

Coercion and Undue Inducement in Research

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Disclaimer and Acknowledgement

- The views expressed are my own. They do not necessarily represent any position or policy of the National Institutes of Health or the Department of Health and Human Services.
- Actually, the views (and material) expressed are not (all) my own. Christine Grady and Neal Dickert have been kind enough to allow me to use slides that they developed.

Bioethics Worries About Money

- Selling Organs
- Commercial surrogacy
- Payments to Research Subjects
 - Professional Guinea Pigs
- Payments to Referring Physicians
- Payments to Researchers?

The basic problem

- Research requires subjects
- Participation may be risky, inconvenient, painful
- Altruism is limited

Walter Reed

- Yellow fever studies in Cuba (1900).
- Intentional exposure.
- Paid \$100 in gold.
- \$100 bonus for successful infection.
- Payable to family in the event of death.



<http://etext.lib.virginia.edu/healthsci/reed/commission.html#vol>

Payment Today

- **“Make \$1,000's... Get paid hundreds weekly in additional cash income, part-time, while relaxing in a million-dollar, get paid research study... Yes, there are thousands of cash paying studies and even free medical care available!”**
- **“Get paid up to \$1,000 weekly for safe sex research?”**

<http://www.rxgetpaid.com>

PROGRAM DIRECTORY	
 Easy Sleep 'ZZZ' Research	 Drive Cars Get Paid
 Alcohol • Medical Marijuana Studies	 Plasma • Blood Donation
 Eat and Shop Get Paid	 Health • Weight Loss Studies
 Safe Sex • Condoms • Sperm Donor	 Surrogates • Egg Donors Wanted
 Anxiety • Depression Bi-Polar Treatment	 Look at Email Get Paid
 Free Samples Get Paid	 Tobacco Smokers • Non-Smokers
 Focus Groups • Product Opinions	 Free Health & Dental Care
 Experimental Drugs and Medications	 PreExisting Condition Studies

Advanced Search

Other Incentives

- Free treatment (or chance of treatment)
- Free medical examinations
- Experimental Treatment
- Post-trial treatment
- Ancillary Care or Incidental Findings

Research in Developing Countries

- Access to ARVs in preventive HIV vaccine trials.
- “In the context of a community in which ARVs are not available, their provision to persons found to be HIV positive at screening or to trial participants who develop HIV during the course of study is obviously undue inducement to participate in the study. Only study participation gives access to ARVs that can forestall what is otherwise certain death from HIV.”
- **Charles Weijer, in Emily Bass, “Ethics, antiretrovirals and prevention trials,” IAVI REPORT 7(3), September 2003-January 2004**

Research in Developing Countries

- Burial expenses deceased children in an autopsy study of cerebral malaria in Malawi.
- “. . . economic pressure and the need to offset expenses related to a decent burial could conceivably become an incentive for many poor families to participate when they might otherwise prefer not to. The voluntariness of the consent could be undermined as much in this case as when, for example, \$10,000 is paid to university students in developed countries for participating in a study that offers no benefits.”

Mfutso-Bengo and Taylor, *Trends in Parasitology*. 2002.

TGN 1412

- TeGenero AG
- Lymphocytic leukemia and rheumatoid arthritis
- Phase I trial by Parexel, American CRO
- Subjects paid £2,000
- 6 subjects had catastrophic system failure

TGN 1412

- Unethical or Bad Luck?
- Consent form?
- Simultaneous Administration
- Undue Inducement/Coercion

TGN 1412

- The consent document stated that “If you leave the study and exercise your right not to give a reason or are required to leave the study for noncompliance, no payment need be made to you.” Greg Koski, former director of the U.S. Office of Human Research Protections, remarked, “That’s very coercive language.”
- Bloomberg. Parexel misled subjects sickened in London study, ethicists say. April 10, 2006. Available at <http://www.bloomberg.com/apps/news?pid=7100000&refer=germany&sid=aG3sg1rkL4U>

Overview

- Canonical Statements
- State of payment in the US
- Coercion
- Undue Inducement
- Exploitation

The Common Rule

“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 influence.”

45 CFR 46, 116

FDA

“Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive... The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence.”

FDA Information Sheets, 1998

OHRP

“... the IRB should review both the amount of payment and the proposed method of disbursement to assure that neither entails problems of coercion or undue influence. Such problems might occur, for example, if the entire payment were to be contingent upon completion of the study or if the payment were unusually large. Payments should reflect the degree of risk, inconvenience, or discomfort associated with participation.”

Office of Human Research Protection. *IRB Guidebook*.

Is Money a Benefit?

- The IRB should not view remuneration as a benefit to offset research risks in deciding whether a protocol should be approved. As in all cases, the IRB is charged with determining whether research risks are justified by the potential benefits of doing the research. Risks that are otherwise unacceptable cannot be made acceptable by offering increasing amounts of money to subjects. (Office of Human Subjects Research, NIH)

Payment in the U.S.

- Payments made in Phase I, II, III
- At least 23% of protocols at academic institutions paid subjects.
 - Few have any method of tracking paid studies
- Frequency of payment higher at independent IRBs and pharmaceutical companies.

Dickert, Grady, and Emanuel. *Annals of Int Med.*
2002

Amount of Money Being Paid (n=467 studies)

< \$100	30.4%
\$100-249	33.6%
\$250-499	21.2%
\$500-999	10.5%
\$>1,000	4.3%
<i>Mean</i>	\$266
<i>Median</i>	\$155

Amounts shown in U.S. dollars

Grady, Dickert, Jawetz, and Emanuel.

How are Decisions Made?

- 8/32 institutions had specific guidance.
- Significant variation within and between institutions in amount of payment for particular procedures, inpatient days, outpatient visits.

Dickert, Grady, and Emanuel. *Annals of Int Med.* 2002.

The State of Payment in the U.S.

- Payment is very common.
- All types of subjects are paid.
- Payment is erratic with little institutional guidance or consistency.
- Payment is generally modest.
- Significant disagreement over payment as incentive or for risk.

What are the worries?

- Subject Protection
 - Coercion
 - Undue Inducement
 - Fair Subject Selection
- Other
 - Commodification
 - Trust in research enterprise
 - Scientific
 - Conceal information
 - Reporting adverse events
 - Skewing population

Consequences of the worries

- Fact that payments are frequently made does not show that worries make no difference (speed limits)
- Not how many protocols are disapproved
- But how many protocols that would otherwise pass muster are not proposed or even considered?
- Does research progress more slowly?

Coercion

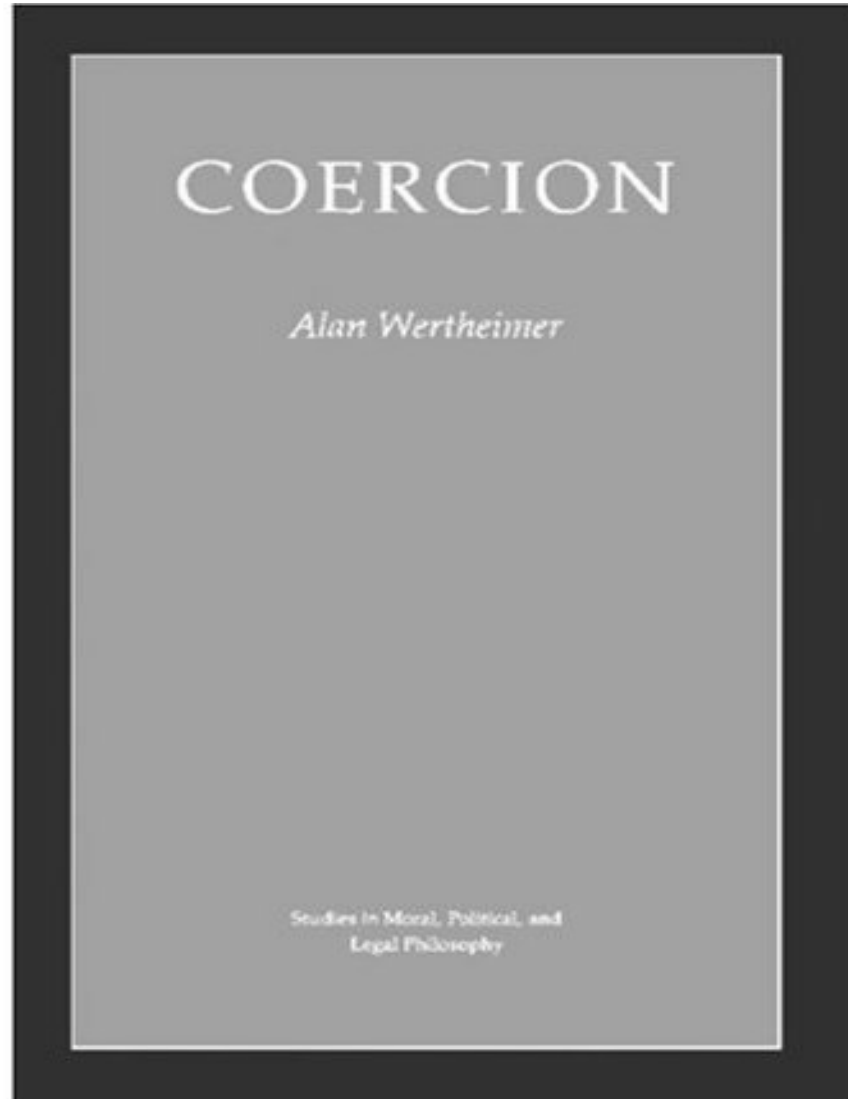
“By now it is an unquestioned ethical precept of biomedical and behavioral research practice that subjects should not be coerced into participating... Those who choose to participate in research should be capable of choosing freely; they must do so voluntarily, willingly, without duress, and without being subjected to threats or the promise of too great a reward.”

Macklin, *IRB*. 1981.

Coercion

- Concept used in many different circumstances.
- Often misunderstood as simply meaning under strong influence.
- Particularly misused to refer to situations in which there are no good options.
- We must be careful.

Subliminal Advertisement



Coercion: Two Views

- A coerces B to do X only if A proposes (threatens) to render B worse off unless B does X. (Threat view)
- A coerces B to do X when A's proposal leaves B with no reasonable alternative but to do X. (No Reasonable Alternative view)

What is Coercion: Threat View

- A coerces B to do X when A threatens to make B worse off if B does not do X.
- Threats v. offers
- Threats reduce options
- Offers enhance options

The Belmont Report

“Coercion occurs when an overt threat of harm is intentionally presented by one person in order to obtain compliance.”

National Commission, 1979

No Reasonable Alternative

- Attractive but mistaken view
- In most cases of coercion, target has no reasonable alternative but to agree.
- “Give me your money or I’ll beat you up.”
- But it does NOT follow that she is coerced BECAUSE she has no alternative but to agree.

No Reasonable Alternative

- Surgery. Doctor tells patient that unless she agrees to surgery, she will die within a year. Patient agrees.
 - Does patient have a reasonable alternative?
 - Has patient been coerced?
 - Can patient give voluntary consent?
 - Has doctor committed battery?
 - Is patient obligated to pay?

Coercive Offers

- Are there coercive offers?
 - “Is it not a coercive offer to force terminally ill pregnant women to choose between joining a placebo-controlled trial which gives them a shot at an established HIV intervention, and no treatment at all?”
Udo Schuklenk
- Offers enhance range of options
- So it seems that offers cannot coerce
- But what about an offer that can't be refused?



Godfather's Offer (Revised)

After original offer of \$10,000 is rejected,
Don Corleone raises the offer to
\$100,000.

The bandleader accepts the proposal.

Can Other Offers be Coercive?

- ARVs in the setting of vaccine trial.
 - Very attractive but not coercive.
- Burial expenses for autopsy study.
 - Very attractive but not coercive.
- In neither case is a subject worse off for refusing than never being asked.
- That people will enroll may be predictable, but this does not make an offer coercive.

Can Payment be Coercive?

- Payment is an offer and not a threat.
- To be coercive, a subject who refuses must be made worse off than if he or she would have been if never asked.
- Payment for research is not coercive.

Coercion is Rare in Research

- Cases where retribution is conceivable.
 - A physician may threaten to abandon a patient who refuses to participate in a study.
 - Explicit v. tacit threats
- Perceived coercion is possible.
 - Patient participates in a study run by his PCP because the patient mistakenly fears his care is contingent on participation.

Inducement

- Inducements are offers that get people to do things they would not otherwise do.
- Inducements are typically unproblematic
 - Jobs
 - Market transactions
 - Need not be financial (“If you do this, I’ll be your best friend.”)

TGN 1412

- Those who participated were members of an “economically vulnerable population; members who, presumably, would have made a different decision had they been in a position in which their personal valuations of the incentive were not *clouded* by their economic standing.”
(emphasis added)
 - Benjamin Hale, Risk, Judgment, and Fairness in Research Incentives, *American Journal of Bioethics* (2007) 7:2, 82 - 83

Undue Inducement

“...monetary inducements may be undue if they alter patients’ decision-making processes such that they do not appropriately consider the risks of participating.” Halpern, et. al. Arch. Intern Med. 2004

Undue Inducement

“An offer one could not refuse is essentially coercive (or “undue”). Undue inducements 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.”

Office of Human Research Protection. *IRB Guidebook*.

Undue Inducement

“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.” CIOMS, 2002, Guideline 7.

Fallacies about Inducement

- It's problematic to get someone to do something that they would otherwise not do.
 - Give blood
 - Give to charity
- It's problematic to get someone to do something against their better judgment
 - Against better judgment NOT COUNTING value of inducement.
 - Against better judgment, counting value of inducement

The Core of Undue Inducements

- Inducements are problematic when they distort the target's decision-making.
- Tunnel Vision
 - Focusing on gain
 - Ignoring cost
- Myopia
 - Overweighting short term gains
 - Underweighting long term costs
 - Hyperbolic discounting

Risky Jobs

- Coal mining
- Logging
- Commercial fishing
- Structural Steel
- Fire fighters
- Soldiers
- Is research different?

Is Undue Inducement a Concern?

- Likely to be rare in protocols approved by diligent IRBs.
- Can neither be completely dismissed nor completely eliminated.
- A reason for caution in settings where subjects likely have values in conflict with the research.
- Not just the IRB's responsibility.

A clear answer?

- “How large a payment constitutes “undue influence” or a coercive offer to participate in research is a question . . . for which no clear answer is forthcoming.”

Ruth Macklin

- A clear answer is forthcoming
 - offers do not coerce
 - A payment constitutes “undue influence” only if it distorts the agent’s judgment or reasoning

Payment Schedules

- Assume that patients have a right to withdraw from research at any time
- “the subject may discontinue participation at any time without penalty or loss of benefits *to which the subject is otherwise entitled.*” The Common Rule
- Do completion bonuses compromise that right?

Payment Schedules

- “Incentives must not be provided on a schedule that results in coercion or undue influence on an individual’s decision to continue participation. That is, incentives must not be withheld as a condition of an individual completing the research. If an individual withdraws early, payments or incentives must be prorated to reflect the time and inconvenience of the individual’s participation up until that point.”
 - Syracuse University IRB Handbook

Are completion bonuses problematic?

- Voluntariness worries
- Fairness worries
- Scientific worries

How much should subjects receive?

- Opportunity cost model
- Wage Payment model

Wage Payment Model

- Treats research as a form of unskilled labor
- Standardized payment for time and for procedures.

Wage Payment Model- Advantages

- Provides consistency.
- Treats research participation as labor.
- Offers appropriately limited protection from undue inducement.
- Prevents unfair advantage exploitation by ensuring reasonable standard payment tied to the nature of the work
- Controls research costs.

Exploitation and Undue Inducement

- Paying more: does it increase the likelihood of undue inducement?
- Paying less: does it increase the likelihood of exploitation?
- Stay tuned

Questions

- Is it right to consider research participation a job like other forms of work?
- Should payment be explicitly offered as an incentive?
- Should we allow payment as compensation for risk?
- Which is the greater problem – paying too little? Paying too much?
- Are there other reasons to worry about inducements?