THE ROLE OF COMPENSATION IN CLINICAL RESEARCH AND THE ETHICAL CONSIDERATIONS

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by
Amie Devlin
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Nicolle Strand, Thesis Advisor, Urban Bioethics

ABSTRACT

In order to ensure the generalizability of clinical research studies, researchers and study sponsors are tasked with making efforts to ensure that research participants are racially and ethnically representative of the population at large. However, minorities and women continue to be underrepresented in medical research studies. To encourage participation in medical research studies, researchers are often inclined to offer compensation for study participation. However, it is vital that researchers consider the ethical implications of monetizing participation in medical research studies.

The first aim of this paper is to discuss the ethical ramifications of providing compensation for research participation. Additionally, this paper will critically analyze the various ways of handling financial compensation for participation in medical research studies involving experimental drugs, devices or surgical techniques. Information for this paper was gathered by conducting a literature review and by analyzing 121 semistructured interviews. Using an ethical framework, and supported by qualitative data from the interviews, this paper will discuss the ethical concerns that researchers must consider when offering monetary compensation in exchange for participation in medical research.

Overall, the paper aims to show that in order for clinical research to be conducted ethically, we must grant potential participants the autonomy to use their own decision making framework when deciding whether or not to participate in a medical research study. While a potential participant's decision to join a research study in exchange for

financial compensation may raise concerns to some people, autonomy requires that the research institution respect each individual's own motivations and decisions.

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CHAPTER 1: HISTORY OF COMPENSATION IN MEDICAL RESEARCH

Participants in medical research studies have received financial compensation for over 100 years. In the early 1800's, Dr. William Beaumont encountered a patient named Alexis St. Martin. Beaumont was not able to close a gunshot wound in St. Martin's stomach, so used this opportunity to study the inter-workings of St. Martin's digestive system. Beaumont paid St. Martin to come back and undergo the desired examinations. "The army surgeon paid the often-reluctant St. Martin $150, plus food, clothing, and lodging, for one year of "reasonable experiments"" (Lederer, 1995).

In 1900, researchers traveled to Cuba in an attempt to prove that mosquitoes were the vector for yellow fever. To do this, the U.S. government paid participants $100 in gold to participate in a medical research study where they were exposed to yellow fever. In addition to the $100 for joining the study, participants would receive an additional $100 in gold if the exposure resulted in them contracting yellow fever. (Cutter, 2016) By the 1920's and 1930's, compensating people financially to participate in medical research studies had become commonplace. This practice was hastened by the financial depression of the era. In 1927, *The New York Times* published an advertisements from a man "willing to sell himself for medical tests. The 50-year old man, who wished to remain anonymous, asked that researchers pay him $50 a week for the rest of his life" (Lederer, 1995).

At the University of Pennsylvania, a researcher interested in testing a new method of intubating patients handed out slips of paper asking unemployed individuals to come

to the hospital for a job which paid $2 per day, sometimes targeting individuals who were spending time under a bridge which crossed the Schuylkill River. (Lederer, 1995) When participants were brought into the research facility, they were asked to sign a legal document which reviewed the procedures of the study. Far from being a modern day informed consent form, these documents more closely resembled indemnification agreements to protect the university from any liability. Seeing the historical rise of compensation for participation in medical research studies, it is easy to see why financial compensation should be carefully considered through an ethical lens.

Despite the questionable methods used, financial compensation for participating in medical research studies originally began as a way to ensure that participants joined studies of their own free will. This practice grew at a time when there was understandable concern regarding whether research volunteers had truly joined voluntarily. Prior to formal regulations regarding informed consent, medical research studies were often conducted using infant volunteers. (Lederer, 1995) Opponents of medical research studies understandably raised concerns about how an infant could truly volunteer to participate. Regarding a study which involved infecting a 12-month old child with the herpes virus, one opponent exclaimed that enrolling the child "was an abuse of power, an infringement on the rights of the individual, and not excusable because the illness which followed had implications for science" (Lederer, 1995). During this time, medical research volunteers included not only children but also prisoners, who were likely to fall victim to coercion.

CHAPTER 2: METHODS

In order to more thoroughly investigate the thoughts, opinions and understandings of medical research among people living in North Philadelphia, 121 semi-structured interviews were conducted with people living in the following ZIP codes: 19120, 19121, 19122, 19124, 19125, 19132, 19133, 19134, 19140, 19141, 19144. Participants in this research study were part of a larger cohort study conducted under the Temple University School of Medicine.

This study was originally proposed in response to the low enrollment rate of minorities into clinical research studies. The goals of this project were multifaceted.

- Learn more about the baseline understanding of clinical research among people living in the Temple University catchment area
- Inform researchers about the most common concerns and misconceptions about clinical research to enable research staff to better communicate with potential research participants
- Create a focused educational program to teach the community about clinical research
- Identify misconceptions in the literature regarding the concerns of people when considering participation in clinical research

The interviews were based on an established interview guide. However, based on the responses of the participants, the interviewers were given leeway to deviate from the

guide to more thoroughly address a concept the participant disclosed. The interview consisted of a combination of open-ended and close-ended questions.

CHAPTER 3: WHY IS IT NECESSARY TO CONSIDER THE ETHICAL IMPLICATIONS OF MONETIZING PARTICIPATION IN MEDICAL RESEARCH STUDIES?

When reviewing protocols for approval, IRB members are tasked with the job of determining whether an investigator has selected an appropriate level of compensation for study participation. Despite little guidance on what makes for an appropriate compensation amount, this job falls to the IRB members. To make this determination, IRB members consider whether the compensation amount constitutes either coercion or undue influence. To begin a discussion of this topic, it is first necessary to define our terms.

The term *coerce* can be defined in several ways. The Merriam-Webster dictionary defines it as "to achieve by force or threat" (Coerce, 2017). However, there also exists a bioethics definition which interprets coercion as "an extreme form of influence by another person that completely controls a person's decision" (Faden, Beauchamp & King, 1986). We begin by analyzing the dictionary definition. In a medical research study, the presence of monetary compensation does not constitute force or threat; therefore, according to this definition, coercion is not the ethical issue that should be considered while determining the appropriate amount of compensation.

The bioethics definition of coercion is more complicated to analyze. Under this definition, it is not sufficient to determine that financial compensation impacts an

individual's decision making process; instead, it is necessary to determine that the compensation completely controls the decision. Additionally, the determination will be dependent on the individual circumstances of each individual person who is presented with a medical research study. In order to determine whether coercion exists under this definition, it is necessary to review a person's entire state of being and then to make value judgements on their behalf. For example, it is not sufficient to determine whether or not a person could benefit from financial compensation. In order to determine whether coercion exists, it is necessary to assess whether that benefit is enough to serve as their complete motivation to enroll in a medical research study. There is a level of paternalism in attempting to determine whether or not financial compensation serves to completely control an individual's decision. In determining how strongly financial compensation influences a person's decision, the outside observer is assessing a person's level of financial desperation based on their own beliefs, values, and biases. As a result, the presence or absence of this type of coercion can only be assessed on a case-by-case basis by the individual faced with the decision.

The second concept of *undue influence*, however, is more appropriate when determining whether a compensation amount is ethical in medical research. Undue influence is defined as "improper influence that deprives a person of freedom of choice or substitutes another's choice or desire for the person's own" (Undue Influence, 2017). As there is a perception that a particularly large amount of compensation could cause an individual to accept the high risks of a study in exchange for financial gain, undue influence is the issue that needs to be considered. Furthermore, there is concern that

undue influence by way of study compensation may potentially cause study participants to be dishonest about their health history in order to join or continue in a research study. (Williams & Walter, 2015) This action could be considered undue influence because a particularly large compensation amount "encourages participant to lie or conceal information in order to participate" (Williams & Walter, 2015).

> Quote from 62 year-old black man from North Philadelphia: *...Like I said, if they needed the money then they probably wouldn't look at everything about it. Their concern be just, "hey, I need this $500," or whatever and they would just go through it. So I guess it would be the people that don't have money would, would, would kind of let things go more, you know. […] You know, maybe, like I said, the side effects or something like… If they take the research studies and it doesn't, and they take the study and something threatens like, like they get sick or something doing the study, they might not say anything cause if they get sick, then they might not finish it and they might not get the money.*

However, the issue of whether a person receiving compensation in exchange for participation is indeed substituting "another's choice or desire for the person's own" is a complex issue. (Undue Influence, 2017) To determine whether it is ethical to use financial compensation to motivate participants to join medical research studies, we should begin by analyzing financial motivators outside of the research arena. One area where financial motivators are routinely accepted is the workforce. Every person who is employed in any capacity is agreeing to receive money in exchange for a task that they would be unlikely to do if the payment did not exist. (Largent, Grady, Miller & Wertheimer, 2012) In the majority of employment transactions, the financial exchange is

to compensate a person for their time and effort. In many regards, this is similar to the compensation scheme of a medical research study.

One area where employment and medical research appear to differ is in the level of risk being assumed. In most medical research studies, study participants assume a certain level of risk. While this same assumption of risk is not inherent in all employment transactions, there are many jobs in which employees are highly compensated due to a high level of risk. In general, society has accepted an employment exchange where employees in risky professions accept a higher wage in order to compensate for the risk. If this type of compensation is deemed ethical, the same logic should extend to compensating individuals for their participation in medical research studies.

> Quote from a 75-year old black woman in North Philadelphia: *Because I remember one time years ago when I use to live in (Neighborhood). There was a neighbor of mine I used to visit once in a while. She had her nephew or cousin or somebody used to live with her. He was like a guinea pig. He was always taking those experimental drugs and stuff like that. And I said, "Well, you don't really know how this is gonna affect you later. Aren't you afraid?" He said no. He just did it for money. That was crazy. Who going to put their life on the line for a dollar? That's crazy.*

In the opinion of this woman, it seemed crazy for an individual to risk their health and safety in exchange for money. However, we as a society accept this type of risk all the time. Dangerous professions, such as fire fighters or police officers, regularly ask their employees to risk their lives in exchange for money.

In risky professions such as those mentioned above, there are built in protections to ensure that employees are taken care of in the event of injury. Two examples of this are Occupational Safety and Health Administration (OSHA) and workers compensation. These systems are in place to ensure that the workers' rights are protected.

Similar to the job market, medical research has a system in place to improve the safety of participants and to protect their rights. That system is the Institutional Review Board (IRB). Prior to any medical research study being approved, the IRB is responsible for reviewing the protocol to ensure that the benefits justify the risks and that all ethical guidelines are followed. Additionally, the IRB is responsible for reviewing adverse events associated with study participation to ensure that participants are not assuming unjustified risks. According to the NIH, for a research study to be ethically sound it must have a favorable risk-benefit ratio. (Emanuel, Abdoler & Stunkel) Therefore, once a study has been IRB approved, a person joining the study should result in a positive net-benefit. As a result, it is fair to say that it would be an ethical action to enroll a participant into that study. A point to consider is that the positive net-benefit may apply to the society as a whole and not to the individual who is participating in the medical research study. However, this misplaced benefit is commonly accepted in risky professions. When firefighters or policemen are at work, they are often times not the direct beneficiary of their actions. Society does not question whether it is ethically acceptable to pay a firefighter to put out a fire at a home that is not his own. Because the actions of the firefighter result in a societal net good, payment of a firefighter for his duty is considered to be ethically sound.

Knowing that the medical research study results in a positive net-benefit, the benefit of any proposed financial compensation can now be assessed. While the IRB is tasked with reviewing and approving the compensation amounts for research studies, this review is done once the study has been found to be scientifically sound and it has been determined that there is a positive risk-benefit ratio. The amount and timing of compensation is not taken into consideration when determining whether a study is approvable. In fact, FDA guidance states that "payment to research subjects for participation in studies is not considered a benefit that would be part of the weighing of benefits or risk" (Payment, 2018). This view is supported by the NIH Department of Bioethics which states that "other benefits, like getting paid, may be important to the subjects. However, such non-medical benefits are not considered in a study's risk-benefit ratio" (Emanuel, Abdoler & Stunkel). While IRBs may consider the amount and timing of financial compensation in their decision of whether or not to approve a medical research study, these conversations do not impact the overall determination of whether the benefits outweigh the risk.

As an example, consider a hypothetical research study where the risks far outweigh the benefits. In order to entice people to participate in the study, researchers decide to offer a large stipend for study participation. According to FDA guidance, the IRB should refuse to approve this study based upon the unjustified risks of the study. Even in the absence of such guidance, approving a study where the benefits do not justify the risks would be unlikely to pass the ethical test of each individual IRB member required to vote to approve the study.

CHAPTER 4: THERAPEUTIC MISCONCEPTION

The particular issue of allowing medical research participants to assume risk in exchange for compensation may be particularly complex due to the relationship between physicians and patients. For example, the fact that a person has presented in a doctor's office indicates that may have some particular illness or injury. The presence of this bodily harm may put the person in a place where they are vulnerable to the suggestions of the physician-researcher. This leads to the discussion of whether the same ethical considerations are present for healthy participants and patient participants.

> Presumably, patient-subjects are considered more vulnerable in research studies than healthy subjects because of the nature of the relationship with their physician and because of possible confusion about the difference between participation in clinical research and the receipt of clinical care — the so called therapeutic misconception. (Grady, 2005)

The therapeutic misconception is the misunderstanding of research participants who believe that the primary goal of medical research is to provide clinical care. In reality, the ultimate goal of medical research is to create generalizable knowledge, regardless of whether the research itself is beneficial to participants. In order for research to be considered ethical, there must be genuine equipoise regarding the effectiveness of the various study arms. In an ideal medical research study, the novel treatment being tested would be found to be more effective than existing treatments. However, by nature, there must be uncertainty about the comparative effectiveness of the treatments. If there is no uncertainty, it would be unethical to assign participants to the less effective

treatment. According to the National Bioethics Advisory Committee "it is not a misconception to believe that participants probably will receive good clinical care during research. But it is misconception to believe that the purpose of clinical trials is to administer treatment rather than to conduct research" (Ethical and policy issues in international research, 2001).

In order to understand the therapeutic misconception, it is important to consider the specific goal of the medical research:

- Only to help patients enrolled in the study,
- Both to help patients enrolled in the study and patients in the future, or
- Only to help patients in the future. (Henderson, Churchill, Davis, Easter, Grady, & Joffe, 2007)

The therapeutic misconception is epitomized by statement number one: the goal of medical research is only to help patients enrolled in the study. However, statement number two is a good example of how and why the therapeutic misconception occurs. While the ultimate goal of medical research is to build generalizable knowledge, the researchers have a hope that the new treatment will prove to be effective and therefore improve clinical care to the patients enrolled in the study.

However, within a clinical trial, there will always be at least two treatment arms. If the researchers believe that the new treatment being tested is superior to the standard of care, then the researchers postulate that they have assigned the participants in the control group to the less effective study arm. This is another aspect of the therapeutic misconception. Even though researchers review a consent form with research participants and explain randomization, many research participants are "unaware of study design

implications, especially random assignment to a control or comparison group, often believing that they were assigned a medication based on what was best for them personally" (Henderson et al, 2007).

The therapeutic misconception is important when considering compensation for study participation because potential participants may erroneously believe that their physicians are offering them a new treatment which is better than existing options. Despite efforts by the research staff to convey the uncertain nature of a research study, potential participants may be completely unaware of the research process. This knowledge gap between the researcher and the potential participant may hinder the effectiveness of the researcher's explanation of medical research. Potential participants may be inclined to follow their physician's recommendation without a proper understanding of the implications. This likelihood is even higher when a potential participant may be under the impression that, in addition to a more effective treatment, they will also be entitled to financial compensation.

> Quote from 51 year-old black woman in North Philadelphia: *So basically, you know, when a doctor ask you, they're asking you because they feel that the research study could benefit, benefit them in the long run. I feel they see some tendencies in you that would, you know, qualify you for that study but there also see, um, how it could benefit their patient.*

CHAPTER 5: FINANCIAL COMPENSATION FOR HEALTHY SUBJECTS

Although the therapeutic misconception has been identified and is well documented, it is extremely pervasive within the research community. There continues to be the assumption that patient-subjects will receive some semblance of direct health benefits. However, what about the motivations of healthy subjects? In Phase 1 studies involving healthy volunteers, there is no need to be concerned about the therapeutic misconception: the volunteers have no ailments for which they are seeking care. Knowing that, what is their motivation to participate? There are two potential answers which could justify a healthy person's decision to join a medical research study: financial compensation or altruism.

The concept of participating in a medical research study for altruistic reasons, particularly one with a high level of risk such as many Phase 1 studies, is noble. However, compensation undoubtedly plays a role in a person's decision making process in some capacity. Accepting this assumption, it is important to decide whether or not it is ethically permissive for researchers to allow participants to join risky Phase 1 studies for financial reasons. Answering this question requires an analysis of the motivations of everyone else involved in the clinical trial pipeline. In a study where the participant joins a study for purely altruistic reasons, the participant themselves may be the only person involved in the medical research study who is not doing so for a financial gain. Consider the research staff, the physician, or the biostatistician at the pharmaceutical company. All of these people are involved in the medical research study in exchange for payment.

While they may have a particular calling which drives them into that specific line of work, it is unlikely that they would show up everyday if it were not for financial compensation. Even the executives at the pharmaceutical company have a financial motivation in the form of profits. While some of the individuals tangentially involved with the research study may be doing so partially due to altruism and a desire to a contribute to the greater good, there is never a debate about whether it is ethical to provide financial compensation to these key players.

In this consideration, is it vital to determine what separates the research participant's role in the study from the role of the administrators, scientists and physicians; that difference is the level of physical risk assumed. The individuals employed in the administration of the clinical research study do not assume any of the physical risk. The entirety of the risk falls to the medical research participants. If the argument is that people should only be involved in medical research studies for altruistic reasons, and should be in no way motivated by financial gain, this argument should apply to all parties involved. However, it is disingenuous to say that everyone involved in a clinical research study is allowed to trade their time and effort for financial gain, except for the person who is assuming the risk. As mentioned previously, society has set a precedent which allows individuals to participate in risky activities, such as dangerous jobs, in exchange for money. Participation in medical research studies, particularly Phase 1 studies which provide no real or perceived health benefit, should be considered no different.

While it is the most ethical solution to have all parties involved in a medical research study do so for purely altruistic reasons, this scenario may be unattainable. In order to attract physicians, chemists, and study coordinators, they must be compensated for their time and effort. Similarly, the research participants themselves should be compensated for their time and effort as they are they ones who give up their bodies, time, and personal comfort in order to test whether new drugs and treatments are safe to test in a larger audience.

CHAPTER 6: FINANCIAL COMPENSATION FOR PATIENT-SUBJECTS

As discussed, there appears to be convincing ethical evidence to allow healthy subjects to receive financial compensation for participating in medical research studies. However, different concerns arise when considering whether to compensation patient-subjects for their role in clinical trials. Some bioethicists wonder whether it is ethical to provide financial compensation to patient participants because "patients are particularly vulnerable, and patients are deriving medical benefit in a way that healthy subjects are not" (Dickert & Grady, 1999). While the argument against paying patient subjects is based on the premise that compensating a sick participant complicates the relationship between patient and physician-researchers, it is the innate nature of research that complicates that relationship.

When a patient is offered an opportunity to join a medical research study, the therapeutic misconception can lead the participant to join the study under the false assumption that participation in the study will be in the best interest of their health. In the situation where a potential participant is choosing to join a research study under the therapeutic misconception, this desperation for a cure could be just as unethical as desperation for financial compensation.

Often times, when talking about the decisions to enter a medical research study, participants talk about using the trial as a last-ditch effort once all other options have proven ineffective. Under this rationale, the participant is joining a study under the assumption that they will receive direct benefits from participating. The alternative to

participating is suffering with an untreatable ailment and, in extreme cases, death from that ailment. Knowing that the primary goal of a medical research study is to contribute to generalizable knowledge and not to provide treatment to the individual patient, it could be considered unethical to allow a patient join a research study under the assumption that it will improve their health.

> Quote from 64 year-old black woman in North Philadelphia: *Yeah, I'd want to know them [risks] but, like I said, I would only be in the study if that was, you know, sort of a last resort, I guess. Or if I had, you know, nothing else I knew of that I tried before had worked and I had exhausted all that I knew, or my doctor knew, to try.*

When a potential participant is hoping to receive a direct benefit from participating in a medical research study, either in the form of financial compensation or improved medical care, at what point do these motivators amount to undue influence? Similarly, at what point does the bioethicist's concern for these motivators become an attack on the potential participant's autonomy?

> What the example of subjects who are desperate for an effective treatment shares with the example of subjects who enroll only for payment is that the autonomy of the subjects seems to be compromised in similar ways. Neither is coerced but both raise the concerns that the transaction is still not morally acceptable. They are making a deal that more fortunate people would find repugnant. They are being exploited. (Kuczewski, 2001)

Perhaps the most important sentiment in the above passages is the phrase more fortunate people. When considering the ethical nature of benefits within clinical research,

does the principle of autonomy require that the more fortunate ensure that the less fortunate are protected for outside forces, or does it require that all individuals, regardless of their health or financial status, are trusted to consider their own situations and make decisions based upon their determination of what is right for them? If the ethical conclusion is that patient-participants should not receive financial compensation because of the potential for undue influence, then the conclusion should extend that patients should also be excluded from treatment trials because desperation for a treatment may have a similarly negative impact. Even if sick participants are aware that their participation in a medical research study is a last ditch effort to improve their health, their participation is being swayed by desperation for something that cannot be guaranteed. Similar to a terminal participant who is considering joining a research study out of desperation to survive, a participant who is struggling financially may decide to join a research study out desperation to get money to pay their mortgage. Arguably, the sick participants desperation is more dire and hence more likely to allow them to be taken advantage of. Furthermore, the health benefit cannot be guaranteed, whereas the financial compensation can be guaranteed. Allowing a terminal ill person to join a medical research study out of desperation is setting the precedent that sometimes desperation is an acceptable motivator. Setting guidelines regarding which types of desperation are acceptable effectively removes an individual's agency and ability to determine for themselves that they deem acceptable.

> Quote from 66 year-old black woman in North Philadelphia when asked whether there are any groups that are more likely to be taken advantage of in medical research: *Depending on if they have a, um, an illness that's, uh, terminal.*

An argument against this is that the researchers can take steps to inform the terminally ill patient that they are unlikely to see health benefits from the research, thus reducing the impact of the therapeutic misconception. However, even the best efforts of the physician-researcher to explain the uncertainty of research may not alleviate this burden. In one study, 89% of participants reported that possible health benefits was a "very important" factor in deciding to participate in the clinical trial. (Nurgat, Craig, Campbell, Bissett, Cassidy, & Nicolson, 2005) In another study, only 33% of participants were able to accurately state the purpose of the trial in which they were taking part. (Daugherty, Ratain, Grochowski, Stocking, Kodish, Mick, & Siegler, 1995) This suggests that potential participants, typically unfamiliar with the field of clinical trials, may be unable or unwilling to separate medical research from routine medical care.

Even if the patient fully grasps the uncertain nature of research, the desperation of their situation remains unchanged. This scenario leads us to make a value judgement between desperation to extend life and financial desperation. There may be an impulse to believe that a person joining a medical research study out of medical desperation is making a more ethical choice than a person joining a medical research study for the financial compensation, yet this results in an outside observer imposing their beliefs upon another person.

Beyond the discussion of desperation, there are some studies where the investigator must recruit both healthy participants and patient participants. In these situations, it would be unethical to compensate healthy participants but not patient participants.

> In studies that offer potential benefits, such as many Phase 3 studies, there may be no reason to pay patients, but it is not clear why it would be unethical to do so simply because they may benefit from participating (Dickert & Grady, 1999).

Once the argument exists that it is ethical to compensate patient participants, as well as potentially unethical to exclude them from receiving compensation, it becomes necessary to investigate the various ways that compensation amounts be determined.

CHAPTER 7: ETHICAL ANALYSIS OF VARIOUS COMPENSATION METHODS

In considering how best to compensate individuals for study participation, there are several different models to consider:

Market Model

The Market Model of compensation is based off the principle of supply and demand. Compensation amount is based off the number of people who are interested in participating. For research studies where many people are interested in participating, the compensation rate will be low. The opposite will happen for studies that are less desirable. The desirability of participation and, hence, the compensation for participation will be based off a combination of the risk, palatability of procedures and extent of time commitment. (Dickert & Grady, 1999) For example, a study that requires a long in-patient stay or risky procedures may require a higher compensation to draw participants. Alternatively, a research study that has a minimal time commitment or benign procedures may only require a negligible compensation payment. This model has some ethical concerns because as the compensation becomes overly enticing, the potential participant may be less inclined to fully consider the risks of the study procedures. (Dresser, 2001)

Under this model, all participants in a research study would receive equal payment for equal participation. This initially appears to satisfy the bioethical principle of justice. However, there could be some serious ethical concerns when considering the

Market Model further. Under the principle of autonomy, potential participants should be allowed to make voluntary decisions without the presence of undue influence or controlling influences. (McCormick, 2017) While a potential participant could be fearful to participate in a particularly risky study, there could be concerns that the higher compensation, in combination with a financial need, may sway them to chose to participate despite their concerns. To satisfy this argument, it is important to think back to employment opportunities in risky professions. The societal-set precedent states that it is ethical to motivate a person to assume physical risk in exchange for financial gain. This precedent follows that the potential participant should be allowed to make the decision for themselves whether they are willing to accept risk in exchange for financial compensation.

While the compensation that study participants receive under the Market Model may be nominally equal, it is also important to understand that the marginal value of that compensation may vary greatly between participants. For example, consider a research study that is compensating $3,000 for a week-long inpatient stay which involves a reasonably risky procedure. Now consider two potential participants: a well-off lawyer who earns $100,000 annually and a single-mother who averages $26,000 a year. While both the lawyer and the mother may bring home the same amount of money from the research study, the $3,000 payment will have a larger impact on the life of the single-mother, as opposed to that of the lawyer. An argument against compensating for research participation is that we must protect the single-mother from being taken advantage of. Yet, do we violate her autonomy by suggesting that the lawyer is more able to make

decisions than the single-mother. Presented with the same information about the study, the principle of autonomy states that we must value both people's decision-making process equally. While it is possible that the single mother may be more likely to consider the financial compensation while making a decision, both individuals should be free to consider the full circumstances of the study and make the decision that is best for them based off the terms.

Wage-Payment Model

A similar compensation strategy is the Wage-Payment Model. In this model, research participation is also considered to be a source of employment. Researchers under the Wage-Payment model create a billing schedule based off a standard hourly rate and bonus payments for completion of particular tasks. For example, a research study could offer $15/hour for the completion of study visits, along with a $50 completion bonus for following the drug schedule and completing at-home diaries. (Dickert & Grady, 1999) This model is based on the assumption that, like other unskilled jobs, research participation requires time and effort.

Through a bioethical lens, this model does appear to satisfy the principle of justice. Within a single research study, all participants are treated equally. Additionally, assuming that the hourly rate is set sufficiently low, there is a low risk that the compensation will result in participants being unduly influenced.

However, as opposed to the Market Model, the Wage-Payment model is based on the assumption that the hourly rate is set low. All research studies involve a certain

amount of risk. Under this type of compensation scheme, participants are being compensated for their time and not necessarily for the risk that they are assuming. In fact, in order for the hourly rate to remain non-influential, the level of risk must not be considered. This raises concerns that participants may not be receiving a far wage in exchange for their assumption of risk.

Reimbursement Model

Differing from the Market Model and the Wage-Payment Model is the Reimbursement Model, which is based on the assumption that participation in a research study should remain revenue neutral. (Dickert & Grady, 1999) According to this model, participants should be reimbursed for expenses they directly incur as a result of participation. This would include expenses such as parking, transportation, meals, and lost wages. In this model, research participants receive reimbursement for expenses related to study participation but are not routinely compensated for study procedures.

The Reimbursement Model appears to meet many of the bioethical principles. As participants are reimbursed based on their expenses, not all participants will receive the same amount of reimbursement. However, as all participant's in a study will remain revenue neutral, the principal of justice is upheld. Additionally, this model may be the strongest when it comes to removing financial motivation from a person's decision of whether or not to participate. Under the Reimbursement Model, participants are not receiving any financial benefits to participation. In lieu of compensation, potential participants must base their entire decision on the logistics of the research study: the

procedures, the time commitment, and the risk-benefit comparison. Yet, this model raises concerns that the person assuming the study risks is the only person not being financially compensated for their time and efforts.

While this model may be ethically strong, it is weak in practice. While this type of model may have some strengths from an ethical standpoint, it is unlikely to encourage research participants to enroll in a study. While it may be important for participants to be reimbursed for their expenses, this model downplays the impact of risks or discomfort on a person's decision whether or not to participate in a research study. While it is important for a participant to be reimbursed for parking at the research site, it is also important to acknowledge that the participant is assuming the risks of the study.

Additionally, various participants in the same research study will accrue different expenses. As opposed to another model where participants receive standard compensation for participation, the reimbursement model creates a logistical burden for the research staff. Under this model participants are required to provide receipts to justify their reimbursement. To accommodate this, the research site must create a tracking and reimbursement system to ensure that participants receive their due compensation and to ensure that all reimbursements are valid.

Appreciation Model

The Appreciation Model is similar to the Reimbursement Model in that it also refrains from considering research participation to be a source of employment. Instead of compensating participants for their time or reimbursing them for their expenses, the

Appreciation Model says that research participants should receive a token payment at the end of the research study to thank them for their participation. This model falls into the same trap as the Reimbursement Model. While it meets the ethical principles, it is likely to be the least effective in recruiting participants for anything but the most minimal research studies.

Sliding Scale Model

An alternative to these models is to compensate the participants according to their current pay rate. Under this model, participation in research studies would be treated as another source of employment, and participants would be compensated according to their hourly rate, set either by their current job or through an estimation of their hourly rate. In this model, researchers would break down the study procedures based off the amount of time it would take to complete each task. Study participants would then bill the researchers, using their assigned hourly rate. For example, a lawyer who decides to participate in a medical research study could receive $150/hour, while a teacher could receive only $25/hour. While this would rectify the concern regarding the marginal impact of compensation on a participant's life, it is in direct conflict with the principle of justice. Instead of everyone receiving the same payment for the same activity, participants with a higher financial situation would receive a higher rate of compensation.This system is unethical because it "encourages unequal pay for equal work" (Williams & Walter, 2015).

CHAPTER 8: IMPORTANCE OF DISCUSSION

In considering which compensation model a person should receive, it is important to understand the effect the these considerations have on the person's autonomy. While the intent of this discussion is to prevent potential participants from being unduly influenced, there is a risk that the researchers drift into becoming overly paternalistic. For example, consider a research study which offers $1,000 if a participant continues throughout the entirety of the study. To fill the required demographic quotas, the researchers have decided to enroll in two locations: Society Hill and Strawberry Mansion. In Society Hill, an average household income could be around $90,000, whereas the average household income in Strawberry Mansion could be mid-$20,000. In the more affluent area, researchers may assume that their participants are likely to base their decision to participate on the risks and benefits of the study. Researchers may therefore be less inclined to worry about the impact of the compensation on a person's ability to make an informed decision.

However, this consideration raises ethical concerns about the researcher's perception of the potential participants. While the researchers may believe that the the large compensation may cause a low-income individual to act against their own best interest, it is important to consider the autonomy of both potential participants in their decision of what qualifies as in their best interest. This type of consideration is based upon the assumption that a less financially stable person is less qualified to make decisions on their own.

Quote from 57 year-old black man in North Philadelphia when asked whether people sign up for research studies for the money: Well sometimes. It can definitely be a lure, you know. It can definitely be a lure, you know. But like I said, who, whichever side of the coin you on, whether it's financially okay, or not financially okay, understand that you still a human being and you have rights and you don't have to get involved with nothing if you don't choose to.

CHAPTER 9: COMPENSATION AND THE HETEROGENEITY OF MEDICAL RESEARCH

When considering the issue of compensating research participants, it is important to highlight the vast differences between medical research studies. A person joining a Phase 1 safety study may have very different considerations than a terminal cancer patient considering a new type of chemotherapy. In order to best test the hypothesis that financial compensation is ethical, this paper examines Phase 1 safety studies, where study participants do not have the condition being studied, as well as later stage treatment trials, where there could be real or perceived health benefits for the study participants. While the argument of agency applies to all types of research, it is easier to consider these types of research separately.

Another complexity to add to this discussion is the heterogeneity of compensation in medical research. When talking about compensation of medical research participants, it is easy to consider one compensation strategy and then mentally apply it to all types of research.

> Quote from 66-year old black man when discussing a person who knows who does medical research studies professionally: *He just goes and they go and he gets compensated for it. […] I haven't seen him get sick from it or anything. […] He was going away a week or two at a time. […] He's been doing this for about a year or two. […] He could stop working and he could do this. He was getting paid. Evidentially the compensation he was getting was almost equal to what he was making at work. […] Sometimes he has to get some kinda, like they give him some chemical some, something I guess they ingest in his system to do it.*

It is true that Phase 1 studies routinely provide compensation that can be in the thousands. However, participants in later stage research often receive only a few hundred dollars for completing a medical research study, which may span several months or years. As a hypothetical example, a Phase 1 study requiring a one-week inpatient stay may compensate participants several thousands of dollars. Yet a late stage study may provide a much smaller amount of compensation. In the qualitative interviews conducted in North Philadelphia, many participants referred to people they know who had participated in what appeared to be Phase 1 studies. In this type of study, there is no real or perceived health benefit to participation. When these studies were mentioned in the interviews, the primary motivator for participation was often financial. When pulling data from these interviews, it is easy for an ethicist to misrepresent or misunderstand these sentiments and proclaim that financial compensation is the primary motivator of low-income people to participate in any type of medical research study.

In Phase 1 studies, there are two logical motivators for participation: altruism and financial compensation. There is likely no ethical argument against an individual participating for altruistic reasons. This is considered to be a noble act as the research participant is willing to risk their health in order to improve the future health of others. This type of research participation is a noble and selfless act, but it is also an act which can result in physical discomfort and tie commitments. For studies involving in-patient stays, participants are willing to forego their regular activities in order to further medical discovery. While it is admirable to think that a person is willing to give up their time and

physical comfort for the sake of the study, it seems unreasonable to expect them to do it without compensation for their time and effort.

A logical next step in this discussion is to determine the appropriate amount of financial compensation which will limit any undue influence on a potential participant. However, stating that there are appropriate and inappropriate compensation amounts concedes that compensation for research participation is ethically troubling. The goal of this paper is to argue that financial compensation, regardless of the size of the payment, does not amount to undue influence. As discussed above, undue influence occurs when a person is deprived of their "freedom of choice or substitutes another's choice or desires" for their own (Undue Influence, 2017).

All medical research studies involving humans are reviewed by the IRB. Prior to approval, the IRB ensures that the informed consent form contains all pertinent information that an individual needs in order to choose whether or not to join the study. When a potential participant reviews this information, they are free to determine for themselves whether or not they will agree to participate. This choice is based off both the information presented in the consent form as well as the particular circumstances of the person's life. Using this compete information, they are then free to determine whether or not participate. As this choice is based off the complete information about a person's circumstances, we have no reason to believe that they are "substituting another's choice or desires" for their own (Undue Influence, 2017).

In the qualitative interviews conducted, it is interesting to note that when people were asked what motivates a person to join a medical research study, they often said that

it was the financial compensation. However, this motivator was often talked about in the context of someone they knew. It is extremely difficult to accurately summarize another person's decision-making process. It may be accurate to say that a friend or loved one joined a medical research study for the money, but this does not necessarily mean that the risks of the study were not taken into consideration.

Despite people's assumption that financial compensation was the primary motivator for participation, when asked what information the participants themselves would want to know prior to joining a medical research study, people cited concerns about safety rather than compensation. This hints that people, even those who would be considered low-income, are able to analyze the complete information and think beyond the mere presence or absence of financial compensation.

> Quote from 51-year old black man when asked whether he had ever considered doing a medical research study: *Like I came really close, I'm like "$500? I could use that." And I-I think I read on a little long and think it was like 30 days like, like, uh, I think you have to stay, you know in a facility for like 30 days or something like that and, and I at that time, y'know I had a family so I was like "Well I'm not gonna go stay for 30 days".*

> When asked why he had never participated in a medical research: *It just wasn't my cup of tea. […] I think it was because I say, just because (friend) didn't have any side effects doesn't mean it's gonna be the same for me. […] If in the event, the volunteer did get a side effect, that they was, it was very easily, you know, rendered with whatever drug or whatever. But I didn't know of that, so I figure, you know, if I had a side effect I might just get stuck with something. So I just left it alone.*

Quote from 80-year-old black man when asked how he feels about people joining medical research studies for the money: *Well, I'm not too fond of it. […] If you going to jeopardize your body and your life just to get a couple hundred dollars or whatever the case may be, I think that's foolish. You have to be committed within yourself to do that and so forth. And not just to think about the money and so forth. You can't think how rich it's going to make me. It's not going to do any good in the long run if the drugs don't work… […] How are you going to spend all that money when you laying up there half way dying and so forth and whatever the case may be because the drug didn't work and so forth?*

CHAPTER 10: JUSTICE AND THE THERAPEUTIC MISCONCEPTION

In discussing the effect of financial compensation on clinical trial enrollment, the conversation often includes a debate about diverse enrollment and justice. According to the Belmont Report, "injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly" (Ryan, Brady, Cooke, Height, Sankar, King, et al., 1979). However, in the discussion of low-income individuals participating in medical research studies, it is hard to see which benefit non-participators are being denied.

In conducting medical research studies, there is an assumption that members of various sex, racial, and ethnic groups should participate in order for researchers to identify whether new drugs, devices or therapies work differently among these groups. While this is very important, it is important to distinguish the importance of racial/ethnic diversity in clinical trials from the effect of financial compensation on enrollment. When discussing the impact of financial compensation on participation, the group dichotomy most affected is low-income individuals versus moderate- to high-income individuals. The offer of a financial incentive is more likely to entice a person who is struggling financially, as opposed to a person of any specific sex, racial, or ethnic group.

In certain geographic locations, low-income populations may be largely composed of racial and ethnic minorities. As a result, opponents of this view may state that offering financial compensation for study participation will result in enticing racial and ethnic minorities to join medical research studies. While this may occur in practice,

the purpose of this paper is to explore the ethical implications of financial compensation in medical research. If it is deemed to be ethically sound to offer financial compensation, there should be no concerns if that compensation results in a higher minority participation in medical research.

An argument often raised to explain why low-income participants should join clinical research studies is that people involved in medical research receive better care than those participating in the traditional medical system. In order to determine the validity of this claim, it is important to break it down. As discussed previously, the therapeutic misconception is the misunderstanding of participants that the primary goal of a medical research study is to provide care, as opposed to contributing to generalizable knowledge. This misconception can affect both the study participants and the research staff. However, awareness of the therapeutic misconception requires us to disregard any possible therapeutic benefit and focus on the goal of medical research to increase generalizable knowledge.

Removing the potential benefit of the clinical trial, some researchers retain the perception that the sheer nature of being in a research study leads to better medical care, regardless of what treatment arm a person is assigned to. In a medical research study, a person often has more frequent study visits than a person undergoing traditional medical care. More frequent monitoring of health by a physician could lead to better health outcomes, even if they are attributed to more attention as opposed to the drug, device or treatment being investigated in the medical research study. As a result, it could be

considered advantageous for a person to join a medical research study. However, this increased monitoring does not affect the ethical principle of justice.

In order for the results of a medical research study to be generalizable to everyone, members of all groups must be represented in the research. This is true for sex, race and ethnicity. The question to be considered is whether income level affects how a drug, device or treatment will affect an individual. In conducting a literature review on this topic, many articles appeared showing that a person's income level is a predictor of their likelihood to participate. However, there were no articles which indicated that a person's income level affected how well a treatment worked in the individual. The absence of this makes sense, as there are not expected to be any genetic or metabolic differences between income groups.

Since researchers are unlikely to expect a drug or device to work better or worse in a person based off their income, it should be examined whether there are other income-related factors that could affect how well a treatment works in an individual. One perceived reason is that low-income individuals could be less likely to adhere to their treatment schedule. In a traditional medical setting, this could be related to prohibitively expensive drugs preventing a low-income person from purchasing their medications. However, in a medical research study the experimental treatments are traditionally covered by the study sponsor which removes the financial burden.

CHAPTER 11: CONCLUSION

There are several arguments against compensating people for their participation in medical research studies; yet these arguments are met with ethical precedent. The argument exists that money should not be used to persuade an individual to do something that the person would not do otherwise; however, this type of transaction is the basis of all employment contracts. Another argument is that people should not endanger themselves in exchange for money, yet this occurs frequently in risky professions. Despite these precedents being set, there is an aspect of payment in exchange for medical research participation that still raises an ethical red flag. One potential cause for this discomfort is a difference in the way that society views medical research.

Table 1

Comparison of Importance, Safety Considerations and Motivation

Comparisons	Firefighter	Medical Research Participants
Importance	Fires are an unfortunate fact of life. In order to minimize harm, we need firefighters to fight the fires.	Illness and injury are unfortunate facts of life. In order to minimize harm, we need to develop new treatments to fight the diseases.
Safety Considerations	There is in implicit risk in firefighting, yet these risks are minimized through safety standards and federal regulations.	There is an implicit risk in medical research, yet these risks are minimized through safety standards and federal regulations.
Motivation	Many individuals become a firefighter for altruistic reasons, yet some do it for the financial compensation.	Many individuals join medical research studies for altruistic reasons, yet some do it for the financial compensation.

For the purposes of this argument, there are several similarities between being a firefighter and a medical research participant; however, the truth is that they are viewed very differently in society. When a low-income person joins the military as a way to pay for college, there is rarely a discussion that he or she has been coerced into doing so. It would be unheard of to suggest that service men and women should no longer receive financial compensation for their service so that we can better ensure that their decision to enlist was truly voluntary. Yet this is the argument that is made when a low-income individual decides to join a medical research study. There are many potential reasons for this difference, such as past research atrocities or a general mistrust of the medical establishment.

Because of these negative opinions of medical research, there tends to be a belief that medical researchers are in a prime situation to take advantage of participants. This attitude remains even in the presence of regulations, review boards, and trainings to ensure that the rights of research participants are properly protected. This negative perception of medical research is even perpetuated by individuals involved in the conduct of the research. Even among medical researchers themselves, there often lingers a belief that a participant in a medical research study is ripe for exploitation or may not be acting in their own self interest. To a certain extent, even discussing the negative effect of financial compensation on voluntary participation perpetuates that stereotype that joining a medical research is a unsavory action. Instead of focusing on the medical research participant as a victim of an objectionable system, the research community should instead

hold up research participants as unsung heroes in the medical community. This attitudinal change would alter the perception of researchers from that of predators into that of trusted physicians.

> Quote from a 57-year old black man in North Philadelphia: *Of course. It's always going to be somebody tooken [sic] advantage of. That the way of the world. But in a, in a sense that some people are, you know, they're not as well informed as others. Or sometimes people, like I said, they people have hidden agendas […] but like I said, the medical professional who's, who you gonna be under this research project with, you would hope that they would be honest as possible with you and have no bias towards you regardless of your color, your religion, your age and take all these matters in consideration before even accepting you into that research study.*

An individual's decision making process is complex and is based upon a host of factors. When presented with all the relevant information, it should be permissible for an individual to consider the financial gain along with all other details of the study. A person's informed choice to participate in a medical research study should not be considered any less noble because their action was motivated by a financial gain.

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