Undue Confusion: The Problem of Inducements to Participate in Clinical Research Trials

by

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Abstract

For decades, researchers have made use of various types of incentives, including financial incentives, to entice individuals to participate in clinical research trials. However, there is concern that the use of financial incentives might exert an undue influence on potential research participants; unable to resist the lure of a large financial incentive, an individual might enroll in a trial against his or her better judgment. The purpose of this thesis is to examine the concept of undue inducement, and determine if the use of incentives in research is really problematic in this way. I suggest that 'undue inducement' mislabels a different problem --inadequate comprehension on the part of potential research participants-- and argue that a strong comprehension requirement is the solution to the real problem raised by the use of incentives to participate in research. I also consider objections to a strong comprehension requirement, and examine whether a strong comprehension requirement provides a solution to the problems of coercion and exploitation in clinical research trials in the same way that it solves the problem of undue inducement.

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Chapter 1: Introduction

1.1 Introduction

Since the emergence of systematic medical research over a century ago, the issue of ensuring that research is ethical has grown both in terms of its importance, and its complexity. While the vast majority of early research trials would not have passed ethical muster by today's standards, it was not until the occurrence of trials which clearly violated important human rights that change began to occur. Important statutes like the Nuremburg Code, drafted in response to the medical testing by Nazi physicians during the Second World War, and later the Helsinki Declaration, played an important role in establishing guidelines for the proper treatment of participants in clinical trials. Most of these ethical guidelines were drafted in response to specific incidents, and as such they often focused their attention on certain ethical requirements, while neglecting others. Recognizing that informed consent alone is neither necessary nor sufficient for ethical clinical research,[1] the seven ethical requirements for clinical research set out in 2000 by Ezekiel Emanuel, David Wendler, and Christine Grady[2] are taken to be the authoritative standard by which a clinical research trial is determined to be ethical. These seven ethical requirements serve to synthesize "traditional codes, declarations, and relevant literature on the ethics of research on human subjects."[3] They provide a general and coherent set of

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[1] Informed consent is generally taken to be a means by which the interests and values of individuals are respected; a person who gives informed consent to participate in research has verified that the terms of participation are in keeping with their interests and values. However, children and adults with diminished mental capacities still have interests and values and ought to be permitted to participate in research, even though they are unable to make their own decisions about participating in research and thus cannot give valid informed consent. Moreover, in emergency situations which preclude the securing of informed consent by either the participant or a valid proxy, research may ethically proceed when conducted under strict guidelines.

[2] Ezekiel Emanuel, et. al., "What Makes Clinical Research Ethical?" *Journal of the American Medical Association* 238.20 (2000): 2701-2711.

[3] Ibid, 2701

guidelines for use by Research Ethics Boards (REBs), who are in turn responsible for ensuring that clinical research trials are ethical, according to these requirements, which are jointly sufficient for ethical clinical research:

1) *Social or Scientific Value*. A treatment or procedure to be studied must have potential to improve health and well being, or increase knowledge. This requirement is meant to ensure that participants are not exploited, and that scarce resources are not wasted.
2) *Scientific Validity*. Research must make use of accepted scientific principles and methods, to produce reliable and valid data. This requirement is meant to ensure that participants are not exploited, and that scarce resources are not wasted.
3) *Fair Subject Selection*. Research must not target stigmatized or vulnerable individuals as participants for risky research, and must not favor rich and socially powerful individuals as beneficiaries for potentially beneficial research. This requirement is meant to ensure that subjects are selected justly.
4) *Favourable Risk-Benefit Ratio*. Ensuring a favorable risk-benefit ratio is a three step process, consisting of: a) Minimizing research risks, b) maximizing potential benefits, and c) making sure that remaining risks to the participant are proportional to the participant and society. Potential risks are minimized by using procedures which are consistent with sound research design and do not expose subjects unnecessarily to risk, while potential benefits are maximized by determining if alterations to the study might enhance participant benefit (this only takes into consideration health-related benefits).

Other participation benefits such as financial inducements are not considered when determining risk-benefit ratios. For those trials which provide no individual benefits to subjects, potential benefit to society must outweigh risks to the subject. This requirement is meant to ensure non-maleficence, beneficence, and to prevent exploitation.

5) *Independent Review*. Research design, proposed subject population, and risk-benefit ratio must be evaluated by individuals unaffiliated with the research. This requirement is meant to minimize conflicts of interest and ensure accountability.
6) *Informed Consent*. Informed consent is typically divided into five components: participant competence, participant voluntariness, disclosure of information by the researcher, comprehension of information by the participant, and token consent by the participant. Researchers must provide information to subjects about the purpose of research, its procedures, potential risks and benefits, and alternatives, so that the individual understands and can make a voluntary choice about enrollment. This requirement is meant to respect subject autonomy.
7) *Respect for Potential and Enrolled Subjects*. Researchers must a) permit withdrawal from trial; b) protect privacy through confidentiality; c) inform subjects of newly discovered risks/benefits; d) inform subjects of results of trials; and e) maintain welfare of subjects. This requirement is meant to respect subject autonomy and welfare.

According to Emanuel et. al.[4] social value, validity, fair subject selection, favorable risk-benefit ratio, and respect for potential or enrolled subjects are each substantive ethical values, and as such they are all necessary for ethical clinical research. On the other hand, independent review and informed consent are procedural requirements whose purpose is to maximize the autonomy of the research participant, and ensure that their values and interests are satisfied by research participation. However, other procedures may serve to satisfy these ends, and thus Emanuel et. al. state that "informed consent requirements can be minimized, and in some circumstances consent can even be waived."[5] As was mentioned in a footnote above, research on interventions for individuals in emergency life-saving situations might be conducted ethically, even in the absence of informed consent by the participant or a proxy. Thus, each of the seven ethical requirements must be satisfied for research to be ethical, although some circumstances might require the adjustment of some requirements, in order to ensure that their intended function is achieved in the absence of the standard procedure for securing this function.

Provided that research trials meet these ethical requirements, an REB can grant their approval, and allow the trials to be carried out in a clinical or independent setting. Of course, REB approval is only half the battle for researchers; the other half is recruiting a sufficient number of acceptable individuals to participate in clinical trials. Generally speaking, a randomized controlled trial (RCT) --taken by most to be the standard for providing reliable research data-- will consist of two or more groups of participants: those receiving a new treatment whose effectiveness is as yet unknown and those receiving a control-treatment by which to judge the comparative effectiveness of the new treatment.

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[4] Ezekiel Emanuel, et. al., "What Makes Clinical Research Ethical?" *Journal of the American Medical Association* 238.20 (2000): 2701-2711.
[5] Ibid, 2707.

Depending on the phase of the trial, I, II, or III, researchers are concerned with a specific notion of 'effect.' In Phase I, the exact effects the chemical ingredients will have on the body are investigated to determine whether it is safe to consume; these trials are usually tested on a small group (20-100 on average) of healthy volunteers. Phase II trials assess how well the drug works, as well as continue Phase I safety assessments on a larger group of volunteers, and are usually tested on slightly larger groups (20-300 on average). They are often divided into two types, Phase IIA and IIB: IIA is designed to assess dosing requirements, while IIB is designed to study efficacy of certain doses. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects. In Phase III the drug is tested on a large population (300-3,000 on average) to determine if its effects are generalizable. The control treatment might be one whose effectiveness is well-established, or it might be no treatment at all. Participants are placed into each group at random, and in a blind study they are not told what group they are in while the trial is ongoing; in the case of a double-blind RCT, the physician-researcher does not know either.

While participants in Phase III trials are necessarily individuals afflicted with some illness, participants in Phase I (and some Phase II trials) are typically healthy volunteers and, as such, they usually stand to receive no direct medical benefit from participation. Though some volunteers are motivated to participate by altruistic tendencies, many others are motivated to participate for other reasons, including financial incentives. Typically, payments received by participants are intended as reimbursement for expenses incurred through participation (fuel costs, transit fares, lost wages etc.),

though some researchers pay participants considerable amounts of money for their services in research trials. While reimbursement is not generally taken to present an ethical problem (it is assumed not to be a strong motivator for participation because the participant is only breaking even), the moral status of large payments are far less clear.

One sort of claim leveled against large financial incentives is that research participation should be altruistically motivated, and that payment undermines the moral quality of the act. Some argue that to volunteer the use of one's body is morally different from selling it, and as such accepting a financial incentive for research participation is a commodification of the body that should be prohibited. For many, this is not a convincing argument. When one considers that participants in Phase I research often have no prospect of receiving health benefits from participation but may incur considerable risks, and that many Phase I trials are conducted by for-profit pharmaceutical companies, it seems at least somewhat idealistic to expect participants to act entirely out of altruism. There is a great deal more to be said about the ethics of commodifying the human body, but I will not pursue those questions here.[6] Instead, I will turn to the arguably more

[6] Most arguments concerning the commodification of the human body rely on a 'broad construal,' which depicts the commodification of a certain object as seeing or thinking about the object as if it is the sort of thing which can be bought or sold, the practice of thinking about interactions as if they were sale transactions, and the use of monetary cost-benefit analysis to judge these interactions. Many theorists argue that to treat a human as a commodity involves some or all of the following features: a) denial of subjectivity, where the commodified object is treated as a thing whose feelings need not be taken into account; b) instrumentality, where the commodified object has only instrumental value; and, c) 'fungibility,' where the commodified object is replaceable with some other kind of object, in this case money. Those who criticize the sale of parts of the human body (blood, tissue, organs etc.) argue that this practice contributes to a society in which the bodies of persons are regarded as resources, and that this is morally wrong. Accordingly, they claim that we ought to prohibit this practice. Currently there is no federal legislation against the sale of organs in Canada, though all provinces and territories (with the exception of Nunavut) have adopted some form of legislation prohibiting organ sales, as have both the United States and the United Kingdom. (Shaun Pattinson, "Paying Living Organ Providers," *Web Journal of Current Legal Issues* 3 (2003): online, 15 Jul. 2010. Available: http:// webjcli.ncl.ac.uk/2003/issue3/pattinson3.html) However, the World Health Organization identifies these nations as among the leaders in 'organ importing countries' (i.e. the country of origin of those patients who venture overseas to purchase organs for transplant.) See: David Resnik, "The Commodification of Human Reproductive Materials," *Journal of*

widespread concern associated with incentives to participate in research, namely the risk that payment may unduly influence the decision making of the potential research participant.

This problem, commonly referred to as 'undue inducement,' occurs when an incentive (typically characterized as a financial incentive, though not necessarily so) is so large that it causes the potential research participant to accept unreasonable risks. There is also concern that large inducements might be irresistible to certain vulnerable groups (those living in poverty for example), and thus result in their participation in research against their better judgment. Put in terms of the informed consent requirement, undue inducement can impede an individual's comprehension, or the voluntariness of their decision to participate. And under normal circumstances, without proper informed consent, (one of the seven requirements for ethical clinical trials) a patient cannot be permitted to enroll in a research trial. This characterization of undue inducement has experienced widespread uptake on the part of REBs internationally, and has proven to be one of the primary concerns when evaluating the informed consent of potential research participants. The fear of unduly inducing a potential research participant has caused some theorists to recommend that low[7, 8], or no[9, 10] payments be offered to research participants. The primary concern is that financial inducements often target individuals in unfortunate situations, who are already vulnerable to exploitation, or who may lack the education to

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Medical Ethics 24.6 (1998): 388-393 and Stephen Wilkinson, "Commodification Arguments for the Legal Prohibition of Organ Sale," *Health Care Analysis* 8.2 (2000): 189-201.

[7] Christine Grady, "Money for Research Participation: Does It Jeopardize Informed Consent?" *American Journal of Bioethics* 1.2, (2001): 40-44.

[8] Neil Dickert and Christine Grady, "What's the Price of a Research Subject? Approaches to Payment for Research Participation," *New England Journal of Medicine* 34, (1999): 198-204.

[9] Paul McNeill, "Paying People to Participate in Research: Why Not?" *Bioethics* 11.5: (1997): 390-396.

[10] Nancy K. Reame, "Treating Research Subjects as Unskilled Wage Earners: A Risky Business," *American Journal of Bioethics* 1.2 (2005): 53-54.

fully comprehend the risks and benefits of a trial. In some cases, individuals might purposely fail to report important health conditions which would otherwise disqualify them from participating, because they are desperate to receive the inducement. However, other theorists[11, 12] counter that minimizing or eliminating incentives only further reduces the options available to potential research participants.

Regardless of one's proposed solution, the problem of undue inducement seems clear: certain inducements to participate in research trials, especially large financial inducements, may cause individuals to accept unreasonable risks and exercise poor judgment or faulty reasoning. In order to protect individuals from themselves, researchers must ensure that any inducements to participate in a trial are not exerting an undue influence on potential patients. However, what it means to 'accept unreasonable risks' or 'exercise poor judgment' is not clear in the context of undue inducements.

In the second chapter of this thesis, I will argue that there are three possible accounts of the problem identified by undue inducement, each of which depends on a certain conception of what things a person ought to value. The first assumes an objective standard of values. In this case, an individual who is unduly induced fails to be motivated by the right values. The second assumes a subjective standard of values. In this case, an individual who is unduly induced becomes confused about which values they actually hold, and the strength with which they are held. I will show that neither of these views can be correct. I offer a third account that also assumes a subjective standard of values, but rejects the idea that one can be mistaken about one's own values. Rather, it is only when a person is confused about which option best satisfies their values and desires that

[11] Martin Wilkinson and Andrew Moore, "Inducement in Research," *Bioethics* 11.5 (1997): 373-389
[12] Ezekiel Emanuel, "Undue Inducement: Nonsense on Stilts?" *American Journal of Bioethics* 5 (2005): 9-13

inducements are problematic. This problem can be addressed by maintaining a stringent comprehension requirement for informed consent. If individuals fully comprehend the pertinent details of participating in a trial, no inducement of any kind can be considered 'undue.' Thus, undue inducement does not identify a unique problem; the real problem is one of ensuring comprehension.

In the third chapter, I will consider a problem referred to as the therapeutic misconception, which will serve as an important example of where a strong comprehension requirement is needed. I will also respond to several of the arguments given by those who believe that a weakened comprehension requirement is satisfactory for ethical research.

In the final chapter, I will argue that a strong comprehension requirement also allays concerns about inducements being coercive and/or exploitative. I will show why inducements cannot be coercive by definition, and I will argue that even in exploitative circumstances, an individual can give fully informed consent to participate in research. In the case of exploitative transactions of the sort which ought to concern us, the ethical issue is not the informed consent of the individual, but the unethical nature of an exploiter making an unfair offer.

Overall, I will show that concerns about undue inducement in clinical research trials are misguided, and that rather than being concerned about whether or not the voluntariness of a potential research participant is compromised by a large inducement, bioethicists ought to be concerned with ensuring the comprehension of potential research participants. It is by focusing their attention on ensuring adequate levels of

comprehension, and not on the status of specific inducements, that bioethicists will most effectively protect the interests of potential participants.

1.2 Informed Consent as Expression of Autonomy

Before proceeding into the discussion of undue inducements, a brief consideration of informed consent is in order. The informed consent requirement has long been a hallmark of ethical clinical research trials, because it helps to ensure that participants know exactly what they are agreeing to by participating in a trial. This not only helps protect research participants from being subject to dangerous or harmful research, but also respects their autonomy by helping to ensure that the values of the patient are respected and that they are treated as ends in themselves rather than means to achieving research data. To be autonomous is to be a self-governing agent: when we act autonomously we determine our own actions, and are free from those influences which do not derive their power from our own authority. An agent possesses the unique power to act for herself -no one else can act for her- and so she is justified in taking as authoritative her own judgment about how to act. If this authority is challenged, (e.g. if someone violates her autonomy), those judgments which determine her actions would cease to be her own; their power to move her would no longer be a reflection of her power to move herself. As autonomous agents, we have the right to determine our own actions.

Autonomy is thus closely tied to personal responsibility; insofar as I act autonomously, I am the architect of my own actions, and may be held responsible for any consequences which might foreseeably arise from these actions. Because I will be held responsible for my actions, it is of the utmost importance that I know (as much as

possible) about what their outcome will be. Within the context of a clinical research trial, if I agree to participate, I am accepting the risks of participation (as well as the benefits); I need to know what I am agreeing to before I can be taken to have agreed to it. As described above, the informed consent requirement is fairly rigorous, and according to the standard view its fulfillment is based on five component parts: competence, voluntariness, disclosure, understanding, and token consent. Under normal circumstances, it is only when these five requirements are met that a potential research participant ethically may be permitted to participate in a trial. Some theorists debate the necessity of each of these components; their objections will be considered later. Of these five requirements, I take four (competence, disclosure, understanding and token consent) to be relatively well understood and so I will only offer a brief consideration of each. However, I take the standard account of voluntariness to be unsatisfactory and so I will consider this requirement in much greater detail. I also take the voluntariness requirement to be of crucial importance to my account of both undue inducement and exploitation, each of which will be taken up in later chapters.

1.3 Competence

While the competence of research participants is presumed to be an important component of ethical research, most regulatory bodies do not provide a satisfactory notion of what constitutes competence. For instance, neither HHS (United States Department of Health and Human Services) nor FDA (United States Food and Drug Administration) regulations stipulate a criterion for competence; while some statutes define incompetence in a treatment setting, none address incompetence in consent to

research.[13] However, these regulations do at least suggest that when a patient is deemed incompetent, a legally authorized representative may consent on their behalf to research participation, though no uniform standard of who is legally authorized to act as a consent-proxy exists. The use of third party authorization must comply with the legal requirements of the jurisdiction where the research is taking place. Tom Beauchamp and James Childress broadly define competence as "the ability to perform a task," the task in question being making a decision to participate in research.[14] Therefore, competent participants must have the capacity to understand (at some minimal level) the information they are presented with.

In addition to the ability to perform a given task, Tom Grisso and Paul Appelbaum argue that participants must also possess some appreciation of the nature and significance of the decision they are being presented with. They claim that in order to truly understand what the decision amounts to, the decision must have some significance for the decision-maker and they must appreciate both that it is their decision to make and will affect their lives once made.[15] Similarly, Allen Buchanan argues that fully competent individuals must understand what it would 'feel like' to be in a future state in which the decision had been made or not, and incorporate these ideas into their decision making.[16] Some theorists also suggest a minimal level of reasoning skills, such as the ability to

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[13] Jessica Berg, et. al., "Fulfilling the Underlying Purpose of Informed Consent to Research," *Informed Consent: Legal Theory and Clinical Practice* (Oxford University Press, 2001): 279-307.
[14] Tom Beauchamp and James Childress, *Principles of Biomedical Ethics* 1st ed. (Oxford University Press, 1979.)
[15] Tom Grisso, et. al., "The MacArthur Treatment Competence Study: I. Mental Illness and Competence to Consent to Treatment," *Law and Human Behavior* 19 (1995): 105-126; Tom Grisso, et. al., "The MacArthur Treatment Competence Study. II. Measures and Abilities Related to Competence to Consent to Treatment," *Law and Human Behavior* 19 (1995): 127-148.
[16] Allen Buchanan, and Dan Brock, *Deciding for Others: The Ethics of Surrogate Decision Making* (Cambridge: Cambridge University Press, 1989).

derive conclusions from premises.[17] Additionally, a competent participant must be able to express their decision in some way; without the ability to express their decision, satisfaction of the other components is rendered moot. However, the inability to express one's competence is typically a physiological issue (e.g. a stroke victim who cannot speak or move but is mentally competent), and so some authors do not consider the ability to express one's decision to be an element of competence in the same way that the other components are.

The MacArthur Treatment Competence Study, which began its initial phase of development in 1988, was designed "to provide information to policy makers and clinicians to help them address questions about the decision-making capacities of people who are hospitalized with mental illness." [18] After several phases of testing, it generated an interview procedure which measures abilities related to four abilities which are deemed legally relevant to competent decision making. This interview, called the MacArthur Competence Assessment Tool-Treatment (MacCAT-T) measures a person's ability to "state a choice, to understand relevant information, to appreciate the nature of one's own situation, and to reason with information."[19] This test allows researchers to screen potential research participants in order to ensure that they are able to satisfy the competency component of informed consent, especially when a person's condition might be suspected of inhibiting their ability to give informed consent (e.g. a patient suffering from a severe mental illness.) Without first satisfying the competence requirement, any

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[17] Benjamin Freedman, "Competence: Marginal and Otherwise," *International Journal of Law and Psychiatry* 4.1 (1989): 53-72.
[18] Tom Grisso, et. al., "The MacArthur Treatment Competence Study: I. Mental Illness and Competence to Consent to Treatment," *Law and Human Behavior* 19 (1995): 106.
[19] Tom Grisso, et. al. "The MacArthur Treatment Competence Study. II. Measures and Abilities Related to Competence to Consent to Treatment," *Law and Human Behavior* 19 (1995): 128.

consent offered by an individual cannot be taken to be informed, and as such cannot be considered valid. The competence requirement ensures that the individual has the *capacity* to understand information presented to them, although it is a further requirement that the individual actually does adequately comprehend this information.

1.4 Disclosure

The third component of informed consent is information disclosure, and its satisfaction depends on the effectiveness of the researcher in conveying all of the pertinent information to the participant in a way which is clear, concise, and phrased in understandable language. Information such as the purposes of the research, the probability and degree of risk and/or benefits to which the potential participant will be subjected, as well details regarding any investigational techniques which might be unfamiliar to the patient, all must be conveyed. Additionally, the participant would be informed about administrative details such as alternatives to participation in the trial, as well as their right to withdraw at any time.

1.5 Comprehension

The fourth component of informed consent is the actual comprehension of the information disclosed to the potential participant. This depends on the ability of the participant to receive and process the information, and furthermore seek clarification on any areas they are uncertain about. Unfortunately, potential participants may not realize that they have misunderstood some of the information about the trial in which they would be participating, and in some cases either no amount of further disclosure by the researcher would rectify the problem, or no further information is provided because the confusion is not known to the researcher. While few (if any) theorists would debate the

necessity of the voluntariness, competence, disclosure or token consent requirements for informed consent, the comprehension requirement is often viewed as somewhat less essential. Perhaps not coincidentally, the comprehension requirement is also typically the most difficult to satisfy, as otherwise competent patients are sometimes mistaken about their own level of comprehension. It is not always easy for researchers to determine whether appropriate levels of comprehension are present; they must rely on indirect evidence gleaned from comprehension tests, or the testimony of the participant.

Consequently, some theorists[20] claim that the requirement places too much weight on the researcher to ensure that comprehension is present, and so a less stringent version of the comprehension requirement ought to be adopted, in which the standard of adequate comprehension is lower. For instance, Gopal Sreenivasan argues that the standard view of informed consent (which asserts a duty to ensure adequate comprehension), is a confusion of "an ethical aspiration with a minimum ethical standard,"[21] where the former is adequate comprehension, and the latter is simply adequate disclosure of information on the part of the researcher. Simply put, researchers obviously hope that participants understand the information being presented to them, but Sreenivasan believes that patient understanding is not necessary for researchers to satisfy the disclosure requirement (the satisfaction of which he believes fulfills their duty to the potential research participant). A closer analysis of this view, as well as criticisms of it, will be taken up later.

1.6 Voluntariness

According to the Nuremburg Code, a decision to participate in research is voluntary when the subject is "so situated as to be able to exercise free power of choice,

[20] Gopal Sreenivasan "Does Informed Consent to Research Require Comprehension?" *The Lancet* 362 (2003): 2016-2018.
[21] Ibid, 2017

without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion."[22] Of course, the fact that a decision is made freely by an individual does not prevent the decision from having been influenced by a variety of factors. As Appelbaum points out, these factors might be internal factors such as a participant's preexisting values and preferences (e.g. inclinations towards altruism or the pursuit of scientific knowledge), or their psychological state (e.g. an increased willingness to accept risk brought on by failure of treatments for a serious illness.) They might also be external factors such as legal pressures, the opinions of family and community, and (lack of) available resources or possible financial or health incentives for participating. According to the standard account offered by Appelbaum, a decision is taken to be involuntary only if it is subject to a particular type of influence, which has all of the following characteristics: the influence must be 1) external, 2) intentional, 3) illegitimate, and 4) causally linked to the choice of the person making the decision. Let us consider each in turn.[23]

First, while internal factors such as fear, hope, or confusion might result in a decision which is unwise or imprudent, only external factors (i.e. those influences which come from outside the person deciding) can render a decision involuntary because they are not always under our control. Internal factors might distort our ability to make a decision which best represents our desires and those things that we value, but Appelbaum argues that there is nothing about them that actually constrains our ability to choose one option over another. Even if internal factors cause us to see the world as offering only one choice, we still could have acted otherwise than we did, although this may have

[22] Paul Appelbaum et. al. "Voluntariness of Consent to Research: A Conceptual Model," *Hastings Center Report* 39:1 (2009): 30-39
[23] Ibid.

seemed impossible at the time. As such, we have acted voluntarily, because nothing actually forced us into the choice we made, though we may have *felt* forced.[24]

Second, the fact that someone is influenced by the actions of another person does not mean that their decision is involuntary. If we are trying to decide between X and Y, and a friend who is unaware of our decision comments on her preference for Y, this might influence us one way or the other, though this was not the intention of the friend, and so could not be said to have affected the voluntariness of our decision. To affect voluntariness, an external factor must result from the deliberate action of another person, whose intention it is to influence the decision to be made. As Appelbaum makes clear, situational constraints such as poverty, lack of treatment options, or the culture of a society or workplace might strongly influence a person's decision, and perhaps make it far more difficult by increasing the number of factors to be considered, without rendering it involuntary.[25]

Third, even if the friend in the above example was intentionally trying to persuade us to select Y, this is not necessarily a problem; in fact, we encounter people intentionally trying to influence our decision making countless times in our daily lives, from unknown advertisers trying to affect our spending habits, to physicians or lawyers giving us expert advice, to friends and family. As Appelbaum argues, external and intentional influences are only problematic when they are illegitimate; that is, when the person exerting the influence is acting in a way that crosses accepted social boundaries.[26] For example, those involved in certain types of relationships in which there is a clear power disparity (e.g. teachers and students, bosses and assistants etc.) are typically discouraged by social

[24] Ibid.
[25] Ibid.
[26] Ibid.

norms from engaging in sexual relationships, because those in the subordinate position often feel that they will face negative consequences if they do not agree to participate. While it might be perfectly legitimate for A and B to engage in a sexual relationship if they had met in some other context, the fact that the person in the dominant position is able to use their position in order to influence the actions of the subordinate makes this type of influence illegitimate. Similarly, if A places a gun to the head of B and demands B's money, this influence would certainly be illegitimate, because A has clearly violated a social (or more specifically, a legal) boundary. By intentionally constraining the possible options which B might choose to a single viable choice, A's method of influence is not legitimate.

Lastly, the influence exerted only negates the voluntariness of the decision if the influence actually caused the decision to be made. In other words, Appelbaum claims, if a person intentionally and illegitimately pressures me to participate in a research trial when I was already inclined to participate and had formed the intention to do so, my decision was still voluntary, although we might still seek to discourage these sorts of influences from being exerted.[27] Of course, it might be difficult to determine exactly what factors are influencing my decision prior to it being made, or even reflecting back after it has been made. (If I had made up my mind prior to the illegitimate offer being made, this would seem to be a less problematic case.) Unless the illegitimate influence is the only motivating factor, it would be fairly difficult to separate its effect from the concurrent effect of the other motivating factors, and unfortunately Appelbaum does not offer any clarification for how the efficacy of a certain influence is to be determined. Perhaps some sort of counterfactual test, where the person would imagine how he would act if the

[27] Ibid.

pressure had not been exerted might illuminate its effect on the decision. However, I would argue that unless a person is completely certain that a particular influence was not a motivating factor (a claim which might be based on this particular potentially motivating factor's opposition to the sorts of things that have motivated the person consistently in the past), we should assume that it played some role in the decision.

Though Appelbaum's four-part account of non-voluntariness is partly correct, it has several significant flaws. More specifically, his illegitimacy component categorizes as involuntary decisions which I will argue ought to be considered voluntary, because the individual who made the decision was able to act in accordance with the most strongly held desire they had available to be satisfied. For example, if I desire to go on a diet, and I do so, than my going on a diet was a voluntary decision. Of course, failure to realize the object of my desires does not render my decision involuntary. If I want to go on a diet, yet fail to do so for whatever reason, this only means that my desire to not diet outweighed my desire to diet. Perhaps some other option presented itself (e.g. an invitation to an all-you-can-eat buffet dinner), and I determined that I valued eating excessively more highly than dieting.

Alternatively, it might be the case that I wanted to have the desire to diet, but I failed to actually realize that desire. This notion of first and second order desires was introduced by Harry Frankfurt,[28] and goes basically as follows: The will of an individual is expressed in the choices that person makes; their motives and desires move them to act in one way instead of another. These desires and motives are 'first-order desires,' because they are desires for, and ultimately result in, some action: 'I want to diet' is a first-order

[28] Harry Frankfurt, "Freedom of the Will and the Concept of a Person," *Free Will*, ed. Gary Watson (Oxford University Press, 2003) 322-336.

desire, and having it explains the fact that I am dieting. Thus, it is impossible to do something without desiring to do it (though in some cases we may not be aware of the desire until after it has been satisfied), unless compelled by some external force (e.g. someone might push me from behind, causing me to fall, even though I did not have the first-order desire to fall).

A second-order desire, on the other hand, is a desire for a first order desire; it reflects a desire to be motivated in a certain way: 'I want to want to diet' is a second-order desire. Frankfurt calls the desire for a second-order desire to be a person's will (i.e. to become a first-order desire) a 'second-order volition.' Thus, it is possible for an individual to have many (and possibly conflicting) second-order desires simultaneously and moreover to have certain second-order desires which they would not want to become their will. I might be curious to know what it is like to be addicted to a certain drug, and so have a second-order desire to desire the drug (a first-order desire). Of course, I may have other first and second-order desires which would be compromised if the second-order desire to desire drugs became a second-order volition, and thus I would not want the object of my second-order desire (drug taking) to be carried out in action.

To return to the dieting example, if I ultimately fail to diet (i.e. my first-order desire to not diet overcomes my first-order desire to diet), this outcome arises for one of two reasons. First, I might have had the second-order desire to not diet, and so my not dieting is the proper expression of my will to not diet. Second, I might have believed myself to have had the second-order volition to diet, but as it turns out, I did not actually have this second-order volition because if I had, I would have done everything I could to make it a first-order desire. If I really wanted to be the sort of person who diets, I would

have done things like focus on all the positive aspects of dieting, and worked hard to convince myself that dieting was the sort of thing that I wanted to do, so that I would be motivated to do it. To have a particular second-order volition is simply to act in a way that will bring about the object of the second-order volition. So if I claim to have the second-order volition to diet, but I do nothing to make dieting a reality, I do not really want dieting to be my will.

In other words, it is impossible for an individual to perform the action (A) if he genuinely believes that it would be better to perform action (B). While he might believe that (A) is superior in certain respects to (B), and inferior in other respects, whatever action he ultimately chooses must be the one which he evaluated as the superior option all-things-considered. This is the sort of view argued for by philosophers like R.M. Hare[29] and categorically denies the possibility of *akratic* or 'weak-willed' action, which is the sort of action which occurs when an individual does (B) even though she is convinced that she would be better off doing (A). Hare argues that it is the purpose of evaluative judgments like 'I ought to do (A)' to guide our actions, and it is only such evaluative judgments which can provide action guidance (i.e. answer the question 'what should I do?'). Thus, if we assent to an evaluative judgment like 'I ought to do (A)', (i.e. we believe that (A) is the best option), this entails our assent to the corresponding imperative 'I will do (A)'. If it is in my power to do (A) now, and I do not do A now, it follows that I did not genuinely judge that I ought to have done (A) now.

Hare argues that any apparent case of 'weak-willed' action falls into two categories. First, the individual is actually unable to do (A) when they judge it to be best.

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[29] Richard M. Hare, *The Language of Morals* (Oxford: Clarendon Press, 1952); Richard M. Hare, *Freedom and Reason* (Oxford: Clarendon Press, 1963).

They may have determined that (A) is the best option and thus ought to be the object of their second-order volition, yet be overcome by emotions which render them psychologically unable to act in accordance with this second-order volition. Second, the individual might simply be mistaken about their evaluation; they do not genuinely believe (A) to be best. Rather, when saying that they believe (A) to be best, they actually mean that most people would consider (A) to be best. Here, the evaluative judgment the individual actually makes is not the same as the one he believes himself to have made, or which he communicates as the evaluative judgment he has made. Nevertheless, the course of action which he inevitably follows is necessarily the one which he thought was best.

Many philosophers have argued against the impossibility of weak-willed action, and their arguments seem to have a degree of intuitive support; it certainly seems like weakness of the will happens all the time. However, as Hare points out, there are serious consequences to accepting the possibility of weak-willed action, namely that it means evaluative judgments are not action guiding. If we can make an evaluative judgment about what is best, yet ultimately choose a different option, there seems to be no connection between our evaluations of what is best and what our actions are.[30]

The important point is this. An action is voluntary when the object of my second-order volition is congruent with my first-order desire; it is voluntary when the object I desire to become my will actually does become my will, and this results in action. And because whatever course of action I pursue is precisely the course of action I wanted to

[30] Donald Davidson and others writing after him have attempted to show that weak-willed action is in fact possible, though with limited success. For an overview of the weakness of will debate, see: Sarah Stroud "Weakness of Will," *Stanford Encyclopedia of Philosophy* (2008): online, 2 Aug. 2010. Available: http://plato.stanford.edu/entries/weakness-will

pursue (because any course of action I pursue is the one I evaluated to be best), any course of action I pursue is voluntary. Thus, if I believe that I want to be the type of person who diets, but come to have the first-order desire to not diet, I did not actually want to be the type of person who diets. My strongest desire ultimately prevailed and as such I acted in the way that I wanted to. More importantly, such a view does entail that the person who finds himself in a situation where he must decide between his money and his life (a classic example of an involuntary choice) does actually have a decision which he makes voluntarily, because if he chooses his life, that was clearly what he desired more strongly. The only time that a decision is involuntary is when I act according to a desire that is not 'my own' (i.e. I am unable to manifest my second-order volition as a first-order desire) or someone else's (and not merely my desire to act according to the desire of someone else.) Of course, it might be the case that I truly had the second-order volition to not give up the wallet, but was so paralyzed by fear that I acted against this desire. However, the point is that only when I act against my will is an action involuntary, and cases like the gun-toting mugger do not necessitate my acting against my own will; it is entirely possible to act voluntarily in these cases because it is entirely possible for me to desire either one of the two options available and act accordingly.

On Appelbaum's account my decision to give up my wallet is involuntary, because the mugger is exerting an illegitimate influence on me. But the fact that I am in a dilemma with no favorable options does not mean that my decision was not voluntary. For example, if I am arrested for a crime that I actually did commit, I might be given the following option: I could plead guilty in exchange for a lesser sentence, or risk a higher sentence by going to court. If I opt to plead guilty, clearly my decision was voluntary,

because this offer was not illegitimate. But let us compare the court case and thief case more closely. Both force me to decide between two choices, both of which are real options (i.e. I could actually choose either one), though neither of which I really want. However, one choice is clearly preferable to the other. The only difference is that the court case is an offer which respects my rights, while the thief case is not. But the type of choice which I am presented with (one which respects my rights versus one which does not) has no effect on the freedom of my will; I am still ultimately selecting the option which best satisfies my desires in either case. As far as the actual decision-making process occurs, both the thief case and court case are the same. If voluntariness is a concept meant to capture the freedom of a choice, how can one decision be voluntary and the other not, if both decisions were made freely? Granted, I should never have been subjected to the choice in the thief case but, given that I have, the choice I ultimately make is arrived at in the same way as in the court case. In this respect, context is not relevant for voluntariness; all that is required is for my actions to be congruous with my will (as expressed by my second-order volition).

It seems that, for Appelbaum, the decision is involuntary because I really desire neither outcome, but rather a third outcome where I keep my wallet and do not get shot. Of course, this would be an ideal outcome. However, it is not one of the available options. As such it cannot truly be an object of my will, because there is no action I could take which would bring about its satisfaction. I might wish that unavailable options were available, but I cannot will the impossible into possibility, because to will something is just to turn a desire into an action. If I could be taken to legitimately will unavailable states of affairs, then virtually all of my actions would be involuntary. Ideally I could

choose to fly to school rather than walk or take the bus. Ideally I could afford to go to a concert every night rather than watch TV or read. However, the fact that I would desire to bring about these states of affairs if they were available options does not mean that my decision to walk to school or watch TV is somehow involuntary because I am acting contrary to what my will *would have been*.

Of course, in a certain respect it is *possible* to not be robbed. We would certainly agree that the thief ought not to rob me, and because 'ought' implies 'can,' it follows that it is possible for the thief not to rob me. However, the fact that it is possible for a state of affairs to exist where the thief does not rob me has nothing to do with the options which are actually available to me, and so ought to have nothing to do with the voluntariness of my action. The fact that my available options have been limited does not impede the functioning of my will, and thus does not affect the voluntariness of my action. Granted, the thief does constrain the number of outcomes which I could make the object of my will, but this is a different matter than saying that I did not will the choice which I ultimately made. The functioning of my will is entirely internal. It can only affect the course of action I ultimately choose to pursue; it cannot affect the range of options available to me. Thus, to evaluate the proper functioning of the will in terms of external factors beyond its range of effect, such as the availability of certain courses of action, is a mistake.

Appelbaum's account is correct insofar as it differentiates between illegitimate and rights-respecting proposals. Obviously, he wants to argue that circumstances like the thief case are unfair in some way, and so we should not be held to the decisions which we make in these situations. Yet their unfairness comes not from the fact that they force us

into making an involuntary choice, (because what other than the absence of a desire is there to prevent us from choosing to be shot) but rather from the fact that we find ourselves in the sort of situation that we can be taken unfair advantage of. In other words, the ethical problem exists independently of any decision being made; whether the decision was made voluntarily has nothing to do with the problem. If there is an ethical problem, as our intuitions indicate, it arises not from the choice being involuntary, but something more along the lines of disrespect for the rights of persons. While I might voluntarily surrender my wallet to the thief, he is violating my right to not be threatened, (or my right to personal property, or my right of bodily integrity etc.) and it is *this* fact that renders the transaction unethical, not the fact that my decision was apparently made involuntarily. Applebaum's account mislabels the source of the ethical problem in these cases of apparently involuntary decisions, and this is why I take his account to be unsatisfactory.

The salient point of this discussion of voluntariness is that even if one is presented with an illegitimate decision, one can still make a voluntary choice; choosing between two unfair options is still a choice. A proper account of voluntariness ought to capture when an individual has acted according to her own will; when we say that a person acted voluntarily, we should be saying that they made the decision they wanted, from the available choices. Appelbaum's account does not do this. Rather, it says that some influences are illegitimate, and this compromises voluntariness. But voluntariness simply tracks the correspondence of my will and my actions, and as such cannot be compromised in the way Appelbaum seems to think. While illegitimate influences might constrict my available options, or present a strong reason to choose one option over the

other, they do not force me to will or desire anything. All they do is create a situation where one option is most congruous with what they take my will to be in the given context. Typically, people value their survival very highly and would desire that it be preserved. Thus, by threatening me with a gun, the mugger assumes that I value my survival and accordingly alters the situation so that satisfying this desire to preserve my survival involves me giving up my wallet. Never do I act in a way that is not in accordance with my will in this case. Of course, it might not have been my will to surrender my wallet prior to entering the mugging situation, but this point is irrelevant, for the reasons already argued. There is an important difference between the person who sees that surrendering the wallet best satisfies his desires, and the person who desires to stand up to the mugger but is overcome by fear and unwillingly surrenders the wallet. While my view can account for this difference by pointing out that in one case I am acting in accordance with my second-order volitions while in the other I am not, Appelbaum labels both of these cases involuntary.

1.7 Token Consent

The last portion of the informed consent requirement is the actual expression of the consent. An individual must in some way acknowledge that they understand what they are agreeing to, and that their permission has been given. Token consent may be expressed verbally, though in the context of clinical research an individual is typically required to sign some sort of legal release confirming their informed consent. This ensures that consent cannot be attributed to an individual who did not actually give consent, and also ensures that a person giving consent does not claim at a later period to

have not given consent. Additionally, the signing of a consent form does not preclude an individual from removing him or herself from the trial at any time.

1.8 Summary

In this chapter, we have closely examined the five components of informed consent, which itself is one of seven requirements for ethical clinical research. I have also argued that contrary to the standard account, voluntariness is simply the congruence of my second-order volitions with my first-order desires. In the Chapter 2, we shall see that the presence of an inducement does not compromise the voluntariness of a potential research participant, and thus the issue of undue inducement is wholly misguided. The real problem which inducements cause is a lack of comprehension on the part of potential research participants, and this requires a different sort of response.

Chapter 2: Undue Inducements

2.1 What Do We Mean By Undue Inducements?

There seems to be fairly broad consensus amongst those who write guidelines for research ethics committees that providing 'undue inducements' to potential research participants ought to be avoided. According to the Council for International Organizations of Medical Sciences (CIOMS) (2002):

> Subjects may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ('undue inducement').[31]

The US Common Rule for the Protection of Human Subjects states that:

> …an investigator shall seek consent only under circumstances that provide the prospective subject or representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue inducement.[32]

Similarly, according to Article 12 of the Council of Europe's Protocol on Biomedical Research (2007), ethics committees approving clinical research must be satisfied that "no undue influence, including that of a financial nature" has been employed to persuade individuals to participate in research.[33] Echoing this sentiment, Canada's Tri-Council Policy Statement (TCPS) (2009) requires that "where incentives are offered to

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[31] Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. (1993, 2002): online, 24 Jul. 2010. Available: http://www.cioms.ch/publications/frame_printable_publications.htm

[32] Ezekiel Emanuel, "Undue Inducement: Nonsense on Stilts?" *American Journal of Bioethics* 5 (2005): 9

[33] Council of Europe, *Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research*. (2007): online, 24 Jul. 2010. Available: http://conventions.coe.int/treaty/en/treaties/html/195.htm

participants, they should not be so large or attractive as to constitute an inducement to take risks that one would otherwise not take."[34]

Each of these requirements for the use of inducements reflects roughly the same concern: inducements such as money or otherwise unavailable medical treatment are sometimes offered in order to persuade people to participate in clinical research trials. This becomes an ethical issue when the inducements offered are so compelling that they cause potential participants to enroll in these trials against their better judgment. The IRB Guidebook, released by the US Department of Health and Human Services, states that:

> [undue inducements] may be troublesome because: 1) offers that are too attractive may blind prospective subjects to the risks or impair their abilities to exercise proper judgment; and 2) they may prompt subjects to lie or conceal information that, if known, would disqualify them from enrolling – or continuing – as participants in a research project.[35]

Similarly, the TCPS warns that "the offer of benefits in some contexts might amount to undue inducement, and thus negate the voluntary aspect of consent of subjects who may perceive such offers as a way to gain favor or improve their situation."[36]

2.2 What Makes an Inducement Undue?

Of course, the issue is not simply whether or not an inducement causes someone to alter their behavior; this is the whole purpose of inducements. When a potential employer offers a pay increase or health benefits to a potential employee in order to

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[34] Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 2nd* edition. (2009): 16 Jul. 2010. Available: http://www.pre.ethics.gc.ca/eng/policy-politique/tcps-eptc/

[35] Office of Human Resources, *Protecting Human Research Subjects: Institutional Review Board Guidebook*. (Washington D.C.: U.S. Government Printing Office, 1993)

[36] Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 2nd* edition. (2009): 16 Jul, 2010. Available: http://www.pre.ethics.gc.ca/eng/policy-politique/tcps-eptc/

entice them into accepting a position, or when a retail store offers discounts on merchandise in order to increase sales, the behaviors of those receiving the discounts or pay increases are being induced; they are behaving in ways that they would not have otherwise. However, few would find fault with such a system of inducements and the consequent behavior of those induced. It is only when the effect of the inducement is to render a decision involuntary that it becomes problematic, and is said to be 'undue'.

Yet it seems that something is missing from this definition: if an inducement is 'undue' when it causes people to act in a way that is not in their best interests, it would seem that we must have some notion of an individual's interests before we can assert that they have been unduly induced. Undue inducements are thought to render certain options irresistible which may compromise the voluntariness of a decision, as evidenced, for example, by individuals accepting unreasonable risks. Thus, it would appear that when ethics committees advocate against the use of undue inducements, they take themselves to be protecting the interests of a potential participant in one of three ways:

View #1: they are ensuring that individuals only enroll in trials for the right sorts of reasons according to some objective standard of values.

View #2: they are ensuring that individuals only enroll in trials for the right sorts of reasons according to the individual's own values; participation for the wrong subjective reasons is involuntary.

View #3: they are ensuring that individuals are enrolling in trials for reasons which are congruous with what is actually being offered in the trial; participation is always voluntary.

As we shall see, neither of the first two options properly capture the real issue which is mistakenly referred to undue inducement, while the third option can be ensured by enforcing a strict comprehension requirement.

2.3 How We Use Values in Making Decisions

We have seen that insofar as undue inducement causes individuals to act against their better judgment by acting in ways which are not voluntary, it appears to present a problem for informed consent in clinical research trials. Before moving ahead, a brief discussion of practical rationality is in order so that we can see how it is that we come to have the second-order volitions whose objects become our first-order desires; it is this progression which 'undue inducement' is argued to disrupt, insofar as it compromises voluntariness. The standard account of practical rationality can be traced back to David Hume, and entails that we are rationally required to pursue those means which will achieve our ends. As David Gauthier explains, practical rationality is concerned with maximizing utility, which is generally speaking the state of affairs that is most preferable (utility also incorporates the likelihood that our actions will bring about these states of affairs).[37]

First, we might suppose that every individual has a set of values arranged in some order based on the strength with which they are held. Furthermore, these values are what motivate our actions; I act in such-and-such a way because I think this is the best way to get what I desire. For example, I might generally value my personal health very strongly, my friendships with others slightly less strongly, and my personal wealth slightly less strongly still, and so forth for all of the things in life that I value. Moreover, if I strongly

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[37] David Gauthier. "Choice: Reason and Value," *Morals by Agreement* (Clarendon University Press, 1986): 21-59.

value my health, I ought to act in ways that will help me to maintain my health. I might see that people who exercise regularly are typically healthier, and as such I should desire to exercise regularly and in fact do so, because this will bring me something that I value, namely health. Similarly, if I value health over money, and am in a situation in which I could act so as to bring about greater health, or bring about greater wealth to an equal degree, I ought to act so as to bring about greater health, because I value it more. In essence, I am rationally required to consult my personal values and decide which things in my life are most important to me, and then act to bring those things about because this is the rational thing to do.[38] So, in the context of a clinical research trial, when I am deciding whether or not I should participate, the standard account suggests that I must consult my set of values and determine whether or not participation helps me to realize these values.

2.4 Objectivism v. Subjectivism

In order to understand why only the third option presented above adequately captures how the use of inducements are problematic in clinical research trials, it might be useful to briefly distinguish between several concepts: intrinsic goods and instrumental goods, as well as objectivism and subjectivism. On the one hand, intrinsic goods are those which are valuable for their own sake, because of a property the good thing has in and of itself; happiness, for instance, is often taken to be intrinsically valuable. On the other hand, an instrumental good is seen as valuable only insofar as it contributes to the realization of some other thing of value (either an intrinsic good or some further instrumental good); its value comes from the relation it shares with

[38] Duncan MacIntosh, "Prudence and the Reasons of Rational Persons," *Australasian Journal of Philosophy* 79.3 (2001): 346-365.

something else. For example, money is generally taken to be instrumentally valuable. As simply a piece of paper or circle of metal it has little value, but it is useful to us insofar as we can exchange it for other things that we want. Additionally, some goods might be simultaneously intrinsically and instrumentally valuable.

Objectivism in the theory of value is the notion that there are certain facts about the world, which obtain regardless of one's perspective. For example, if I say that X is inherently better than Y (not better for some instrumental reason, but simply because of its nature), and you say that X is not inherently better than Y, one of us is correct and the other is not. There is a fact of the matter about value judgments, such that they can be true or false. Subjectivism treats intrinsic value judgments as neither true nor false; as such they are merely a reflection of one's personal attitudes and beliefs. On a subjectivist account, when I say that 'family is the most important thing in life,' I am neither correct nor incorrect, and in fact likely just mean that 'I think that family is the most important thing in life.'[39]

Of course, there seem to be different appropriate responses to value which depend not only on features of the things being valued themselves, but also the agent doing the valuing. Depending on my unique set of desires and experiences, a certain object might have a particular value for me and a completely different value for someone else. If I am stranded on a desert island with no food, and I am offered a year's supply of rice or $5000, it might be an objective fact that the year's supply of rice has a greater value than the $5000, given my situation, even if a year's supply of rice is only worth $100. Thus, an objective ranking is based not simply on descriptive facts about the items being

[39] Albert P. Brogan, "Objective Pluralism in the Theory of Value," *International Journal of Ethics* 41 (1931): 287-295.

ranked, but also the situation in which the person finds themselves. Thus, an objectivist would hold not simply that food is more valuable in all times and places than money, but rather that in this specific circumstance it is an objective fact that I ought to find food more valuable than money.

While we do judge some values as being better or worse for a person to hold, it is only insofar as they are beneficial to the individual or society as a whole in achieving some end which is thought to be good. In other words, we can objectively judge certain values to be instrumentally good. For example, if I value good health, it is an objective fact that my valuing exercise is an instrumentally good value to have, if indeed exercise leads to good health. If exercising does not actually lead to good health, it would be an objective fact that my valuing exercise lacks instrumental value.[40] Similarly, we tend to view as good those values which contribute to the sort of society that the majority of people would want to live in (values such as honesty, tolerance, charity, respect for property etc.) because the having of these values, and moreover their being acted upon, is believed to foster the sort of society where intrinsic goods can be realized. Contrarily, values like deception, vengeance or violence are seen as less favorable because they detract from society as a whole, and in many cases are not even beneficial values for those holding them. For example, someone who strongly values violence might exert physical harm on someone else, yet will still be subject to the legal ramifications of this action; the satisfaction of one value, namely violence, conflicts with another value, namely not being imprisoned. Still, the 'goodness' of these values is not necessarily an intrinsic goodness, but merely a reflection of what the majority of people think is valuable.

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[40] Nicholas Rescher, *Introduction to Value Theory* (Prentice-Hall, Inc., 1969) 128-141.

2.5 View #1: Undue Inducement is Being Motivated by Bad Values

Consistent with the objectivist account of values, it does not matter whether or not a person actually does value, say money over health, or if they only think that they do because of the excessive nature of the offer. The problem is that choosing, for example, money over health in a specific case involves an objectively wrong choice; given the circumstances of the individual, and the various elements of participation in a research trial (i.e. the risks and benefits of participation), there is an objective fact about what the individual ought to do, yet they failed to act accordingly. When this is the case, they have been unduly induced. I will argue that this view of undue inducement is untenable.

Critics of providing inducements to potential research participants often argue that "a subject's decision to take part in medical research should not be primarily because of money," because it "might override more valuable reasons for taking part in research, such as the opportunity to contribute to scientific progress, [or] help other people…"[41] Research participation ought to come from a sense of altruism, (Phase I and II) or the desire to improve one's own health (Phase III). In other words, if someone is persuaded to participate in a trial because they value the money being offered, this is the wrong sort of reason for participating. As Christine Grady states,

> …it is sometimes argued that since research participants volunteer with altruistic motives, money has no place in this arrangement. The ethical concern, then, is not simply that some might find the offer of money irresistible, but also that money is simply not an appropriate motivating factor for research participation.[42]

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[41] Trudo Lemmens and Carl Elliot, "Guinea Pigs on the Payroll: The Ethics of Paying Research Subjects," *Accountability in Research* 7, (1999): 6.
[42] Christine Grady, "Money for Research Participation: Does It Jeopardize Informed Consent?" *American Journal of Bioethics* 1.2, (2001): 42.

Paul MacNeill argues that because "financial inducement to participate in research exposes people to risk they might not otherwise accept," we should not pay people to participate in research.[43] He claims that "payments cannot be justified when they act as an inducement to volunteer,"[44] especially because those most susceptible to inducement are the poor or socially disadvantaged. Since money can be such a strong motivator for these sorts of individuals, MacNeill claims that even 'out-of-pocket' reimbursements should not be offered in exchange for research participation because it can be difficult to determine when such compensation for inconvenience acts as an inducement.

Similarly, Ruth Macklin argues that "it is ethically inappropriate to pay patients to be research subjects [because] it is likely to be coercive, violating the ethical requirement that participation in research be fully voluntary."[45] Neither MacNeill nor Macklin seems to be against clinical research trials on the whole, rather they are merely opposed to financial inducements because of the effect they seem to have on potential participants.

Of course, a potential research participant has to be motivated in some way to participate in a trial (or else there would be literally no reason for them to participate), and so it seems safe to assume that both MacNeill and Macklin would agree that some reasons for participating in research (e.g. one's health interests) are better than others (e.g. money). Lynn Jansen argues that "people should be permitted to assume risks for

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[43] Paul McNeill, "Paying People to Participate in Research: Why Not?" *Bioethics* 11.5 (1997): 393.
[44] Ibid, 395.
[45] Ruth Macklin, "The Paradoxical Case of Payment as Benefit to Research Subjects," *IRB: A Review of Human Subjects Research* 11.6 (1989) 3.

the sake of contributing to the development of medical knowledge, especially if they care deeply about the cause," greater risks even than if they are motivated by personal gain.[46]

This seems to presume a sort of objective hierarchy of values which individuals ought to have (though in fact they may not, for whatever reason). Thus, when someone is 'unduly induced' to participate in a research trial, what has gone wrong is that they have been induced by the excessive offer to act according to values incongruous with the objective standard. There is some way that my values *should* lead me to act, but I am not properly motivated by these values. If a reasonable person (a person with their values 'properly' arranged and properly weighted according to the given circumstances) would not accept risk X in exchange for benefit Y, then a person who *would* accept such an arrangement must have their values improperly ordered as a result of the inducement; this is precisely what makes the inducement undue. If I was aware that benefit Y was the wrong sort of value to be motivated by given my situation, I would not have been motivated to accept risk X.

For example, I might be offered the chance to participate in a Phase I research trial offering me $5000 which I desperately need, but which will also result in considerable damage to my health. We might express this situation in the following way: I stand to keep 3000 units of health by not participating, and I stand to gain 5000 units of money by participating. Moreover, it is an objective fact that given my situation, every unit of health is equivalent to 0.8 units of value, while every unit of money is equivalent to 0.3 units of value. (We might even stipulate that it would be worth 0.2 if I were not financially desperate.) Thus, it is an objective fact that I ought to decline participation, because the value of declining (2400 units) exceeds the value of accepting (1500 units).

[46] Lynn Jansen, "The Ethics of Altruism in Clinical Research," *Hastings Center Report* 39.4 (2009): 26-36.

However, I do in fact accept, because I determine that every unit of health is actually equivalent to 0.6 units of value, and every unit of money is equivalent to 0.5. The presence of the inducement prevented me from recognizing that my value-calculus was improperly set, which resulted in my being unduly induced and consequently making the wrong choice.[47]

In fact, proponents of the sort of objectivist view discussed above would seem to hold that in the context of virtually all clinical research trials, the value which health ought to be assigned far exceeds the value which money ought to be assigned, such that virtually no amount of money would ever be more valuable than one's health. Thus, when potential research participants elect to place their health at risk in exchange for money, it is thought that they are almost invariably succumbing to undue inducement. It is important to emphasize that according to this conception of undue inducement, the ethical issue is not necessarily one of voluntariness being compromised. Rather, it is a separate issue pertaining simply to being motivated by the wrong sorts of values; this might happen even if my second-order volitions are congruent with my first-order desires. It might be that the course of action which I judged to be best all-things-considered, and thus made the object of my second-order volition, is the course of action I pursued and so my action was voluntary. However, I was simply wrong about what the best action all-things-considered actually was. Thus, undue inducement is problematic because it results in my making the wrong calculations about what would be the best course of action.

[47] Note that I might have the proper 'value order,' (i.e. I still value health over money, even in the unduly induced case) yet still make the wrong choice, because the amount of money offered is so large.

2.6 Even if True, Objectivism is Paternalistic

Even if we are willing to accept that unbeknownst to us an objective standard of values does exist, such that for a given situation there is an objectively correct course of action an individual ought to pursue, it not only seems to be beyond the capacity of REBs and researchers to make that determination, but would be paternalistic to do so. Paternalism can be generally defined as the interference by (A) into the affairs of (B), against (B)'s will, with the motivation that (B) will be made better off by the interference of (A).[48] In some instances paternalism is taken to be an acceptable practice, namely in cases where the person being interfered with is taken to be less than fully rational (e.g. young children, those suffering from severe mental illness etc.) However, paternalism in those sorts of cases where the individual is fully rational is arguably a violation of that individual's autonomy. Moreover, determining the objective value of certain actions and values would involve a very complex calculus, which would have to take into account a plethora of factors, and it is not unreasonable to suppose that an individual might have a better sense of what the objectively correct course of action is in a given situation.

Furthermore, even if a researcher *did* have a better sense of the objectively best course of action for an individual to take, it is the responsibility of the individual as an autonomous agent to determine if a particular course of action is the one they want to pursue, and to force them into making a particular choice by preventing them from participating in the research trial (on the grounds that their motivations are faulty) is a violation of their right to act autonomously. Perhaps the individual does not agree with the objective standard being used to evaluate the possible courses of action because it is not in keeping with their subjective values; maybe they simply do not care that one

[48] Gerald Dworkin, "Moral Paternalism," *Law and Philosophy* 24.3 (2005): 305-319.

choice is clearly superior according to some objective measure and they simply prefer the other choice. Individuals must be permitted to make their own choices with regard to pursuing the best life possible for themselves, and even if participating in a clinical research trial turns out to be contrary to this end, they still have the right to make the choice to participate.

2.7 View #2: Undue Inducement is the Confusion of My Value-Order

Contrary to View #1 above, perhaps what makes an inducement undue is not that it results in an individual making a decision that is incongruous with some objective set of values which he or she ought to have. Perhaps the problem will be found if we relinquish the notion of an objective set of values, and merely assume that each individual person has their own unique set of values which help to motivate their decisions. Under this framework, an undue inducement causing a person to act 'against their better judgment' might mean that they are acting in a way that is incongruous with their own values. For example, I might strongly value my personal health, and less strongly value money, but when offered an excessive amount of money to participate in a research trial which presents a significant risk to my health, the magnitude of the offer causes me to overestimate the degree to which I value money, and underestimate the degree to which I value my health. Were the amount not so excessive, I would see that I actually value health more than money, and would not agree to participate in the trial. Thus, by accepting the offer I am acting according to the wrong values *for me*; I only think that participation is in my best interests because I am confused about what I really value, and this confusion is caused by the excessive nature of the inducement. Thus, because I actually value (A), but choose (B), my voluntariness is compromised; the

course of action I 'actually' desired (insofar as it was apparently a proper reflection of my values) is not the course of action I took and so my second-order volitions were not congruous with my first order desires. Although this view seems more plausible than the previous view, it too fails to capture what makes an inducement problematic.

We can see this by considering what exactly it means to 'overestimate' or 'underestimate' the strength with which we hold a certain value. The way we determine the strength with which we hold values is by looking at the actions we would take to realize them; we do not simply decide how much we value something, and then act accordingly, but rather come to realize how much we value something by the lengths we are willing to take to realize it. (We might do this prospectively, by estimating what lengths we would be willing to go to realize a certain value, or retrospectively, by examining the lengths we have already taken.)

Recall our earlier discussion of second-order volitions: the action which I choose is necessarily the action I evaluated to be the best course of action all-things-considered. The fact that I am willing to work very hard to maintain my health is precisely what it means to strongly value health, while the fact that I am willing to work moderately hard to earn money is precisely what it means to value money less strongly. If I perform a certain action, this entails that I believed it to be best; I determined it to be the course of action most highly valuable. So, the notion of 'overestimating' or 'underestimating' how much we value something is incoherent; to value something is just to do it and we either pursue the course of action, or we do not. Or, perhaps to 'overestimate' the degree to which I value (A) over (B) would be to 'actually' value (A) more strongly, yet choose (B), thinking that I valued (B) more strongly. But precisely what it means to value

something is to choose it; whatever action I choose is necessarily the one I valued most. 'Overestimating' (or conversely 'underestimating') a certain value is thus akin to the sort of weak-willed action rejected in Chapter 1. It is impossible to value (A) over (B) all-things-considered and still choose (B), as doing so would mean that I really valued (B) all along.

Of course, the strength with which we hold our values (i.e. the lengths we would go to realize them) can change over time as we come to value different things more highly; while we might have been willing to devote significant amounts of time to the pursuit of money in early adulthood, we might be more inclined to devote time to family in later life. Similarly, if I am desperate financially I might value $1000 more so than I would if I were well off; I would be willing to do more for that $1000 in my current circumstances. So, if I agree to participate in a research trial because of the financial inducement, I am not compromising my values in doing so, because in the current circumstances, the financial inducement is something I value highly enough that I am willing to risk my health. An inducement does not change my values, but rather caters to certain values which I may or may not have, and the fact that an inducement might cause me to accept a certain risk in one circumstance while the same inducement would fail to entice another person, or me in a different circumstance, is not an indictment of the inducement (i.e. it does not make it 'undue'), because I am able to have any values I choose.

My right to autonomy implies that my desires, values, and whatever else moves me to act, are authentically mine and not externally imposed upon me. To limit the sorts of values it is acceptable for me to have amounts to a sort of oppression. While I might

not be *free* to act in any way I choose (i.e. I may not be able to act without external constraints like laws, or I may lack the resources to fulfill my desires), I surely have the right to determine those things that I value. Autonomy helps to ensure my responsibility for my actions, because those factors which motivated me to act in a certain way were genuinely my own, and present an accurate reflection of the type of person that I am or desire to be. In other words, my second-order volitions are congruous with my first-order desires, and as such my actions are voluntary. (However, the fact that certain inducements might appeal to me in certain circumstances, and those happen to be the inducements being offered by researchers, might be problematic in another way; specifically, this might be a case of exploitation. This point will be taken up in greater detail in Chapter 4.) The point is that the mere fact that an inducement is deemed excessively large does not make it ethically problematic, nor does the fact that the presence of an inducement causes a person to take on larger risks than might be considered reasonable; whatever course of action an individual pursues, whether it is to accept the large inducement and participate in a risky trial or not, is necessarily the one they valued most highly. As such, it is a proper reflection of their will and is therefore voluntary.

2.8 A Version of View #2: Emanuel

A good example of this second notion of undue inducement is captured by the work of Ezekiel Emanuel. In his 2004 and 2005 papers, Emanuel provides four criteria which he claims are necessary for the presence of undue inducement in a given case. [49]

[49] Ezekiel Emanuel, "Ending Concerns About Undue Inducement," *Journal of Law, Medicine & Ethics* 32 (2004): 100-105; Ezekiel Emanuel, "Undue Inducement: Nonsense on Stilts?" *American Journal of Bioethics* 5 (2005): 9-13.

First, some good must be offered which is valuable or desirable in exchange for performing some action. If someone is harmed as a result of poor judgment but no good was offered which led to their exercising poor judgment, the individual is merely imprudent or foolish. Second, this offered good must be sufficiently large or excessive that it is irresistible to the person to whom it is offered, in the context in which it is offered. If an offered good is only moderately large, it exerts less internal pressure on the person being induced and thus does not affect the ability of the person being induced to reason properly. Third, the offer must lead to poor judgment on the part of the individual, and fourth this poor judgment must lead to a "sufficiently high probability that he or she will experience a harm that seriously contravenes his or her interests."[50] If an individual is harmed, though not as a result of poor judgment on their part, they are simply unfortunate. Each of these criteria must be satisfied for undue inducement to occur.

Emanuel also claims that some harms are sufficiently mild that even when coupled with an excessive offer and poor judgment by an individual, they fail to result in a case of undue inducement. He argues that although reasonable people might disagree about what constitutes a 'serious risk of harm,' undue inducement applies to those risks which are clearly unreasonable. Daily activities such as driving a car, engaging in sports, or even riding in an elevator involve a degree of risk, though few people would consider these activities unreasonable because the severity of potential harm and the likelihood of its occurrence are sufficiently low. Though there appear to be a few difficulties with this definition (such as how large an inducement can be before it affects reasoning), it largely captures what bioethicists view as problematic about undue inducements, namely that they cause people to engage in risky behaviors or act in ways which are not in the best

[50] Ibid, 9.

interests of their health. Emanuel claims that we can apply a standard of what is excessive risk of harm for the average reasonable person in order to determine when an individual is unduly induced. He states that although the precise location of this boundary between reasonable and unreasonable cannot be strictly defined, we need not be concerned with where it falls exactly. Rather, we need only avoid those instances where a certain risk is clearly unreasonable. This is unsatisfactory for several reasons.

2.9 Why Emanuel's Account is Unsatisfactory

To begin with, it is entirely possible that the boundary between reasonable and unreasonable risk might differ significantly between otherwise reasonable people, simply because they happen to have different interests and values. While there may be some hypothetical clinical research trial that had such a high degree of risk that no reasonable person would participate in it, such a trial would never receive the approval of an REB because it would never satisfy the requirement of a positive risk-benefit ratio. It is *precisely those trials* which possess a degree of risk straddling the line between reasonable and unreasonable levels of risk which we must concern ourselves with when it comes to undue inducement. If a trial has a 99% chance of resulting in death (or some other clearly unacceptable risk), no amount of inducement would make accepting this risk seem reasonable. Contrarily, when the risk to the individual is just slightly above what they would normally subject themselves to, the presence of an inducement is just enough to overcome their risk aversion and cause them to participate in the trial.

Moreover, one cannot simply assert that activities such as skydiving or mountain climbing are such that no reasonable person would participate in them. While the risk of participation in such activities may not fluctuate significantly between individuals, the

value of the risk involved might differ greatly between them, such that participating in risky activities is entirely reasonable for some because it properly reflects their values. In fact, the whole reason that people engage in risky clinical trials is because they have determined the incentive to be of sufficient value that it is worth the risk. If this assessment is correct, then participation is *entirely reasonable*, because it is the course of action which will most likely satisfy their strongly held desires and values.

Emanuel also suggests that simply eliminating inducements for participating in trials is not an adequate solution to the real issue that preventing 'undue inducements' is attempting to address. His proposed solution to the problem is to simply prevent the possibility of clinical research trials which involve participants taking unreasonable risks. His argument is as follows: undue inducement can only occur when there is an unreasonable risk for an individual to accept. Under normal circumstances the individual would not accept the risk involved with participation, but given the presence of an excessive inducement, they act in a way contrary to their own notion of reasonableness (i.e. what they would recognize as unreasonable if they were not being influenced by the inducement), because the inducement is too highly valued to refuse. He claims that we ought not to simply get rid of inducements altogether as a way of avoiding this problem, because removing an inducement, undue or not, does not transform an unethical trial into an ethical one. In other words, if a research trial poses such unreasonable risk that participants ought not to be induced to participate, they should not be participating even if they are not induced.

Conversely, if a trial is such that unpaid participation is acceptable because it does not pose any significant risks to the participant, Emanuel argues that there can be no

problem with paid participation, because a necessary requirement of undue inducement, namely the presence of excessive risk to the participant, is absent. It is important to point out here that when determining the favorability of a risk-benefit ratio for a given trial, REBs should not take into account the inducements themselves as forming a portion of the aggregate benefits against which the risks of participating in the trial should be weighed. The risks must be reasonable only when compared to the benefits of taking the drug or receiving the procedure itself; it is here that a bioethicist would employ the requirement that risks not exceed the minimal possible level, or barely exceed this minimal level. If the ancillary benefits of participation (e.g. financial inducements in Phase I and II trials) are taken into account as benefits, an exceedingly large inducement might barely outweigh a still significant risk. In other words, researchers would be able to justify conducting trials with very high risk on the grounds that they have a positive risk-benefit ratio, though this favorability only results from the presence of excessive inducements.[51]

Unfortunately, Emanuel's solution is inadequate on several fronts. First, it fails to take into account the fact that ethical issues might occur even in cases where a participant is not subjecting themselves to an 'unreasonable risk,' and so eliminating clinical research trials which exceed a certain risk level would do nothing to prevent participation in these sorts of cases, because the level of risk is not the problem. Emanuel's assertion that greater focus ought to be paid to ensuring positive risk-benefit ratios likely stems from the fact that participants' health is seen as the greatest concern because it is a fairly ubiquitous value; nevertheless it is not unique in its importance. An individual might be

[51] Recall however, that according to the fourth requirement for ethical research, only health benefits are considered by REBs when determining risk-benefit ratios; financial benefits and the like are not considered.

induced into forsaking other strongly held values which have no impact on their health, and which more importantly may not derive from the riskiness of the trial. These values need not even be common; they might be highly idiosyncratic, yet strongly held by the individual and as such a person forsaking these values ought to be as pressing a concern as the forsaking of values pertaining to health.

For example, an individual might be extremely patriotic and only use products grown or manufactured in Canada. Yet the presence of a large financial incentive results in her participating in a Phase I research trial in which the drug being tested was not manufactured in Canada. In this case, the value compromised has nothing to do with her health and so it would still have been violated even if the trial posed minimal risks to her health. While an individual risking his or her health by participating in research is certainly a concern, participation in research trials might have a significant impact on more than just one's physical health. By preventing individuals from subjecting themselves to certain risks, Emanuel is guarding against individuals forsaking only one possible value.

Second, we might dispute whether we ought to prevent individuals from participating in behavior which is risky to their health in the first place. In fact, we allow individuals to participate in all sorts of behaviors which are not in the best interests of their health. Smoking cigarettes, as well as the excessive consumption of alcohol, are known to have adverse effects on the body, yet adults are not prohibited from engaging in either activity. Moreover, individuals participate in contact sports or other activities where risk of bodily harm is high, because the inducements to participation (i.e. the camaraderie and enjoyment of competition involved in team sports, or the adrenaline rush

of risky behavior like skydiving or swimming with sharks) are taken to be more important (i.e. more highly valued) than the risks involved (i.e. the preservation of one's health). So not only does Emanuel's account privilege the individual's health and dismiss other values which a person might have, it is not clear that we ought to limit the risks a person can take with their health to the degree he argues.

Third, empirical evidence suggests that potential research participants are rarely persuaded by financial inducements into accepting significant risks. According to Cynthia Cryder et. al.,[52] potential research participants typically associate greater financial inducements with greater health risk, and consequently they tend to investigate more closely those trials offering high inducements. In 2008, Cryder and colleagues conducted three experiments using participants from both high and low income/education groups in the Pittsburgh area. In the first experiment, participants were asked to evaluate the risk level of a study. One group was informed that participation offered $1000, while the other was informed that it offered $25. The $1000 group rated the study as significantly riskier than did those in the $25 group, with the findings being consistent across income/education level. A second experiment involved patients who believed they would be participating in the study, and measured the amount of information they sought. Those who were being offered more money sought significantly more information about the risks of the trial. In the third experiment, when participants were explicitly informed that there was a positive correlation between payment and risk, participants' wariness of the higher paying trial increased, and led to more information seeking.

[52] Cynthia Cryder, et. al., "Informative Inducement: Study Payment as a Signal of Risk," *Social Science and Medicine* 70 (2010): 455-464.

These findings suggest that rather than patients being less cautious about participating in a research trial with high inducements, participants might actually be *more* cautious when evaluating a potential research trial; moreover, some participants might underestimate the risks involved in trials with minimal inducements. Evidently, accepting a significant risk against one's better judgment (i.e. without adequate consideration of those risks that one is accepting) is not necessarily a result of high financial inducements; as such, Emanuel's proposed solution to undue inducements is one which potentially overestimates the problem.

2.10 View #3: Inducements Are a Problem When I Mistakenly Think an Option Satisfies My Desires

It seems then, that when ethicists take themselves to be talking about 'undue inducements,' the only thing they could actually be referring to are cases of inadequate comprehension by research participants. The knee-jerk reaction when a research trial offers an incentive and this leads to a participant accepting a significant risk is to claim that the participant has been 'unduly induced.' However, this conception of the problem is incorrect. Either the participant acted according to his or her strongly held values in making the decision, or they are experiencing a lack of comprehension. As a concept, 'undue inducement' simply does not do the work that its supporters believe it to be doing. Additionally, the mislabeling of certain sorts of problematic cases as issues of 'undue inducement,' erroneously suggests that a remedy to the problem is eliminating all of a certain kind of inducements. (In fact, we may want to consider offering greater incentives to participate in research on my view; this issue will be discussed later.) As we have seen, not only is there no such category of inducements which are uniformly 'undue' such that

we can simply prevent their use as participation incentives, but more importantly this distracts us from the real problem of inadequate comprehension on the part of participants.

The solution to preventing those problems that both Emanuel and other advocates of the 'undue inducement' concept fail to resolve must be one which addresses the problem at its source. This will ensure not only that potential research participants do not inadvertently subject themselves to excessive risks, but also any situation which might lead to the unintentional compromising of strongly held values. More specifically, the solution I will offer is to maintain a strict comprehension requirement for informed consent; if a participant fully comprehends the circumstances into which he or she is entering (the research trial), undue inducement is impossible. Emanuel claims that we must focus on ensuring that trials have favorable risk-benefit ratios, and not the status of inducements. Conversely, I believe that we must focus on ensuring that adequate comprehension is achieved by would-be participants; if this occurs, the presence of inducements becomes irrelevant to an otherwise ethical research trial (i.e. one in which coercion or exploitation does not occur, and that satisfies the seven requirements for ethical clinical research). Researchers do not need to stop offering inducements to potential research participants for fear that individuals might be unduly induced. Rather, they need only to ensure that a potential research participant fully comprehends the offer being made, and has a clear understanding of what the risks and benefits actually are; only the potential participant can properly evaluate these risks and benefits and in so doing arrive at the decision that is best for them in their present circumstances, provided they meet the other standards of informed consent.

2.11 Undue Inducement Does Not Identify a Unique Problem

The problem with the use of the term undue inducement is that it erroneously conveys the existence of a specific category of inducements which can justifiably be called undue, when no such category really exists. Granted, the presence of an inducement might be problematic in a given case: namely, if its presence contributes to the exploitation of a potential participant, or if it disrupts their comprehension and thus their informed consent. Yet these are very different problems, addressed with differing solutions. Moreover, inducements exist in *every trial* that researchers conduct; insofar as the participant has a reason sufficiently compelling to cause their enrollment, some element of the trial induced them to participate, whether it is some direct benefit they will receive, or because participating in research satisfies a strongly held value in some way. An inducement need not be of a certain magnitude or type (financial, health-related etc.) in order to generate a problem, and so it is misleading to single out only a certain type of inducement as 'undue.' Furthermore, the mere presence of an inducement is not in and of itself problematic; only when coupled with how it is perceived by the person being induced can ethical issues arise. The simple prospect of improved health might persuade an individual to participate in a Phase III trial in spite of significant risk, while an identical inducement would be insufficient to persuade a different person. This point alone seems to reveal a certain sort of hypocrisy in arguing for eliminating financial incentives for research participants: by allowing any research trials to occur in which there is some health-related incentive to participation, which by definition would appear to be all Phase III trials (because all involve at least the possibility of a health benefit), we

seem to be assenting to the propriety of offering at least *some* kinds of incentives to participate in research.[53]

2.12 Eliminating Inducements is Not the Solution

It follows from the subjective nature of what counts as an inducement for an individual that ethics committees often cannot know if the presence of a certain inducement will turn out to be ethically problematic; an inducement only functions as such when it is valued by the potential recipient. Consequently, eliminating a certain type of inducement is only effective if this type of inducement typically causes decisions against one's better judgment, in most cases. However, we have seen that no such class of inducements really exists. Nevertheless, the fact that the term 'undue inducement' is of minimal use does not mean that inducements to participate in clinical research trials are never an ethical concern. In fact, there seems to be one way in which the presence of inducements might turn out to be problematic, namely when the presence of an inducement prevents us from accurately determining whether or not participating in the trial actually satisfies the values that we have. Here, the issue is not whether our values are in the proper order, or whether we are acting on the correct values, but whether or not we are agreeing to what we think we are agreeing to. Consider a case of an extremely ill patient, who is offered the chance to participate in a trial which poses significant risks, in addition to the slim prospect of recovery. Because several other treatments have failed, the patient is willing to try virtually anything which might improve her condition. Thus, she agrees to participate in the trial because she believes it will be beneficial to her

[53] While one might make the argument that financial inducements are different insofar as they are akin to commodifying the body and this is objectionable, this is a different matter altogether from the one at issue here, namely whether or not incentives impede the exercise of an individual's better judgment when making decisions.

health, even though the trial actually poses significant health risks, such that participation would actually conflict with her strongly held values. The inducement of improved health renders her unable to fully comprehend the risks of participation, and consequently she fails to see that participation is not actually congruous with her strongly held values, because had she been able to understand, she would not agree to participate. It is important to realize that her decision to participate was still voluntary, because her evaluation of participation being the best option all-things-considered led to the formation of a second-order volition to participate, which she satisfied. However, the inducement prevented her from taking into account all of the pertinent information about the trial, and incorporating this information in her determination of which option was best all-things-considered. The inducement was all that she focused on, and on these grounds alone she determined that participation was the best option all-things-considered. This is precisely the purpose of a strong comprehension requirement: to ensure that potential research participants fully appreciate the details of each option, and are able to make a well-informed calculation of which option best satisfies their desires all-things-considered. It is critical to point out that the problem is *not* simply that the participant was persuaded by the inducement because they placed too high a value it, and on this basis decided to participate. Rather, the problem is that they did not understand their options. If the individual realizes the risk of participation but still determines the inducement to be sufficient incentive to participate, this is perfectly acceptable.

Or consider the case of a man who values money highly, and so agrees to participate in a Phase I trial for an arthritis medication in exchange for $1000. However, the man is also a vegan, a value he holds even more strongly than money. Unbeknownst

to him, the arthritis medication contains small amounts of fish oils, and so is a violation of his vegan practice; he was so enticed by the prospect of money that he was unable to take into account the possibility that other strongly held values might be compromised. In other words, he thinks that he is acting in a way that is in keeping with his strongly held values, but because he does not understand what is actually occurring, it turns out that he is acting in a way which forsakes strongly held values. It is important to differentiate between this case and one where the man is cognizant of the presence of fish oils, but forsakes his vegan values; this second case is merely a case of the man coming to realize which values he actually holds most strongly.

2.13 A Stronger Comprehension Requirement is the Solution

The problem which is erroneously labeled 'undue inducement' appears to involve a lack of comprehension by the participant; participation in the trial is mistakenly believed to satisfy the values of the participant when in fact it does not. While we might assume that an excessive offer would be the most likely candidate for a claim of undue inducement, this need not be the case. Rather, any sort of inducement whose presence causes the participant to mistake the treatment they will actually be receiving with the treatment they believe that they will be receiving ought to be considered 'undue' because it is causing the participant to make a decision that they did not want to make (i.e. they believe that they are agreeing to something other than the treatment being offered). So long as I am competent and fully understand what is being offered in the trial, any decision I make will properly reflect my current values, and so be reasonable in the given context. However, *any* inducement which contributes to my inability to comprehend the details of participation in clinical research trials is equally as problematic ethically, even

if the same inducement is taken as perfectly reasonable in other sorts of cases. It need not be a financial inducement, or an inducement which could be taken as excessive. By the same token, an extremely large financial inducement need not be labeled undue, so long as it does not impede the comprehension of the potential participant. It may properly be labeled exploitative (i.e. it is only reasonable for the participant to accept the risks of participation because of their dire financial situation), but this is not an issue specific to large inducements; the source of the ethical problem in this case is the unfavorable conditions in which the potential participant finds himself. (This will be discussed in greater detail in Chapter 4.)

Indeed, it is possible that potential research participants might lack the comprehension necessary to make their participation in a clinical trial ethically permissible, even where no inducement is present. These sorts of cases might be difficult to distinguish from cases of comprehension failure as a result of large inducements, but this may not be a significant problem. The purpose of comprehension tests which researchers administer to potential research participants is to ensure comprehension, not merely to ensure that the presence of an inducement is not disrupting comprehension. If there is some other factor which is preventing the individual from achieving an adequate level of comprehension, their participation is not ethically acceptable. The presence of a large inducement is one likely cause of comprehension failure, but it is surely not the only cause.

We might be concerned that a strong comprehension requirement would end up disqualifying many potential research participants, even those with clearly defined values. However, there seems to be no other way to ensure that an individual is actually

pursuing the course of action that best reflects their values than to make certain that they actually understand the course of action they are pursuing. Opponents of a strong comprehension requirement might suggest the following objection: (A) knows that he values money above all else, and so desires to participate in a research trial on the grounds that it will provide him with money. However, he is unable to comprehend the terms of the trial and is not permitted to enroll, even though both he and the researcher know that enrollment is in his best interests because it will provide him with money.

I would respond to this sort of case by pointing out that if both (A) and the researcher knew which course of action best satisfied the desires of (A), yet comprehension still could not be achieved, there might be legitimate questions about (A)'s competence to participate in research anyway. Setting this issue aside, it does seem possible that some individuals might be unnecessarily disqualified by a strong comprehension requirement, but I feel that this is a worthwhile cost for the benefit of ensuring that individuals are not enrolled in trials which violate their strongly held values and desires.

Another concern of those seeking to prohibit the use of large inducements which has only briefly been acknowledged so far is the risk of potential participants failing to report important health information so that they can remain in a research trial. For example, an individual who desperately needs the $500 offered for participating in a Phase II trial might hide the fact that he has had two heart attacks in the past 5 years because he knows revealing this information will disqualify him from the trial, even if the researcher screening potential participants warns him that the trial drug poses potential heart risks. I think it is unlikely that an individual with a full understanding of the risks

involved in a trial would believe it a good idea to omit important health information even if this meant disqualification; a strong comprehension requirement would work against individuals underestimating the risk of trials, which seems to be what leads to these sorts of cases.

However, we have seen that in some situations it is in an individual's best interests to accept significant risks. If the man in the above Phase II trial needs $500 to pay his rent by tomorrow, participating in research might actually be the best of a bad range of options. If individuals genuinely understand the risk of participation, they should be allowed to participate in spite of the risks to their health. Preventing high-risk individuals from participating in research trials seems essentially to be based on the notion that some risks simply are not worth taking, and so no competent person would take them. However, taking a large risk does not make a person incompetent, nor does it entail that they do not understand the magnitude of the risk they are taking. Individuals should not have to lie about medical conditions in order to remain in research trials; they should be warned at the outset of the risks to their health, and in those rare cases where a person actually determines that accepting this large risk is in their best interests, they should be permitted to do so. In short, if individuals are lying because they are underestimating the risks involved and want to continue in the trial, a strong comprehension requirement should prevent this.

Conversely, if individuals are lying because it is in their best interests to do so and they are fully aware of all the risks, this is not an issue of the sort typically characterized as undue inducement. The only foreseeable problem is that a lying participant might necessarily be unable to achieve full comprehension; in virtue of the fact that the

researcher is unaware of the potential participant's condition, they might not provide an adequate account of risk. In this case, the comprehension requirement is not met and so the individual should not be allowed to participate. This simply shows the importance of emphasizing all potential risks of participation, even if certain risks do not appear pertinent to a given individual, and ensuring that a potential participant comprehends even those risks which they claim do not apply to them. Again though, this would be a problem of comprehension, and not a case of a person being induced into acting against their best interests.[54]

In fact, as Cryder's research suggests, the presence of an inducement might actually contribute to comprehension, at least of the risks involved in participation. If individuals tend to correlate financial inducement with increased risk, a lack of financial inducement might prove to be more problematic than offering a considerable sum; no financial inducement seems to make potential participants less cognizant of risk and so impedes their comprehension. It seems that the presence of an inducement might work to compel potential participants to ensure their own awareness to a greater degree; the fact that they are enticed by the financial inducement is unproblematic if participation is in keeping with their strongly held values, and the presence of the inducement makes them more likely to verify that participation actually is in keeping with their strongly held values. Furthermore, it seems reasonable to extrapolate from these findings to a clinical setting, insofar as we might suspect that the presence of a significant financial

[54] Of course, a further important concern is that individuals who omit important health information are a risk to confound research data and thus impact the validity of the research trials in which they participate. However, this is neither an issue of informed consent to participate on the part of individual participants, nor is it more generally a concern about individuals being induced by excessive offers to act against their best interests. Certainly, researchers ought to be concerned about the possibility of potential participants providing inaccurate information, but this problem falls outside the scope of this paper.

inducement might be sufficient to break the therapeutic misconception (a topic to which I will turn in Chapter 3.) If this turns out to be the case, the expected decrease in research participants as a result of strict comprehension requirements might be offset, not only by a larger number of potential participants induced by financial incentives, but an increase in participant comprehension, brought on by the greater attention to detail a large financial inducement seems to generate. A paradigm example of the sort of undue inducement which will be eliminated by the comprehension requirement exists in cases of the therapeutic misconception.

2.14 Summary

In this chapter, I have considered three possible conceptions of the problem labeled undue inducement. The first view conceived of undue inducement as causing an individual to act according to the wrong objective values, while the second view conceived of undue inducement as causing an individual to act according to the wrong subjective values. I concluded that neither of these views is correct, and moreover that the problem typically mislabeled undue inducement is actually a problem of comprehension, and thus the solution is a comprehension requirement that is taken very seriously, and not the prohibition of certain types of incentives to participate in research.

Chapter 3: Informed Consent

3.1 A Distinction Between Research and Practice

Before examining the therapeutic misconception and the role of comprehension as a necessary component of informed consent in clinical research trials, it is important to first draw a distinction between treatment and research in a medical context, and to identify what constitutes consent in these contexts. Generally speaking, the overall goal within the treatment context is the promotion of the individual patient's health. Both physician and patient share this goal; the actions of the physician are understood to be in the best interests of the patient at all times. Of course, physicians and patients might disagree as to what the best interests of the patient in fact are or how to go about achieving the goal of patient health, but the salient point is that there is only one set of interests being served between the two parties: those of the individual patient. Charles Fried calls this coalescence of interests 'the principle of personal care,' and it is according to this principle that interactions between patients and physicians are governed.[55] As such, where the interests of the patient are represented merely by the restoration or preservation of health (and not necessarily the means by which this end is accomplished), a patient grants consent to a physician to perform those procedures which are necessary in routine physician-patient interactions, such as drawing blood, simply by appealing to the physician for help. For the sake of efficiency, the patient may not be fully informed as to the specific details or purpose of a given treatment or procedure, though it is understood to be acceptable by both parties on the basis of the principle of personal care; moreover, the patient always has the right to request further information.

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[55] Jessica Berg, et. al., "Fulfilling the Underlying Purpose of Informed Consent to Research," *Informed Consent: Legal Theory and Clinical Practice* (Oxford University Press, 2001): 279-307.

However, many patients seek the advice of a physician simply because physicians are presumed to be experts, and those patients are more than willing to simply take physician's advice in good faith. As we shall see, the difference between the context of care and the research context is the already established understanding between physician and patient that the primary concern is health. In cases where the only concern is the health of the individual patient, the patient has already given 'informed consent' (in a matter of speaking) to the physician, insofar as they understand that the physician will do everything they can to preserve or restore the health of the patient, and they consent to whatever treatment that might entail, provided that treatment does not involve serious risk.

Contrarily, in the context of medical research the physician- researcher is concerned primarily with the acquisition of generalizable knowledge. When the required steps for valid research diverge from offering the best care possible to the patient, this former interest supersedes that of individual health promotion; the researcher might take steps to ensure valid research data at the expense of the patient receiving the sort of care they would outside the research context. While some research participants are perfectly healthy (Phase I trials) and may in fact volunteer for clinical trials for altruistic reasons, and thus might have the same interests as the researcher, in most cases (Phase III trials) research participants are people who are ill and seeking treatment. In these circumstances, the interests of the physician-researcher and patient are not congruous. The difficulty stems from the fact that the patient assumes the existence of the principle of personal care because they find themselves in a situation sufficiently similar to a normal physician-patient encounter; namely, they are ill and are seeking treatment.

However, in order to gain the sort of information which is the purpose of a clinical trial (more specifically, RCTs), the standard view is that a physician must avoid providing care which is tailored to the individual's needs, so as not to confound the research data. Supporters of these sorts of trials assert that most RCTs are motivated by 'clinical equipoise' on the part of physicians: there is no clear consensus on which of several treatments is the most effective. As such, assigning patients randomly to one of several trial groups does not diminish the likelihood of their receiving beneficial treatment, because all patients are receiving what is, at the outset , thought to be equivalent treatment, regardless of the group to which they are assigned.

However, this ignores an important benefit of the principle of personal care by mistakenly presuming that all research subjects are equal. While RCTs attempt to provide the most generalizable data by controlling all variables except those to be tested, it is impossible to ensure that all subjects are 'the same' except for certain key areas. In a treatment setting, a physician might use her experience with this patient in the past, specific combinations of symptoms, or encounters with similar patients to inform her speculation about a potential diagnosis or to determine the best course of action. This sort of individualized care is typically lost to the participant of a research trial. Moreover, the level of informed consent which exists in the treatment context no longer applies within the research context, because the very thing that informed this consent, namely the principle of personal care, is no longer present. In such circumstances, it is extremely important that research participants make informed decisions, so as to determine the course of action which best suits their own ends.

3.2 The Therapeutic Misconception as a Paradigm Case of Comprehension Failure

Of course, these matters might not present such a difficulty for determining the ethical validity of RCTs if research subjects were aware of the divergence of interests between physicians and themselves. In many cases however, research subjects fall victim to a 'therapeutic misconception,' whereby they confuse typical treatment interactions between patient and physician with the different sort of interaction which occurs in a research context. As a result, research participants might overestimate the therapeutic benefit of participating in research and mistakenly assume that they will be receiving the best individualized treatment possible. According to Appelbaum's original statement of the therapeutic misconception in 1982 and reiteration in 1987, a person is under therapeutic misconception if they "deny the possibility that there might be major disadvantages to participation in clinical research that stem from the nature of the research process itself."[56] Subsequent interpretations have shifted the meaning of therapeutic misconception to include any mistaken belief held by subjects that research projects will directly benefit them, and not simply as a result of confusing the aims of research with practice;[57] however I will use it according to Appelbaum's original intent.

Research subjects under the therapeutic misconception mistakenly believe themselves to be entering into a trial with certain conditions, and it is because of their belief that these conditions are congruous with their values and preferences that they agree to participate. The problem is not merely that potential participants might

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[56] Paul Appelbaum, et. al. "False Hopes and Best Data: Consent to Research and the Therapeutic Misconception," *The Hastings Center Report* 17.2 (1987): 20.
[57] Jonathan Kimmelman, "The Therapeutic Misconception at 25: Treatment, Research, and Confusion," *The Hastings Center Report* 37.6 (2007): 36-42.

inadvertently agree to take on certain risks, but also that the lack of comprehension implies a violation of participant autonomy (in virtue of their lack of informed consent); they have not agreed to whatever is involved in participation because they did not comprehend exactly what participation amounted to.

For example, a participant in a research trial might be informed that half of participants will receive a new medication for arthritis pain, while the other half will receive the standard treatment, and that she will be randomly placed in one of the groups. While she understands in principle what the term 'random' means, she mistakenly assumes that those trial participants who are in need of care (which presumably would be all of them) will receive it, and consequently her participation in the trial would be a benefit to her. Of course, the chances that she will end up in the experimental treatment group are equal to the chances of ending up in the standard treatment group; as such, there is no guarantee that she will incur any direct health benefit from participation, because the experimental treatment may not be effective. Because the therapeutic misconception is based on a notion of the physician-patient relationship which is deeply entrenched in the minds of most research participants, it is extremely difficult to bring to people's attention; the presence of the therapeutic misconception at the very least poses a significant obstacle to the comprehension requirement of informed consent on the part of research subjects.

Consider an individual (A) who is suffering from a serious illness, which causes her great pain and discomfort. Her physician suggests participation in a Phase III trial for a new treatment which might help her condition. The physician informs her of the details of the trial, and estimates that participation has a 5-10% chance of improving her

condition, though there is a 40-50% chance that the medication will cause her additional suffering (with negligible long-term improvement). Conversely, the standard treatment for the particular stage of her illness has a 3-5% of improving her condition, but with only a 10% chance of causing her additional suffering. Because she is desperate to lessen her suffering, and because she mistakenly assumes that any treatment her physician would recommend could not would worsen her condition, which is something she seeks to avoid more than she values improvement, she agrees to participate. Now, consider another individual (B) who unfortunately finds himself in the same set of circumstances. The difference is that (B) fully understands that the chances of improvement are slight, yet feels that the risk is worth it. Even though both patients are accepting a significant risk to a strongly held value (i.e. their health), the fact that (A) lacks comprehension makes her case ethically problematic, while (B)'s case is not. Both patients have the right to act according to their strongly held values, and insofar as (A) fails to comprehend that the experimental treatment is much more likely than the standard treatment to cause her additional suffering (and not just slightly more likely to lessen her suffering), she is unable to make the decision that she wanted (i.e. that was most in accordance with her values.)

It is important to realize that because comprehension is necessary for subjects to ensure that they are able to choose the best course of action according to their values, comprehension is necessary even in those cases which are *prima facie* ethically unproblematic. For example, participating in a Phase III clinical research trial might appear to be in the best interests of a certain patient, because chances of success for the new treatment are high and risks are minimal. However, if the patient does not fully

comprehend the nature of the trial, researchers cannot be certain that participation really is in the best interests of the patient, according to the *patient's* values. They might believe that they are benefiting the patient by allowing them to participate in the trial, yet without the informed consent of the patient (which entails comprehension), this assumption is unjustified. As mentioned previously, the patient might have some distinctive value which is held very strongly, and violated by participation. Yet even if the participation *really is* in the best interests of the patient, but for whatever reason they fail to fully comprehend the nature of the trial, allowing them to participate is not justified.

For example, a patient suffering from arthritis might be given the choice between the standard medication, and the chance to participate in a Phase III trial to test a new arthritis medication against the standard treatment. His physician informs him that the current medication is moderately effective in 50% of patients, with no side effects, while the test medication has so far been highly effective in 75% of patients with only 2% of patients experiencing mild side effects (e.g. a slight headache lasting for 5 min after the medication is taken). According to the patient's own values, participation would be the best option. Unfortunately, the patient does not fully comprehend the offer and decides to participate because he believes that that his physician would only recommend the best possible treatment option. The patient was motivated by the inducement of improved health to participate, but the reason participation was interpreted as the best option was not because the patient actually recognized the greater effectiveness of the test medication but because of the therapeutic misconception. The presence of the therapeutic misconception removed (or at the very least mitigated to a sufficient extent) any

awareness of the negative aspects of participation, and so even though the patient would have participated if he had comprehended, the fact is he did not comprehend.

In short, the patient made the right decision (because as it turns out participation was in his best interests) but for the wrong reason. In this particular example the value violated was the patient's health, though the therapeutic misconception might have caused the participant to be ignorant of the violation of any sort of strongly held value; this would be equally problematic. Just as the importance of patient autonomy ought to allow research participants to justifiably subject themselves to a significant risk because a certain inducement is highly valued, the importance of patient autonomy ought to prevent researchers from subjecting research participants to even those trials where participation is believed to be in the best interests of the patient, unless patient comprehension is fairly certain.

Unfortunately, the therapeutic misconception seems to occur in a significant number of clinical research trials. In a study of potential clinical research trial participants by Appelbaum and Lidz, 69% of participants were unaware that their assignment to treatment interventions would be randomized, while 40% said explicitly that they expected assignment to be made on the basis of need, and 44% failed to recognize that the use of placebos and non-treatment control groups meant that some participants would not receive the experimental treatment.[58] Even more problematic is the fact that the therapeutic misconception need not even be the reason that patients do not comprehend the details of a trial. As we have seen from prior examples, one's dire straits might render one unable to comprehend the specifics of trial participation. Of course, as noted earlier,

[58] Charles Lidz and Paul Appelbaum, "The Therapeutic Misconception: Problems and Solutions," *Medical Care* 40.9 (2002): 55-63.

inducements are a part of every research trial; without an inducement (be it financial reasons, health reasons, altruistic reasons, the desire to please an authority figure, desire for human contact, entertainment, and so on) there is literally no reason to participate in a trial. It seems then that every conceivable trial is necessarily at risk of being ethically invalid, because the presence of any inducement might impede comprehension. It is for this reason that many theorists, such as Sreenivasan,[59] advocate a weakening of the comprehension requirement in order to prevent clinical research from grinding to a halt due to lack of suitable participants. There is no doubt that some otherwise suitable participants will be prevented from participating in research trials. However, the pivotal role a strong comprehension requirement plays in ensuring that patients act according to their own strongly held values more than outweighs the risks of decreased enrollment.

3.3 The Need for a Strong Informed Consent Requirement

One of the primary criticisms of the informed consent condition for ethically valid clinical research is that it is no longer required to ensure that participants are not entering into trials that are unfavorable to their health. Unfortunately, some research trials do not present a benefit to the participants but only to others (e.g. future patients), either because participants end up in a control group which does not receive treatment, or for other reasons. According to this line of reasoning, it is the role of REBs to examine and allow only those research trials where "risks to subjects are minimized," and "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be reasonably expected to result."[60] Thus, trials which exceed a

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[59] Gopal Sreenivasan, "Does Informed Consent to Research Require Comprehension?" *The Lancet* 362 (2003): 2016-2018.

[60] Charles Weijer and Paul B. Miller, "When Are Research Risks Reasonable in Relation to Anticipated Benefits?" *Nature Medicine* 10.6 (June 2004): 570.

minimum threshold of risk or whose potential benefits do not sufficiently offset the risks involved are not permitted; research participants never even get the opportunity to unwittingly stumble into them. Perhaps unsurprisingly, there is considerable debate as to how these imperatives are to be applied. Nevertheless, let us assume for the sake of argument that a valid notion of risk-benefit ratio exists, and that it adequately captures the spirit of protecting patients from research trials which place them at unacceptable risk. It would arguably follow from the necessary presence of a favorable risk-benefit ratios that any trial in which one could participate is sufficiently low-risk that a patient need not be informed about the trial in order to protect himself from undue risk; whatever he was protecting himself from by being informed has already been removed, and so there is no need for informed consent. Emanuel[61], Sreenivasan[62], and Truog et. al.[63] each hold something approaching this view.

The problem with this view and those approaching it is that it grossly oversimplifies the role of informed consent in research trials, and mistakenly reduces it to a means for patients to avoid trials with unfavorable risk-benefit ratios. In actuality, informed consent functions in much more important ways, not the least of which is to ensure that participants in research trials are treated as persons and not merely as illnesses which need to be cured or as research 'guinea pigs'. As we have seen, there may be other values informing the patient's decision to pursue a certain course of action besides simply ridding themselves of the illness; a patient's reasons for desiring a certain treatment are

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[61] Ezekiel Emanuel, "Undue Inducement: Nonsense on Stilts?" *American Journal of Bioethics* 5 (2005): 9-13

[62] Gopal Sreenivasan, "Does Informed Consent to Research Require Comprehension?" *The Lancet* 362 (2003): 2016-2018.

[63] Robert Truog, et. al., "Is Informed Consent Always Necessary for Randomized, Controlled Trials?" *The New England Journal of Medicine.* Vol. 340.10 (1999): 804-807.

important to the overall goal of health as the treatment itself, and must be respected. Thus, to weaken the informed consent requirement is to presume that researchers can adequately capture and accommodate all of the possible values of potential research participant within the context of a clinical research trial, such that for any patient if they were informed, they would still participate in the trial. Quite simply, this is a virtually impossible task, and any attempt would reduce complex people into simplistic types. Simply requiring that researchers disclose all of the important information does not ensure that potential research participants comprehend the terms of the trial to the degree necessary to determine if participation is consistent with their strongly held values. Critics like Sreenivasan argue that the minimum standard of disclosure required of researchers cannot be whatever it takes to ensure comprehension. Yet, it is only when a high level of comprehension is achieved by the potential participant that we can be sure that their desires and values are not compromised by participating.

For example, consider two treatments for some non-life threatening affliction A. Treatment 1, a long-established treatment, consists of injections once daily, and Treatment 2, a Phase III experimental treatment consists of taking a pill every other day; though Treatment 1 is quite effective, Treatment 2 has been shown to be slightly more effective in earlier trials, and is presumably much more convenient. However, a certain patient (x) might be extremely averse to taking medication orally, because he has a sensitive stomach. Yet Treatment 2 may be a more effective treatment strictly in terms of curative power, and so enrolling in this trial is what (x)'s physician recommends. Yet had he been informed of the details of the trial, (x) would have chosen to forego participation and simply opt for Treatment 1. Individuals might have highly idiosyncratic reasons for

preferring one sort of treatment to another, and to presume that a certain procedure will accommodate these values without asking the individual in question is paternalistic at best. There is no objective standard of whether or not the risk-benefit ratio of a trial has been assessed 'correctly,' (though perhaps there is some wide range that everyone would fall into) because it is only within the context of a participant's value system that risks and benefits can be given the proper weight for the individual participant.

Moreover, enrolling subjects into trials even with favorable risk-benefit ratios without proper informed consent is a violation of an individual's right to autonomy, because it treats them as a means to achieving research data, rather than an end in themselves. Because the end goal of research trials is generalizable knowledge and not necessarily individual care, some philosophers like Hans Jonas and Paul Ramsey[64] have argued that the only way to avoid treating research participants as means is if they so strongly identify with the cause of the researcher that they take it on as their own. I do not believe that quite so strong a stance is necessary; it seems to me to be sufficient that the physician-researcher and potential research participant work collaboratively to achieve the goals of the patient and by consequence achieve the unique goals of the researcher. By providing the research participant with all of the information possible, and ensuring that she understands, the physician-researcher enables the participant to make the decision which serves to best bring about the potential participant's desired outcome. Whether that turns out to be participation in the study or not depends on what the individual identifies as the 'best' treatment for her. If the potential participant has been properly informed and genuinely wants to participate in the study, it is inconsequential

[64] Jessica Berg, et. al., "Fulfilling the Underlying Purpose of Informed Consent to Research," *Informed Consent: Legal Theory and Clinical Practice* (Oxford University Press, 2001): 279-307.

that she happens to be serving the needs of the researcher as well. While she is being used as a means to acquire research data, she is also being treated as an end in herself via the satisfaction of her desire to participate in the study; the presence of her desire to participate --motivated by a desire for health which she determined was best realized through participation-- resulted in her participation.

By the same token, unless a participant is provided with all of the information possible, their ability to make a decision which maximally realizes their values is impeded. If an uninformed individual makes a decision regarding participation in a clinical trial, it would only be by coincidence that her ends are met if this is the way things work out. In other words, in order to fully respect individual autonomy it is not enough that the individual choose the course of action that they would have chosen anyway had they been fully informed, but rather they must choose the course of action they do because they are fully informed and have been able to weigh all of the information pertaining to each alternative, and incorporated their unique values. Also, there are unavoidable differences between the circumstances of the participant and researcher, even if the research participant does end up adopting the ends of the researcher as her own. The participant is accepting virtually all of the risks of treatment (complications of the treatment, even death), and so ought to have these possible conflicts of interest emphasized rather than glossed over in the name of unifying participant and researcher ends.

Critics such as Sreenivasan argue that this notion of the ‘privileged authority’ of participants as the most familiar with their own desires and values only works up to a

point.[65] He argues that individuals are not always infallible judges of their own interests, and points to the therapeutic misconception as an example of where individuals fail to recognize what is in fact in their best interests. This is supposed to show that individuals are not necessarily better judges of acceptable risk-benefit ratios than REBs, and thus a strong comprehension requirement is unnecessary. However, Sreenivasan seems to conflate an individual's knowledge of what is in their best interest, and the recognition of what actual course of action represents this interest. When a person is under the therapeutic misconception, they are not mistaken about what their interests are, they are mistaken in thinking that the treatment they have actually chosen is 'the same' as the treatment they have envisioned as satisfying their best interests. If Sreenivasan wants to claim that an REB is better able to tell what an individual's values are than the individual herself, he is surely mistaken. Conversely, if what he really intends to argue is that sometimes individuals make mistakes about what course of action is in their best interests, it is unclear how *removing* the only means by which they can determine the proper course solves anything. Rather than taking the decision out of the hands of the participants on the grounds that they sometimes make mistakes, a better solution is to put in place comprehension requirements which ensure that individuals are not making mistakes.

Moreover, placing this responsibility in the hands of an REB does nothing to remedy the situation unless we suppose there to be a 'correct' assessment of risk-benefit ratio, which as mentioned above is an untenable position. A strong comprehension requirement helps to ensure that potential research participants do not agree to participate

[65] Gopal Sreenivasan, "Does Informed Consent to Research Require Comprehension?" *The Lancet* 362 (2003): 2016-2018.

in research which is contrary to their own strongly held values and desires, by requiring that potential research participants actually know and understand the research conditions. In this way, they are able to make an accurate comparison between what the trial actually involves and what they desire from the trial, and on this basis evaluate the benefit of participation. A strong comprehension requirement helps to ensure that individual's are actually doing what they want to do. It might appear that a strong comprehension requirement is equally as paternalistic as views I have rejected earlier. The difference is that a strong comprehension requirement does not make any evaluation of the values or desires by which an individual is motivated to act; it is meant only to ensure that the course of action an individual chooses is actually the course of action they meant to choose because it will lead to the outcome they desire, without making an evaluation of the outcome. Determining what the best interests of the individual are is left to the individual, while the sort of paternalism I reject is the type which does make an evaluation of potential outcomes, and restricts an individual's actions to those which would be best for the individual, whether the individual thinks so or not.

3.4 Informed Consent as an Expression of Autonomy

At this point, we have seen that informed consent by research participants is an integral component of an ethically valid research trial. In the absence of informed consent, there is no genuine consent of any sort, because the consent given lacks a real object and thus lacks content. Moreover, informed consent is not merely a method of protecting participants from risky trials, but rather a vehicle by which they can ensure that their autonomy and personhood is respected. Clearly, to dispense with informed consent would be a mistake. However, the very reason its critics are motivated to

attenuate it as a requirement is worthy of criticism as well; it is a problem which pervades all sorts of issues in bioethics and philosophy at large. Those who oppose a strong informed consent requirement argue that it is an impediment to valuable research, and if we restrict the pool of potential participants by disallowing those who cannot give fully informed consent, research will grind to a halt.[66] There are a number of problems with this view, the first of which is quite straightforward. The purpose of ethical principles governing science of any kind is to articulate those standards which our society takes to be valuable and wants preserved; they are not supposed to be applied only when doing so is easy. Research practice ought to accommodate ethical principles and not the other way around.

Furthermore, critics of the informed consent requirement might argue that it places too great a responsibility on researchers to ensure participant uptake; in some respects this is not something they can control. If researchers provide all of the relevant information and explain it in a clear and concise fashion, there is little else that they can do to create understanding; some responsibility has to fall to the patient to ask questions when they do not understand. As well, the already complex task is made more so by the fact that it is difficult to evaluate whether or not uptake has actually been secured. A patient might mistakenly think that they understand, yet still be under the therapeutic misconception. While I am sympathetic to the difficulty of overcoming the therapeutic misconception and ensuring patient understanding, the fact remains that it is not the *right* of researchers to do research; more specifically, just because most researchers prefer RCTs, they are not therefore entitled to conduct them in all cases. Simply because an

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[66] Robert Truog, et. al., "Is Informed Consent Always Necessary for Randomized, Controlled Trials?" *The New England Journal of Medicine* 340.10 (1999): 804-807.

REB gives approval to a trial does not mean that it ought to be conducted, but only that it is permitted on the assumption that willing participants can be recruited.

Similarly, if the concern is that fully informed patients do not want to participate in trials and consequently research grinds to a halt, this would seem to be an indication by the public that they do not value the type of research being done, or the method by which it is being done. The fact that a participant would likely refuse to participate if they were informed is *more* of a reason to require informed consent, not less, even if it would result in few research trials being conducted. This should incite researchers to change their methodology, perhaps by more readily accepting data acquired by less stringent research methods than RCTs (or by variations of RCTs that allow for things like tailored dosing), and not seeking to relax the requirements upon which ethically valid research is based.

Sreenivasan argues that informed consent is not required to protect patients because REBs do a much better job of assessing the favorability of a trial's risk-benefit ratio than an individual patient. As we have seen, this claim is false because the risk-benefit ratio of a trial should also be assessed on an individual level, so as to properly incorporate patient values. Moreover, he argues that individuals "retain the right not to enroll in a trial…Even without comprehension, individuals are always free to choose not to participate in research."[67] While this might be true in some sense, it is a gross oversimplification of the issue; of course participants are not forced into trials, but this is not the problem. The problem is that the basis on which a participant 'freely chooses' to enroll in or withdraw from a trial might be faulty. His second-order volition has as its object participation in the trial, and in participating he realizes the object of his will.

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[67] Gopal Sreenivasan, "Does Informed Consent to Research Require Comprehension?" *The Lancet*, 362 (2003): 2017.

Therefore, his participation is voluntary. However, the participant determines participation to be the best option all-things-considered on the basis of faulty evidence; the reason he believes that the particular course of action he chose was best all-things-considered is because he did not fully comprehend the nature of the options available. Surely he *could* refuse to enroll, but given his (mis)understanding of the trial, he *would* not. In fact, many physician-researchers are averse to discussion of their own uncertainty about the best possible treatments. As such, they can "underplay, distort, or even conceal information that would ordinarily be considered important in disclosure prior to obtaining consent."[68] Insofar as he lacks a reason to refuse enrollment, the participant cannot refuse without acting irrationally; and it does not make sense to suppose that he would knowingly act contrary to his beliefs about what will improve his health, if his goal is to improve is health. Given the possibility that researchers are providing participants with a biased version of what a potential treatment will actually amount to, the reasons a participant has for enrolling are similarly biased; as we have seen, a participant's consent must be informed in order to be meaningful. So perhaps Sreenivasan is strictly speaking correct that participants are free to enroll and withdraw even if they are uninformed; however, this is point is rather inconsequential. The real issue is what decisions a potential participant would make, given the circumstances and the amount of information they have.

3.5 Summary

In this chapter, I have examined the effect of the therapeutic misconception on potential research participants, and argued that the best way of overcoming this obstacle to informed consent is to require a high level of comprehension from research

[68] Ibid, 2017.

participants. I have also argued against the views of those opposing a strong comprehension requirement, who claim that minimizing risk is the primary purpose of informed consent, and that other methods are more effective in accomplishing this task. What these critics fail to acknowledge is the diverse role of informed consent in not only protecting patients from harms, but respecting their autonomy.

Chapter 4: Conclusion

4.1 Inducements and Coercion

We have seen so far that the notion of an 'undue inducement' is not useful in evaluating the ethics of clinical research trials. An inducement is only problematic when it impedes the comprehension of a potential participant, and because inducements of some kind are necessarily present in clinical research trials, seeking to eliminate certain types of inducements misses the real issue. Thus, it seems that the use of inducements is unproblematic in any case, provided participant comprehension meets a sufficiently high standard; this standard must ensure that participation is congruous with the strongly held desires and values held by the potential participant, because it is these values and desires which motivate decision making. Yet we might worry that the presence of inducements could create ethical problems in other ways than by compromising the voluntariness of potential participants; namely, they might be exploitative, or coercive. It is to these issues which we now turn.

4.2 What is Coercion?

A cursory discussion of coercion is in order here. The Belmont Report defines coercion as occurring when "an overt threat of harm is intentionally presented by one person to another to obtain compliance,"[69] while the TCPS states that coercion "involve[s] a threat of harm or punishment for failure to participate. Coercion would negate the voluntariness of a decision to participate in a research study."[70] A coercive

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[69] Alan Wertheimer and Franklin Miller, "Payment for Research Participation: A Coercive Offer?" *Journal of Medical Ethics* 34 (2008): 389.

[70] Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 2nd* edition. (2009): 16 Jul. 2010. Available: http://www.pre.ethics.gc.ca/eng/policy-politique/tcps-eptc/

offer involves the constraining of one's options such that the best available option is the one which the coercer wants the person being coerced to choose; the person being coerced has no reasonable alternative but to accept the proposal of the coercer. Additionally, both Alan Wertheimer and Franklin Miller[71] and Jennifer Hawkins and Ezekiel Emanuel[72] claim that the narrowing of one's options has to be the result of someone else's purposeful manufacturing. If certain random occurrences leave us in a bad situation, the choices we make are not necessarily coerced.

Importantly, determining whether someone is made 'worse off' by a supposedly coercive offer is dependant on where we establish the moral baseline relative to which someone is better or worse off. In a patently coercive case, this baseline is quite clear; in the 'your money or your life' example, not only is the person who is coerced into surrendering his money made worse off, but he clearly has the right to keep both his money and his life. Conversely, if a transaction renders a person worse off than if no transaction had occurred, but the consequences of refusing the offer do not violate the rights of the person to whom the offer is made, the transaction is not coercive. Wertheimer provides this example: (A) might be charged with a crime unless he testifies against (B), in which case he will be given a lesser sentence. While (A) is certainly worse off if he does not cooperate and is charged (refuses the transaction) than if he had never been charged (no transaction), his being charged would not be a violation of his rights, and so his accepting the deal is not coerced.

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[71] Alan Wertheimer and Franklin Miller, "Payment for Research Participation: A Coercive Offer?" *Journal of Medical Ethics* 34 (2008): 389-392.
[72] Jennifer Hawkins and Ezekiel Emanuel, "Clarifying Confusions About Coercion," *Hastings Center Report* 35.5 (2005): 16-19.

4.3 Inducements Cannot Be Coercive

As Wertheimer and Miller[73] suggest, some theorists maintain that offers of financial payment can nevertheless be coercive because the person being offered the inducement has 'no reasonable alternative,' but to accept. On the one hand, the difference between one offer and the other might be so large that only one offer would be reasonable to accept. Of course, this alone does not entail coercion. I might be offered $1000 to walk my neighbor's dog, and because the difference between my two options (walking the dog and receiving $1000, and not walking the dog and receiving $0) is so great, I have only one reasonable course of action. Yet this is clearly not a case of coercion, because my choices are not actually constrained; the 'unreasonable' option of not walking the dog is still open to me, I have just determined it to be ridiculous to pass up the other alternative. In fact, if having 'no choice' in this sense impeded voluntariness in a way that negated informed consent, it would seem that informed consent could only occur when there was little difference between the two options.

On the other hand, I might be faced with a terrible situation if I refuse the offer. For example, I might die of cancer if I refuse to consent to life-saving surgery and thus I have no choice but to consent to the surgery. Yet this is not coercion either, for the same reasons as before. It is important to distinguish between ethical problems in the background situation, and ethical problems with the offer itself, and so the fact that one has no reasonable alternative but to accept an offer does not in itself imply coercion. Moreover, if the concern with coercion is that it forces individuals into choosing one of

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[73] Alan Wertheimer and Franklin Miller, "Payment for Research Participation: A Coercive Offer?" *Journal of Medical Ethics* 34 (2008): 389-392.

two or more intrinsically unwelcome choices, it is difficult to see how the situation is improved by removing the best of their options.

As Janice Richards correctly argues, if the constriction of circumstances leaves people incapable of making rational decisions, their informed consent is invalidated by their failure to satisfy the competence requirement; the problem is not one of voluntariness.[74] Voluntariness corresponds to whether or not a person acted according to a will that was free when they made their decision; if my house burns down and I need to sell a kidney to feed my family, I am still acting according to my strongly held desire to feed my family by selling a kidney. Of course, the stress of this catastrophe might have rendered my basic reasoning skills ineffective. If this is the case, I am either failing to understand that selling a kidney is actually *not* in the best interests of feeding my family, (a comprehension problem) or I lack the capacity to understand this fact altogether (a competence problem).

I agree with Wertheimer and Miller, as well as Hawkins and Emanuel that coercion is ethically problematic, though not because it renders an individual's decision involuntary (as the standard account dictates), but because it is a violation of individual autonomy. As we saw earlier, voluntariness is compromised only when an individual does not act in accordance with their own will, and this is not necessarily the case in a coercive situation. Coercion involves the constricting of an individual's options in a way which is unjustified, and though it typically renders one possible option overwhelmingly more reasonable than another, this does not force the individual into selecting this option.

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[74] Janice Richards, "Consent with Inducements: The Case of Body Parts and Services," *The Ethics of Consent: Theory and Practice* eds. Franklin Miller and Alan Wertheimer (Oxford University Press, 2010): 281-305.

In other words, it is entirely possible to be coerced into making a decision, with this decision nevertheless being made voluntarily.[75]

However, there is another sense in which we can argue that coercion is ethically wrong, namely that it renders an individual 'less free' in some interesting way. While the decision the coerced individual ultimately makes might still be 'free' insofar as it is congruous with her will, the fact that choices available to her were unjustifiably constrained is an impingement of her freedom to act. For example, the gunman who threatens to kill me if I do not surrender my wallet is making a coercive offer; he is making one of my available options far less appealing than the other, in order to obtain my compliance. Once I am in this circumstance, whatever decision I make is voluntary, because I can determine which of the two unfavorable options best satisfies my desires and values. However, the coercive offer eliminates the option where I get to keep my wallet and not be shot; a valuable option has been eliminated, and thus I am less free.

Importantly, not all cases in which my available options are constrained entails coercion; only when such constraint is unjustified. While the gunman has no right to threaten me with harm, the government may be within its rights to threaten me with prison if I rob a bank. Here, I am prevented from robbing the bank and avoiding prison (which is a constraining of one of my options), but this sort of constraint is justified, because it actually contributes to the freedom of society (and thus my own freedom) by ensuring that a system of property can exist. In short, because it violates their freedom in an illegitimate way, individuals have the right to not be subject to coercive transactions.

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[75] I recognize that this may sound strange to most people, given the standard definition of voluntariness. Recall however that on my account an action is voluntary when the first-order desires which motivates my action is congruous with my second-order volitions. Even in a coercive situation there is one action which I would prefer to the other and thus would desire to become my will and manifest itself in action, even if both are very bad.

Nevertheless, the simple fact that an inducement expresses a genuine offer entails that by definition it cannot be coercive. As such, we need not worry about inducements functioning in a coercive way.

So far, I have argued that inducements to participate in research do not compromise the voluntariness of potential research participants, and that a strong comprehension requirement will serve to eliminate the ethical issues which arise from the presence of inducements to participate in research. I have also argued that inducements to participate in research are not coercive. The last problem to consider is whether or not inducements are exploitative, an issue to which we now turn.

4.4 What is Exploitation?

At a very general level, the sort of exploitation to be considered here amounts to person (A) taking unfair advantage of person (B). However, the broadness of this definition allows for varying accounts of whether or not a particular situation is genuinely exploitative. Much like the concept of 'undue inducement,' the readiness with which accusations of exploitation are made shrouds the fact that it is a concept not easily captured. As Alan Wertheimer argues in his "Exploitation in Clinical Research", many theorists seem to accept what he calls the 'exploitation argument': 1) If a practice is exploitative, it should not be permitted. 2) Placebo-control trials (PCTs) such as the Surfaxin[76] trial are exploitative. 3) Therefore, PCTs should not be permitted.[77]

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[76] In 2000, Discovery Labs proposed a research trial comparing Surfaxin, (a treatment for Respiratory Distress Syndrome (RDS) in infants), with the treatment Survanta. Although placebo-controlled trials of surfactants are considered unjustifiable because so much is already known about these sorts of drugs, Discovery proposed to go ahead with a two-arm placebo controlled trial in Bolivia with a study population of 650 infants. Discovery planned to provide endotracheal tubes, ventilators and antibiotics for all study participants, although there was no plan to market Surfaxin in Latin America. Parents of infants with RDS would provide consent, at which time the infants would be intubated, and either receive air suffused with Surfaxin, or air without any drug. This trial was thought to be exploitative because those participating had a 50% chance of being placed in the placebo group, in which they would receive no treatment.

Wertheimer states that this argument moves too quickly, and he is certainly correct. It is not always clear when a certain trial is exploitative; though many theorists would claim to know an exploitative research trial if they were presented with one, the usefulness of such knowledge is limited unless accompanied by some definition on which to base their claims. Moreover, it is not clear that all clinical research trials which are exploitative should not be conducted. If it is possible that those being exploited can nevertheless give adequate informed consent, perhaps the trial should not be prevented. We saw earlier that as long as research participants exhibit full comprehension, they ought to be able to accept any offer made to them by researchers. I argue here that even if the inducement is exploitative, the presence of informed consent by an eligible participant to which an offer of participation is extended makes their participation ethically acceptable. However, this does not mean that exploitative trials ought to be allowed to occur. Let me explain how these two seemingly contradictory claims can be resolved.

Two questions must be addressed. 1) Can a person give genuine informed consent in an exploitative situation, and if so, 2) does the presence of informed consent on the part of the person being exploited make the exploitation acceptable? Before answering these questions, a more detailed definition of exploitation is in order. Wertheimer usefully distinguishes between two different sorts of exploitation: harmful exploitation, and mutually advantageous exploitation. As its name might suggest, harmful exploitation occurs when the exploited party is harmed by the exploitation; slavery would be one such example because the slave-master gains significantly from the unpaid labor of the slave, while the slave is worse off than he would be if he was not a slave. On the other hand,

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[77] Alan Wertheimer, "Exploitation in Clinical Research," *Exploitation and Developing Countries: The Ethics of Clinical Research* eds. Jennifer Hawkins and Ezekiel Emanuel (Princeton University Press 2008): 63-104.

mutually advantageous exploitation occurs when both the would-be exploiter and exploited reasonably expect to gain from the transaction; both would be better off than if they did not make the transaction. This can often be difficult to determine, though an obvious sort of case might be between an athlete and team owner; the owner uses the athlete to make money selling tickets, while the athlete gets paid a salary which is far less than the amount which he generates for the owner. The owner profits from the work of the player, and the player makes more money than he would if he did not play; both parties are better off than if they had not made the agreement.

What exactly does it mean to 'take unfair advantage of' someone? Wertheimer claims that we can understand this notion in one of two ways.[78] First, we might believe that the outcome of the exploitative transaction is unfair; either because (A) has no right to benefit from (B) in this way (e.g. because of harms incurred by (B)), or because the benefit incurred by (A) is so much greater than that incurred by (B). Second, we might believe that there is some problem with the process by which the outcome is brought about; (A) might deceive (B) or fail to provide (B) with important information.

As Wertheimer points out, (A) can only take *unfair* advantage of (B) if (A) actually receives some benefit from the transaction. Thus, cases of oppression or discrimination in which the oppressing or discriminating party does not incur a benefit are not exploitative, though they may be morally reprehensible for other reasons. Conversely, (A) can exploit (B) even if (A) has good intentions and a benevolent end in mind. For example, a charity might exploit a celebrity to generate funds for a relief effort.

Clearly, (A) must benefit to exploit (B). For any transaction, there can be one of three potential outcomes for (B). Either there is no effect, a positive effect, or a negative

[78] Ibid.

effect. A transaction which has no effect on (B) is one where (A) takes advantage of (B), yet (B) is no worse off. If (B) is reading a newspaper on the bus and leaves it when he is finished, and (A) picks it up and reads it, (A) is better off because of (B), but (B) is no worse off. Most cases of exploitation are taken to have a negative effect on the exploited party, where (A) gains by harming (B). Slave labor, extortion, and fraud are obvious examples of negative outcomes.

The more interesting sorts of exploitation are those resembling the athlete example, where both parties appear to be better off than they would be if no transaction had occurred. Wertheimer insists that when assessing apparent benefit, it is important to take an 'all-things-considered' approach, because certain aspects of almost any transaction will be negative and certain aspects will be positive. If I desire to sell my car and do so for a fair price, the fact that I no longer have a car is certainly a negative aspect, yet as Wertheimer points out it would be a mistake to think that this fact means I was harmed in the transaction, because I received fair compensation. Additionally, if it later turns out that I could have sold the car for a much higher price, I have not thereby been harmed in the transaction which I did make; prior to making the deal it was a clearly beneficial transaction, and although it turned out after the fact to have been a mistake, it was not a morally problematic transaction.

Wertheimer also argues that one party's taking advantage of the other's vulnerabilities does not necessarily amount to exploitation, provided that the distribution of the benefits is fair. Taking advantage of an individual's unfair circumstances is not in and of itself morally objectionable; it is only when one party uses the vulnerabilities of the other to take unfair advantage of them that problems arise. For example, if (B) is very

ill and (A) offers to sell her medicine which will cure her illness for a fair price, this is not a case of exploitation. The fact that (B) is ill puts her in the market for (A)'s services, and (A) is merely taking advantage of this fact, she is not taking unfair advantage of (B) because she is not using (B)'s unfair circumstances against her and treating her unfairly in light of her situation.

It seems that neither the presence of a negative aspect to the transaction or unfair circumstances in which the transaction takes place, are sufficient to render a mutually advantageous transaction unfair and thus exploitative. One might suppose that certain types of goods are simply incommensurable, and so any transaction involving goods of this type are unfair. We might think that it is impossible to put a fair price on one's kidney, and so the sale of a kidney could never be fair, because one party would always gain too much. However, whether a transaction is exploitative or not cannot simply be determined by the relative gains of each party. Consider a doctor who charges a patient far more than his normal rate for lifesaving surgery. We might justifiably claim that the doctor has exploited the patient, even though all things considered the patient gains a greater benefit than the doctor relative to the condition in which the transaction had not taken place. The doctor makes more money than he would have, but the patient's life is saved. As Wertheimer points out, the power of the exploiter typically stems from the very fact that the exploited has so much to gain that he cannot simply walk away from the transaction, and thus might be willing to agree to a transaction in which he recognizes that he is being treated less than fair. Thus, we ought to evaluate the fairness of transactions using a normative standard of how much benefit each party ought to receive. I will return to this discussion later in the chapter.

4.5 Informed Consent Can Be Given to an Exploitative Offer

We have seen that genuine exploitation occurs when (A) takes unfair advantage of (B), relative to some baseline condition, and that exploitation can occur even when both sides benefit. We can now turn to questions of informed consent in these genuinely exploitative situations in which both parties receive a benefit, and determine whether one can truly give consent which meets the requirements of voluntariness, competency, and understanding.

If we bear in mind the earlier discussion of coercion, it seems fairly obvious that the voluntariness requirement *can* be met even in exploitative situations. The fact that an individual (B) has 'no reasonable alternative' but to accept (A)'s offer, as is generally the case in exploitative situations, does not imply a lack of voluntariness on my account. Even though neither option is particularly appealing, one option must be preferable to the other in some way (or else there would be no grounds for choosing between them), and because one option is more desirable than the other, the individual prefers that this option come about rather than the other, less desirable option. Thus, (B) forms the second-order volition that the more desirable option become the object of her will, and in carrying out this option her action is wholly voluntary because she is choosing the option she most desires.

It also seems that the competency requirement can be satisfied in exploitative situations. Recall the definition of competency set out in Chapter 1, which claimed that a competent individual is one who is capable of making a decision with an appreciation of its consequences. We might be tempted to think that individuals lose the capacity for rational thought when they find themselves in unfavorable circumstances (the very sort

where they would be vulnerable to exploitation). While this might be true in some cases (e.g. those with mental impairments, or those suffering severe emotional trauma), the fact that one is agreeing to be exploited does not entail incompetence. For example, an individual might be renting an apartment for $500 each month. The landlord knows that the individual has every intention of renewing the lease, because he just started working at a business very close to the house and moving would force him to purchase a car. When the end of the lease is reached, the landlord decides to increase the price of rent to $650 each month; he is exploiting the tenant's reluctance to move. The tenant agrees to pay the higher rent even though it is unfair (no improvements were made to the house, and the increase is far greater than normal inflation). He determines that paying the higher rent leaves him financially better off than moving and purchasing a car; surely we would not say that the tenant is incompetent, even though he is effectively agreeing to be exploited. Conversely, agreeing to an exploitative transaction might be entirely reasonable given their circumstances; having weighed all their options, and according to their own desires and values, agreeing to a risky research trial or selling a kidney might be the best option.

Additionally, though the standard of competence we could justifiably require is often dependant on the circumstances (e.g. (B) might be competent to determine what kind of clothes to wear, but not whether to sign a mortgage contract), it seems reasonable to presuppose a baseline level of competence in most adults, as it relates to their carrying out everyday activities. Most adults are extended the benefit of the doubt when it comes to making decisions about fulfilling their basic interests (i.e. day to day activities). Accordingly, we ought to extend the same privileges to them in research contexts; the

burden of proof should be on researchers to show that potential research participants are not competent, rather than assuming that their unfortunate circumstances render them incompetent and thus incapable of making important life decisions. They are apparently competent enough to make other important life decisions, as evidenced by the fact that they have done so for themselves up to the point of the research trial. It would be paternalistic to suppose that a person's level of competence suddenly drops when they are placed in a new situation; if we have allowed a person to decide what is best for themselves prior to the time when they may consent to being exploited, what has changed?

Certainly, our evaluation of an individual's competence is in many ways task and time specific. While I might be competent to coach a Little League baseball team, I might not be qualified to coach a Major League baseball team. Similarly, I might be competent to drive a car unless I am intoxicated, in which case I am no longer competent to do so. However, the introduction of new variables to a situation does not necessarily mean that an individual becomes incompetent. Suppose I am sufficiently competent to determine a healthy diet for myself. It is unreasonable to think that I suddenly lose the capacity to determine what constitutes a healthy diet when I become very poor. Of course, this new circumstance might limit my ability to obtain healthy foods, but it does not limit my capacity to determine what foods are healthy. Similarly, if a potential research participant has always been deemed competent to determine what is in the best interests of their health, the fact that they are living in impoverished conditions does not *necessarily* render them incompetent to make this determination now. Unless we suspect that they have made the wrong decision according to their own standard of value and their own desires

(which would be an issue of comprehension), it is a mistake to deem them incompetent just because they are agreeing to something that they would not have agreed to if they were not in such unfortunate circumstances.

Even in developing countries, where those life decisions an individual makes might have greater consequences for survival, an individual ought to be assumed to be competent, unless proven otherwise. As Christine Grady argues:

> it is at least plausible that coping with limited resources renders one better able to protect one's own interest, not necessarily less able. Such individuals make daily decisions balancing limited means…why should research participation create more of a risk for impaired decision making than other dilemmas they face?[79]

While we might find flaw with the fact that individuals have found themselves in these unfortunate circumstances in the first place (e.g. through their own poor decisions but also through bad luck, an oppressive government or other factors which are out of their control), these circumstances do not automatically render an individual incompetent.

Moreover, it is important to prevent the competence and comprehension requirements from collapsing into each other, by recalling that competence is simply a *capacity* to understand. Thus, when theorists assume that an individual's lack of education renders him or her incompetent to participate in research, they are conflating the individual's capacity for understanding with the individual's actual understanding (i.e. the level of information that the individual has been given). This is an important distinction to draw, because it shows that individuals who find themselves in desperate circumstances or are lacking education are not necessarily incompetent, and thus cannot be prohibited from participating in research on these grounds. Of course, the comprehension requirement must still be satisfied, but again, this is a separate

[79] Christine Grady, "Vulnerability in Research: Individuals with Limited Financial and/or Social Resources," *Journal of Law, Medicine & Ethics* (2009): 22.

requirement from ensuring participant competence. It seems at least possible that an individual can both competently and voluntarily agree to an exploitative transaction. Let's turn then, to comprehension.

There is no reason to think that an individual *necessarily* lacks comprehension when engaging in an exploitative transaction. Of course, one of the reasons that we might consider a transaction exploitative is because the exploiter purposely omits information which thereby impedes the exploited person's ability to determine whether the transaction really is in his or her best interests. However, this would be a case in which the researcher fails to fulfill the disclosure requirement of informed consent, which would render the potential participant's enrollment unacceptable. Still, if all of the relevant information is presented to the exploited, it is entirely possible that he or she will understand it completely. We might suspect a problem similar to the one which seemingly arose in problems of undue inducement, namely that because of one's circumstances one would not be able to properly evaluate the circumstances; if one is desperate for money, one is liable to downplay the risks involved in participating in a Phase I research trial. While this is a definite concern for researchers, the solution is to take additional steps to ensure that the patient does fully comprehend the consequences of participation.

Even an unfairly exploitative transaction might be the course of action which best satisfies the values and desires of the potential participant, and it is at least in principle possible that they might come to this realization and thus satisfy the comprehension condition. For example, an individual desperately in need of money to keep their home from being foreclosed on might agree to participate in a Phase I research trial in exchange

for $500, knowing full well that the researchers could afford to pay more, and that participants in equivalent research in the past had received far greater compensation. Yet because they really need whatever money they can get, they might be willing to accept their own exploitation, and satisfy all of the conditions for informed consent.

4.6 Fairness

The source of ethical discomfort with exploitative transactions does not seem to be the fact that they violate informed consent; it seems at least possible for an individual to give valid informed consent to being exploited in a mutually advantageous transaction. Rather, it is with the fact that the transaction is seen to be unfair; perhaps the exploited people willingly accepted the offer, but they would have accepted anything. It is arguably the responsibility of the 'exploiter' to offer a fair set of options, because of the exploited's rights as a person. Thus, we might see exploitative inducements as problematic even if participants give valid informed consent. The problem comes down to this: does comprehension (and in a larger sense informed consent), make exploitative transactions acceptable, in the same way that informed consent (specifically the comprehension requirement) renders permissible the acceptance of significant risk by potential research participants?

I take a 'fair' transaction to have at least two elements. To begin with, the benefits received by each party ought to be roughly equivalent to the costs or risks of their participating in the transaction; call this 'intra-party fairness.' For example, if my car is said to be worth $5000, a fair offer would be for at least that amount. Or, if I am a participant in a Phase I research trial, the compensation I receive for participating ought

to be commensurable with the risks or discomfort of participating such that the more risk or discomfort I accept, the more I am compensated.

At the same time, the benefits received or the risks or costs incurred by one party should in some way reflect the gross benefits and costs of the entire transaction, such that one party does not receive a proportion of the benefits which does not reflect the risks or costs they have accepted through participation; call this 'inter-party fairness.' For example, if a large company achieves record profits over a given period, this ought to be reflected by an increase in employee wages or by employee bonuses. Similarly, if one pharmaceutical company stands to earn $10 million through the sale of a drug (x) and another stands to earn $100 million through the sale of another drug (y), the amount of compensation provided to the individuals or community involved in clinical research ought to be larger in the case of drug (y), in order to reflect a fair share of the overall benefit. It seems that 'intra-party fairness' helps to ensure 'inter-party fairness', because if individuals are given what they deserve, there should not be a significant disparity in the proportion of gross benefits received by each party in a transaction. However, both elements are necessary for a fair transaction.

It seems entirely possible that at least some exploitative clinical trials in which the dispersion of benefits is unfair might nevertheless be ethically permissible. Consider the sorts of trials where individual participants accept significant risk of harm with minimal direct benefit, but where the potential for future benefit to others is very high. I might agree to be a participant in a clinical research trial for a heart medication that might make me violently ill, but whose later development could cure heart disease. The overall risk-benefit ratio for me personally is low, but the potential benefit for others means that the

study has a very high risk-benefit ratio overall. If I am a very altruistic person, and I believe in the value of clinical research, I might agree to participate in this trial. Clearly I am being exploited (insofar as I am receiving very little benefit in exchange for accepting considerable risk, while the researchers and future patients are gaining a great deal through my participation), but it seems reasonable to think that the fact that I am giving informed consent to participation, coupled with the fact that the research has high social value (one of the seven requirements for ethical clinical research), makes the trial ethically permissible.

If we are to truly respect the autonomy of individuals, we must permit them to participate in any trials they choose, provided they satisfy the strong informed consent requirement, *even if the transaction is unfair*. A fully competent person might fully understand the potential risks and benefits involved in participating in a clinical research trial, and determine that participation best satisfies their desires. Moreover, they can do so voluntarily even if they are presented with two unfair options, because voluntariness is simply a congruity between my first-order desires which cause my actions, and my second-order volitions which are a reflection of my will. To prohibit unfair transactions like this might be seen as justified insofar as it 'protects the individual from himself or herself'; even if an individual does give informed consent to the transaction, their predicament is such that they would have accepted anything, and it is wrong on the part of researchers (or whoever is making the unfair offer), to take advantage of this situation to increase their own level of benefit. But to prohibit the transaction altogether only makes things worse for the individual, by removing their best possible outcome.

This is precisely the argument made earlier against the prohibition of inducements which were mistakenly categorized as undue. Undue inducements are prohibited on the grounds that they might cause potential participants to accept unreasonable risk, or act against their better judgment, and so we should simply remove the option to accept them. Preventing individuals from participating in exploitative research where both parties receive benefit, but the exploited party is nevertheless treated unfairly (the benefit is too small, the benefit to the exploiter is too large relative to the benefit of the exploited etc.), prevents people from accepting an option that we do not think they should accept by simply removing it. If the individual believes that the option best satisfies their values, they have every right to accept it, provided that they can give informed consent.

For example, a person who is desperate for money might agree to enroll in a Phase I research study which poses moderate health risks. While he would not normally agree to participate in an activity that might endanger his health, the fact that he is desperate for money causes him to rearrange his values such that money now takes a higher priority than health. Some would argue that this is a classic case of undue inducement, because the presence of the financial incentive causes the man to alter his values. As we have seen, this is a mistake. What causes the man to alter his values is his desperate financial situation, and as such the presence of the inducement itself does not cause the man to act in a way which violates any strongly held values; he is merely acting according to a new set of values which places financial interests first.

Of course, we might still feel there is something wrong with this situation, and there may be. By catering to certain interests, those offering the incentive are attempting to attract a certain type of person, namely those who value what is being offered. If the

motivation for offering a given incentive is to entice members of a certain vulnerable group (e.g. the financially desperate), so as to profit from their circumstances, we would have reason to call this exploitative. That being said, the mere fact that certain individuals find themselves in desperate situations is not necessarily the responsibility of those organizations sponsoring research to remedy (though it may be if they have something to do with causing or proliferating the bad situation). If a research group is offering incentives, though not with the specific aim of targeting a vulnerable group, though it happens to be the case that a certain group is more persuaded by the incentive offered, we may want to consider other alternatives to simply banning the use of incentives, as this is merely denying an opportunity to those who need it and thus violating their autonomy. Of course, it might be argued that the offering of incentives which are too good to refuse is a violation of autonomy. However, this would be an erroneous claim because those who are accepting the incentives are still acting according to their values and preferences, and could still elect to refuse the offer to participate. Simply put, the unfairness of a trial does not entail that an individual cannot provide informed consent to participate.

This view appears to leave us in a morally awkward position. It seems that an exploiter can propose an unfair transaction (e.g. participation in a research trial where the potential participant accepts significant risk with a moderate probability of direct benefit from the trial, but where the tested treatment will not be made available to the test population, and the research sponsor stands to make significant profit having invested only minimally in the test), and an exploited individual can accept it, and so nothing immoral has occurred. The participant is better off, so intervening does not benefit them

in this circumstance.[80] This is why the fair-subject selection requirement for ethical research, another of the seven requirements for ethical research, would not necessarily work to prevent the occurrence of exploitative research trials. Emanuel et. al. indicate that "groups or individuals should not be excluded from the opportunity to participate in research without a good scientific reason or susceptibility to risk that justifies their exclusion."[81] Thus, the fact that a certain population would be more likely to accept certain risks of participation in exchange for fewer benefits offers no grounds for excluding them from participation. The fair subject selection requirement does prohibit the selection of individuals or groups on the basis of vulnerability or privilege, so some exploitative trials might be prohibited in these grounds, though it is entirely possible that a population will be targeted for legitimate reasons (i.e. the high incidence of the disease being studied), and then be exploited. Intuitively, some clinical trials just should not be permitted at all, either because they have no social value, are exceedingly risky, or some combination of the two. However, this is a different claim than the one made earlier, namely that individuals should be permitted to enroll in any trial to which they can give informed consent.

So why do we feel that we need to intervene on behalf of those individuals who are engaged in mutually advantageous exploitative transactions? Not only is the exploited party receiving a benefit such that they are better off than they would have been had the transaction not occurred, but they have given informed consent to the transaction. The

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[80] Of course, it might benefit them in the long-term depending on the outcomes of the trial (namely if the risks involved result in harm to the participant), or insofar as refusing to participate might act as leverage for the exploited person. For example, if many potential participants refuse, and the researchers have no other place to conduct their research, they may be forced to further increase the benefit to participants. However, this only works if sufficient numbers refuse, and if researchers cannot simply relocate their trial.
[81] Ezekiel Emanuel, et. al., "What Makes Clinical Research Ethical?" *Journal of the American Medical Association* 238.20 (2000): 2701-2711.

reason an exploiter should not be able to make an unfair offer is *not* because the exploited individual might accept. It is because making unfair offers violates one's rights as a person, namely rights to benefits which are simply not offered in the sort of mutually advantageous exploitative transactions which seem to be an ethical concern.

Let us consider the case of the altruistic research participant again, as it is closely related to the sorts of issues being considered. Both the altruism-exploitation case and the mutually advantageous yet unfair exploitation case share key features: they are mutually beneficial (I would argue that the altruistic person is receiving some sort of benefit from participation, such as feeling good about themselves for helping their fellow human beings), and they involve a wide disparity in the benefits received by the exploiter and exploited. They both involve informed consent on the part of the exploited. Yet the altruistic case seems to involve a less ethically problematic case of exploitation. I think this is because in the altruistic case, one's motivation for participating is not to receive a direct benefit from participation. The good feeling one gets is a residual effect of participation; it is not the sort of benefit calculated in a risk-benefit ratio and as such exists outside the scope of the trial. As such, one might say that the altruistic person surrenders her claim to a share of the direct benefits of participation. This does not mean that the altruistic person surrenders her rights to be treated respectfully (as it relates to the seven requirements discussed earlier), or agrees to any compromise in the quality of her medical treatment. It simply means that she is in effect refusing some benefit to which she is entitled. This is why we view those who participate in research for altruistic reasons as morally exemplary; they are going beyond their duties as persons.

On the other hand, those who are participating in trials for financial gain or to improve their health are entitled to a proper share of the benefits of the research as well, only they are choosing to accept these benefits and are well within their rights to do so. So when a desperate individual agrees to participate in a research trial for less than his fair share of the benefits of research, he is exercising his right to surrender some of the benefits in exchange for the greater assurance of being included; this is why there is no ethical issue in agreeing to participate in mutually advantageous though unfairly exploitative research. However, it *is* beyond the rights of research sponsors and researchers to offer an individual less than their fair share of research benefits. It does not matter if the individual would accept the offer or not; the reason the unfair offer is not ethically valid is not because the individual would accept it when they should not, but rather because it violates the individual's right to a fair offer.

This point is critical: *it is unethical to make an unfair offer.* So even though I have argued that it is acceptable for an individual to accept the terms of an unfair offer within the context of clinical research, this should never be a possibility because potential research participants should never be extended an unfair offer. The point of the above discussion was to show that, contrary to most accounts, the reason unfairly exploitative trials are unethical is not because individuals cannot give informed consent to participate in them, but because exploiters cannot ethically extend unfair offers.

Of course, we often see unfair offers extended in the real world, and for practical reasons we might permit them; this does not make them any less unethical.[82] However, in

[82] An individual might agree to an unfair deal simply because they are ignorant of the value of the goods being exchanged. For example, I might sell my $10,000 car for $5,000 simply because I did not know its worth. This would be an unethical transaction, though one might dispute whether it is the responsibility of the exploiter to ensure the comprehension of the exploited, and so one might dispute whether such a

the case of institutions like law or medical research, the need for the preservation of ethical principles is even higher than in day-to-day life, because there is a degree of trust extended to these institutions by society which is necessary for their effectiveness. Individuals need to believe that the court system enforces fair laws in a fair way (e.g. with fair punishment for breaking the laws) in order for society to respect them. Similarly, individuals need to believe that the research community is performing valuable research in an ethical way, in order for them to trust researchers and volunteer their services to them. Though unfair offers are unethical in virtually all circumstances, we might treat them with reluctant acceptance in some cases: clinical research cannot be one of those cases.

4.7 Competing Accounts of Fairness: Responsiveness and Fair-Benefits

In an attempt to overcome the exploitation of research participants, many international statutes require that clinical research trials be limited to those trials which are responsive to the health needs of the community in which research is taking place. This is typically referred to as the 'responsiveness and reasonable availability' requirement, and is articulated by the CIOMS as follows:

> Before undertaking research in a population or community with limited resources, the sponsor and investigator must make every effort to ensure that the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.[83]

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transaction would be acceptable. However, in cases of exploitative clinical research trials, the problem is not necessarily the ignorance of the exploited, but rather their lack of leverage in compelling researchers to increase the benefits being offered. These exploited groups do not have the means to prevent their own exploitation, while the ignorant person does by simply becoming better informed.

[83] Christine Grady, "Ethics of International Research: What Does Responsiveness Mean?" *Ethics Journal of the American Medical Association* 8.4 (2006): 236.

By integrating the needs of the host community into the research to be conducted, the hope is that research groups will not simply impose their desires on a community that is desperate for any sort of benefit which might be offered, but rather conduct research whose findings would be useful to that community. In short, the research community will receive some part of the benefits of research for which they have borne the majority of the burdens. However, requirement provokes several important questions. First, must all research be limited to only those health concerns which are of a high priority in a specific region? As Grady points out, conducting a study of malaria treatments in a region with a high prevalence of malaria seems to address an important health need, and could thus be judged more 'responsive' than a study on breast cancer or depression; however, it should not follow that breast cancer or depression research is unethical.[84] Clearly there must be more to responsive research than the prevalence of the disease.

This is typically where the reasonable availability component of the responsiveness requirement is brought to bear: 'responsiveness' can only be fulfilled if successful interventions or other health benefits generated by research are made available to the population. Yet it is not clear who is responsible for disseminating these benefits; is it the researchers, the host community government, or some combination? Moreover, it is not clear whether a 'reasonably available product' is one which is provided at no cost to the host community, or provided at an affordable price, or simply making it available in the host community. These are all questions which REBs must contend with in evaluating the ethics of a research trial.

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[84] Christine Grady, "Ethics of International Research: What Does Responsiveness Mean?" *Ethics Journal of the American Medical Association* 8.4 (2006): 235-240.

Critics of the responsiveness requirement argue that to emphasize the type of benefit received by the host community is misguided. If the overall aim of the responsiveness requirement is to reduce exploitation, ethicists ought to focus on the 'level' of benefit received by the host community, and there are many different sorts of benefits associated with clinical research such as therapeutic benefits to study participants, ancillary benefits to participants or others, generalizable knowledge for the community, infrastructure building, training of medical staff, and other economic benefits like increased employment. It seems entirely reasonable to suppose that if a host community wanted researchers to build a roadway or well in exchange for participating in the research trial, this might be considered a fair benefit, even if the benefit had nothing to do with the nature of the research to be conducted. To require a host community to accept a certain benefit from participating in research, when the community might prefer a different benefit, is paternalistic. Moreover, in those cases where no intervention can later be made available to the host community (either in cases of Phase I trials, or unsuccessful Phase III trials), the host community is left essentially empty-handed.

The response to the apparent shortcomings of the responsiveness requirement has been the 'fair-benefits' requirement, which would allow host communities to bargain with researchers for a wide range of benefits, including those which do not pertain to the information or intervention strategies the intended research is designed to generate. As Alex London states, it is the host population which must determine fairness: "whether the

benefits are fair and worth the burdens of participation cannot be entrusted to people outside the population, even if those parties are well-intentioned."[85]

In order to make certain that host populations are in a position to determine the fairness of a research trial, the fair-benefits approach makes use of the collaborative partnership requirement.[86] This requirement ensures that a negotiation takes place between the researchers and host community to generate a package of benefits which both sides believe to be fair. This process is to be regulated by a principle of transparency, which is designed to give the host community access to information regarding the level of benefits received by host communities for similar research in the past, and thus reduce deception or fraud by researchers.

However, the notion of a trial with 'intra-party' and 'inter-party fairness' (which the fair-benefits account seems to accept) seems to be at odds with an account of fairness in which the host community is the ultimate arbiter of fairness. As London points out, in practice the fair-benefits approach proceeds like an auction, with potential host communities each vying for the privilege of acting as the trial population. In order to secure the research trial, each host community will naturally attempt to make itself the most appealing to researchers by offering the lowest costs, which in turn would grant the researchers a larger share of the benefits. Such a method of determining fairness seems to be inconsistent with the original intention of the fair-benefits account, which was to ensure that research populations were not being exploited. Yet it seems clear that the mutual desire of the various potential host populations to act as the pool of research

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[85] Alex London, "Research at the Auction Block: Problems for the Fair Benefits Approach to International Research," *The Hastings Center Report* 40.4 (2010): 36.

[86] This eighth requirement was added to Emanuel et. al.'s seven requirements for ethical clinical research in 2002: Ezekiel Emanuel, et. al., "What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research," *The Journal of Infectious Diseases* 189 (2004): 130-37.

participants is being used to drive down the benefits the research group will have to dispense.

4.8 The Need for an Objective Account of Fairness

Clearly, an account of what constitutes a fair share of benefits must not simply depend on what an individual or group is willing to accept. There must be some normative standard of fairness, or else a 'fair' transaction will simply amount to the sort of transaction all parties would consent to. Of course, we have already seen that both the exploiter and exploited can agree on the terms of a transaction which is ultimately unfair for the exploited party. The problem is often that the exploited party has very little negotiating power; they simply agree to take what they can get. This is the short-coming of most 'fair-benefits accounts' of exploitation, like those argued for by Emanuel et. al., and Segun Gbadegesin and David Wendler.[87] If we rely on a procedural notion of fairness of the sort they argue for, questions of exploitation merely collapse into questions of consent; if a fair transaction is merely one to which both parties consent, then all consensual transactions are 'fair.'

Since we have already seen that an individual can consent to an unfair transaction, a procedural notion of fairness is obviously inadequate. Say a certain population A is willing to agree to participate in an RCT, on the condition that all participants will receive the best available treatment at the conclusion of the study. If another population B is willing to participate in the same RCT, but does not require that all participants receive the best available treatment at the conclusion of the study, it would certainly be more cost

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[87] Angela Ballantyne, "'Fair Benefits' Accounts of Exploitation Require a Normative Principle of Fairness: Response to Gbadegesin and Wendler, and Emanuel et. al.," *Bioethics* 22.4 (2008): 239-244; Ezekiel Emanuel et. al., "Moral Standards for Research in Developing Countries: From 'Reasonable Availability' to 'Fair Benefits,' *Hastings Center Report* 34.3 (2004): 17-27; Segun Gbadegesin and David Wendler, "Protecting Communities in Health Research from Exploitation," *Bioethics* 20.5 (2006): 248-253.

effective for the researchers to choose population B. If we take the fair benefits approach of Gbadegesin and Wendler, and Emanuel et. al.,[88] it would seem that whether the researchers choose A or B, both populations are treated fairly, because both are giving informed consent to participation. But if a significant benefit is 'fair' for A, while a minor benefit is 'fair' for B (perhaps because B is desperate they are willing to accept less, and thus it might be reasonable for them to do so), this seems to suggest that population B is somehow entitled to less than population A. But this cannot be correct; just because they have agreed to accept less, does not mean that they are entitled to less. So any notion of fairness cannot be drawn from the consent of the individual or population, because an individual can give informed consent to an unfair transaction.

It seems that any useful notion of fairness will be one which places an objective worth on the goods or services to be exchanged, and ensures that the both parties are able to command at least the objective value of that which they are offering in the transaction. When an individual consents to participate in an unfair transaction, it might be reasonable for them to do so because of the subjective value of the benefits offered. The $500 that I would receive for participating in a trial might be worth far more to me because I am desperate for money, than it would be to someone who was very wealthy. The subjective worth I assign to the benefit I receive outweighs the subjective risks of participation, and so it would be reasonable for me to participate. However, the objective value of the benefits I will receive may be far less than the objective worth of my participation to researchers, supposing that they stand to make a significant amount of money based on the results of the trial. If a research sponsor stands to make $50 million from the sale of the drugs tested, the actual worth of the research participants is fairly high; without their

[88] Ibid.

participation the research sponsor would not earn the $50 million. A potential participant might realize that they are being given far less than what they are worth (and thus view the transaction as unfair), yet still determine that the benefits of participation make participation reasonable. A fair trial ought to closely approximate the objective worth of the goods or services being exchanged, because this ensures that the circumstances of the individual parties involved do not influence the amount of benefits being offered.

An individual might believe that a transaction is fair, but only because he does not fully comprehend the circumstances of the arrangement. For example, I might own a painting which unbeknownst to me is extremely valuable. If someone offers me $1000 for it, I might take this to be a fair deal. However, if the painting is actually worth $10,000 this was not a fair deal, because the person that purchased the painting received a huge benefit while I received a far smaller benefit. The fact that all parties consent to participate in a transaction fails to render it fair not only because we can consent to a transaction we know is unfair, but also because we can mistake an unfair transaction for a fair one. This means that a transaction is either fair or unfair *regardless* of the opinions of those involved; just because I believe a transaction to be fair does not mean that it is (as the above example shows). 'Fairness' is an objective property of transactions, and its presence does not depend on the opinions of those involved. Rather, it is derived from the commensurability of the objective worth of the goods being offered; if each party receives a proportion of the actual benefits of participation which accurately reflects the actual costs of participation, the transaction is fair.

What exactly is meant by the 'objective worth' of a good? I take this term to refer to the value of a particular good, independent of any specific individual valuing it; in

other words, its actual value. In some manner of speaking, the value of anything is ultimately subjective, because the worth or value of a good is nothing more than what people are willing to pay for it. However, the notion of the 'objective worth' of a good attempts to remove as much as possible the effect of an individual's desires and beliefs on their determination of an object's value. For some goods, determining objective value is simple. For example, money has a clear objective value. A $20 bill is worth the same as two $10 bills, regardless of any characteristics of the person who possesses the $20 bill. Typically, the objective worth of a good tracks its cost, because generally the cost of an item is determined by what the average person would pay for it. Those selling the item are not aware of the specific values or desires of any potential customer, and so are compelled to offer the highest price that the majority of potential customers would accept. Thus, if a transaction is fair, the vast majority of people would agree that it is fair because the benefit received from participation is commensurate with the cost of participation. They might not agree that it is reasonable *for them* to participate in the transaction, but this is only because they are not interested in the benefit being offered. A transaction is not fair *because* all parties involved agree to participate; rather, a transaction is fair when the benefits to the exploited are commensurable to the benefits to the exploiter.

It is important to differentiate between the sort of 'objective' value being referred to here, and the objective calculation of value rejected in Chapter 2. Objective value in the current context does not presume to be a 'correct' value assigned to the particular good in question, but rather refers to an assessment of value made by an individual or group of individuals who exists outside the context of the transaction and are thus able to

make a disinterested evaluation of the value of the goods in question. For example, contract disputes between professional athletes and management often go to an arbitrator, who determines the 'objective worth' of the player in question, so that he or she might be awarded a fair contract (i.e. one where salary is commensurable with contribution to the success of the team.) Contrary to the sort of objective value discussed in Chapter 2, the arbitrator is not claiming to determine the one true value of the player in question, but is rather making a determination based on the community's inter-subjective assessment of value. The arbitrator is qualified to make such a recommendation because they do not have a stake in the result of the arbitration, and so are able to remain impartial. Moreover, their recommendation is not paternalistic because it does not violate the autonomy of either group; both sides are free to accept or reject the terms set out by the arbitrator. The paternalistic researcher takes their own assessment of value to be objectively correct and prevents those who do not adhere to this standard from participating in research in order to protect them from themselves. Conversely, the arbitrator's purpose is not protect the potential participant/research population from themselves because these parties can agree to participate or not, whether they agree or disagree with the arbitrator's assessment of the value of the goods being exchanged.

In the case of a clinical research trial, a disinterested third-party would judge the value of the service to be provided by the research population, and determine a commensurable benefit to be conferred by the research group. In some cases, the amount of benefit to be conferred by researchers could be determined prior to a research population even being selected, with the type of benefit worked out in collaboration with the research population.

4.9 Generating an Objective Account of Fairness

Ultimately, to what degree the benefits of participation for the exploited must track the benefits received by the exploiter is an educated estimate. Within the context of a clinical research trial, Angela Ballantyne suggests that an 'infrastructure charge' of 10-15% of the cost of the trial for publicly funded research and 20-30% of the cost of the trial for privately financed research be contributed to the trial population to fund health-care infrastructure that would benefit the research population and host community.[89] She argues that the difference in infrastructure charge is meant to reflect the difference in aims of each type of research sponsor, with privately financed research typically being more profit-driven. By increasing the benefits extended to the trial population, the degree of unfairness is reduced to the point that conducting the trial is ethical. Moreover, we might emphasize the role of the 'eighth ethical requirement' for clinical research in this context: collaborative partnership.[90] Ethical research involves working in partnership with the larger community from which the trial population is selected, both in designing and overseeing the trial, as well as sharing benefits within the community. The infrastructure charge should not only be given to the host community, but be invested in collaboration with the input of the host community. While this sort of system pertains to the benefits which ought to be conferred on a trial population, a similar system would work to generate a fair benefit for individual research participants.

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[89] Angela Ballantyne, "Benefits to Research Subjects in International Trials: Do They Reduce Exploitation or Increase Undue Inducement?" *Developing World Bioethics* 8.3 (2008): 178-191.
[90] Ezekiel Emanuel, et. al., "What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research," *The Journal of Infectious Diseases* 189 (2004): 130-37.

In their 1999 paper, Lemmens and Elliot[91] suggest comparing the relationship between researchers and healthy volunteers to labor contracts, in order to generate a notion of what constitutes a fair benefit for participation. It is important to point out that such a market-model depends on a clear distinction between clinical research on healthy volunteers, and those research trials in which already ill patients participate. While I argue that exploitation is a concern in both cases, it seems that within the sphere of the already ill volunteer, unfair exploitation is only ethically problematic in those cases where the potential participant fails to provide adequate informed consent. The issue of 'fairness' does not really arise, because researchers are not withholding any health benefits from the potential participant such that it is in their power to make the transaction 'more fair.'

For example, a terminally ill patient might agree to participate in a risky trial, because she believes that the benefit being offered, a slight chance of recovery, is worth any risks incurred through participation. While researchers might be exploiting her desperation (because the risks are so high and the potential for benefit is so small), this is not an 'unfair' transaction because the researchers could not augment the transaction to make it more beneficial. Lemmens and Elliot argue that treating research participants like labourers recognizes that many healthy subjects volunteer to participate in research primarily out of financial need, and it is precisely this financial need that is the source of their vulnerability, as it pertains to receiving fair compensation for their participation. By establishing some sort of objective account of what constitutes fair compensation for participation in research, potential research participants are less likely to be undermined

[91] Trudo Lemmens and Carl Elliot, "Guinea Pigs on the Payroll: The Ethics of Paying Research Subjects," *Accountability in Research* 7 (1999): 3-20.

by their own desperation, because researchers will be forced to provide a level of benefit which might exceed what a desperate potential participant would be willing to accept.

The salient point is that potential research participants are not typically in a position to be making demands of researchers to increase the benefits of participation, and so a model which determines a fair level of compensation for potential participants must not rely on what either party would be willing to accept, but rather equate fairness with each party getting what they deserve. Although a commercial model of the sort that Lemmens and Elliot propose is not perfect (because even within already established payment structures, some feel that certain occupations are unfairly compensated), it at least provides one possible method for providing an objective account of fairness with which to evaluate exploitative research trials.

Importantly, it seems that if the concern with unfair mutually-advantageous transactions is that the exploited party is receiving too small a proportion of the benefits, fairness can only be arrived at by *increasing* the incentives offered to individuals to participate in research. Surely, we need not be concerned with an individual receiving too great a benefit for participating in research (i.e. where $500 would have been a benefit commensurable to the risks of participation, the individual receives $1000). This provides a further reason to abandon the notion of prohibiting incentives for research participants; if we are concerned with treating them fairly, we ought to offer more for participation and not less.

Moreover, it is worth pointing out that a proper notion of fairness is restricted to ensuring that the proportionality of costs and benefits incurred by each party in a specific transaction are roughly equal. Thus, the circumstances in which an offer is made does not

influence whether or not the transaction is fair, though it may influence whether or not the transaction is ethical and thus ought to be permitted; we could certainly conceive of cases where a transaction might be fair, and voluntarily agreed to by both parties, yet nevertheless be unethical. For example, I might own a classic car worth $80,000. If a person places a gun to my head, and demands that I sell him the car for $85,000 it is probably reasonable for me to do (because I prefer receiving $85,000 and not being shot, to keeping the car and being shot.) Thus, because I am a competent individual who comprehends fully the terms of the transaction, and because selling the car is congruous with my desire to not be shot, I can give fully informed consent to the transaction.

Moreover, it appears that the transaction is fair because I am receiving a benefit proportional to the cost of participating in the transaction (i.e. I am giving up the car, but receiving more than its value in return.) Nevertheless, the transaction is unethical; because I was coerced into selling the car, my autonomy was violated. By constricting my choices in such a way that it was no longer possible for me to both keep the car and not be shot (an option which the gunman is not justified in removing), the gunman exerts an illegitimate influence on my decision-making; by exerting his dominance over me (a dominance which stems from the fact that he has a means to harm me, while I lack proportional means to defend myself), he reduces my freedom.

Thus, it seems that it is entirely possible for an individual to give informed consent to a mutually beneficial yet unfairly exploitative offer; the acceptance of an unfair offer does not invalidate any of the requirements of informed consent and so there is no reason to prohibit individuals from accepting these sorts of offers. However, it is *not* acceptable for those parties who are in a position to exploit to make unfair offers because

individual's have a right to be offered benefits commensurable to the costs of participating in a transaction. Moreover, what constitutes a fair level of benefits to be received by each party cannot simply be a product of what both sides are willing to accept but must be determined objectively. In short, when exploitation is wrong, it is not wrong because it violates the informed consent of those being exploited, but because it is unfair or coercive.

4.10 A Practical Example: The Surfaxin Trial

How would this notion of exploitation apply to a practical case? Recall the real-world example of the Surfaxin trial in Bolivia, described earlier in note 72, where researchers sought to test the non-inferiority of Surfaxin using a placebo-controlled trial. This trial has often been cited as a paradigm case of exploitation in clinical research, because it contains several examples of research procedures which are taken to be unethical. One of these issues is the ethical requirement to provide the standard care to research participants. According to the Declaration of Helsinki, "in any medical study, every patient –including those of a control group, if any- should be assured of the best proven diagnostic and therapeutic method."[92] Some opponents of this view argue that we should adopt a 'local' standard of the best proven method, and thus in the case of the Surfaxin trial, the local standard was no treatment and as such all participants received at least the local standard of care, since the control group received placebo. I will not argue for either of these positions in detail here, though it seems reasonable to think that if an offer to participate in a clinical research trial is objectively fair, this will not be according to a local standard.

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[92] Alan Wertheimer, "Exploitation in Clinical Research," *Exploitation and Developing Countries: The Ethics of Clinical Research* eds. Jennifer Hawkins and Ezekiel Emanuel (Princeton University Press 2008): 96.

Another of the criticisms of the Surfaxin trial is that its participants did not give valid informed consent to participate. Let us first assume that the Surfaxin trial was mutually-beneficial; Discovery Labs received the benefit of trial participants with which to test its drug, and those consenting to participate received a 50% chance of medical treatment for their illness (or, more specifically their child's illness.) Some critics of the Surfaxin trial worry that participants did not give informed consent to participate in the trial, because they did not understand the conditions of the trial. If this is the case, the enrolment of such participants is clearly unacceptable on the account proposed in this paper. However, it is reasonable to think that at least some of the participants did understand what they were consenting to, or that the majority of participants *could* have given informed consent. It is important to distinguish this type of concern from the more general concern that participants could never have given informed consent to participate in the Surfaxin trial. Theorists who espouse this view argue that the nature of the trial and its intended population compromises the voluntariness of participation. However, we have already seen that individuals can give informed consent even when faced with 'no reasonable alternative' to participation.

Moreover, we might worry that the Surfaxin trial constituted a seductive offer and distorted the judgment of the potential participants, such that they mistakenly believed participation to be in their best interests. Again, this issue is one of comprehension, and clearly if the potential participant does not comprehend the details of the trial (such that they mistake trial participation which is not in their best interests for one which is), they should not be permitted to participate. Yet we might also be concerned that given the circumstances of the participant, it is rational for them to participate in an exploitative

research trial. I have argued that there is no reason to prevent participants from participating in research trials if doing so is truly in keeping with their best interests and that by denying them the ability to enrol in trials like the Surfaxin tiral, we eliminate what is potentially the best option available. While we might worry about the objective state of those in impoverished or other unfortunate circumstances, we are not justified in imposing our own judgment about their capacity to act in their own best interests by preventing them from participating in mutually-advantageous exploitative trials. It was entirely rational for the Surfaxin participants to enrol their children in the trial, if in fact it was in keeping with their strongly held values and desires to attempt to improve the health of their children.

However, the Surfaxin trial fails to pass ethical muster insofar as the research participants did not receive a fair proportion of the benefits of the trial; they did not receive a benefit commensurable to the risks and burdens they undertook by participating. While some received treatment, many others did not, and though all received some moderate benefit from participating (even if only the examination of a qualified physician or the use of hospital equipment), this is far less than what they should have received, especially given the significant benefit received by Discovery Labs, and the comparatively minimal investment. Here is where a system like Angela Ballanytne's 'infrastructure charge' would serve to increase the fairness of the transaction (by requiring an increase in the benefits given to the participant population), and thus help to eliminate this particular ethical issue.

Similarly, we might imagine that the Surfaxin trial had been a Phase I trial and the concern was that participants received too little compensation (instead of receiving too

little medical benefit). In this case, a market model of the sort mentioned earlier could be utilized to determine an objectively fair level of compensation for the research participants.

4.11 Summary

By this point, I take myself to have shown first and foremost that concerns about incentives to participate in research trials acting as undue inducements are misguided; there is no such thing as 'undue inducement' as commonly referred to in the bioethics literature. Rather, the sorts of problematic cases often mislabeled 'undue inducement' are actually cases where the potential participant lacks an adequate level of comprehension, and thus mistakenly believes that participation in the research trial will satisfy her strongly held desires and values.

Second, inducements might impede comprehension regardless of their size (even a very small benefit might end up motivating an individual to participate in a research trial), or their type (an inducement need not be financial). Thus, prohibiting the use of large financial inducements mischaracterizes the diverse nature of individuals' values; anything which an individual values might act as an inducement to participate in research and thus might compromise an individual's comprehension. Contrary to the standard account, which suggests that any incentives to participate in research must be minimal, I argue that incentives can be of any type or size, provided that the individual achieves adequate levels of comprehension. In fact, larger incentives might be more conducive to comprehension because individuals tend to associate larger incentives with greater risk and so use greater care. Similarly, participating in research might compromise something other than an individual's health, and so prohibiting those trials which involve

considerable risk to participant health is also too narrow a solution. A strong comprehension requirement helps to ensure that the strongly held values and desires of research participants are respected, and in so doing helps to protect their right to autonomy. (This was precisely the concern with undue inducement in the first place, namely individuals being persuaded by excessive offers to act in ways which were not in their interests.)

Third, I have argued that inducements to participate in research cannot be coercive, because inducements to participate are genuine offers which expand the range of options available to a potential participant, and thus by definition cannot be coercive. I also argued that coercive transactions were bad, though not because they compromise voluntariness (as typically conceived by most standard accounts). Rather, I argued that they are ethically problematic because they reduce an individual's freedom in an illegitimate way. I claimed that contrary to the standard account, voluntariness is simply the congruence of my actions with my will, and so I can act voluntarily even within the context of a coercive transaction; the problem arises not because my choice is involuntary, but because certain options were eliminated which I ought to have been able to choose from.

Fourth, because of this account of voluntariness it is entirely possible for an individual to provide informed consent to participate in an exploitative transaction. Contrary to the standard account, I argue that if a certain transaction is unethical, it is not because the exploited party could not provide adequate informed consent. Instead, I claim that the unfairness of the transaction is what renders it unethical, and so no transactions which are unfair are ethically permissible. A fair transaction cannot simply be one where

both parties agree to the terms, because it is entirely possible that an individual might agree to an unfair transaction. Instead, a fair transaction is one where an exploited individual receives benefits commensurable to the risks of participation, and proportional to the benefits received by the exploiter. Moreover, what constitutes this proportionality must be determined in an objective way (i.e. by parties with no stake in the transaction). Consequently, in order to provide research participants with a fair amount of benefits for participation, it is likely that the amount of benefits they receive ought to be *increased*, rather than decreased as proponents of the concept of undue inducement believe.

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