About Schulman IRB

- Established in 1983
- Superior audit history with FDA—six consecutive audits with no findings
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA, OHRP and Health Canada requirements

- Full Board meetings **five days a week**
- Dedicated **daily expedited review** of qualifying minimal risk protocols
- Review outcome provided within **one business day** of new study review
- **One business day** turnaround for complete new site submissions
About Schulman IRB

- Dedicated streamlined processes tailored to **Phase I timelines**
- **Expert oncology IRB members** experienced in all phases of oncology research
- Customized services for **institutions**
- **Experienced primary points of contact** for sponsors, CROs, institutions and sites
- **Institutional biosafety committee (IBC) services** for clinical, pre-clinical and non-clinical research
About Schulman IRB

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About Today’s Presenter

Luke Gelinas, PhD
Petrie-Flom Center Fellow in Clinical Research Ethics, Harvard Law School
Schulman IRB Member

- PhD in Philosophy/Ethics from University of Toronto; MA in Religion from Yale Divinity School
- Most recently completed a Postdoctoral Fellowship in Bioethics at National Institutes of Health and training in Clinical Ethics at Albany Medical College
- Research currently focused on regulatory, ethical, and practical aspects of recruiting and retaining research participants
- Work has been published in several academic journals, including *Hastings Center Report*, *American Journal of Bioethics*, and *Journal of Medical Ethics*
Objectives

- Understand foundational regulatory and conceptual issues around paying subjects
  - Understand how payment relates to key regulatory concepts of ‘coercion’ and ‘undue influence’

- Propose a framework for evaluating payment that can facilitate review
  - Based on different reasons for paying subjects: reimbursement, compensation, incentives
Case Study

- Investigator A is planning a clinical research study on the treatment of seizures.

- Study involves 5 long hospital visits (4-6 hours each) during which subjects will undergo uncomfortable interventions, including:
  - Blood draws at each visit
  - 2 lumbar punctures
  - 2 MRI scans

Investigator A wishes to reimburse subjects for expenses and also pay them for their time and burdens during the hospital visits.

Investigator A has had trouble recruiting for similar studies in the past and wishes to offer enough payment to motivate people to enroll in the study.
Poll 1

- Investigator A wishes to pay subjects an hourly wage to compensate subject for the time they spend undergoing burdens in the hospital, similar to how (say) firefighters and police officers are paid an hourly wage to undertake burdens for the public good.
- The wage Investigator A proposes is significantly higher than the local minimum wage (say, $5 more per hour).

- Not acceptable to pay subjects by the hour or offer any hourly wage.
- Acceptable to offer hourly wage but not acceptable to offer more than local minimum wage.
- Acceptable to offer hourly wage higher than local minimum wage.
Poll 2

Would it be acceptable for Investigator A to offer payment explicitly for recruitment purposes, if this was likely to motivate some people who would not otherwise enroll in research to participate?

- Yes
- No
Regulatory and Conceptual Considerations
Basic Assumptions

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

- Why are we discussing it?
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 …
‘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."

BUT

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

- Difficult and controversial concepts
- Not everyone understands them the same way: academic debate and different understandings among IRB members and researchers
- May often be used imprecisely or interchangeably → risk of talking past each other or using these terms as conversation-stoppers
- Motivation to adopt shared understanding of these concepts!!
Defining ‘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.”

Threats of harm differ from offers of reward.

OHRP Informed Consent FAQs
Implication…

- If ‘coercion’ always involves a threat of harm…
- Offers of payment will not be coercive, since they involve an offer of some good (i.e., money) that expands options, not a threat of harm.

Example of coercion:
Prisoners threatened with loss of privileges unless they participate in study.

Offering payment is not like this.
The Main Concern...

- Risk that offers of payment will **unduly influence** people to participate in research.
- But what exactly is ‘undue influence’?
  - Involves an offer of some good or reward
  - That influences people to participate in research

What does ‘undue’ mean?
Not All Influence Is Undue

- Often acceptable to be motivated by money to undertake burdens and risks.
  - For example, typically acceptable for firefighters, miners, fishers, and so on, to be motivated by money.
  - Typically allow individuals to decide what level of pay makes the burdens/risks worth it to them.
  - FDA and OHRP guidance assume that payment is an acceptable form of influence: mere vs. undue
Poll 2

- Would it be acceptable for Investigator A to offer payment explicitly for recruitment purposes, if this was likely to motivate some people who would not otherwise enroll in research to participate?

- This by itself = mere influence, not worrisome.
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.*” [OHRP Informed Consent FAQs](#)
  - Empirical question; some data that payment *increases* perception of risks and caution among subjects (Cryder et al., Halpern et al.)
Unpacking OHRP’s Definition…

- If an individual’s decision-making is distorted, they may make a **bad** decision to participate in research.
  - ‘Bad’ decision = research is unreasonably risky for a subject or conflicts with their personal values

Shifts emphasis away from how subjects process offers of payment and toward issues over which IRBs have better grasp (risk level, study design, population)
The Main Regulatory Concern

- I.e., minimize situations where payment might influence subjects to make a bad choice to participate in research, when doing so is unreasonably risky for them.
Undue Influence and the IRB’s Risk-Benefit Determination

- IRBs have an independent duty to ensure…
  - (i) Risks to subjects are justified by individual and social benefits
  - (ii) Risks are generally reasonable (not above some ceiling or threshold)
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.

Thus, for most, being influenced by payment would not raise concerns about undue influence.

- 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.
First Half Takeaways

- Main ethical/regulatory concern with payment is risk of **undue influence** (not coercion).
- Payment may motivate research participation without being ‘undue’ or problematic.
- Minimize chance that payment will influence people to participate in research that is unreasonably risky for them.
- The IRB’s independent risk-benefit analysis itself guards against payment unduly influencing research participation.
A Practical Framework for Proposing and Evaluating Payment
A Practical Framework for Proposing and Evaluating Payment

- Payment is offered for different reasons...

What is the rationale or justification for payment—what is payment for?
Three Main Reasons/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
The extent to which payment amounts are acceptable may depend on category/why it is offered.

- Clearer regulatory guidance on reimbursement than compensation and incentives.

For reimbursement and compensation, fairness to the subject may be relevant and balance concerns; for incentives, study completion is relevant.

Breaking down payment in terms of these categories can facilitate proposal and review.
Reimbursement

- Reimbursement for reasonable expenses incurred during research is widely accepted
  - “Research participants should be reasonably reimbursed for costs directly incurred during the research, such as travel costs....” CIOMS Guideline 13, 2016 revision
  - Not a net benefit; restores subjects financially to pre-research baseline.
    - Examples: travel, meals, lodging, child care
Reasonable reimbursement does not raise concerns about undue influence and should be the default

- Subjects should be reimbursed unless there are good reasons that outweigh (e.g., very limited study budget)

But IRBs may differ over ...

- What counts as a reasonable type of eligible expense (e.g., child care)
- What counts as a reasonable amount for reimbursement ($10 versus $20 for meals)
Compensation for Time/Burdens

- Paying people for time/burdens is widely accepted outside research.
  - Would be considered unfair not to compensate people for time/burdens, or to compensate less than is deserved, in employment contexts.
Compensation for Time/Burdens

- Presumption that compensating subjects for time/burdens is likewise fair and acceptable.
  - OHRP: “Remuneration for participation in research should be just and fair.” [OHRP Informed Consent FAQs](#)
Compensation for Time/Burdens

- Presumption that compensating subjects for time/burdens is likewise fair and acceptable.
  - OHRP: “Remuneration for participation in research should be just and fair.” [OHRP Informed Consent FAQs](#)
  - Fairness may involve acknowledging time and burdens through remuneration.
  - Assumes that research is analogous to non-research endeavors, such as employment.
What Counts as Reasonable Compensation?

- If compensation is excessive (i.e., more than time/burdens are worth), it may raise concerns about undue influence.

- No real regulatory guidance on reasonable compensation rates and wide variation in actual practice...
What Counts as Reasonable Compensation?

- But if we continue the analogy with non-research endeavors…
  - Compensation for time could be benchmarked to local minimum wage as baseline.
  - With possibility for higher rates, if time is spent in particularly uncomfortable or demanding ways.
  - Ask:

  Given the burdens subjects are undertaking during the time frame, what would be a fair wage in employment contexts?
Compensating for Risks?

- Think back to the study on seizures…
- In addition to foreseeable burdens (blood draws, lumbar punctures), the study also involves the risk of side effects from an experimental drug…
  - E.g., headaches, nausea, high blood pressure, stroke

- **Burdens** = will occur, part of study design (blood draw)
- **Risks** = may or may not occur; **not** part of study design (potential side effects of experimental drug)
Poll 3

- Investigator A wishes to compensate subjects for the risks of side effects from the experimental drug.
- Is this acceptable?

- Yes
- No
Compensation for Risks?

- OHRP seems to acknowledge that compensating for risks is acceptable.
  - “[R]emuneration to subjects may include compensation for risks associated with their participation in research and … compensation may be an acceptable motive for agreeing to participate in research.” [OHRP Informed Consent FAQs](#)

- But **not** as a benefit that offsets risks
  - “OHRP continues to assert that IRBs should not consider remuneration as a way of offsetting risks.”
Compensation for Risks?

- Studies must have a favorable risk-benefit ratio **apart from any consideration of payment** in order for them to merit IRB approval.

- When (and only when) this is the case, payment for risks may be acceptable.

What is an appropriate wage, given the burdens and risks?
Recruitment Incentives

- Payment is sometimes offered to incentivize recruitment and increase participation rates.
  - Not exclusive category: offers of reimbursement and compensation may also incentivize recruitment.
  - Clearest case of recruitment incentive…
    - Researchers wish to offer *more* payment than would be justified for reimbursement and time/burdens
      - E.g., large payment sums for participating in SBER or a simple interventional study with one blood draw.
Recruitment Incentives

- Most controversial category…
Recruitment Incentives

- For reimbursement and compensation, payment to the subject is fair and deserved, within reasonable range.
  - Acknowledges burdens and functions to make subjects whole.

- Recruitment incentives go beyond this: explicit aim is not to restore subject financially but to improve recruitment.
  - Highlights risk of undue influence
Recruitment Incentives

- But incentives not inherently problematic.
  - They may merely, not unduly, influence.
Recruitment Incentives

- But incentives not inherently problematic.
  - They may merely, not unduly, influence.

- And regulatory guidance does not prohibit ...
  - 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.”

[Source: FDA Payment to Research Subjects—Information Sheet]
Recruitment Incentives

- Reason for incentives is to facilitate recruitment.

- Should IRBs be concerned about recruitment when evaluating incentives?
  - *Is low recruitment a subject protection issue?*
Should IRBs Be Concerned About Low Recruitment?

- Ethical/subject protection reasons to ensure (or do best to ensure) that studies approved by IRB meet recruitment targets.
  - The IRBs risk-benefit analysis is based on the assumption that the study will answer the research question and in doing so deliver socially valuable knowledge.
  - Under-powered and early terminating studies that do not answer the research question expose subjects to risk for limited or no social good.

Significant problem: As of 2011, over 47,000 subjects participated in under-powered clinical trials. (Carlisle et al.)
Recruitment Incentives: Balancing Act

- On one hand, guard against the risk of undue influence when evaluating recruitment incentives.
  - Don’t assume incentives are inherently problematic.
  - Be specific. Is undue influence in this case likely? Why?
Recruitment Incentives: Balancing Act

- On other hand, acknowledge the ethical reasons in favor of facilitating recruitment and the role recruitment incentives might play.
  - Not same as reasons in favor of reimbursement and compensation (fairness), but still important and relevant for subject protection.
Applying the Framework

- Earlier case study on seizures…
  - Reimbursement
  - Compensation
  - Recruitment incentives
The study involves **five hospital visits** (4-6 hours each)

- **Transportation**
  - Round trip = $20 (max) x 5 visits = **$100**

- **Meals**
  - $10 (max) per meal x 5 meals = **$50**

- **Child care**
  - $15/hour x 25 hours (5 visits of 5 hours) = **$375**

**TOTAL** **$525**
Compensation for Time

- The study involves five hospital visits (4-6 hours each), where subjects will undergo blood draws at each visit, two lumbar punctures, and two MRI scans.
  - Hourly wage for hospital visits
    - Assume local minimum wage is $10/hour
    - Proposed $15 per hour, due to significant burdens
    - $90 per visit ($15 per hours x 6 hrs)
    - $90 x 5 visits

  TOTAL $450
Recruitment Incentive

- Investigator A has had trouble recruiting for similar study in past and wants to offer recruitment incentive.

  - Recruitment incentive
    - Proposed $500
    - TOTAL $500
Totals

- Reimbursement: $525 max
- Compensation: $450
- Recruitment incentive: $500

TOTAL: $1475
Totals

- **Reimbursement** $525 max

- Presumed non-problematic, fair, and default.
- Are the types of expenses and amounts reasonable?
- Does not typically raise concerns about undue influence.
Totals

- **Compensation**
  - $450

  - Presumption in favor, based on analogy to non-research/employment and regulatory guidance.
  - Is the rate fair, given what subjects are being asked to do?
    - Compare to wages for similarly burdensome work.
    - If fair, does not raise concerns about undue influence.
Recruitment incentive $500

- Not inherently problematic, but be aware of risk of undue influence.
- Considerations of fairness not relevant.
- But relevant ethical reasons in favor of facilitating recruitment/retention.
- Balance study-specific risk of undue influence against importance of recruitment and study completion.
Wrapping Up

- Be clear about the definitions of key regulatory terms!
  
  - Adopt shared understanding of ‘undue influence.’

- Do not be concerned about the mere influence of payment as a motivating factor!

- Recognize the role that the IRB’s risk-benefit analysis plays in mitigating risk of undue influence!
Wrapping Up

- Be clear about **why** payment is being offered!
- Within reasonable range, reimbursement and compensation are fair, work to make the subject whole, and do not raise ethical concerns.
- Recruitment incentives pose the greatest challenge for IRB review but are not inherently problematic.
Thank you!

Questions? Comments?

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Evaluating Payment to Participate in Research: Ethical and Regulatory Issues

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