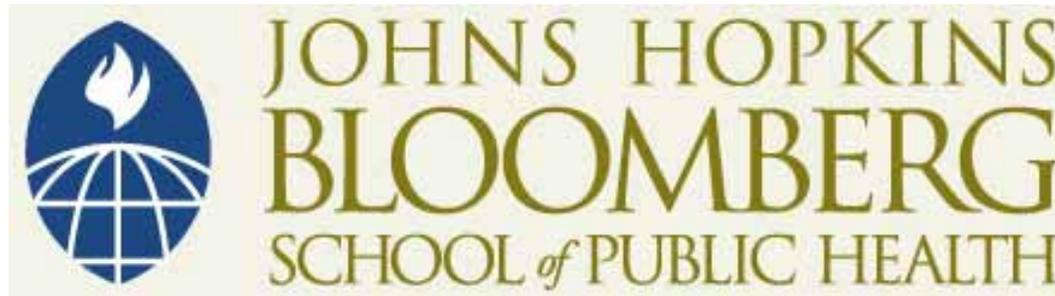


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*Coercion and  
Undue Inducement in  
Research:  
Money and Other Offers*

Neal Dickert

Johns Hopkins School of Medicine and  
Bloomberg School of Public Health

# *Question of the Day*

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- Asking your student to give a lecture in class is :
  - A) Coercive
  - B) Unduly influential
  - C) Exploitative
  - D) None of the Above
  - E) A Nice Gesture
  - F) Torture for the audience

## *Alexis St. Martin*

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- “The Intrepid Guinea Pig of the Great Lakes”
- In 1822, accidentally shot in the gut and left with a permanent gastric fistula.
- William Beaumont paid him room, board, and \$150 a year for use of his stomach.

<http://www.guineapigzero.com/AlexisStMartin.html>

# *Walter Reed*

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- 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*

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- “**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>

## *Payment Today*

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“There are lots of good reasons to rent your body to science: the advancement of knowledge, the opportunity to help future generations - oh, who are we kidding? The bottom line is that by "volunteering" to participate in medical experiments (a.k.a. being a "human guinea pig"), you can pick up some well-earned cash.”

[http://www.soyouwanna.com/site/syws/guineapig/guinea\\_pig.html](http://www.soyouwanna.com/site/syws/guineapig/guinea_pig.html)

# *Other forms of payment*

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## **Research studies and opportunities for free treatment**

- There are lots of ways to fight eating disorders. One way is to participate in research. Well-done studies help us understand why people become eating disordered, how they recover, and how treatment can be made more effective.
- In addition, it's sad but true that treatment for an eating disorder is prohibitively expensive for many people, and insurance coverage tends to be minimal at best. Many research projects offer free treatment to qualified participants. Some even pay stipends, and procedures are supervised by clinical staff with professional credentials.
- The treatment you receive in a study probably will not last for the several months, or even years, required to support full recovery, but it certainly can help you define the path you need to follow. And give you hope that recovery is possible.

<http://www.anred.com/res.html>

# *Research in Developing Countries*

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- Access to ARVs in preventive HIV vaccine trials.
  - Clearly desired by any subject participating
  - Raised concerns that it is “too attractive to refuse.”
- Burial expenses for an autopsy study of cerebral malaria in Malawi.

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

# *Payment Concerns*

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- Deaths of paid research subjects
  - Nicole Wan
  - Ellen Roche
- “Stuck for Money- To Screen New Drugs for Safety, Lilly Pays Homeless Alcoholics.”

Cohen L. *Wall Street Journal*. Nov. 14, 1996.

## *Tensions Today*

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“Because payment for participation can have coercive or exploitative effects on potential subjects, institutional review boards (IRBs) generally take into consideration the amount and distribution of proposed monetary payments to subjects to ensure that subjects in the study will not be unduly influenced to participate.”

Schonfeld, et al., *IRB*. 2003.

# *Overview*

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- State of payment in the US
- Coercion
- Undue Inducement
  - Existing Views
  - A New Definition
- Exploitation
- Data on Ethical Concerns in Practice

## *The Common Rule*

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“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

“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

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“... 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*.

## *Payment in the U.S.*

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- 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.
  - “most” and “about 80%”

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

## *Types of Studies Paying Subjects (n=467 studies)*

Phase I	26	5.6%
Phase II	58	2.4%
Phase III	100	21.4%
Phase IV	36	7.7%
Physiologic	88	18%
Behavioral	82	17.6%
Other	77	16.5%
<i>Total</i>	467	-

Grady, Dickert, Jawetz, and Emanuel. *In press*

# *Amount of Money Being Paid* *(n=467 studies)*

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< \$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. *under review***

# *How are Decisions Made?*

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- 8/32 institutions had any 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.

## *How is Payment Described? (n=31)*

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	Academic (n=9)	Pharm/ Biotech (n=6)	CROs/ SMOs (n=8)	Indep. IRBs (n=8)
Incentive	4	4	5	5
Time	7	6	6	8
Travel	6	5	5	5
Inconvenience	8	6	6	6
Risk	3	0	1	6

# *The State of Payment in the U.S.*

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- 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.

# *Ethical Concerns*

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- Concerns focus on the enrollment of vulnerable populations.
  - Poor and homeless
  - Sick patients
  - Children
- Often cast as worries about coercion, undue inducement, and exploitation.

# Coercion

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“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

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“... [A] patient suffering from a life-threatening disease may feel as though she has little choice regarding treatment. Physicians should be aware of how vulnerable patients may be to the coercive influence of unrealistic hope, especially those suffering from chronic, life-threatening disorders.”

Berg, Appelbaum, Lidz, and Parker, *Informed Consent: Legal Theory and Clinical Practice*. 2001.

# *Coercion*

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- Used in many different circumstances, often incorrectly.
- Often misunderstood as simply meaning involuntary or under strong influence.
- Particularly misused to refer to situations in which there are no good options.
- Because coercion is not a benign accusation, the concept is in need of clarification and should be used carefully.

# *The Belmont Report*

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

National Commission, 1979

# *Coercion Requires a Threat*

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- Classic case- “your money or your life”
- Structure- *A* wants *B* to do *X*. If *B* does not do *X*, *A* will make *B* worse off than *B* was before the interaction.

Wertheimer, *Coercion*. 1987.

- *If B refuses, B will be worse off than if A had never approached him.*
- Some may claim that *B*'s decision may be voluntary in some strict sense. The problem is that it's made under a threat of harm.

# *Can Payment be Coercive?*

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- 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.

# *Can Other Offers be Coercive?*

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- ARVs in the setting of vaccine trial.
  - Very attractive but not a threat.
- Burial expenses for autopsy study.
  - Very attractive but not a threat.
- 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.
- Cell phones for IPT study in S. African mines?

# *Coercion is Rare in Research*

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- Cases where retribution is conceivable.
  - Inmate may receive poor treatment for refusing.
  - A physician may threaten to abandon a patient who refuses to participate in a study.
- Perceived coercion is possible.
  - Patient participates in a study run by his PCP because the patient fears his care is contingent on participation.
- Payment or other incentives may be involved in these cases, but they have nothing to do with coercion.

# *Inducement*

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- Inducements are offers that get people to do things they would not otherwise do.
- Acceptable inducement
  - Higher salaries or other perks for jobs.
  - Giveaways by stores induce us to shop.
  - Advertisements
- Inducements in research
  - Any activity to encourage participation.
  - Pure reimbursement- pay for parking.
- What inducements are acceptable?

# *Undue Inducement*

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“...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

# *The Belmont Report*

---

“Undue influence... occurs through an offer of excessive, unwarranted, inappropriate, or improper reward or other overture in order to obtain compliance.”

National Commission, 1979

# *Undue Inducement*

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“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.

# *Undue Inducement*

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- Individuals induced by large amounts of money are acting involuntarily and may be exposed to significant risk.
- They may be blinded to the risks of participation and thus make uninformed decisions.
- They may lie or conceal information.

# *Undue Inducement*

---

- There is an offered good.
- The good is excessively attractive.
- It leads people to exercise *poor judgment*.
- Participation involves a *risk of serious harm*.

Emanuel, *J Law Med Ethics*. 2004.

# *Undue Inducement*

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- Payment cannot be undue inducement in an appropriately approved study.
  - Enrolling in such a study cannot represent poor judgment.
  - IRBs should not approve studies that expose subjects to serious risk of harm.
    - Limited agreement with McNeill's argument.

Emanuel, *J Law Med Ethics*. 2004.

# *Undue Inducement*

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- Concern seems misdirected if a study involves no risk.
  - No worry about paying \$500 to ask people about their favorite color or to do a fingerstick blood glucose test.
  - Participating in research is generally very safe.
  - If it isn't, the problem is with the IRB and not with the money.

# *Undue Inducement*

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- Concerns about voluntariness are counter-intuitive.
  - Why would payment for research compromise voluntariness when it doesn't in other settings?
  - Doing what you *want* is typically thought of as voluntary.

# *Undue Inducement*

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- Concerns about consent are misdirected
  - If consent is compromised, improve the consent process.
  - It isn't clear that changes in payment are the right solution.

# *Undue Inducement*

---

- There is an offered good.
- The good is excessively attractive.
- It leads people to exercise *poor judgment*.
- Participation involves a *risk of serious harm*.

Emanuel, *J Law Med Ethics*. 2004.

# *Undue Inducement*

---

- Two concerns with this view:
  - Reasonability of risks to different people varies.
  - Non-risk determinants of poor judgment that involve violations of fundamental values or important preferences.

# *Reasonability of Risk Varies*

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- Risk tolerance lies on a spectrum from extreme daredevil to extreme caution.
  - IRBs simply cannot, and should not, accommodate the whole range of risk tolerance.
  - But, as studies get riskier, and as payment goes up, it becomes more likely to induce people to take risks that make them very uncomfortable.

# *Reasonability of Risk Matters*

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- Risk tolerance is an important part of one's self-conception.
- The meaning of exceeding risk tolerance will vary but can be significant.

# *Non-Risk Determinants of Judgment*

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- Values other than risk may make people significantly averse to particular studies.
- *Example:* Some people have value-based objections to getting undressed in front of members of the opposite sex. A study paying a lot of money but requiring them to disrobe may lead them to act contrary to those values.
- They may not be *wrong* to override these values or strong preferences, but it may be worrisome to institutionalize practices that encourage them to do so.

# *Undue Inducement- New Definition*

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*Undue inducements are excessively attractive offers that lead people to do something to which they would normally have real objections based on risk or other fundamental values.*

- Acting contrary to important values better captures the nature of undue inducement concerns.
- In most cases, risk will be the primary objection but is not the only consideration.

## *But why is this really wrong?*

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- Worrisome to institutionalize practices that express disregard for human values and dignity.
  - Especially in the setting of institution designed primarily to improve health.
- More to respect than just honoring the decisions of capacitated adults.

# *Is Undue Inducement a Concern?*

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

# *Examples*

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- ARVs in vaccine study.
  - Depends on the nature of the study.
  - If a Phase III study where risks are low and no reason to think subjects object to participation, little concern about undue inducement. To what would they object?

# *Examples*

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- Burial expenses for autopsy study.
  - More complicated case.
  - Depends on how autopsy is viewed and the attractiveness of burial expenses.
  - May be unduly influential if participants likely to feel they have violated their values, undermined their dignity.
  - Not undue inducement if subjects likely to accept wouldn't do it otherwise but basically accept the need for the study and feel comfortable about participating.
  - Shows the importance of careful local review.

# *Exploitation*

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- Raised as a concern when enrolling vulnerable populations.
  - Enrolling Cambodian sex workers without access to care in RCT of tenofovir for HIV prophylaxis.
  - Enrolling prisoners in a malaria study
- “An exploitative transaction is one in which A takes unfair advantage of B.”  
*Wertheimer, Exploitation. 1999.*

# *Exploitation*

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- Solution- Offer more?
  - Exactly what participants suggested in Cambodia.
- Hardly satisfies opponents and raises concerns about undue inducement.
- Significant tension exists between concerns about exploitation and undue inducement.

## *Exploitation and Undue Inducement*

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- Issues of exploitation are central and are far from settled.
- Figuring out how to fix unfair advantage exploitation will require confronting undue inducement.
- Highlights the importance of clarity on undue inducement as a concern.

# *Concerns about Justice*

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- Pay will lead the poor to accept a disproportionate research burden.
  - Empirically unknown- On a broad level, we don't know who participates in research.
- What is the worry if risk is acceptable?
- What if people enrolling see participating as a net benefit and not a net burden?

# *Concerns about Justice*

---

- The only true fix is to pay people according to existing income or not at all.
  - Unequal pay also seems to violate justice.
- The real worry is one about exploitation, about taking advantage of people.

# *Scientific Impact of Payment*

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- Do people conceal information to get into studies?
- Are they unlikely to report adverse events, compromising science and jeopardizing safety?
- Does payment skew the population in scientifically relevant ways?
- The answer- we don't know.

# *What do the Data Show?*

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- Motivations of paid subjects
  - Money is important but not the only factor.
  - 50-95% of subjects motivated primarily by money.

Bigorra and Banos, 1990; Vrhovac, Francetic, and Rotim, 1990; van Gelderen, et al., 1993; Novak, Seckman, and Stewart, 1977; Martin, et al., 1968; Hassar and Weintraub, 1976; Aby, Pheley, and Steinberg, 1996.

- Very little data on the kinds of tradeoffs subjects will make for money.

# *Negative aspects of research*

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- None 20.0%
- Pain/side effects/scarring: 21.7%
- Poor procedures (painful blood draws): 20.0%
- **Uncertainty of the risks and unknown: 20.0%**
- Time commitment: 16.7%
- Lack of activities/bad or no perks: 16.7%
- Staff mean/unpleasant 15.0%
- Not home/with family: 5.0%
- **Didn't pay enough 5.0%**
- Restrictions on diet/drugs/cigs/alcohol: 1.7%
- Other 1.7%

**Kass, et al. do not cite.**

# *What do subjects want?*

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- Interviewed 963 Ugandans
  - Participants (paid/unpaid), decliners, residents of uninvolved communities, and community leaders
- 72 % said subjects should be compensated
  - 40% money
  - 15% food
  - 22% health care
  - 5% health item

Grady et al., do not cite

# *What do subjects want?*

---

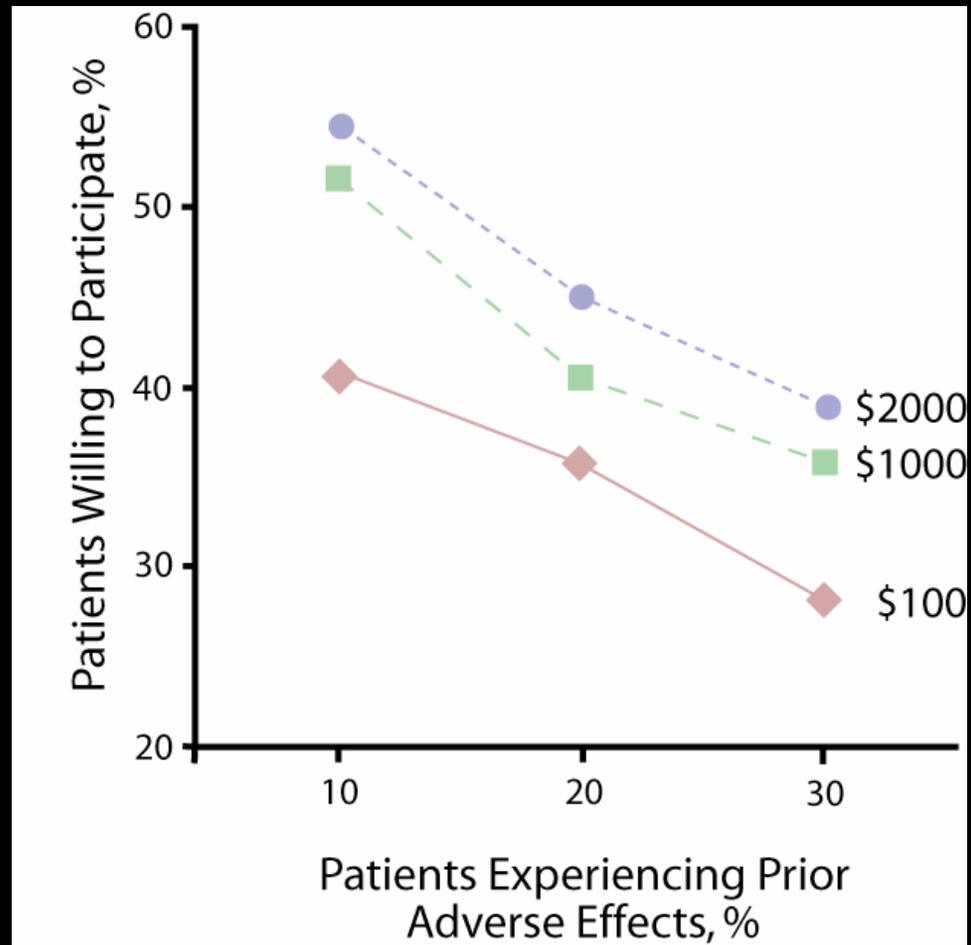
- Of those who wanted money
  - 27% < 10,000 Ush
  - 42.6% - 10,000-50,000 Ush
  - 30.3% > 50,000 Ush
- Hypothetical vaccine trial
  - 43.9%- Travel \$ and health hygiene- related item
  - 22.2%- Health hygiene related item alone
  - 21.6%- Travel \$ and small payment in Ush

Grady et al., do not cite

# *Influence of Payment on WTP*

- Payment influences willingness to participate.
- Influence of payment may level off.
- Relative influence of payment seems stable as risk increases.

**Halpern, S. D. et al. *Arch Intern Med.* 2004**



## *Effect of payment on understanding*

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- No interaction between amount of money and risk rating in hypothetical scenarios.  
*Bentley and Thacker, J Med Ethics. 2004.*
- No data on understanding in actual subjects who are paid versus unpaid.

## *Summary*

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- Coercion requires the presence of a threat of harm if a subject refuses participation.
- Undue inducements are very attractive offers that lead people to do something to which they would normally have real objections based on risk or other fundamental values.
- Exploitation and undue inducement exist in tension.

# *Recommendations*

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- More empirical work
  - Tradeoffs people will make for different kinds of offers.
  - Concerns people have about participating in research.
  - Impact of offers on safety and data integrity.
- Focus on the study first, then the offer.
  - Undue inducement is important to consider at the limits of approvability and when fundamental values are known to be stake.

# *Wage Payment Model*

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- Treats research as a form of unskilled labor
  - Mere reimbursement
  - Market-based payment/incentive
- Standardized payment for time and for procedures.
- Payment based on the unskilled labor market.
- Particularly opposed to McNeill's objection to considering research participation to be work.

# *Wage Payment Model-Advantages*

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- 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.

# *Questions*

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- Is it right to consider research participation a job like other forms of work?
- Should payment be considered an incentive?
- Should we allow payment for risk?
- What is the right fix for the tension between undue inducement and exploitation?
- Was I coerced, unduly influenced, exploited, or none of the above?

# *Cases*

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- IPT Case Study from last week
  - Is the provision of cell phones problematic from an ethical perspective?
- Autopsy Study in Malawi
  - Does payment of burial expenses constitute undue inducement?
- ARVs in vaccine studies
  - Is undue inducement a concern?