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A Case for More Generous Compensation for Human Research Subjects in Non-Therapeutic Research

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How much payment participants in human research clinical trials should be allowed to receive continues to stir significant debate. Federal regulations state: "An investigator shall seek…consent only under circumstances…that minimize the possibility of coercion or undue influence".[1] When surveyed, Institutional Review Board (IRB) members and human subjects protection professionals "indicated considerable ethical concern that payment could constitute coercion or undue inducement".[2] Although historically viewed with misgiving, compensating research subjects is both acceptable and ethically warranted by the principles of autonomy, non-maleficence, beneficence and justice, particularly in non-therapeutic research. Although current guidelines stress the dangers of paying research subjects too much, we should be more concerned about whether we are paying them too little.

One illustrative example involves the analysis of a situation where a commercial entity seeks to recruit healthy volunteers to participate in a Phase I clinical trial evaluating the safety, side effects, and appropriate dose range for a new drug. The trial may involve identifying the drug's maximum tolerated dose, defined as the highest dose that can be taken without unacceptable side effects. This research is non-therapeutic in nature: participants do not stand to reap medical benefit, and, in fact, may undertake significant risk. Furthermore, even if the drug is eventually approved by the United States Food and Drug Administration (FDA), the volunteers are not likely to benefit from the its commercialization. In contrast, the pharmaceutical company's shareholders and corporate officers do stand to gain financially from the eventual sale of this new treatment. Though the costs of research and development are great, once a drug is approved and on the market, future profits should recoup monetary investments.

The fear that compensation causes undue inducement amongst research subjects is based on reasoning that autonomy might be compromised if participants are given enticements that render them unable to make rational decisions that uphold their own self-interest. An undue inducement occurs when "the offered good leads to poor judgment which makes us take unnecessary, unreasonable, and excessive risk of harm, whether physical harm or the harm of violating important values".[3] Many have argued that the rationale for undue inducement is paternalistic, and that restricting the range of options for research participants places unreasonable limits on their freedom.[4]

As reported in a recent *Wall Street Journal* article, scientists from the Walter Reed Army Institute of Research are considering whether to go forward with research that involves infecting healthy people with dengue fever.[5] Although volunteers will be paid, ethics committees will weigh "what would be reasonable and what would be considered coercive".[5] The article includes a comment from bioethicist Dr. Arthur Caplan, who explains that compensation that would lead participants to dismiss the risks is typically considered too high[5]. Empirical studies also suggest that limits are being placed on compensation to research participants. Largent et al. found that 80% of surveyed IRB members and human research professionals "judged that the offer of payment constitutes undue influence simply because it motivates someone to do something they otherwise would not"[2]. These authors argue that the professionals may be "adopting a conception of undue influence in

research that is radically different from the conception they employ in other areas of life".[2] As an example, they suspect that "respondents are unlikely to think that a bioethicist is *unduly* influenced if the offer of $1,000 as honorarium to give a presentation motivates him to do so when he otherwise would not".[2] We need to consider carefully whether we are paternalistically discounting the ability of research participants to make autonomous decisions and unfairly precluding their opportunities for compensation.

Compensation provides clear benefits to research participants, thereby upholding the principle of beneficence. Contrary to the idea that compensation blinds participants to the risks, some have pointed out that compensation may actually *warn* would-be volunteers to potential risks. Lack of or low payment may create the false impression that participation is risk-free, or even that it provides therapeutic benefit when none is present.[4] Therefore, providing compensation may benefit the participants in three ways: 1) actual value of the compensation; 2) communication to the participant that they are making a contribution, and 3) communication to the participant that they are taking on risk.

With respect to non-maleficence, clearly, most researchers do not intend to cause injury to participants in the course of clinical trials. Yet, clinical trials are experimental, and in the case of Phase I trials with new drugs and other non-therapeutic research, the effects cannot be completely known. The principle of non-maleficence is violated because there are inherent risks and a chance that participants will be harmed in some way. Some voice concern that providing compensation may increase the riskiness inherent in trials, if IRBs factor compensation as a benefit to be weighed against potential harms. However, as Ezekiel Emanuel rightly points out, review committees are tasked to ensure that "the anticipated risks are not excessive and, therefore, that it is reasonable for individuals to participate in the research trial".[3] The committees are also "required not to consider the incentives as a benefit in their assessment".[3] The Office for Human Research Protections (OHRP) also "continues to assert that IRBs should not consider remuneration as a way of offsetting risks".[6] It is important to note OHRP's position that "remuneration to subjects may include compensation for risks associated with their participation in research and that compensation may be an acceptable motive for agreeing to participate in research".[6] Given that IRBs should only approve protocols they believe warrant participation from volunteers without consideration of offsetting compensation, the amount of compensation that is given to participants should not be limited.

Issues of justice also require examination. The literature suggests that potentially coercive effects of undue inducement are particularly worrisome in vulnerable populations, such as those that are economically or educationally disadvantaged. However, restricting compensation effectively reduces options for those who are already financially strained. Particularly in circumstances where a human research subject does not have potential to benefit from participating in research, we must be sure that policies aimed to protect do not enable exploitation. The issues raised in Rebecca Skloot's *The Immortal Life of Henrietta Lacks* seem pertinent here. Although the researchers that propagated the HeLa cells obtained from Lacks' tumor did not believe they had infringed upon her rights, one can certainly sympathize with her relatives' feelings that Lacks' contribution to both

research and commercial products was not adequately compensated.[7] We should not expect participants to be motivated by altruism alone. It seems reasonable that participants in clinical trials be compensated. Participants may deserve a financial reward when a drug is approved and commercialized. After all, research participants clearly contribute to the process because the drug cannot achieve approval without them.

Today's emphasis on avoiding undue inducement may actually have the unintended consequence of allowing corporate sponsors of human research to undercompensate research participants. Although undue influence is a valid concern, application of the principles of autonomy, non-maleficence, beneficence, and justice demonstrates that compensation for research participants should be less restrictive. One suggestion is to create a separate mechanism for the evaluation of a research study's compensation component. The remainder of a research proposal can go through the regular IRB review process. Another idea might be to allow research participants to receive stock options (i.e., participate in the financial success of a drug if it does eventually make it to market). Perhaps medical federal regulations need to be revised and clarified in order to allow research participants to receive the full compensation they deserve.

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1. United States Department of Health and Human Services, Office of the Secretary, Office of Public Health and Science, Office for Human Research Protections, *Protection of human subjects: Title 45, Code of Federal Regulations, Part 46, revised January 15, 2009,* Bethesda, MD.

2. Emily A. Largent, Christine Grady, Franklin G. Miller, and Alan Wertheimer, "Money, coercion, and undue inducement: attitudes about payments to research participants," *IRB: Ethics & Human Research*, 34(1) Jan/Feb 2012: p. 1-8.

3. Ezekiel J. Emanuel, "Undue inducement: Nonsense on stilts?" *American journal of Bioethics*, 5(5), 2005: p. 9-13.

4. Ari VanderWalde and Seth Kurzban, "Paying human subjects in research: where are we, how did we get here, and now what?" *J Law Med Ethics*, 39 (3) 2011: p. 543-58.

5. Shirley S. Wang, "Dengue Fever Researchers in Military Weigh Infecting Volunteers," *The Wall Street Journal*, November 13, 2014.http://online.wsj.com/articles/dengue-fever-researchers-in-military-weigh-infecting-volunteers-1415908102.

6. United States Department of Health and Human Services, Office of Human Research Protections. "Human Research Protections FAQ: When does compensating subjects undermine informed consent or parental permission?" October 18, 2013, http://answers.hhs.gov/ohrp/questions/7251.

7. Rebecca Skloot, *The Immortal Life of Henrietta Lacks* (New York: Crown Publishers, 2010).