisting confusion and potential solutions to it, beginning with an overview of extant analyses.

Analyses of vulnerability in clinical research attempt to address three primary questions.⁹ First, the concept of vulnerability itself: what does it *mean* for an individual or group to be vulnerable? Second, analyses attempt to determine *which individuals or groups* are vulnerable, along with the sources of their vulnerability. Third, as a practical matter, *what requirements or guidelines* are needed to protect these individuals? Much of the literature assumes, often implicitly, that an analysis of vulnerability should answer all three questions. A proper understanding of what vulnerability means will reveal which individuals are

vulnerable, and a proper understanding of which individuals are vulnerable will clarify what steps are needed to protect them.

This approach has the potential to succeed only if the significance of claims regarding vulnerability remains constant across the three domains. Against this, a pragmatic analysis suggests that the practical significance of claims regarding vulnerability is not determined strictly by the meaning of the claims, but depends on the context in which they are used. Hence, analysis of the meaning of vulnerability will not identify which subjects are vulnerable. Moreover, since the practical significance of claims regarding vulnerability can vary by context, identifying which subjects are vulnerable will not be sufficient to identify what steps are needed to protect them. A pragmatic analysis thus has the potential to resolve the central contradiction that arises from a combination of the claims that vulnerability applies to everyone and it applies only to those who are especially vulnerable or vulnerable in certain contexts.¹⁰ What appears to be a contradiction involves different uses or senses of vulnerability.

EXISTING ACCOUNTS

Scholarship on the concept of vulnerability in clinical research has been significantly influenced by the US regulations,¹¹ and by the recommendations of the National Commission on which the US regulations are based.¹² The National Commission was formed in response to condemnation of the Tuskegee syphilis study and was charged with identifying ways to protect the subjects of clinical research.¹³ The Commission argued that independent review and respect for the capacity of competent adults to make their own decisions represent the fundamental protections for research subjects. On the assumption that independent review is possible for all relevant studies, this analysis suggests that vulnerable subjects are those who are not able to consent for themselves. This conclusion led the Commission to propose additional protections for four groups: pregnant women/fetuses/neonates, prisoners, children, and the mentally infirm. The first three sets of recommendations were eventually incorporated into US regulations, with some modifications, while the proposed additional protections for the mentally infirm were rejected out of concern that they might block valuable and appropriate research.¹⁴

Subsequent efforts endorsed the Commission's approach of identifying subjects for whom the requirements of independent review and informed consent were not sufficient and then proposed additions to the list. The Belmont report adds racial minorities, the economically disadvantaged, and the very sick.¹⁵ The final US regulations mention subjects who are 'likely to be vulnerable to coercion or undue influence,' including mentally disabled persons and economically or educationally disadvantaged persons. Another account argues that concern should focus on research subjects who are at risk of not being treated equally,¹⁶ while still other accounts combine several of these and other elements.¹⁷ The legacy of these incremental and well-intended additions has been confusion over what to do in the face of an ever-expanding universe of vulnerable subjects.

One of the most influential responses limits the scope of vulnerability to those who need protection beyond what is needed for the paradigmatic research subject:

While I shall assume in what follows both that the existing guidelines are sufficient to deal ethically with the paradigmatic research subject, and, further, that all those standard protections are reliably in place, the vulnerable research subject nonetheless requires ethical consideration going beyond that baseline.¹⁸

This account goes on to describe six sources of vulnerability that could lead to ‘non-paradigmatic’ individuals needing additional protection: cognitive, juridic, deferential, medical, allocational, and infrastructural.

The claim that vulnerable subjects, at least frequently, are those for whom baseline regulations are not sufficient represents a crucial insight. The proposed list of different sources of vulnerability is also valuable for providing insight into some of the potential ways in which individuals may become vulnerable. For example, inclusion of ‘deferential’ vulnerability emphasizes the fact that the inability to make one’s own decisions is not limited to those who suffer from cognitive impairments that undermine their capacity to make decisions. It also includes individuals who have the cognitive capacity to make decisions, but whose relationships with others are such that they are not able to decide based on their own preferences and values. Individuals who are so awed by white coats that they cannot refuse invitations from physicians are vulnerable, even when they have the cognitive capacity to understand the study in question and recognize that it conflicts with their fundamental values.

At the same time, this approach attempts to derive the sources of vulnerability from an analysis of the concept of vulnerability. It thus illustrates the prior claim that the meaning of the term provides little guidance for determining precisely which individuals or groups are vulnerable. As a result, one is left to highlight what seem to be some of the most important sources, in this case, listing six sources. However, the fact that these sources are not complete and the potential to go on to an ever increasing list is suggested by the addition in a later work of a seventh source, social vulnerability.¹⁹

A related account attempts to limit the scope of vulnerability by limiting the potential harms that research regulations should attempt to address. On this account, vulnerable subjects are defined, not as individuals or groups who are at increased risk for any harm whatsoever, but as those who are ‘at risk of being enrolled in research in violation of one or more of the deal’s basic premises.’²⁰ The idea here is that vulnerable subjects are those for whom existing regulations may not be sufficient to realize the primary protections that are due to all research subjects. On this basis, the author concludes that there are three general vulnerabilities: consent based, risk based, and justice based. For example, the requirement for informed consent is not sufficient to protect the interests of those who cannot give consent.

This account offers another critical insight, namely, that appeals to vulnerability in clinical research depend on an understanding of which safeguards are needed for research subjects. Whether a potential threat renders some individuals or groups vulnerable *qua* research subjects depends on whether the threat has the potential to undermine one or more of the safeguards for research subjects. To consider a specific example of what this account does not include, empirical studies find that participation in research can undermine the jobs of

some subjects.²¹ Nonetheless, potential participants with limited work flexibility do not constitute a vulnerable group of research subjects. Why not? The plausible answer proposed by the present account is that research regulations are not intended to protect subjects from every possible harm that might arise from their participation in research. Hence, being at increased risk for some harms does not render one a vulnerable subject.

Recognizing the insights provided by this account, it is not clear which protections are the basic or primary ones and why protection of vulnerable subjects should be limited to them. What if a subject is vulnerable as the result of a failure of a *secondary* safeguard? More importantly, this analysis also seems to attempt to derive the sources of vulnerability from an analysis of the meaning of vulnerability. It tries to determine which groups are vulnerable from the claim that vulnerable subjects are those who are ‘at risk of being enrolled in research in violation of one or more of the deal’s basic premises’. Unfortunately, as we will consider in greater detail below, there are countless ways in which individuals may be enrolled in research inappropriately. This fact underscores the aforementioned claim that analysis of the concept of vulnerability provides little guidance for determining which specific groups or individuals are vulnerable. The present approach deals with this challenge by listing three general sources of vulnerability: consent based, risk based, and justice based. Notice that these three sources closely mirror the Belmont Report’s three ‘basic ethical principles’ for human subjects research: Respect for persons, Beneficence, and Justice.²² This makes sense to the extent that one assumes the Belmont principles accurately represent the core or primary protections needed for research subjects (with the substitution of non-maleficence for Belmont’s beneficence). However, this approach seems to either leave the question of which subjects are vulnerable or leads to a very extensive list in order to capture all the individuals who might be wronged, harmed, or not treated fairly.

A third account attempts to limit the scope of vulnerability in the context of clinical research by distinguishing between the potential to be harmed and ‘susceptibility’.²³ Because all human beings can be harmed, the author concludes that all human subjects are vulnerable. Rather than concluding, in line with the previous accounts, that we need to limit the scope of vulnerability, the author instead proposes to focus on the susceptible: individuals who have suffered previous injuries which predispose them to additional harm. This analysis suggests that the central challenge for protecting research subjects is to develop requirements and regulations to ensure that the needs of individuals who have previously been injured, such as the poor and the sick are ‘met by specific care and remedial measures’.²⁴

This account points to the need for an analysis of the extent to which researchers and funders are obligated to assist those in need, even when they are not responsible for their injuries. For example, to what extent do clinical researchers who propose to study a stigmatized group have obligations not just to avoid exploiting them, but to positively address the prevailing effects of the exploitative behavior of others? Answering this question is important. At the same time, focusing on those who have been previously injured seems too narrow. An individual who understands only Farsi may be vulnerable if they try to enroll in research in the United States, even though the inability to understand English frequently does not trace to prior injustice and does not constitute an injury. Similarly, working for the

principal investigator of the study in question can make a potential research subject vulnerable even though the job is a prestigious one.

In response to the limitations of these accounts, some commentators and guidelines work at a more general level and attempt to define what it *means* to be vulnerable. The most prominent approach in this regard defines vulnerability in terms of an increased potential for harm. For example, vulnerability has been defined as an ‘increased potential that one’s interests cannot be protected.’²⁵ This definition suggests that vulnerable subjects are those who are ‘relatively (or absolutely) incapable of protecting their own interests.’²⁶ This approach avoids the apparent arbitrariness of targeting specific sources of vulnerability (e.g. inability to consent) by regarding individuals or groups as vulnerable to the extent that they cannot protect themselves from specific threats, independent of what explains their relative lack of capacity. Yet, this approach still seems too broad and too narrow.

It is too broad because some harms are not relevant to vulnerability in research, even though they may occur in the research setting. We saw this previously with respect to the fact that individuals with limited work flexibility can be at greater risk of economic harm as a result of their participation in research. Nonetheless, these individuals do not constitute a vulnerable group of research subjects. The potential for this approach to be overly narrow traces to the fact that some, although not all, of its proponents focus on harms to subject welfare, thus ignoring the possibility that subjects may be vulnerable in virtue of being at increased risk of not being treated with respect.

This possibility forms the basis for a different approach, which defines vulnerability in terms of ‘identifiably increased likelihood of incurring additional or greater wrong.’²⁷ The practical importance of this emphasis is illustrated by research with stored biological samples. Regulations for research with stored biological samples need to protect donors’ welfare. For example, they need to protect donors from the possibility that research on their biological samples will lead to job or insurance discrimination. Regulations also need to ensure appropriate respect for donors. They need, for example, to protect donors from the disrespect that occurs when their samples are knowingly used for research, such as research on human cloning, that conflicts with the donors’ values.

Recognizing the importance of respect, some wrongs that might occur as a result of one’s participation in research do not seem relevant to research vulnerability, suggesting that this account is too broad as well. Consider an investigator who occasionally has lunch with her subjects in the cafeteria. Both buy for themselves and they sit together. Imagine that the investigator arranges these meetings in advance and agrees to meet the subjects. The investigator thereby makes a commitment to the individuals and acts wrongly if she fails to show up (without sufficient justification). Now imagine that this investigator implements the research regulations scrupulously for all groups, but she is more inclined to break these lunch dates with respect to a particular group. It follows that these individuals are at *identifiably increased likelihood of incurring additional wrong* compared to other individuals who enroll in her trials. Still it seems mistaken to say that, as research subjects, these individuals are vulnerable. The explanation seems to be that, as with potential *harms*, research regulations are not designed to protect subjects from all possible wrongs. Hence,

being at increased risk of being wronged does not necessarily make one vulnerable; it depends on the potential wrong in question.

By defining vulnerability in terms of wrongs, this account also seems too narrow. It misses sources of vulnerability that trace to the potential for increased harm rather than increased wrong. For example, young children are vulnerable because they are not able to understand important aspects of clinical trials. It is for this reason that children need special protections. Of course, investigators may fail to recognize children's vulnerability and they may thereby fail to implement the additional protections called for by children's lack of capacity. And this may result in the children being wronged. Yet, the obligations of investigators to protect children are not the source of their vulnerability. Instead, these obligations arise from the fact that children are unable to understand the research in question. If all investigators faithfully enact the additional protections for children, it would follow that pediatric subjects are not at increased risk of being wronged. Nonetheless, additional protections would still be needed because children are vulnerable.

More recent commentators argue that definitional approaches to vulnerability fail because they fail to recognize that vulnerability depends on the context: 'An individual's needs for special protections in the research context may depend more on personal factors, characteristics of the research and the research environment, available alternatives, and other factors than merely on that person's inclusion in a particular sociodemographic group.'²⁸ Whether women are vulnerable depends on whether they live in a society which respects them.²⁹ Whether individuals who work in a research lab are vulnerable depends on who has authority over the study. One proposed explanation for this context dependence cites the claim that vulnerability is essentially relational. A research subject is vulnerable to a researcher, and the fact of their vulnerability implies obligations on the researcher to protect them.³⁰

The claim that vulnerability in clinical research is context dependent provides a crucial component of an overall account and helps to explain the fact that many analyses are both helpful and too broad. They are helpful to the extent that they identify individuals and groups that are vulnerable. But, they become too broad and vulnerable themselves to counterexamples when they suggest that the cited individuals are vulnerable in all cases. This implication also raises the potential mentioned at the outset for lists of vulnerable subjects to become stigmatizing.

The fact that a context dependent analysis has these virtues may lead one to conclude that the prior conclusion—all human beings are vulnerable— must be mistaken. Yet, it seems undeniable that, in some sense at least, all human beings are vulnerable. Our bodies, our hopes, our relationships, our projects, are all under threat from others and the environment. Indeed, it has been argued that developing appropriate protections for human subjects depends on recognizing that all subjects are vulnerable. The author argues that contextual accounts ignore this critical aspect of vulnerability and goes on to express surprise that it has 'taken so long to recognize this to be the case.'³¹ This seems both clearly right and fundamentally problematic. All human beings can be harmed. But regarding all humans as

vulnerable seems to undermine rather than promote appropriate protections for research subjects.

To consider one final account, it has been argued that the solution to all of this confusion lies in more extensive conceptual analysis.³² The authors agree with those who regard ‘more than ordinary’ vulnerability as involving an increased risk of harm or wrongs. To individuals who are at risk in this sense, the authors propose a typology that links the different sources of vulnerability with specific obligations to address them. Specifically, the authors argue that there are three overlapping sources of vulnerability: inherent, situational, and pathogenic. Inherent sources of vulnerability trace to the nature of human beings, including our ‘corporeality, our neediness, our dependence on others, and our affective and social natures.’³³ Situational sources are context specific and include the personal, social, political, economic or environmental situation of a person or social group. Pathogenic sources of vulnerability involve the subset of situational sources that arise from ‘dysfunctional social or personal relationships.’

Attention to the vulnerabilities that result from dysfunctional social or personal relationships highlights the importance of ensuring that enrollment in clinical research does not make subjects significantly worse off. It also raises the question of whether investigators have greater obligations to address vulnerabilities that trace to human agency versus vulnerabilities that trace to human nature. Recognizing the importance of these theoretical questions, the proposed typology seems to underscore the point made earlier that analysis of the meaning of vulnerability does not provide insight into which individuals are vulnerable in the context of clinical research. Given that all threats arise from humans’ nature or their circumstances—the kind of beings we are or the situations in which we find ourselves—the proposed typology does not seem to provide insight into when protections are needed for research subjects.

To see this concern, consider the authors’ example of a proposed (albeit never conducted) trial of sex workers in Cambodia. The authors argue that the researchers had an obligation to compensate participants for any research related injuries and should have consulted with the sex workers in a respectful way. Both of these claims are undeniable. Yet, the claims that participants should be treated respectfully and compensated for research related injuries does not seem to depend on any particular conceptual analysis of vulnerability. Put differently, it is not the proposed typology that is doing the normative work here. Rather, it is other familiar considerations in research ethics, such as avoiding harm and minimizing risks, promoting autonomy and agency.³⁴

The present overview has inevitably left out a number of accounts and has analyzed the included accounts in insufficient detail. It nonetheless seems sufficient to justify the claim that the literature on vulnerability in clinical research is something of ‘a mess’.³⁵ As we have seen, the literature includes a range of accounts of vulnerability in clinical research that provide important insights and also contradict each other. It suggests that all human subjects are vulnerable, a claim that is supported by ever expanding lists of vulnerable groups. But, it also suggests that vulnerability is comparative and context dependent, so that only some individuals are vulnerable and only in some cases. To try to make sense of this apparent

contradiction, it will be helpful to start with a conceptual analysis of vulnerability as it is used in other contexts and consider what that analysis implies for clinical research.

THE CONCEPT OF VULNERABILITY

Very generally, the claim that an individual or group is vulnerable refers to the possibility that things might go worse for them in ways that are not fully within their control. For example, Merriam Webster defines a vulnerable individual or group as one which is: 'capable of being physically or emotionally wounded'; 'open to damage'; or 'assailable'.³⁶ Not surprisingly, the research ethics literature focuses on the fact that individual humans and human groups can be harmed. They can be mistreated; they can feel pain; they can suffer; they can die. And these possibilities are, at the very least, not fully eliminated by enrolling in a clinical trial. It follows that, in some sense, all human research subjects are vulnerable.

While all human beings are vulnerable, not all vulnerable individuals are human beings. Suffering typically involves a harm to those who suffer, and at least the vast majority of sentient beings (gods may represent an exception) are not fully in control of whether they suffer. This suggests that all sentient beings are vulnerable. Next, disease frequently represents a harm to living beings, even those who are not sentient. For example, it is commonly said that the roots of many grapevines are vulnerable to secondary fungal infections following attack by *phylloxera vitifoliae*, a pale yellow sap-sucking insect. This is not to say that the vulnerability of plants is necessarily a matter of moral concern. It seems difficult to see how the vulnerability to infection of a single common plant living in isolation is morally relevant. If that is right, it suggests that vulnerability is a sufficiently capacious term to include concerns from the morally irrelevant to the morally pressing.

Finally, in standard English at least, it makes sense to say that many non-living things are vulnerable. Cars are vulnerable to rust and decay, and the Titanic taught us that even very large ships are vulnerable to icebergs. One might object that these appeals to vulnerability ultimately refer to the human beings who can be harmed. The claim that the Titanic was vulnerable to icebergs really means that the owners and the passengers are so vulnerable. While this response makes sense, it does not seem to capture the ways in which vulnerability is used. Consider an historic example. Following the First World War, Billy Mitchell advocated for the development of a U.S. Air Force by trying to demonstrate that battleships are vulnerable to attack from the air. The climax of Mitchell's efforts took place on July 21, 1921 when bombs dropped from several of his planes sank the captured, and widely assumed to be unsinkable, German battleship *Ostfriedland*. This demonstration was widely regarded as establishing something about the nature of battleships, not just something about their owners and passengers, namely: Battleships are vulnerable to attack from the air. This implication is underscored by the fact that, at the time of the demonstration, the ship belonged to the U.S. Navy, which was not harmed by its sinking. Moreover, for the central character in the episode, Billy Mitchell, establishing the vulnerability of battleships was an important victory.

Individuals and groups that are vulnerable tend to be vulnerable in myriad ways. According to one of the most prominent accounts of human well-being or welfare, things go better for

human beings when their (reflectively endorsed) preferences are satisfied and things go worse for them when their preferences are frustrated.³⁷ Given that human beings have preferences about countless different things, from whether it rains and who wins the game, to their relationships, their health, and the future of humankind, this account suggests that the ways in which humans can be harmed are essentially endless.

The analysis to this point highlights the practical limitations of a conceptual analysis of vulnerability for the purposes of ensuring appropriate protections in practice. First, vulnerability applies to a broad range of individuals and things. Indeed, the conclusion that X is vulnerable does not even specify whether X is a human being or a plant or a car. Second, vulnerability applies to threats and potential harms that are of significant moral concern, as well as threats and potential harms that in their own right are not morally relevant (e.g. whether a single plant in the middle of a forest develops a secondary infection). Third, there is a sense in which all human beings are vulnerable. Fourth, there are countless ways in which human beings can be harmed or wronged. Hence, the sources of vulnerability for human beings are endless.

These conclusions illustrate why appeals to the concept of vulnerability do very little normative work in practice. In particular, they illustrate why analyses of the concept of vulnerability in clinical research are not sufficient to determine which subjects or subject groups are vulnerable. While these conclusions help to make sense of the current impasse with respect to vulnerability in clinical research, they do not seem to provide any insight into how we might resolve it. Instead, this analysis supports the claim that all human beings are vulnerable and also supports the claim that whether and how an individual is vulnerable depends on the context. Moreover, these conclusions are not peculiar to clinical research or to human beings. It seems to be the case that almost all things are vulnerable and, at the same time, whether a thing is vulnerable depends on the context. All ships are vulnerable and whether a given ship is vulnerable depends on whether there are planes that can carry bombs of a sufficient size.

While this apparent contradiction has led to significant confusion in research ethics, the same result is not apparent in other fields. Despite the contradiction, readers of the history of the US navy understand the point of claims regarding the vulnerability of ships. And botanists and winery owners understand and take effective steps to address the vulnerability of vines to phylloxera (a common tactic is to graft the vines on to American rootstock, which has evolved defenses against phylloxera). The question for present purposes, then, is how they manage this. Given that vulnerability appears to be both universal and context specific: How do stakeholders in other fields understand vulnerability and take steps to address it in practice?

A PRAGMATIC ACCOUNT OF VULNERABILITY

The theory of pragmatics points out that the same statement can have very different practical significance depending on the context in which it is used.³⁸ This possibility is often described in terms of the difference between the meaning and the conversational implicatures of an utterance.³⁹ To appreciate this difference, and consider how it might help

to address the confusion regarding vulnerability in clinical research, consider different ways in which we might discuss the fact that cars are vulnerable to theft

Imagine that you turn to me at a dinner party and state ‘All cars are vulnerable to theft’. I would be puzzled. I understand what the claim means but, in that context, I don’t understand the point or the significance of your making it. What is it that you want me to do? Now imagine a different context in which you make the same claim. Imagine I give you a ride to the train station in my 20 year old car with a big dent and 250,000 miles. We park, leave the car, and start walking toward the station, at which point you state ‘All cars are vulnerable to theft’. Strictly speaking, this statement has the same meaning as the statement I found so puzzling the night before. But, rather than leaving me puzzled, I turn back and lock car doors before we continue on our way.

In the second context, your use of the claim that all cars are vulnerable to theft essentially reminded me that existing protections, such as laws against theft and police patrols, are not sufficient to protect cars, including my car, against theft. In that location at least, I should implement the additional protection of locking my doors. This example illustrates the extent to which the three questions regarding vulnerability are independent. The meaning of vulnerability in terms of the potential for damage or harm does not reveal that cars, unlike grains of sand, are vulnerable, much less that they are vulnerable to theft. To realize that cars are vulnerable one needs to understand whether there are ways in which they can be damaged. And to understand that they are vulnerable to theft in particular, one needs to know a good deal about people’s preferences and informal markets and the ease of transport. Similarly, recognition that cars are vulnerable to theft does not reveal what steps are needed to protect them. Your statement that all cars are vulnerable to theft does not clarify whether locking my doors is sufficient. To make that determination, one needs to know a lot about the context in question: how do people break into cars and what measures might stop them?

Notice that we judge my response not based on whether it eliminates all chance of harm, but on whether it offers sufficient protection against the harm in question. Even with my doors locked, my car might still be stolen. If this risk is sufficiently low, the protections I took are sufficient. If not, I should move my car to a safer location. The general point is that no set of protections, no matter how comprehensive, can render a previously vulnerable individual invulnerable. The only way to do that is to strip everything of value from the individual. At the extreme, if the risk remains too high no matter what we do, the proper response to vulnerability may be to avoid the context in question. With respect to the potential for theft, we may leave the car at home, and take a cab. This often is the appropriate response when there is no independent value to driving. The analogous response to vulnerability in the context of clinical research is simply to not enroll in the study in question. While this makes sense, it raises competing ethical concern when the study in question offers the potential for clinical benefit.

This pragmatic analysis suggests that the way to make progress on addressing the confusion around vulnerability in clinical research is to draw two distinctions. First, is the distinction between categorical and comparative claims regarding vulnerability. The categorical claim ‘all cars are vulnerable to theft’ means that all cars can be stolen. Categorical claims take the

general form of 'X is vulnerable to Y', where X is an individual or group and Y is a bad outcome (for X). These claims refer to the possibility that all the members of a group or class are vulnerable. The comparative claim that 'Hondas are vulnerable to theft' is not intended to suggest that other cars are not vulnerable to theft. Instead, these claims typically mean that 'Hondas are *more* vulnerable to theft *than other cars*.' Comparative claims take the form: X is (more) vulnerable to Y (than Z), where the comparison is often suppressed. These claims highlight the fact that some individuals or groups are more vulnerable than others.

Categorical claims regarding vulnerability can be puzzling because they frequently seem so obvious that it is not clear why one would expend the time and energy to express them. As I was thinking at the dinner party: Don't we know that all cars can be stolen? And, assuming we do, what is the point of pointing this out? How can it be helpful to state something that we all already know? This question brings us to the second distinction: the difference between the meaning and the practical significance of claims regarding vulnerability.

Comparative claims regarding vulnerability highlight the fact that protections in place for the class in general might not be sufficient for members of the cited subclass. Take the previous claim that 'Hondas are vulnerable to theft'. This claim typically means that 'Hondas are *more* vulnerable to theft than other cars' and thereby highlights the fact that existing background protections are not sufficient, in that context, for all members of a group. If you own a Honda, locking your doors may not be enough. You might want to consider a fancy alarm system. Clarifying the difference between categorical and comparative claims thus clarifies how it can make sense to cite specific individuals as vulnerable, even though we recognize that, in another sense, all human beings are vulnerable. These claims essentially assume that all individuals in the class are vulnerable and make the point that those in the subclass are more vulnerable (in that context). This aspect of vulnerability is reflected in the literature by views which propose that claims regarding vulnerability in clinical research refer to the fact that some individuals are more vulnerable than paradigmatic subjects. Specifically, this is true to the extent that one is considering a comparative claim regarding vulnerability.

VULNERABILITY IN CLINICAL RESEARCH

Analyses of vulnerability in clinical research have come to two apparently contradictory conclusions. The first, supported by ever expanding lists of vulnerable groups, is that all human subjects are vulnerable. This conclusion raises the question of what stakeholders are supposed to do in response to the claim that essentially everyone is vulnerable. The second conclusion, ostensibly inconsistent with the first, is that vulnerability in clinical research is comparative and context dependent, such that only some individuals are vulnerable and only in certain contexts.

A pragmatic analysis suggests that the way to address this dilemma is not to investigate what claims regarding vulnerability mean. Instead, it is to clarify the point of making them. The claim that all human *beings* are vulnerable makes sense to the extent that one wants to call attention to the need for societal norms, laws, and regulations to protect human beings from

harm.⁴⁰ For example, it has been argued that human vulnerability points to the need to recognize that we all have special obligations to protect and assist those who are vulnerable with respect to us.⁴¹ What then is the point of the claim that all human *subjects* are vulnerable? Doesn't this simply follow from the fact that all human beings are vulnerable and human subjects are human beings?

The claim that all human subjects are vulnerable, like the claim that all cars are vulnerable to theft, is a categorical claim. It means that all human subjects may be harmed. This claim makes sense to the extent that general protections for human beings may not be sufficient to protect human subjects. The presence of laws, police officers, and social norms may not be sufficient to protect research subjects. For example, the claim that all human subjects are vulnerable implies that the general right to sue those who cause harm may not be sufficient; we may need research specific protections. To consider a specific example, based on the fact that all human subjects are vulnerable, Grinnell argues that current approaches to risk assessment and compensation for research injuries need to be revised 'analogous to the way that the precautionary principle moves forward environmental action in the absence of scientific certainty.'⁴² The point for present purposes is not whether one agrees with his proposal, but to note that, in a context in which one is evaluating whether existing research regulations in general are adequate, it makes sense to claim that all human subjects are vulnerable.

Determining whether a given set of research regulations are adequate requires an analysis of what human subjects regulations should cover and to what extent. As noted, one cannot determine which regulations are needed simply by analyzing the concept of vulnerability or the meaning of claims regarding vulnerability. This suggests that some debates, which appear to involve disagreements regarding the nature of vulnerability, are really debates over which protections are needed for research subjects. For example, there has been significant attention to concern regarding the potential for exploitation in the context of multi-national research.⁴³ In particular, there is concern that sponsors and investigators will use lower-income countries to test products and interventions that are intended for high-income countries. One proposal to address this concern is the 'fair benefits' framework.⁴⁴ This framework specifies that individuals and host communities in lower income-countries should receive a fair level of benefits, given the risks they face and the extent to which others benefit from their participation in a given trial.

A number of commentators have criticized the fair benefits framework on the grounds that it is limited to compensating individuals and host communities for the risks and burdens that occur in the context of a given trial.⁴⁵ This debate provides just one example of the more general question of whether investigators' obligations with respect to individuals who have been harmed or wronged in the past are limited to not exploiting their circumstances. Or do investigators have positive obligations to partly address past injustices, even when the investigators are not personally responsible for them? This is not a question that can be answered by appeal to the concept of vulnerability. Instead, it requires a determination of whether research regulations should address conditions of background injustice (whether investigators and/or funders have an obligation to do so). Clearly, research regulations should protect subjects from exploitation by investigators. And previously we concluded that

research regulations should not attempt to protect subjects from the possibility that researchers may fail to honor lunch dates with them. The question of whether investigators have positive obligations to partly address historic injustices seems to lie somewhere between these two clear cases, thus leaving the challenge of determining whether this concern should be addressed by research regulations in particular or whether it should be left to more general guidelines and regulations governing international relations.

To consider a second example, most research regulations and guidelines do not place an upper limit on the net risks to which competent adults may be exposed. The US regulations mandate that risks must be minimized and the remaining risks to subjects must be 'reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result (45CFR46.111). The regulations do not prohibit a study that poses high risks to competent adults, provided the risks cannot be reduced and they are justified by the social value of the information to be gained. Thus, consider a competent adult with reduced kidney function who is at very high risk from participating in a phase 1 study of an experimental drug that is excreted by the kidneys. Is this individual vulnerable (in this context) in the comparative sense of being vulnerable relative to competent adults with normal kidney function? Certainly this individual is at greater risk of experiencing harm as a result of participating in the study compared to adults with normal kidney function. However, whether that increased risk of harm suggests that the individual is vulnerable depends on the proper scope of research regulations. Should research regulations protect competent adults from high net risks? Or should they be limited to ensuring that competent adults understand the risks they face and voluntarily agree to accept them?

Analysis of vulnerability in clinical research thus underscores the need for more work to determine the extent to which research regulations should protect subjects. Once we have an account of what protections are appropriate for human research subjects in general, we can determine what regulations are sufficient to realize those protections. And once general protections have been adopted and sufficiently reliable implementation of the protections is in place, categorical claims regarding the vulnerability of all human subjects become analogous to claims made at dinner parties that all cars are vulnerable to being stolen. They remain true, but they lose their practical significance (except as an explanation for why there are research regulations in the first place). This is the case even though, as noted previously, sufficient protections are not foolproof; even with sufficient protections in place, human subjects are still vulnerable in the sense that they can still be harmed as a result of their participation in research.

In the US, this process played out in roughly the following way. Awareness of problematic cases, including the Jewish Chronic Disease hospital case and the Tuskegee syphilis study, highlighted the fact that general laws and societal norms were not sufficient to protect research subjects. It was not sufficient protection, for example, to maintain that research subjects or their relatives could sue investigators. Hence, in that context, all research subjects were vulnerable and the US National Commission was charged with developing regulations for human subjects in general. Its recommendations, which form the basis for subpart A of the US regulations, focus on independent review and voluntary informed consent.

With those recommendations in place, the Commission turned to a comparative evaluation of vulnerability, assessing whether there might be groups who are more vulnerable than other subjects and for whom the proposed requirements for independent review and consent might not be sufficient. Here the Commission identified individuals who cannot give their own voluntary and informed consent, and recommended additional regulations for four groups: fetuses/neonates, prisoners, children, and adults with mental infirmity. This brings us to the present time when commentators focus on what other individuals or groups might be vulnerable in a comparative sense. Again, we should not expect an analysis of vulnerability to clarify the contexts or groups for which this is true. Instead, one needs an understanding of the general protections that should be realized by research regulations and guidelines, and an understanding of the extent to which they may not be sufficient in a particular context, or for a particular type of research. Which individuals are at increased risk of things going worse for them in that context and what additional requirements or safeguards might protect them from the increased risks in question? For example, potential subjects who do not speak the language that is used at the research site raise the need for interpreters and translated documents. Because there are so many different possible reasons why existing protections might not be sufficient for a particular group, the attempt to develop a general and exhaustive account of vulnerable subjects inevitably leads to extensive lists.

Finally, it will not be possible in all cases to address individuals' vulnerability. While researchers should attempt to accommodate a broad range of languages, it is unrealistic to assume that even the most well-funded study site will be able to provide interpreters for every possible language. And telephone interpreters have their limitations as well. These cases raise the question of what should be done when individuals have certain vulnerabilities that cannot be fully addressed by additional safeguards or protections. The most obvious possibility is to consider whether these individuals should be excluded from the research in question. In some cases, that may represent an important protection for them. In others, especially when the research offers sufficient potential for benefit that is not otherwise available, exclusion may begin to seem more like a kind of discrimination. Here too more work is needed to identify the proper balance in individual cases between protecting subjects from risks and allowing them access to potential benefits. And this brings us back to the question of what should be the general requirements for clinical research. In this case, should they be limited to protecting the interests of individual subjects? Or should research regulations also try to protect investigators from harming subjects and try to minimize the aggregate harms caused by research?⁴⁶

CONCLUSION

The literature on vulnerable in clinical research appears to lead to a theoretical impasse. The conclusion that all human subjects are vulnerable seems both correct and incapacitating. What are stakeholders supposed to do in response to this conclusion? Moreover, the conclusion that everyone is vulnerable seems inconsistent with the claims that vulnerability is comparative and context dependent. And if that is right, it will be impossible to develop a comprehensive account of vulnerability that is internally consistent. The present analysis suggests that the solution to this dilemma lies in recognizing that the practical significance

of claims regarding vulnerability is not determined fully by their meaning; it depends on the context in which they are used and can vary from context to context.

This pragmatic analysis reveals that many of the existing accounts of vulnerability in clinical research are not inconsistent. Instead, they provide a proper understanding of different aspects of the overall topic. The claim that all subjects are vulnerable makes sense in the context of assessing whether general research regulations are appropriate. Are protections for human beings in general, such as laws as against battery and assault and the right to sue, sufficient for ensure adequate protection of research subjects? Or are research specific protections needed? And this analysis is consistent with the claim that only some subjects are vulnerable in the context of assessing whether there are individuals for whom the general protections are not sufficient.

Finally, the present analysis suggests that we should stop asking too much of general accounts of vulnerability. The way to ensure appropriate protections for research subjects is not to undertake an analysis of the concept of vulnerability and, on that basis, attempt to develop comprehensive lists of vulnerable groups. Instead, we need to develop guidelines of which individuals and groups are vulnerable in the context of different studies and circumstances, and what steps might help to protect them in those contexts. This process involves at least seven steps.

First, we need an account of vulnerability in clinical research, with an understanding of the ways in which things can go worse for individuals—they can be harmed or wronged—as a result of their participation in research. Second, more work is needed to define the proper scope of protections for research subjects. For example, research regulations should protect subjects from being exploited by investigators. Should they also require investigators to address existing injustices that trace to the problematic actions of others? Should research regulations protect competent adults from high net risks or only mandate that they consent to facing such risks? Third, it will be important to develop general mechanisms to realize the called for protections. Clearly, independent review and informed consent are vital here. But, it does not follow that they are sufficient. We also need to determine whether research regulations should protect even consenting adults from high net risks and, if so, how should this risk limit should be defined and implemented? Fourth, it is important to identify contexts in which the general mechanisms are not adequate to ensure the appropriate protections for one or more groups of subjects. To what extent are independent review and informed consent sufficient for research with pregnant women? Fifth, what harm or wrongs might occur as a result? Sixth, what additional protections can protect subjects against these harm or wrongs? Seventh, in cases where it is not possible to identify sufficient protections for the added potential harms or wrongs, analysis will be needed to determine when exclusion from research is appropriate and when it is excessive.

Conceptual analysis of vulnerability is needed to answer question one and can help with questions two and three. In contrast, no general conceptual analysis of vulnerability, including the present one, will yield answers to questions four, five, and six. These questions, which represent the primary focus of current scholarship, concern not the meaning of vulnerability, but the practical significance of claims regarding vulnerability. As

we have seen, the practical significance of claims regarding vulnerability depends on the context in which they are used. And their practical significance can vary across different context. Hence, appeal to the concept of vulnerability offers very little in terms of making progress on the crucial questions. Instead, what is needed is expertise regarding the specific individuals and contexts in question. What threats are present and how can they be addressed? The answers to these questions will vary widely. The concerns that are raised by research on older patients in a French ICU, and what is needed to address them, will be very different from what threats are present and what safeguards are possible for a survey of adolescents at risk for HIV in Zimbabwe. This suggests that implementing the present approach will require more time and expertise than would be required by a single analysis that covered all the relevant aspects of vulnerability in clinical research. But, in the end, this approach hopefully will lead to greater clarity in the literature and better protections in practice.

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References

1. Levine, C. Research Involving Economically Disadvantaged Participants. In: Emanuel, EJ., et al., editors. *The Oxford Textbook of Clinical Research Ethics*. New York, NY: Oxford University Press; 2008. p. 431-436.
2. Ruof MC. Vulnerability, Vulnerable Populations, and Policy. *Kennedy Inst Ethics J*. 2004; 14:411–425. [PubMed: 15812988]
3. Coleman CH. Vulnerability as a Regulatory Category in Human Subject Research. *J Law Med Ethics*. 2009; 37:12–18. [PubMed: 19245598]
4. Council for International Organizations of Medical Sciences (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland: 2002. Available at: http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm [Accessed 12 Sept 2016]
5. Levine C, Faden R, Grady C, Hammerschmidt D, Eckenwiler L, Sugarman J. Consortium to Examine Clinical Research Ethics. The Limitation of 'Vulnerability' as a Protection for Human Research Participants. *Am J Bioeth*. 2004; 4:44–49.
6. Danis, M., Patrick, DL. Health Policy, Vulnerability, and Vulnerable Populations. In: Danis, M., Clancy, C., Churchill, L., editors. *Ethical Dimensions of Health Policy*. New York, NY: Oxford University Press; 2002. p. 310-334.
7. National Ethics Advisory Committee. *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities*. Wellington, NZ: 2012. Revised edition Available at: <https://neac.health.govt.nz/system/files/documents/publications/ethical-guidelines-for-observational-studies-2012.pdf> [Accessed 17 Oct 2016]
8. Ibid: 26
9. For a variation on this typology, which identifies four questions that need to be addressed by a general analysis of the ethics of vulnerability, see: Mackenzie C, Rogers W, Dodds S. 2014 *Introduction: What is Vulnerability, and Why Does it Matter for Moral Theory? Vulnerability: New Essays in Ethics and Feminist Philosophy*. Mackenzie C, Rogers W, Dodds S. Oxford, UK Oxford University Press: 1–29.

10. Rogers, W. Vulnerability and Bioethics. In: Mackenzie, C. Rogers, W., Dodds, S., editors. *Vulnerability: New Essays in Ethics and Feminist Philosophy*. Oxford, UK: Oxford University Press; 2014. p. 60-87.
11. Department of Health and Human Services. [Accessed 18 Nov 2016] US Code of Federal Regulations, 45 CFR 46. 1991. Available at: [http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/Food and Drug Administration](http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/Food%20and%20Drug%20Administration). [Accessed 18 Nov 2016] US Code of Federal Regulations, title 21, part 50. Available at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50>
12. US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Guidelines for the Protection of Human Subjects of Research*. Washington, DC: US Government Printing Office; 1979. Available at: <http://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/> [Accessed 23 Nov 2016]
13. Jonsen, AR. Commissioning Bioethics: The Government in Bioethics 1974–1983. In: Jonsen, AR., editor. *The Birth of Bioethics*. New York, NY: Oxford University Press; 2003. p. 90-124.
14. Childress JF. The National Bioethics Advisory Commission: Bridging the Gaps in Human Subjects Research Protection. *J Health Care Law Policy*. 1998; 1:105–122. [PubMed: 15573433]
15. Belmont Report, *op.cit.* note 12.
16. Garcia S, Sandra A. Equal Protection Clause Enforcement as a Model for Protecting Vulnerable Human Research Subjects. *Am J Bioeth*. 2004; 4:81–82. [PubMed: 16192155]
17. Nickel PJ. Vulnerable Populations in Research: The Case of the Seriously Ill. *Theor Med Bioeth*. 2006; 27:245–264. [PubMed: 16763881] Macklin R. Bioethics, Vulnerability, and Protection. *Bioethics*. 2003; 17:472–486. [PubMed: 14959716]
18. Kipnis, K. Ethical and Policy Issues in Research Involving Human Participants. National Bioethics Advisory Commission; Bethesda, MD: 2001. *Vulnerability in Research Subjects: A Bioethical Taxonomy*.
19. Kipnis K. Seven vulnerabilities in the pediatric research subject. *Theor Med*. 2003; 24(2):107–20. This work also includes situational vulnerability, but not infrastructural vulnerability.
20. Coleman. *op. cit.* note 3.
21. Lazovski J, Losso M, Krohmal B, et al. Benefits and Burdens of Participation in a Longitudinal Clinical Trial. *J Empir Res Hum Res Ethics*. 2009; 4:89–97. [PubMed: 19754238]
22. Belmont Report, *op.cit.* note 12.
23. Kottow MH. Vulnerability: What Kind of Principle is it? *Med Healthcare Philos*. 2004; 7:281–287.
24. Ibid: 281.
25. Agrawal M. Voluntariness in Clinical Research at the End of Life. *J Pain Symptom Manage*. 2003; 25:S25–S32. [PubMed: 12691694]
26. Levine, RJ. *Ethics and Regulation of Clinical Research*. 2. New Haven, CT: Yale University Press; 1988.
27. Hurst SA. Vulnerability in Research and Health Care: Describing the Elephant in the Room? *Bioethics*. 2008; 22:191–202. [PubMed: 18405317]
28. Grady C. Vulnerability in Research: Individuals with Limited Financial and/or Social Resources. *J Law Med Ethics*. 2009; 37:19–27. [PubMed: 19245599] Welch MJ, Lally R, Miller JE, et al. The Ethics and Regulatory Landscape of Including Vulnerable Populations in Pragmatic Clinical Trials. *Clin Trials*. 2015; 12:503–510. [PubMed: 26374681]
29. Luna F, Vanderpoel S. Not the Usual Suspects: Addressing Layers of Vulnerability. *Bioethics*. 2013; 27:325–332. [PubMed: 23718852]
30. Finder S. Vulnerability in Human Subject Research: Existential State, not Category Designation. *Am Journal Bioeth*. 2004; 4:68–70. [PubMed: 16192149] Thomasma D. The Vulnerability of the Sick. *Bioeth Forum*. 2000; 16:5–12.
31. Grinnell F. Subject Vulnerability: The Precautionary Principle of Human Research. *Am J Bioeth*. 2004; 4:72–74. [PubMed: 16192151]
32. Lange MM, Rogers W, Dodds S. Vulnerability in Research Ethics: A Way Forward. *Bioethics*. 2013; 27:333–340. [PubMed: 23718774]
33. Ibid: 336

34. Luna F. Rubens, Corsets and Taxonomies: A Response to Meek Lange, Rogers and Dodds. *Bioethics*. 2015; 29:448–450. [PubMed: 25186280]
35. Kipnis K. The Limitations of Limitations. *Am J Bioeth*. 2004; 4:70–71. [PubMed: 16192150]
36. [Accessed 17 Nov 2016] Merriam Webster Dictionary. Available at: <http://www.merriam-webster.com/dictionary/vulnerable>
37. For perhaps the classic account of this view, see: Griffin J. 1986 *Well-being*. Oxford, UK Oxford University Press
38. Korta, K., Perry, J. Zalta, EN., editor. [Accessed 19 Sept 2016] *Pragmatics*. The Stanford Encyclopedia of Philosophy. 2015. Available at: <http://plato.stanford.edu/archives/win2015/entries/pragmatics>
39. Grice, HP. *Logic and Conversation*. In: Grice, HP., editor. *Studies in the Way of Words*. Cambridge, MA: Harvard University Press; 1989. p. 22-40.
40. Kottow MH. The Vulnerable and the Susceptible. *Bioethics*. 2003; 17:460–471. [PubMed: 14959710]
41. Goodin, RE. *Protecting the Vulnerable: A Reanalysis of Our Social Responsibilities*. Chicago, IL: University of Chicago Press; 1985. p. 35
42. F. Grinnell. *op. cit.* note 30, p.73.
43. Shapiro HT, Meslin EM. Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries. *New Engl J Med*. 2001; 345:139–142. [PubMed: 11450665] Varmus H, Satcher D. Ethical Complexities of Conducting Research in Developing Countries. *New Engl J Med*. 1997; 337:1003–1005. [PubMed: 9309109]
44. Participants. Fair Benefits for Research in Developing Countries. *Science*. 2002; 298:2133–2134. [PubMed: 12481120]
45. Lavery JV, Bandewar SVS, Kimani J, et al. Relief of Oppression: An Organizing Principle for Researchers' Obligations to Participants in Observational Studies in the Developing World. *BMC Public Health*. 2010; 10:384. [PubMed: 20591194] London AJ. Justice and the Human Development Approach to International Research. *Hastings Cent Rep*. 2005; 35:24–37.
46. MacKay D. Fair Subject Selection in Clinical Research: Formal Equality of Opportunity. *J Med Ethics*.

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