Undue inducement in clinical research in developing countries: is it a worry?
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Ethical controversy has surrounded biomedical research in developing countries. Major concerns include (1) the standard of care used in the control arm of trials, (2) the requirement to provide ancillary care during the trial, (3) the availability of interventions at the conclusions of the trial (reasonable availability), and (4) the quality of informed consent. Increasingly, people worry that undue inducements for research participants in developing countries compromise the voluntariness necessary for informed consent. In general, these research participants are poor, poorly educated, with access to few health-care services. They are often powerless, especially compared with pharmaceutical companies and researchers from developed countries. When outside researchers and funders provide research related payments and/or advanced health-care services that are otherwise unavailable, these individuals are forced to enrol in the research trial; it becomes an offer they can’t refuse. As Annas argues:

“You can tell a person [in a poor developing country] that this is research, but they hear they have a chance to get [health] care or else refuse their only good chance at care. How can you put them in that position and then say they are giving informed consent?”

In addition to monetary payment, concerns about undue inducement are raised regarding the provision of antiretroviral therapies for HIV-infected research participants in developing countries. As one researcher and sponsor asks: “If we provide antiretrovirals, will it create . . . an unreasonable inducement to participate in clinical trials?”

When is providing advanced medical services or payment undue inducement? How should biomedical research be done when the interventions offered are more generous than the standard medical services individuals receive or are entitled to?

A confused concern

There is something strange about this worry. Antiretroviral treatments for people with HIV are recognised as a tremendous benefit. They prolong and greatly improve quality of life, and they allow people to return to productive economic, social, and family lives. Proponents are tirelessly campaigning to secure these drugs for people in developing countries who cannot afford them. Critics seem to worry that although getting the drugs is clearly desirable and reasonable, receiving them as part of an otherwise ethical research study makes research participation unethical. This seems confused if not an outright contradiction. To appreciate fully why this concern is mistaken we need to understand the nature of inducements.

Differentiating inducement from undue inducement

Not every inducement is undue. Classifying inducements as undue is logical only if there are inducements that are due or appropriate. Nor can an inducement that changes a person’s action, making them do something they would otherwise not have done, be sufficient to make inducement undue. After all, the purpose of any inducement is to change behaviour. If all behaviour-changing inducements were by definition undue, there would only be attempted inducements and undue inducements, and no simple unqualified inducements that do not raise ethical worries, which cannot be correct.

Inducements are pervasive aspects of everyday life. Goods are constantly offered to change people’s behaviour without raising ethical concerns about violating autonomy or voluntariness. People are offered more money, more vacation time, or easier work schedules to induce them to change jobs; they are offered good salary, educational benefits, and other goods to join the military; they are offered coupons or discounts to buy one product rather than another. Such cases are not ethically problematic and do not constitute undue inducements even when people’s behaviour actually changes. The offers are intended to change people’s judgments and actions—they may change how people balance benefits and risk. Indeed, when related to taking a job, inducements could very well entail people assuming greater risk. However, the judgments and actions to take a job with more pay or vacation time despite the risks are still people’s own, and therefore are consistent with respecting their autonomy.

When is inducement undue?

Although commonly invoked as an ethical transgression, including specific admonitions in the US Federal regulations on informed consent and many other ethical guidelines for research, undue inducement is rarely explicitly and precisely defined. The main worry seems to be that individuals are offered some good that leads them to use poor judgment and assume substantial risks of harm that compromise their welfare. As the Council for International Organizations of Medical Sciences puts it in their Guideline 7:

“Payment 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.”
This definition suggests four necessary aspects of undue inducement:15 (1) an offered good—individuals are offered something that is valuable or desirable in order to do something; (2) excessive offer—the offered good must be so large or in excess that it is irresistible in the context; (3) poor judgment—the offer leads individuals to exercise poor judgment in an important decision; (4) risk of serious harm—the individuals’ poor judgment leads to sufficiently high chance that they will experience a harm that seriously contravenes his or her interests.

As related specifically to clinical research, undue inducement typically means that individuals are offered financial payment, medical services, or some item of value such as a shirt, toothbrush, or transport of a casket for burial that is so attractive it leads them to exercise poor judgment to either overestimate short-term benefits or underestimate long-term costs. Because of this poor judgment, they enrol in a research trial that poses a substantially unfavourable risk-benefit ratio, thereby compromising their interests.5–11,13

Each of these elements is necessary for inducement to be undue; without any one there is no undue inducement. Harm without poor judgment—being struck by lightning—is just misfortune. Harm from poor judgment without an offered good—swimming in crocodile infested waters—is imprudence.

Importantly, some harms are relatively minor or mild. They might be embarrassing, annoying, unfortunate, or even painful, but are neither sufficiently severe nor permanent to constitute undermining of a person’s fundamental interests.5–14 For instance, being embarrassed at participating in a reality TV programme, sustaining a painful but transient injury from trying a new sport, or selecting a boring job for a higher salary are harms, but these are minor or transient harms. Undue inducement requires substantial risk of serious physical, psychological, economic, or others harms, which threaten a person’s fundamental interests. Although reasonable people might disagree about the seriousness of some risks, undue inducement relates to risks that are clearly unreasonable. The kinds of harms that people assume and sustain in everyday life are reasonable because they are not of sufficient magnitude or seriousness to constitute the substantially unfavourable risk-benefit ratio necessary for undue inducement.

Furthermore, the evaluation is not of harms posed by individual elements.15 Many isolated factors—actual work or an injury—can be harmful or undesirable in themselves. When the work is balanced by the salary or the risk of injury by the exhilaration of a sport, the risk-benefit ratio must not be excessively unfavourable. The key ethical issue is not the harm of each individual element, but the net risk-benefit ratio.15

### Differentiating undue inducement from coercion

Frequently, undue inducement is conflated with coercion, exploitation, injustice, deception, misunderstanding, and other ethical transgressions as if they were equivalent or interchangeable.15,16 It is important to distinguish these violations not merely for philosophical fastidiousness, but because they entail distinct wrongs, and practically because they require different solutions (table).7

<table>
<thead>
<tr>
<th>Definition</th>
<th>Classic example</th>
<th>Solution</th>
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<tbody>
<tr>
<td>Undue inducement</td>
<td>Offer of a desirable good in excess such that it compromises judgment and leads to serious risks that threaten fundamental interests.</td>
<td>“I’ll pay you $1 million to ...” Traditional solution: reduce the quantity of the desirable good. Actual solution: reduce risks or improve risk-benefit ratio.</td>
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<tr>
<td>Coercion</td>
<td>Threats that make a person choose an option that necessarily makes him or her worse off and that he or she does not want to do.</td>
<td>“Your money or your life” Prevent or remove the threat.</td>
</tr>
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<td>Exploitation</td>
<td>Unfair distribution of burdens and benefits from an interaction.</td>
<td>&quot;That deal is unfair, you are charging too much (or you aren’t giving me enough)&quot; Increase benefits to the party receiving the inadequate level of benefits or assuming excessive burdens.</td>
</tr>
<tr>
<td>Injustice</td>
<td>Unfair distribution of resources before any interaction, in the background circumstances.</td>
<td>Lack access to antiretroviral drugs because of poverty Redistribute resources, increasing resources of worst off before the interaction.</td>
</tr>
<tr>
<td>Deception</td>
<td>Intentional withholding or distortion of essential information to mislead or create a false impression.</td>
<td>“This won’t hurt at all” Disclose accurate information.</td>
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<tr>
<td>Inadequate disclosure</td>
<td>Providing insufficient information.</td>
<td>Disclose all relevant information.</td>
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<tr>
<td>Misunderstanding</td>
<td>Inadequate comprehension of essential information.</td>
<td>“I did not know I might get a placebo” Improve comprehension through more discussion between researcher and participant, enhanced disclosure forms, or post-decision questionnaires.</td>
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**Table: Distinct ethical violations and their solutions**

Undue inducement is frequently conflated with coercion.8,9,11,16 Both make a person do what may be unethical, illegal, or imprudent. However, they are different. Undue inducement dangles a positive good, a tempting offer that can cause the bad judgment that leads to harm, while coercion entails a threat that the person considers a worse circumstance if they do not do the desired action.10–15,17,18 The “your money or your life” threat of coercion is clearly different from the “million dollar” offer of undue inducement. Consequently, the remedy for coercion is to eliminate the threat, whereas for undue inducement it is to reduce the value of the offered good.
to more, to increase the amount of benefit to the exploited person, whereas for undue inducement the traditional solution is to give less, to reduce the incentives provided to the person.

Differentiating undue inducement from unfortunate circumstances

Many worry that poverty or otherwise compromised circumstances may force people to take an inducement that people in a better situation shun. Because of people’s unfortunate circumstances, these tempting offers are said to undermine autonomy and voluntariness and, therefore, informed consent.

Distressing circumstances that create limited options do not necessarily compromise the autonomy and voluntariness of decisions. A person suffering from terminal heart disease or cirrhosis who decides in favour of an organ transplant may be in desperate circumstances, may feel his choice is forced, and may have no other viable options, but no one would claim such a choice is involuntary or lacks autonomy—no one would reject consent to a transplant in these circumstances as invalid.

More importantly, tempting offers in desperate situations that have clear good results are not undue inducements. Offering a poor person with no other options a good salary for reasonable work cannot be undue inducement even if it constitutes an irresistible offer because of the person’s poverty. Therefore, being forced to make a decision because of a tempting good in unfortunate circumstances is insufficient to compromise autonomy and create an undue inducement.

Irresistible offers become undue inducement only when the person’s unfortunate circumstances and compromised judgment are combined with accepting a seriously unfavourable risk-benefit ratio that threatens fundamental interests. By pre-empting the risk of serious harm, tempting offers become good rather than ethically worrisome undue inducements.

Undue inducement in clinical research

Although it is a pervasive worry, undue inducement cannot happen in clinical research that fulfils basic ethical requirements. Independent review of clinical research by institutional review boards (IRBs) or ethics review committees (ERCs) should exclude trials exposing participants to substantial risks of serious harms. Thus, even if the participants exercise poor judgment, they are protected from research with unfavourable risk-benefit ratios.

To be ethical, a research study in a developing country must fulfil eight ethical requirements: (1) collaborative partnership; (2) contributing social value; (3) being designed in a scientifically valid manner to generate reliable and valid data; (4) recruiting participants fairly; (5) having a favourable risk-benefit ratio; (6) undergoing external review to ensure that these requirements are fulfilled; (7) obtaining individuals’ informed consent; and (8) respecting the enrolled participants and their communities. The fundamental function of independent review by an IRB or ERC is to ensure fulfilment of these ethical requirements. In particular, IRB or ERC review is meant to preclude research trials that pose unfavourable risk-benefit ratios because they are likely to pose excessive risks that would be imprudent for most reasonable people to participate in. Obviously, IRBs or ERCs must permit some risks associated with research. What they preclude are substantially unfavourable risk-benefit ratios that—although some people may want to assume them—most reasonable people would not.

Importantly, in making a decision about the acceptability of research risks in light of expected benefits, IRBs or ERCs must not count as a benefit in their assessment any financial payments, added medical services, or other inducements. Normally, incentives, especially financial incentives, are balanced against risks of harm, and are typically integral to “all things considered” decision-making. For instance, in deciding whether to accept a risky job, such as being a miner or construction worker, people typically consider the salary and other benefits. Excluding financial and other inducements from the benefits considered by IRBs or ERCs makes their evaluation of a clinical research study more conservative than the decisions individuals make about taking jobs, joining the military, or even enrolling in research trials.

In its initial decision, an IRB or ERC can only consider prospective risks based on available data. In fact, because of knowledge gained through the research, the risks may turn out to be higher than anticipated. But this information is not available when decisions by the IRB, ERC, or individual had to be made at the start of the trial. Data safety and monitoring boards provide oversight during the course of the trial to minimise actual but unexpected harms. Consequently, the protection is not from actual harm but from substantial risk of harm anticipated at the initiation of the research trial.

In a clinical research study that fulfils the eight ethical requirements, there might be an offered good that leads to poor judgment, but substantial risk of serious harm that might threaten an individual’s interests should be prevented by the process of independent review. Without the possibility of a substantial risk of serious harm, undue inducement is not possible.

Real concerns masquerading as undue inducement

Much of the concern about undue inducement seems to be a misguided worry that IRBs and ERCs are not functioning properly and are ineffective at assessing the
constitute undue inducement. The antiretroviral drugs are available only on a restricted basis—does not otherwise ethical research trial in a developing country in
undue inducement and HIV/AIDS research trials incidental effect of adjusting inducements.
information, it should be addressed directly, not as an standing. If the ethical concern is comprehension of
method of improving research participants' under-
to improve the review system, to focus resources on better improvements of research protocols.
The solution to mistaken assessments of research risk and benefit levels is not to prohibit inducements, but to improve the review system, to focus resources on better training of IRB and ERC members and better evaluations of research protocols.

Sometimes, the worry is that beyond voluntariness, high inducements undermine potential research participants' ability to understand and appreciate the disclosed information. No data indicate that payment leads to poor comprehension, or that high inducements make comprehension worse. Indeed, the problem of poor comprehension in developed or developing countries is not unique to research studies with high inducements. The best solution to poor comprehension by research participants is to use interventions that have been shown to improve participants' understanding, such as more discussion between the researchers and participants. Adjusting incentives is at best an indirect and unproven method of improving research participants' understanding. If the ethical concern is comprehension of information, it should be addressed directly, not as an incidental effect of adjusting inducements.

Undue inducement and HIV/AIDS research trials
Providing antiretroviral medications as part of an otherwise ethical research trial in a developing country in which such medications are not generally available—or are available only on a restricted basis—does not constitute undue inducement. The antiretroviral drugs might serve as an inducement, and their availability in the trial could lead some, maybe even many, to change their actions and judge that enrolling in the research trial is worthwhile. However, assuming the trial is otherwise ethical—that it will provide valid and socially valuable data, the participants are selected fairly, and the overall risk-benefit ratio is favourable—these individuals would not be exposing themselves to unreasonable risks of serious harms by enrolling in the trial. Indeed, for HIV patients, access to antiretroviral medications will probably constitute for them a substantial net benefit of the research trial, not a risk that compromises their autonomy or core interests. It would be reasonable for any person to enrol in such a trial, and it might be unreasonable not to. Offering antiretroviral drugs to HIV positive people is not an undue inducement causing poor judgment but an incentive reinforcing prudent judgment; offering antiretroviral drugs as part of a research trial enhances rather than compromises autonomy.

Similarly, for individuals who consider enrolling in an HIV vaccine or microbicide trial, the offer of antiretroviral drugs if they become HIV positive does not constitute an undue inducement. After all, no person would become HIV positive just to get antiretroviral drugs; they are not intrinsically valuable. If research participants in HIV vaccine or microbicide trials were disinhibited and increased their risky behaviour, for example having unprotected sex more frequently, this would constitute poor judgment leading to a compromise of fundamental interests. Is this undue inducement? Only if the offer of antiretroviral drugs led to the poor judgment. On this logic, we would never offer research participants—in developed or developing countries—antiretroviral therapy if they seroconvert because it might induce poor judgment and risky behaviours such as unprotected sex.

There is no reason to think participants in developing countries are more susceptible to such poor judgment than participants in developed countries. Crucially, the unreasonably risky behaviour that might be associated with vaccine or microbicide trials is much more likely to arise from the sense of invincibility or from misunderstanding of the trial's goals and procedures, rather than from the offer of antiretroviral drugs for seroconversion. Since the drugs neither directly nor independently induce bad judgment nor constitute a risk of serious harm, they cannot "create . . . an unreasonable inducement to participate in clinical trials" that otherwise fulfil ethical requirements.

Talk about undue inducement in HIV vaccine, microbicide, or treatment trials in developing countries that provide antiretroviral drugs should desist. This does not mean HIV treatment, microbicide, or vaccine trials are inherently ethical. There might be other ethical transgressions, such as violations of the eight principles for ethical research. However, there is no undue inducement from the offer of money or antiretroviral treatments if participants seroconvert.
Conclusion
There are pervasive worries that clinical research in developing countries that offers payment or medical interventions generally not available to the participants creates ethically worrisome undue inducements. Too many people confuse any inducement that changes behaviour with an undue inducement. This notion is mistaken. Undue inducement requires offering something valuable that leads to both bad judgments and exposure to unreasonable risks. As long as the research is otherwise ethical, inducements do not lead people to assume unreasonable risks because an essential element of ethical research is a favourable risk-benefit ratio. As long as a review board determines that it would be reasonable for individuals to participate in the research study, then providing an inducement to participate cannot lead to substantial, prospective risks of serious harms, and therefore cannot be undue. Independent review boards might approve research with unfavourable risk-benefit ratios, but then the problem is the risk-benefit assessment and not the inducement. The remedy for such a problem is reform of the review process rather than reduction of the level of inducements.

Ultimately, researchers working in developing countries should focus on ensuring that their research is ethical and presents a favourable risk-benefit ratio. If they fulfill these ethical requirements for research, there is no need to worry about undue inducement.

Conflict of interest statement
The authors are engaged in HIV-related research in developing countries. EJE spoke for Merck twice in 2003. AH served as a principal investigator of a training programme funded by Bristol-Myers Squibb in sub-Saharan Africa from 1999–2003, and is currently serving on the Board of Trustees of an advocacy group based in Washington, DC, USA, that receives some of its funding from GlaxoSmithKline.

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References
17 Pace CA, Emanuel EJ. The ethics of research in developing countries: assessing voluntariness. Lancet 2005; 365: 11–12.