Ending Concerns About Undue Inducement

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For decades, worries about undue inducement have pervaded clinical research, and are especially common when research is accompanied by payment or conducted in developing countries. Few ethical judgments carry as much moral opprobrium or are thought to undermine the ethical soundness of a clinical trial as thoroughly as undue inducement. Indeed, the admonition to prevent undue inducement is one of the few explicit instructions in the “Common Rule’s” requirements for informed consent.

Despite their long history and pervasiveness, charges of undue inducement in clinical research are almost always mistaken. Indeed, I will advance an even more radical claim: A research trial that otherwise fulfills the fundamental ethical requirements for human subjects research inherently cannot create the possibility of undue inducement because substantial risk of serious harm is precluded. Charges of undue inducement tend to express displaced and mislabeled ethical concerns about other aspects of human subjects research. Consequently, claims of undue inducement should rarely be made, and when they are advanced should be treated with skepticism, placing a heavy burden of proof on those advancing such charges.

WHAT CONSTITUTES UNDUE INDUCEMENT?

The “Common Rule” states that

An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue inducement.

Ironically, it provides no definition of undue inducement, implying that the notion is either self-defining or obvious. Similarly, the IRB Guidebook fails to list or define undue inducement in its glossary.

Undue inducement is sometimes thought of as an “offer that is too good to refuse,” one which makes people do something they would not otherwise do. That definition, however, is too simple. Incentives related to a job, such as a higher salary, more vacation time, flexible schedules, or fewer hours, are also intended to make people do something they would not otherwise do, that is take the job. Yet such incentives are not ethically objectionable. Indeed, inducements are so commonplace and acceptable that our daily lives would be drastically different if they were all prohibited as unethical.

What makes an inducement undue?

Inducements prompt ethical concern when they distort people’s judgment, encouraging them to engage in activities that contravene their interests because they are harmful. This view seems consonant with the IRB Guidebook’s statement that undue inducement may be troublesome because: (1) offers that are too attractive may blind prospective subjects to the risks or impair their ability 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.
and the Council for International Organizations of Medical Sciences (CIOMS):

Payments in money or in kind to research subjects should not be so large as to persuade them to take undue risks or volunteer against their better judgment. Payments or rewards that undermine a person's capacity to exercise free choice invalidate consent.10

These considerations suggest there are four key characteristics of undue inducements. First, they entail an offer of a welcomed good, a positive incentive.11 The induced person is getting something he or she deems desirable. Second, the incentive, by some metric, appears excessive or irresistible. While there is no physical force or external psychological pressure, there is considerable internal attraction because of the quantity or type of the incentive. Third, the incentive does not just make the person do something they are not otherwise inclined to do. The incentive must produce bad judgments. Finally, the bad judgments must in turn engender ethically, legally, or prudentially undesirable activities. The activities are undesirable because they contravene the person's interests and thereby harm them. While bad judgment is necessary, alone it is insufficient to constitute undue inducement. Undue inducement requires the action entail a substantial risk of serious harm that contravene a person's interests. That is, there must be a risk of a serious adverse effect for the person. Absent potentially serious adverse consequences of the bad judgment there is no undue inducement.12

**Distinguishing Undue Inducement From Coercion And Exploitation**

These characteristics differentiate undue inducement from coercion and exploitation, with which it is frequently conflated.13 Undue inducement is the diametric opposite of coercion. While both make a person do what may be unethical, illegal, or imprudent, the former dangles a good, a positive offer to induce bad judgment that leads to harm, while the latter entails an overwhelming threat.14 The "your money or your life" threat of coercion is clearly different from the $1 million offer of undue inducement. Coercion requires a threat of what the person considers a worse consequence, while undue inducement offers a positive good.

Exploitation is about the unfair distributions of goods that arise from an interaction.15 One party gets too little, while the other gets too much. Often, but not always, the unfair distribution arises because one party to the interaction is in a weak position, due to poverty, ignorance, or extreme urgency, which the other party can take advantage of, offering few benefits. Remedy exploitation entails providing more benefits to one party.16 Thus, exploitation is about giving too little so the interaction is unfair, while undue inducement is about giving too much, leading to bad judgments and harmful consequences.

**Inducements Outside Of Human Subjects Research**

Undue inducement in research can be helpfully illuminated by considering inducements in non-research contexts. Different types of activities can be distinguished along a spectrum with one end encompassing ethical, legal, and prudent activities, such as taking a regular job or engaging in a hobby. At the other end of the spectrum are the clearly unethical and illegal actions, such as murder or plagiarism. Close to regular jobs are actions that are ethical and legal but are silly, foolish, or embarrassing, such as appearing on a reality television show, or (most) fraternity initiation rites. Further along the spectrum are ethical and legal activities, such as tongue piercing, that may be imprudent because they create discomfort or pain but lack serious or permanent risks. Even further along the spectrum are activities that are ethical and legal but risky. At low levels of pain or risk, reasonable individuals may participate in these activities, but as the levels of pain or risk increase more individuals will view them as imprudent. Indeed, there are levels of pain or risk that surpass a threshold, becoming objectively unreasonable. But even beyond the threshold, Evil Knevel-type characters may engage in such high pain or high-risk endeavors as part of their self-conception. Nevertheless, for you and I these actions are unreasonable, because while legal and ethical they threaten our prudential interests.

How do these different types of activities relate to undue inducement? Despite millions in salary, no one claims that Michael Jordan is unduly induced to play basketball, or Julia Roberts is unduly induced to perform in a movie. When a person is offered a huge salary for a reasonable, and otherwise ethical and legal job, no one worries that its high level will unduely induce the person to take the job.17 Indeed, the higher the salary for a specific job, the better off a person is deemed to be. Monetary inducements for an ethical, legal, and reasonable activity are deemed "due" no matter how high. In these cases, undue inducement is not even a conceptual possibility.

Payment to induce a person to perform an unethical, illegal and imprudent activity raises concern, but less because of the amount of money exchanged than the ethics of the underlying activity. The ethical problem of an incompetent student paying someone to take a test for him is not the amount of money transferred—it would be unethical even if no money were exchanged—but the fraud.

The proper sphere of concerns about undue inducement are activities that are ethical and legal, but seemingly imprudent. Payment for imprudent but not dangerous activities is not ethically worrisome; without a serious harm,
it is the proper sphere of a person's autonomous decisions to decide how to balance incentives with other demands. Absent serious harms, even high payments for such imprudent actions do not create concerns of undue inducement.

Therefore, ethical concerns about undue inducement arise only when the imprudence might eventuate in substantial risk of serious discomfort or harms. Since risks are ineliminable from living a full life it is reasonable for people to assume some risks. Likewise, most people can agree that there is a threshold above which it is unreasonable for people to take risks of serious harm whatever the incentives. However, there will be a middle range of pain and risk where there will be disagreement; risk takers will find the risks tolerable, risk-averse individuals will find them excessive. Moreover, there is an interaction of risk of serious harm and incentives. Individuals usually evaluate risks in relationship to benefits that might accompany them, accepting greater benefits, including financial incentives, to balance greater risks. Indeed, in some cases payment can transform imprudent into prudent activities. Below the threshold, society usually allows individuals to decide what risks, undue inducement plays no role in clinical research. Just as acting in a movie or any other job—even with some allure of money from experiencing the adverse consequences of those bad judgments by prohibiting research trials that are either unethical for reasons other than risk or anticipated to expose people to excessive risks. If the excessive discomforts or risks are precluded by the research oversight system, then there should be no worry about the consequences of high incentives.

Another way to see the inapplicability of the charge of undue inducement to clinical research is to consider the following paradox. That a clinical trial fulfills all the ethical requirements for human subjects research implies that it is ethical, legal, and reasonable for people to enroll in the trail. This raises the question: How can it be reasonable to invite people to enroll in a particular trial for no money, but unreasonable—even unethical—to invite them to enroll in the same trial for $100, $1,000 or even $10,000? Just as acting in a movie or any other job—even with some risks—does not become unreasonable if the salary is stratospherically high, participating in a legitimate research study does not become unethical because the incentives are high.

**Undue Inducement in Clinical Research**

Because independent review of clinical research excludes trials exposing participants to excessive discomforts and risks, undue inducement plays no role in clinical research. To be ethical, a research study must fulfill a series of requirements—contributing social value, being designed in a scientifically rigorous manner to generate reliable and valid data, recruiting fairly, having a favorable risk-benefit ratio, undergoing external review to ensure these requirements are fulfilled, and providing individuals informed consent. The fundamental function of independent review, typically performed by an IRB or ERB, and potentially other oversight bodies, such as the Recombinant DNA Advisory Committee (RAC) or the Joint United Nations Program on HIV/ AIDS (UNAIDS), is to ensure fulfillment of these ethical requirements and, especially, to proscribe any research that is likely to pose excessive discomforts or risks, and would be imprudent for a reasonable person to participate in. Importantly, in making this determination, independent review boards are required not to consider the incentives as a benefit in their assessment which makes their evaluation more conservative than in other aspects of life where incentive levels are typically integral to decision-making. Passing independent review ensures the anticipated risks are not excessive and, therefore, that it is reasonable for individuals to participate in the research trial.

In everyday life, society permits people to decide about participating in legal and ethical activities, even if they entail substantial and excessive pain or risk, and even to receive incentives to do so. Conversely, through independent review, the clinical research enterprise protects individuals who might make bad judgments under the allure of money from experiencing the adverse consequences of those bad judgments by prohibiting research trials that are either unethical for reasons other than risk or anticipated to expose people to excessive risks. If the excessive discomforts or risks are precluded by the research oversight system, then there should be no worry about the consequences of high incentives.

**Three Objections Considered**

Those who believe undue inducement is a serious ethical concern for research might raise three objections. While IRB review may indicate that it is reasonable for the average person to participate in a research trial because it does not pose excessive risks, there may be particular individuals who fulfill the eligibility criteria for whom participation is nevertheless excessively risky. High incentives may induce these people to participate against their individual interests. Independent review of any research trial is not meant to evaluate the ethics based on the special interests or idiosyncrasies of particular individuals. Since independent review occurs before a research trial begins, any consideration about the particular individuals who might participate and their circumstances is hypothetical at best. Restricting incentives because of concerns about its effect on a few of the potential research participants who, ultimately, may not even enroll, penalizes the majority of participants for whom these individualized concerns are irrelevant and who would stand to benefit from higher incentives. Further, determining how incentives relate to their personal interests is the proper sphere of individual's autonomous decision-making.

Personal physicians aspiring to the deliberative ideal should advise patients on how medical decisions, such as participating in a research study, will affect and embody their particular values and well-being broadly considered.
But IRBs do not have this role or relationship; they do not interact with much less advise individual participants, and their decisions are meant to apply to average, reasonable individuals.

The second common concern is that some research, such as Phase I studies, poses net risks to the participants but are justified by their social value. In such trials, high incentives might lead people to make bad judgments and enroll in trials that pose serious harms.  

In general, society expects people to assume some risks and inconvenience for the benefit of others. The principle of mutual aid underlies Good Samaritan laws and justifies the claim that people should jump into a pond to rescue a drowning person unless it poses serious risks of harm. Similarly, IRB review of research trials that pose net risks to individual participants but have social benefits are justified by the balance of net risks to the individuals versus the benefits for others. Posing enormous risks to individuals for trivial benefits to society would be unethical. (The current regulations appear to be flawed by failing to specify that research with net risks to the individual can only be justified when these risks are comparable to what society can reasonably expect—in other circumstances—a person to undertake to benefit others.) The IRB review affirms that the net risks to the individual are not excessive in regards what society can expect regarding risks individuals should assume for the benefit to others. Thus, even in Phase I trials, IRB review provides a failsafe check ensuring that an individual who might exercise bad judgment from high incentives is still prevented from excessive risks.

Finally, it might be objected that IRB approval confirms a trial is ethical but only if informed consent is fulfilled. One of the problems is that high inducements cloud people’s ability to understand and appreciate the information provided and thereby invalidates the informed consent process.

There are no data that payment leads to poor comprehension, or that high inducements make comprehension even worse. Indeed, the problem of poor comprehension is not unique to research studies with high inducement. The best solution to poor comprehension is to utilize interventions, such as post-decision assessments of understanding, that improve understanding. Adjusting incentives is at best an indirect and unproven method of improving understanding. If the concern is comprehension this should be addressed directly, not as a peripheral issue.

The Real Worries Behind the Undue Inducement Charge

If a properly functioning oversight system prevents undue inducement in research not by preventing distorted judgments but by preventing the excessive harms that might accompany them, then why all the concern about undue inducement? Many other worries seem mistakenly lumped under the rubric of undue inducement. One worry is that while the oversight system should exclude excessively risky research studies, it fails to work. Obviously the solution to an Oversight system prone to mistaken risk assessments is to fix the system. No research participant should be exposed to excessive risk, even when incentives are not offered. There is no suggestion that this risk assessment problem is more likely for research offering incentives. Indeed offers of inducements are likely themselves to induce IRBs to more carefully scrutinize the risks. But if there is a problem, the entire process of risk assessment is what would need to be improved. Focusing on undue inducement as the ethical concern is a mistake because it diverts attention and resources from correcting the more fundamental problem.

Alternatively, this concern might reflect the fact that risk averse people disagree with the judgments of others about the middle category of riskiness. Inevitably, reasonable people will disagree about what constitutes imprudent risks. But this is not a problem the research oversight system should worry about. As long as substantial risk of serious harms are prohibited, valuing autonomy means empowering individuals to make their own determination within this broad range of not unreasonable risks. The charge of undue inducement may be surreptitious paternalism by risk averse individuals over decisions properly left to autonomous individuals.

A second concern conflated with undue inducement is that of justice and exploitation. It is claimed that the poor are more likely to be lured by incentives and assume the risks of research for the benefit of the well off. After all, poor people tend to value a specific amount of money more, and could more easily be subject to undue inducement.

Not only is there no data supporting this claim, it confuses exploitation and undue inducement. The solution to exploitation is more not less, giving more benefits to the poor, not eliminating incentives. Moreover, if the worry is attracting a disproportionate number of poor people to participate in research, the solution would seem to be to raise the incentives to make the rich deem it worthwhile to participate too.

A third misplaced worry is that high incentives will induce people to falsify information in order to enroll in research. One well-publicized case involved an anorexic/bulimic woman who enrolled on a low risk sleep study but lied about her condition. Ultimately, she died because of self-induced vomiting causing a potassium imbalance and a cardiac arrest. This was a terrible tragedy, but it had nothing to do with financial incentives inducing bad judgment which lead to enrollment in excessively risky research. The vomiting appears to have occurred independent of the research study and even before the actual interventions. It is unclear that such lying is a general problem;
extreme cases are not good grounds for formulating public policy. In cases where researchers can independently validate patients' condition with diagnostic tests, incentive induced lying is not a concern. Since lying by participants threatens the validity of the research, researchers themselves will have to evaluate how much potential for lying is tolerable and calibrate their incentives accordingly.

Finally, there is a worry that the motivations of people who enroll in research for high incentives are somehow suspect. Jonas argued against using payments because he believed research should only enroll people who identify with ends of the research trial. Consequently, people participating for payment should be excluded because they would not identify with the ends of the research trial.

This idea is strange. We do not let people only take jobs in which they share the goals of the employer. Why should we add this requirement to research participation? Participants' motivations are irrelevant to determining the ethics of a research trial. Consequently, IRBs should never consider the research participants' motivations in their evaluations of research trials. While friends—and personal physicians—of research participants may question their motivations, and deliberate with them about whether research participation fulfills their life plans, it is inappropriate for IRBs to do so.

Jonas's view also embodies a faulty human psychology. People do not have some fixed set of goals; they have multiple goals, whose importance and value are frequently being re-evaluated and re-balanced. Some of these goals may overlap with the ends of research and others of which might not. Incentives are all about inducing people to re-examine their motivations and goals. Appealing to these non-overlapping goals to make participation in research more desirable is problematic only if they are unethical, illegal or imprudent. Typically getting more money to pursue one—legitimate—goal rather than another is not considered unethical, illegal, or imprudent, just part of the process of re-evaluating and balancing of goals we are all constantly engaged in.

**APPROPRIATE INCENTIVES**

These considerations do not require much less justify high incentives in clinical research, they are merely arguments to cease allegations of undue inducement. Indeed there may be other arguments against incentives for research, such as wanting to avoid the commodification or commercialization of research or of the human body. Importantly, such concerns are conceptually distinct from the ethical issue of undue inducement.

What should we pay research subjects? Defining a fair wage is highly controversial. However, consistency with payments for activities that entail similar levels of skill, harm, and social contribution suggests that appropriate payment for research subjects corresponds to the remuneration for unskilled labor. This argues against a market among research trials to directly determine payments. If remuneration for unskilled labor becomes high—either through market forces or campaigns for a living wage—then the payment to research subjects should be commensurate.

**CONCLUSION**

There is a real concern that prospective research participants should not be enrolled in excessively painful or risky research trials. Once an independent review affirms that a trial fulfills all the ethical requirements for research, it affirms that the pain or risks of the trial are anticipated to be reasonable. This means inducing a person to enroll in an approved trial, even from poor judgment because of a high incentive, cannot lead to excessive risks and is not an ethical worry. Just as we do not worry about excessive pay or other incentive from an employer—as long as the underlying job is not excessively risky or otherwise imprudent—so too there is no justifiable ethical concern about high incentives for participation in research that is not anticipated to have excessive risks. Charges of undue inducement reflect misplaced worries and can distract IRBs from focusing on real ethical concerns. We need to stop talking about undue inducement in clinical research.

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**REFERENCES**

2. 45 CFR 46, supra note 1.
3. 45 CFR 46, supra note 1.


30. 45 CFR 46.


42. Emanuel and Emanuel, *supra* note 27.

43. Grant, *supra* note 6; Emanuel and Emanuel, *supra* note 27.
