Research Participant Compensation: What is Fair?

Clinical Research Education Series (CRES)
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Consider this example . . .

Lilly's 'Quick Cash' to Habitués of Shelters Vanishes Quickly (Phase 1)
by Laurie P. Cohen, Wall Street Journal – Nov 14, 1996

"INDIANAPOLIS -- Sitting in a drab hospital room at the Lilly Laboratory for Clinical Research, his home for 57 days, Mr. C lifts the sleeve of his navy-blue scrubs to display a right arm that is badly bruised and scarred from being pierced dozens of times.

Homeless and a hard drinker, Mr. C can't say what kind of drug is being tested on him, although he has signed an informed-consent form. Nor has Eli Lilly & Co.'s "Subject No. 7" reported to the researchers any of the head and muscle aches he has suffered in recent weeks, as Lilly requires. He reckons these are simply the price of quitting drinking cold turkey to get into the study, not the possible side effects of Lilly's experimental drug, known only as LY315920."

*Varespladib - is an inhibitor of the IIa, V, and X isoforms of secretory phospholipase A2 enzymes (sPLA2)PLA2 (sPLA2). Since 2006, it has been under active investigation by Anthera Pharmaceuticals as a potential therapy for several inflammatory diseases (e.g., Acute Chest Syndrome).
Lilly's 'Quick Cash' to Habitués of Shelters Vanishes Quickly

• Volunteers as "retired or temporarily employed."
• “Subjects welcome the free physical exams and the money they get, Dr. McKinney [executive director of clinical pharmacology] said, and, above all, are driven to participate "by altruism ... . These individuals want to help society."
• Room and Board - several weeks or months of free room and board
• Grateful participant for "easy money."

What are the challenges to meeting your recruitment goals?

Relative few people volunteer

Increases time and cost to meet recruitment goals

Studies closely monitored or closed.
Topics covered include . . .

- Ethical issues
- Payment models
- Vulnerable groups
- IRB recommendations

Have you ever had trouble meeting your recruitment goals?
Did you ever reevaluate your payments to participants?

Recruitment

4% of the U.S. population participated in a clinical trial

NIH $28 billion in medical research (2010)
- 85% of NIH trials don’t finish on time
  • due to low patient participation
  • 30% fail to enroll even a single participant

https://www.researchmatch.org/
Terms to keep in mind . . .

Altruistic: Principle or practice of unselfish concern for or devotion to the welfare of others

Reimbursement: Payments to cover out-of-pocket expenses (e.g., taxi fare, parking, lunch)

Compensation: Something, typically money, awarded to someone as a recompense for loss, injury, or suffering

Inducement: A thing that persuades or influences someone to do something

Coercion: Use of force or intimidation to obtain compliance

Ethical dilemmas . . .

Altruistic
To give consent the subject must:
• identify with the aims of the experiment and
• must be devoted to advancing the goals of the research.

Hans Jonas
(1903 –1993) philosopher

Philosophical Reflection on Experimentation with Human Subjects, 1969
Ethical dilemmas . . .

"Do not do unto others what you do not want done unto yourself."

Hans Jonas
(1903 –1993) philosopher

Philosophical Reflection on Experimentation with Human Subjects, 1969

In the 1960’s concerns were raised . . .

What if research subjects are harmed and sue us?

Researchers – Believed informed consent protected them from tort claims. But did it?

Standardized research compensation?
Run the risk of having the research industry shut down.
In the 1960’s paternalistic attitudes were starting to be questioned . . .

Could liability insurance be funded by a sponsor, society, and/or the federal government?
No-fault compensation for injury

In the 1960’s others questioned . . .

How can we tell if adverse events are due to research or underlying illness?
Administrative cost [ to compensate subjects] would be too high!
1960 - Donald Dietrich wrote in the Duke Law Journal that . . .

“Mere knowledge of the facts which create the risk of harm is not enough unless there is a true appreciation of the nature and extent if the risk. . . .” (consent form)


1970’s - What about compensation for harm suffered?

Based on respect for the person who takes a risk for society.

“Research subjects should be cared for if they are injured whether enrolled in therapeutic (may benefit) or non-therapeutic research.”

James Childress

Philosopher and theologian, biomedical ethics

1970’s - What about compensation for harm suffered?

“Subjects do get hurt in research no matter how careful one is.”

Compensation would provide incentive to industry to minimize risk.

Clark Havighurst
Professor of Law - Health Care
Law and Policy


1970’s – Re-thinking the issue of compensation for research subjects?

Cardon et al. study 1976

Sponsor? Department of Health, Education, and Welfare

Why? Estimating the incidence of research-related injuries, with a view to determining the feasibility of compensating subjects injured during research.

Sample: 331 investigators conducting research over prior 3 years (133,000 human subjects)

Measure: Telephone survey

1970’s – Re-thinking the issue of compensation for research subjects?

Results:
• 85 investigators ≥ 1 injury per research subjects
• 4,957 reported injuries
  - 79% classified as trivial
  - 20% temporarily disabling
  - 1% death or permanent disability (stroke, cancer chemotherapy)

Conclusion about risk:
• Nontherapeutic studies – no greater than everyday life
• Therapeutic studies - no greater than treatment in other settings.


1970’s - Re-thinking the issue of compensation for research subjects?

“stop circling the wagons” Bernard Barber editorial in NEJM

Research on Human Subjects: Problems of Social Control in Medical Experimentation, 1979
1970’s - Re-thinking the issue of compensation for research subjects?

1978  Common Law amended – compensation and type, has to be stated as available or not in the consent form - at federally funded institution

1990  Industry - no-faulty compensation is too expensive - excluded women

1991  England - 0.005% participants submitted no-fault compensation claims in clinical trials over 5 yrs
   - England = economically viable choice
   - U.S. = economically unnecessary

45 CFR 46 Subpart A: Basic DHHS Policy for Protection of Human Research Subjects

(a) Basic elements of informed consent. Except as provided in paragraph ‘c’ or ‘d’ (waive informed consent) of this section,) in seeking informed consent the following information shall be provided to each subject:

6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained (about compensation)

http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
Models purposed for paying research subjects

**Market** – incentive

**Wage payment** – compensation

**Reimbursement** – reimbursement

**Appreciation** - reward

**Altruism** – belief in study aims and goals


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**Appreciation Model**

Payment - token of appreciation

**Advantages**
- Thank you gift
- Avoids risk of inducement

**Disadvantages**
- No impact on recruitment
- Hard to be consistent over studies

Reimbursement Model

Payment – expenses (e.g., travel) and possible lost wages

Advantages
- Little risk of inducement (neutral)
- Little/no financial sacrifice

Disadvantages
- No impact on recruitment
- Hard to be consistent among subjects (wages)


Wage-Payment Model

Payment – standardized “wage” for an unskilled - essential job

Advantages
- Recognizes subjects contribution
- Uniform payment
- Less risk of undue inducement

Disadvantages
- Little impact on recruitment
- May under compensate some subjects

Market Model
Payment – supply and demand

Advantages
• Possible profit for participants
• Increased recruitment
• Completion bonuses – enhance retention

Disadvantages
• Undue inducement (less attention to risk/benefit)
• Concealing information to meet eligibility
• Multi-site studies – different payments


Offering fair compensation for research participation also demonstrates that society values clinical research and is grateful for subjects contribution to the common good.

Christine Grady, Ethicist

Are there benchmarks/guidelines for paying participants?


Purpose: Understand the inconvenience (units) assigned for 21 common procedures out of 36,273 reviewed by researchers

Examples:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Observations</th>
<th>Inconvenience units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood draw</td>
<td>5,212</td>
<td>2 (1 – 2)</td>
</tr>
<tr>
<td>24-hr urine collection</td>
<td>224</td>
<td>2 (1 – 2)</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>48</td>
<td>5 (1 – 19)</td>
</tr>
<tr>
<td>Functional MRI</td>
<td>204</td>
<td>10 (5 – 10)</td>
</tr>
</tbody>
</table>


Formula for using inconvenience units

• Number of inconvenience units = assigned to procedure based on ability to pay (researcher) and discomfort
• Multiple by $10 per inconvenience units
• Example: Functional MRI (fMRI)
  – 10 units X $10 = $100

fMRI is a technique to detect changes in blood oxygenation and flow that occur in response to neural activity in the brain and spinal cord. http://psychcentral.com/lib/
Are there benchmarks/guidelines for paying participants?


Purpose: Guideline for calculating payment for time spent in research as outpatient or inpatient.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Amount</th>
<th>Additional time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>$40 per night</td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>$20 for 1st hour</td>
<td>$10</td>
</tr>
</tbody>
</table>

Patient’s travel time, check-in 30 min early, testing time, and loss of work time.

**Are there benchmarks/guidelines for paying participants?**

**Purpose**

Use a national **survey** of NIH-funded **principal investigators** and **IRB chairpersons** to identify their considerations and practical application of these considerations in **case studies**.


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**Methods used to test Wage-payment and Reimbursement?**

**Sample and Setting:** Web-based survey completed by 455 NIH funded investigators (28%) and 353 IRB chairs (19%) in the U.S.

**Models:** Wage-payment (time & discomfort) and Reimbursement (subjects expenses)

**Survey:** Anonymous, 6 activities (i.e., clinic visit, blood sample, urine sample, x-ray, overnight stay, one-hour questionnaire) and 6 case studies:

1. Registry, Phone Survey and Medical Record Review
2. Substance Abuse Survey
3. Survey of Twins, DNA
4. Cancer Treatment Trial
5. Healthy Volunteer Pharmacokinetic Study
6. Hypertension Study

**Is there a benchmark for payment?**

What would you recommended as a payment for these study procedures?

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Therapeutic trial</th>
<th>Non-therapeutic trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overnight stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-hr questionnaire</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Average recommended payment for study procedures by investigators and IRB chairperson were:**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Therapeutic trial</th>
<th>Non-therapeutic trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic visit</td>
<td>$25</td>
<td>$26</td>
</tr>
<tr>
<td>Blood sample</td>
<td>$16</td>
<td>$20</td>
</tr>
<tr>
<td>Urine sample</td>
<td>$12</td>
<td>$12</td>
</tr>
<tr>
<td>Overnight stay</td>
<td>$120</td>
<td>$129</td>
</tr>
<tr>
<td>1-hr questionnaire</td>
<td>$21</td>
<td>$22</td>
</tr>
</tbody>
</table>

**Is there a benchmark for payment?**

Which payment schedule do you feel is most appropriate? (If choosing money payments, please fill in the amount you would suggest.)

a. No payment [altruism]

b. Payment for parking or bus fare [reimbursement]

c. A gift from a catalog or movie tickets [appreciation]

d. Money [wage-payment]

1. At completion of study $_____ (suggested amount).

2. Prorated $_____ (suggested amount) for each completed set of surveys and drug screen.

3. Prorated with a completion bonus $_____ (suggested amount) for the baseline set of surveys and drug screen, and $_____ for the final set and drug screen.


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**What did they find?**

<table>
<thead>
<tr>
<th>Case study</th>
<th>Pay by activity</th>
<th>Pay by time</th>
<th>No or token</th>
<th>Total dollar amount (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone survey 4 over 30 min for 2 years.</td>
<td>Surveys: $44</td>
<td>$7.25/hr = $15 $10/hr = $20 $20/hr = $40</td>
<td>60%</td>
<td>Single: $18 ($5-50) Prorate: $36 ($7-200)</td>
</tr>
<tr>
<td>Hypertension Study (RCT PLA) 6 visits (1.5 hrs) &amp; travel</td>
<td>Clinic visits &amp; travel: $210</td>
<td>$7.20/hr = $126 $10/hr = $150 $20/hr = $240</td>
<td>22%</td>
<td>Single: $208 ($25-600) Prorate: $196 ($48-750) Prorated with bonus: $184 ($45-750)</td>
</tr>
</tbody>
</table>

Average recommended rate for activities were: clinic visit $26, blood and urine sample ($20, $12), overnight stay ($129), and 1-hr questionnaire(s) ($22). WA minimum wage is $9.19.

What about studies of healthy volunteers in a phase 1 PK study?

<table>
<thead>
<tr>
<th>Inconvenience</th>
<th>Pay by activity</th>
<th>Pay by time</th>
<th>No or token</th>
<th>Total dollar amount (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low 12-hr stay</td>
<td>1 visit, travel, 2 hr set-up, 10 blood draws: $236</td>
<td>$7.25/hr = $312</td>
<td>3%</td>
<td>Single: $277 ($50-2,500)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$10/hr = $350</td>
<td>Prorate: $852 ($150-3,000)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$20/hr = $490</td>
<td>Prorated with bonus: $914 ($170-3,500)</td>
<td></td>
</tr>
<tr>
<td>Medium 48-hr stay</td>
<td>1 overnight, travel, 20 blood draw: $668</td>
<td>$7.25/hr = $773</td>
<td>4%</td>
<td>Single: $363 ($15-2,000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$10/hr = $910</td>
<td>Prorate: $1,850* ($15-2,000)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$20/hr = $1,410</td>
<td>Prorated with bonus: $819 ($100-3,250)</td>
<td></td>
</tr>
<tr>
<td>High 96-hr stay</td>
<td>4 overnight, travel, 30 blood draws: $1,126</td>
<td>$7.25/hr = $1,321</td>
<td>5%</td>
<td>Single: $509 ($25-3,000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$10/hr = $1,540</td>
<td>Prorate: $644 ($150-1,500)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$20/hr = $2,570</td>
<td>Prorated with bonus: $768 ($50-3,900)</td>
<td></td>
</tr>
</tbody>
</table>


What did you see?

- High percentage of token payments recommended
- Cost to participant is often not considered
- Concern that small studies can not afforded to compete with larger well funded studies so not done
- Ability to conduct research harder if payments become the norm (Toumbourou et al., 2004)

Best Practice:
- Identify all the costs to participant
- Payment should compensate the true cost to the participant or explain why
- Included payment information in the consent form

Local Studies
Effects of Simvastatin on CSF AD Biomarkers in Cognitively Normal Subjects

Study Description (RCT):
• 12 months and involves 9 visits to our clinic. The visits last from 1/2 hour to 4 hours.
• Study procedures include blood draws and memory testing. Study participants will also be asked to have a lumbar puncture (or "spinal tap") two times during the study.

Compensation:
• Participants will receive $650 total if they complete the entire study. Reimbursement is based on the number of study visits completed.


What about vulnerable populations?
Children
Poor – Homeless
Mental Illness
Children

Baby Observational and Nutrition Study (BONUS, cystic fibrosis)

Compensation for the visits required by the study will be provided. Request more information

Compensation
• Injuries (e.g., $20,000 for medical care, [Seattle Children’s Hospital])
• Time
• Inconvenience
• Parent’s wages
• Prorated or single payment to child or parent or both


Children

CF Therapeutics Development Network Reimbursement Policy

<table>
<thead>
<tr>
<th>Type of expense</th>
<th>Time</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient study</td>
<td>&lt; 2 hour</td>
<td>$30</td>
</tr>
<tr>
<td></td>
<td>2-4 hours</td>
<td>$60</td>
</tr>
<tr>
<td></td>
<td>4-8 hours</td>
<td>$85</td>
</tr>
<tr>
<td></td>
<td>8-12 hours</td>
<td>$115</td>
</tr>
<tr>
<td>Inpatient study</td>
<td>Per day</td>
<td>$170</td>
</tr>
</tbody>
</table>

Also mileage and other costs such as parking, meals.

Persons with poor or homeless

Hard to find studies on how actual compensation rates differ from middle class participants.

- Inducement (money) - overwhelm a person’s good judgment of risk (e.g., Phase-1 trials)
- Pre-existing disorders - never diagnosed
- Compensation – harm due to adverse events
- Adverse events - unwilling to report so not disqualified


Persons with mental illness – 1:5 people

Issues that restrict research involvement

- Behavioral and cognitive function
- Decisional capacity – have the ability or education
- Stigma – decrease
- Diminished social opportunities – want to contribute
- Proxy decision makers
- Educate researchers

Payment advice from an Institutional Review Board . . .

- Payment is not a benefit.
- Amount should be related to time, effort, and/or inconvenience, not the level of risk involved in participating in the research.
- IRB is responsible for ensuring that the subjects will be appropriately informed about . . . any payment.

http://www.washington.edu/research/hsd/docs/1271

 Payment advice from an Institutional Review Board . . .

Payment - cash or other value provided to human research subjects, . . .
  - Examples: cash, check, gift, gift card or certificate, voucher, services, merchandise, class credit.

Not a payment
  - Compensation for injury or adverse events that result from research participation
  - Reimbursement for direct research-related expenses such as parking or meals
  - Test results

http://www.washington.edu/research/hsd/docs/1271
Payment advice from an Institutional Review Board . . .

Responsibilities of the Researcher

2.1 Total amount to offer - check with IRB
2.2 Full disclosure to subjects, usually via a consent form
2.3 Obtain and report certain subject information in connection with payment, to fulfill federal and University policies and requirements.

Subject Payment, Confidentiality, & Income Tax

http://www.washington.edu/research/hsd/docs/1271
