Ethical Issues in Providing Payment for HIV and Drug Use Research

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Objectives

Case study

Personal interest

How payment is used in research

Why should we care

Potential solutions

Case Study

"We are conducting a HIV cure study among positive injection drug users. You may not directly benefit from participation in this study. For more information please contact Brandon Brown at 951-990-9899"

Text: **We are conducting a [1] HIV cure study among positive injection drug users. You may not directly benefit from participation in this study. [2]**

	Including text	Proposed amount	
		Agree	Disagree
	No additional text	$0	
1	biomedical, multiple visit, 2 year	$5,000	
1 & 2	biomedical, multiple visit, 2 year In order to participate, you must halt the use of your antiretroviral treatment, which may make you sick or infectious	$50,000	

Case study-what are the issues?

There is diversity in decision making

- Wording+details
- altruism
- experience in research
- Perceptions
  - Payment & safety

Case study-other issues

Would knowing what has been provided in past studies help your decision?

Is there something other than monetary payment that should be considered?

If your role changes, does your suggested payment change?

- Imagine you are:
  - the participant
  - the IRB
  - the PI of the study
  - the study sponsor (funder)

Main concern

What is the main question or concern with payment from an ethical and regulatory perspective?

Regulatory Parameters

The regulations instruct IRBs to minimize the possibility of coercion and undue influence during informed consent.

- Neither the Common Rule nor FDA regulations explicitly connect payment with ‘coercion’ or ‘undue influence’ or discuss payment at all
- But payment is discussed in an Office of Human Research Protections (OHRP) ‘FAQ’ and an FDA Information Sheet …

OHRP, Informed Consent FAQs

‘When does compensating subjects undermine informed consent or parental permission?’

- “Paying research participants in exchange for their participation is a common and, in general, acceptable practice.”

“IRBs should be cautious that payments are not so high that they create an **‘undue influence’** or offer **undue inducement** to participate in research.”

OHRP Informed Consent FAQs

The Regulatory Challenge…

So, according to regulatory guidance…

- Payment is generally acceptable …
- So long as it does not **‘unduly influence’** or **‘coerce’** individuals to participate in research.

‘Coercion’ and ‘Undue Influence’

OHRP’s definitions…

- **“Coercion** occurs when an overt or implicit **threat of harm** is intentionally presented by one person to another in order to obtain compliance.”
- **“Undue influence**, by contrast, often occurs through an **offer of an excessive or inappropriate reward** or other overture in order to obtain compliance.”

OHRP Informed Consent FAQs

What Is '**Undue**' Influence?

OHRP: undue influence occurs when payment **distorts** an individual's decision to participate in research

- Payment as undue influence = "**compromise a prospective subject's examination and evaluation of the risks or affect the voluntariness of his or her choices**."
- Empirical question; some data that payment **increases** perception of risks and caution among subjects

If the IRB Independently Determines the Risks to Be Reasonable...

For most people in the study population, participating will not be a bad or unreasonably risky choice.

- If it were, something has gone wrong with risk-benefit analysis.

Does not eliminate risks of payment entirely but should significantly diminish concerns.

- Some people may have idiosyncratic situations or values that IRB cannot be expected to anticipate.

Three Main Payment Categories

Reimbursement

- Payment for out of pocket expenses incurred as part of research participation

Compensation for time/burdens

- Subjects paid for time and undertaking burdens of research

Recruitment incentives

- Offered to improve recruitment and participation rates

Incentives are everywhere

Sometimes acceptable, sometimes not

Sometimes you pay, sometimes get paid*

‘Real life’ different than research

- In research, usually talk about participant getting something

When some people think of incentives ($$$)...

Initial Interest in incentives

Incentives provided to similar participants in three studies of infectious diseases in Lima, Peru

	Study 1	Study 2	Study 3
Money	None	U.S.$7.00	**None**
Gifts	Watch, makeup, purse, wallet	Annual birthday present, watch, perfume, makeup purse, wallet, hair dryer, lunches	**Nothing**
Health services	Birth control, genital wart removal, condoms and lubricants, and HIV testing	Birth control, genital wart removal, condoms and lubricants, STD treatment and **medical attention for participants and family**, annual breast exam and Pap smear, and HIV testing	**Genital wart removal, HIV testing, annual Pap smear, and syndromic treatment**

IRB: Ethics and Human Research. 2013;35(2):14-7.

Retrospective analysis of participation in clinical trial

Measure	Agreed	Disagreed
Study well described in consent	14	2
Participation is voluntary	16	0
Felt they could withdraw at anytime without loss	13	3
Enjoyed participating in the study	15	1
Primary reason for participating was CC screening	16	0
Study should have paid us	3	13

Ethics and Behavior 2015; 25(2), 115–128

Incentives History: Tuskegee Experiments

1932-72, Tuskegee, Alabama

Public health doctors (NIH) followed African American men with syphilis

- Goal of learning about the disease history

Did not tell participants they had syphilis

When Penicillin became available (1947), did not treat

- "It was important that they were untreated, and it would be undesirable to go ahead and use large amounts of penicillin to treat the disease, because you'd interfere with the study"

For participants: free medical care, meals, and burial insurance

For investigators…

Willowbrook state school Experiments

Children with intellectual disability-NY

1956-1972, children *intentionally infected* with hepatitis
- Study sponsored by US army
- Goal to develop vaccine

Given facility conditions, PI argued children would be exposed naturally

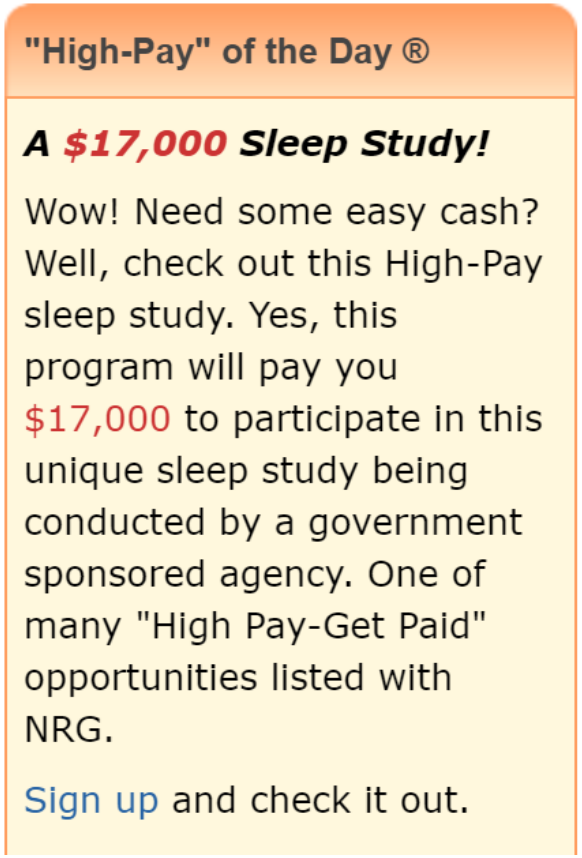
Issues
- Long waiting lists for children to be admitted to the school
- **Parents consenting to participate in the study allowed to enroll their disabled children**
  - **Only school of its kind at the time in the area**

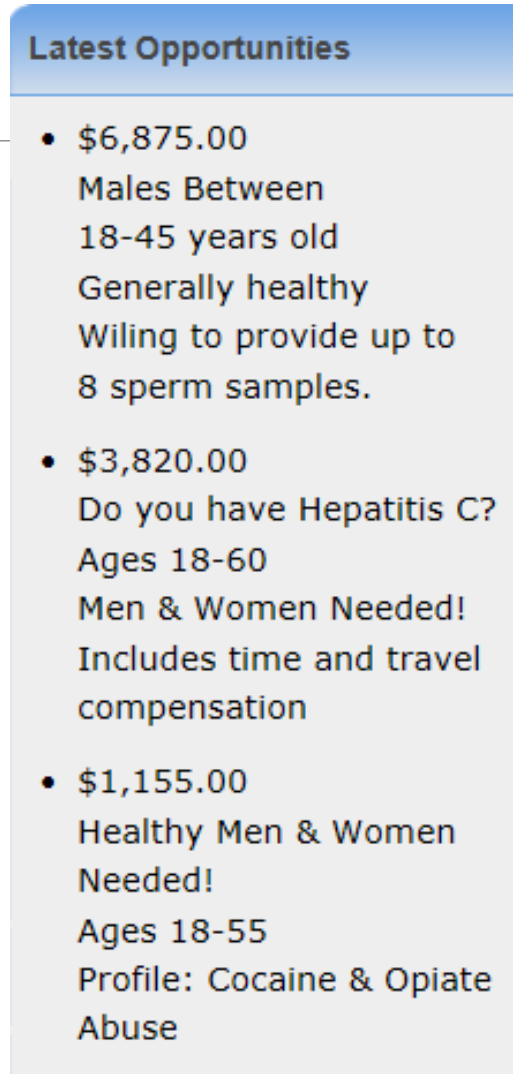
Incentives in research

money, snacks, health care, gifts

means of encouraging participation*

- Skewed sample selection?
  - Marginalized-risk*





Planning a new HS research study*

What are appropriate incentives?

- Who should be making the decision?
- How should this decision be made?*
- Decision can be hard
  - Transparency-reference data

Brown B et al. Transparency of participant incentives in HIV research. Lancet HIV 2016.

We have few incentive data

Currently no public record of incentives

- Not easily searchable-IRB

No guidance on what types/amounts to provide*

No working definition of excessive incentives

- Undue inducement*

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

Why should we care about incentives?

Impact research outcomes
- Enthusiasm to join, not adhere
  - Examples of this in HIV research

Professional research subjects
- Fabricate/conceal-symptoms/behaviors*

Research studies “monetizing” acts-HIV testing*

http://betablog.org/croi-2013-voice-trial-results-on-daily-hiv-prevention-for-women/
http://www.hivequal.org/hiv-equal-online/prep-works-for-transgender-women-but-only-if-they-use-it

Incentives in the literature

Few publications report incentives/payment

Dickert et al 2002 ‘Paying research subjects’

- 37.5% of orgs had policies on payment
- 20% of groups knew what % of their studies paid

Grady et al. 2005 ‘Analysis of US Practices’

- 467 clinical studies with range of payment $5-$2000
- Unexplained variation

Incentive Decision Making

Perfect world
- study team engages potential participants beforehand*
- Review of previous studies, contact PIs
  - Lengthy process

Real world
- Make quick decisions, deadlines
- depends on budget, beliefs, standards

IRBs review incentive amounts proposed by investigators
- Approve or deny
- May rely on investigator to do ‘due diligence’

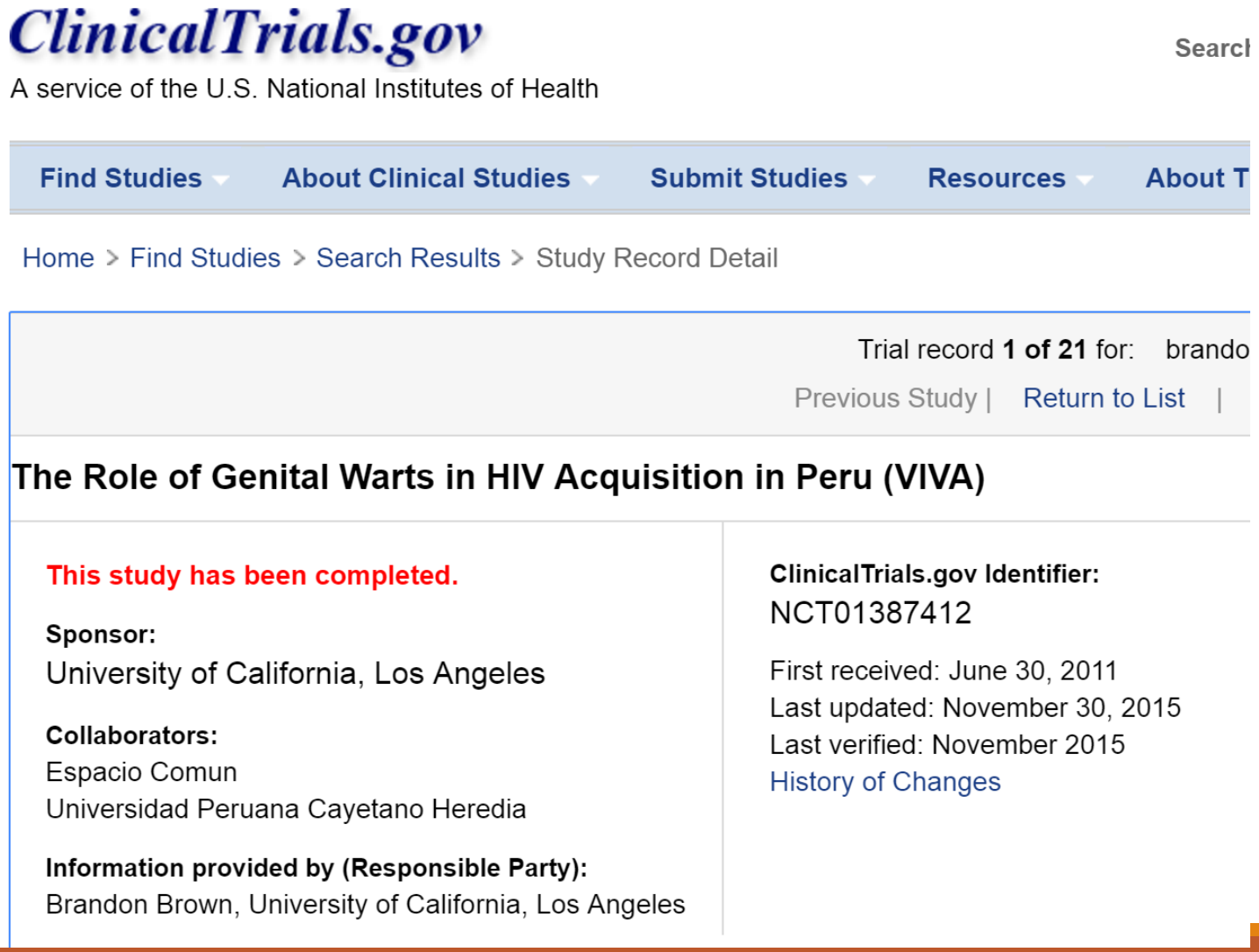
Ex: How payments are evaluated (IRB)

The purpose of this worksheet is to provide support for the convened IRB or Designated Reviewers when evaluating payments to subjects or their legally authorized representatives. This worksheet is to be used. It does not have to be completed or retained.

1	**Requirements for Payments** (Check if **"Yes"**. All must be checked)
☐	All payments are described in the protocol including: (Check if **"Yes"**. All must be checked)
	☐ Amount
	☐ Method
	☐ Timing of disbursement
☐	Credit for payment accrues as the study progresses.
☐	Payment is not contingent upon completing the entire study.
☐	The amount of payment and the proposed method and timing of disbursement is neither coercive nor presented undue influence.
☐	Any amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.
☐	All information concerning payment, including the amount and schedule of payments, is in the informed consent document.
☐	Compensation does not include a coupon good for a discount on the purchase price of the product once it has been approved.
☐	For studies that compensate subjects, the following statement is included in the consent form: 'According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income.'

Determining appropriate incentives*

- Query of incentive amounts/types across studies
- Full reporting DNE



First Step-Get Input from stakeholders

Query Investigators and IRB members

- How they think about incentives

Que Participants

- Fair and unfair payment/incentives
- Do incentives make a difference

Second step-Consensus

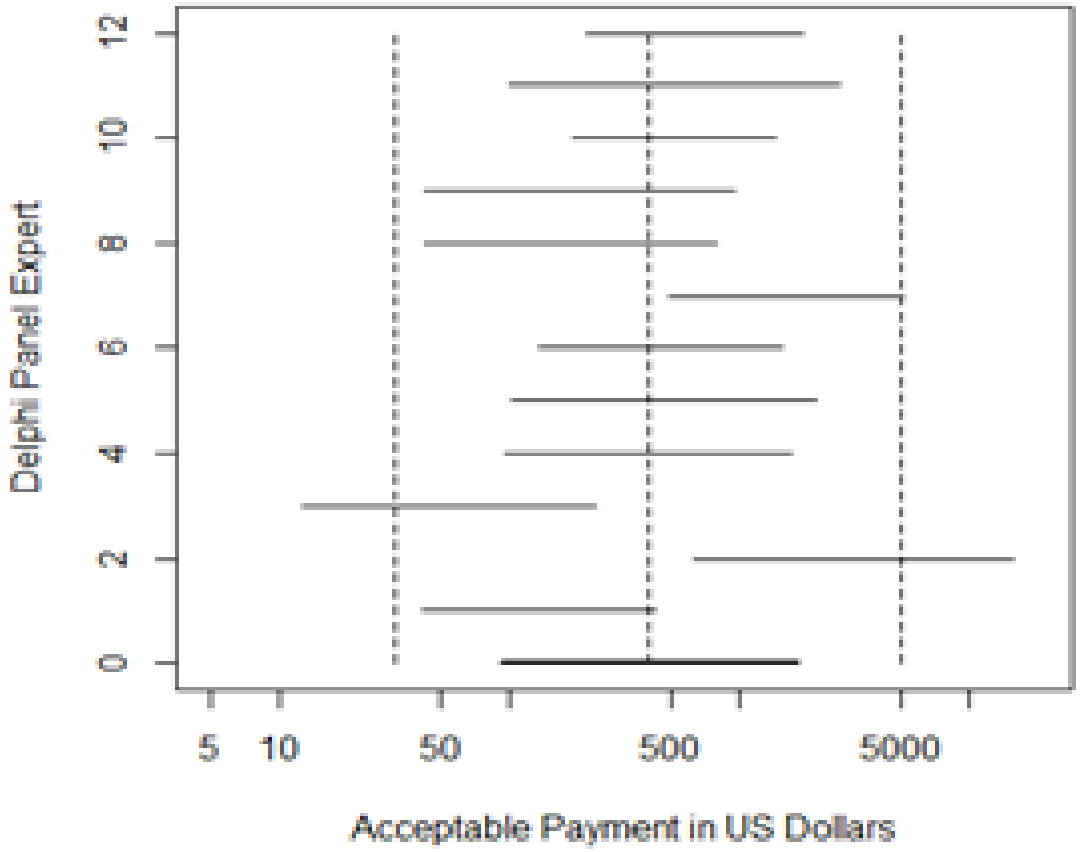
Decide on relevant parameters related to incentives*

Context	Research	Incentives
Location Average income Morbidity/mortality Health services available Health literacy	Condition under study Study population (age, sex, race) Risks and burdens Benefits (direct, indirect) Study procedures (time, visits)	Type (money, gifts, services) Amount (set, varied) Frequency Post-trial access Reimbursement

Third Step-Delphi Panel with vignettes

Judge 3 values per vignette

- Appropriate, too much, too little
- Ex: values are $100, $500, $2000



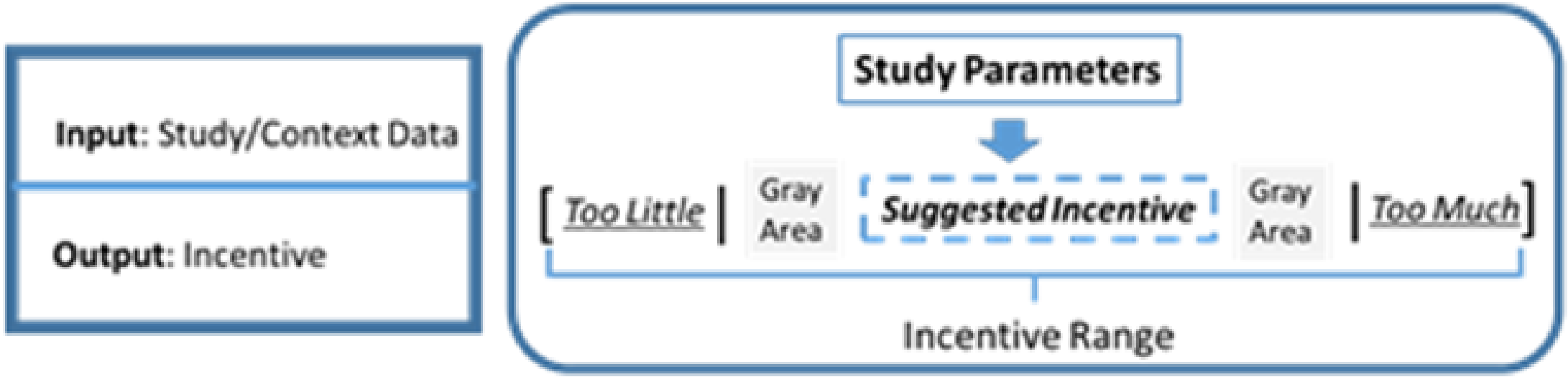
Sample Vignette (variables from Table):

You have been HIV positive for X years. For the past year your health has been Y. You have the opportunity to participate in a phase II study of HIV cure including an intervention which has proved safe in phase I trials but with unknown efficacy, and with a Z risk of adverse health effects. In order to participate in the trial, you must halt your antiretroviral medications for the duration of the study period AA. Your income is BB. Would $500 be an appropriate incentive to participate?

Years w/HIV	Health Status	Study Risk	Study Time in Years	Income
X	*Y*	*Z*	*AA*	*BB*
1	Poor	High	1	Low
5	Okay	Medium	2	Medium
20	Excellent	Low	10	High

Last step

Figure 5: Incentive decision making schematic



Potential benefits of the results

- Aid incentive decision making in HS research
  - Report results of tool
- Empower participants/community leaders

Additional benefits

Use incentive tool/database to…..

- analyze impact of incentives on recruitment/retention*
- Discuss what incentives are appropriate*

What about the risks

Transparency means access

- Participants say no

Underfunded studies not allowed to proceed

If you don’t buy my arguments

- Its OK!
- HPTN
- PCORI
- IRB
- Harvard Payment working group
  - Making guidance document
  - NIH, OHRP, IRBs, CDC, Universities, pharma

Hypothesis-‘going rate’ of incentives in research

Market forces for going rate

- How much to pay someone for a FG

Ex outside research

- short trip from Los Angeles to New York City
- Oversold flight
  - Offers for taking later flight-incremental incentives
    - $200+flight
    - $250+dinner voucher+flight
    - $300+dinner voucher+flight

Next steps

Interviews with participants for a hypothetical HIV cure study

- Varying payment amount, asking about participation, asking about risk
- Answer Q: ‘Does high payment suspend people’s ability to see risk or to act on it’

PCORI methods grant

- Fingers crossed

Questions?

"We found the donut to be more of an incentive for him."