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Much Ado about Subject Compensation

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One of the most ethically perplexing questions in clinical research is proper compensation for study subjects. By setting compensation (stipends) at a reasonable level, we protect the subject's right of autonomy. If set too high, it constitutes undue influence; if set too low, it constitutes exploitation. Consistent levels of compensation across sites and subjects prevent inequities. However, in the same study, some investigators offer compensation of hundreds of dollars, while other investigators offer no compensation at all.[1] Both cannot be ethical according to a single standard of ethics.

Every investigator and ethics committee (IRB/IEC) may agree, for example, that $50 per visit is proper compensation for a given study. But, we know that the amount is wrong for most subjects. For some, it is unduly influential; for others it is exploitative. A variety of compensation models exist that generate different payments for different subjects, but none can satisfy everyone on the criterion of fairness.[2] For example, physician-subjects can argue that they deserve more compensation than nurse-subjects because their salaries are higher. Nurses can argue that compensation should be the same because higher salaries do not make people intrinsically more valuable. Nurses may further say that physicians can afford to donate their time to the study for free because they are paid so highly. On the other hand, perhaps a nurse can take time off for study visits without losing salary, while a physician cannot. Perhaps a physician's spare time is totally consumed as the primary caregiver for a parent, while a nurse's avocation is cat burglary. The complications are endless.[3]

U.S. federal regulations offer no specific guidance on subject compensation, just a caution to "minimize the possibility of coercion or undue influence." (45 CFR §46.116 and 21 CFR §50.20) The FDA information sheet "Payment to Research Subjects" states: "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 [21 CFR §50.20]." ICH E6 §3.1.8 similarly states: "The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects." Interestingly, FDA and ICH do not express any concern for compensation that is exploitative, i.e., unfairly low. Nor do they discuss fairness of compensation across sites or individual subjects.

For subjects who are otherwise undecided, compensation may be the deciding factor. Many subjects care passionately about compensation that they perceive to be too low. Impoverished people have a legitimate reason to complain, but even wealthy people care. There are two primary reasons: First, nobody wants to be taken advantage of, especially for measurable out-of-pocket costs of transportation, childcare, lost wages, etc. Why should the subjects subsidize the profits of a pharmaceutical company? If the pharmaceutical company can afford to conduct the trial, it can certainly afford a few more bucks to cover such expenses. Second, when people make decisions, they perceive a large, qualititative difference between "free" and "low-cost." [4] In this context, a few dollars can make an outsized impact on the subject's decision to participate. With a few more dollars, a small profit is infinitely larger than none at all when measured by percentage.

There is some confusion about whether compensation is a "benefit" to the subject. From the subject's perspective, it clearly is. In Phase I studies, it is recognized as the primary benefit. The compensation-as-benefit problem in Phase II-IV studies relates to any tradeoff between

compensation and health risk to the subject. It is generally considered unethical to pay a study subject to risk his or her life or health. (In contrast, relatively high payments to endure long, painful procedures are generally considered ethical.) When evaluating the merits of a study, the IRB is thus prohibited from weighing subject risk against compensation. To minimize the influence of compensation, study advertisements may disclose but not emphasize it. Informed consent forms discuss compensation and benefits in separate sections, but that is not giving much credit to the subjects' intelligence.

As if the ethical practicalities of subject compensation are not complicated enough, we must also consider other practicalities. For example, it is more difficult to enroll subjects in some studies than others. Some studies have more generous funding or greater urgency than others. From an ethical perspective, such factors should play no role, but they do in the real world. Nevertheless, just because a study is underfunded, is it ethical to set the level of subject compensation at zero? A reasonable compromise is to allow these factors to shift compensation amounts, but not substantially.

Despite these apparently insurmountable obstacles, we can do a lot better than the haphazard approach to setting subject compensation that is common today. In particular, we can adopt a method to systematically determine appropriate subject compensation. At minimum, we can move toward consistency across studies and sites. We can validate the method with external data and shape it with human judgment.

A Model for Determining Subject Compensation

Table 1 presents most of a subject's benefits and costs in a clinical trial:

Table 1. Benefits and Costs of Participating in a Clinical Trial

Benefits	Costs
Receive an experimental medication that treats disease better than S.O.C. drug	Receive an experimental medication that is worse than S.O.C. drug.
Receive medication at no cost	Experience minor pain or discomfort
Discover undiagnosed health problem that can be treated	Experience minor adverse event
Learn more about medical condition	Experience moderate adverse event
Receive physical exams, treatments, lab tests, and extra attention at no cost	Experience severe adverse event
Receive stipend	Experience death
Help medical science, community, etc. (altruism)	Expend funds (transportation, child care, etc.)
Enjoy social contact (visits)	Take off time from work (hours)
	Consume personal time (hours)
	Expend mental & physical energy

We can incorporate these benefits and costs in a spreadsheet model (available at www.firstclinical.com/journal/2008/0809_Cost-Benefit.xls) to measure their effects on a subject's decision to participate in a clinical trial. The model can be used for a "typical" subject or a specific subject. In Table 2, the model is populated with hypothetical but plausible values. In this example, the benefits and costs almost exactly balance.

Table 2. Model with Example Data

	Benefits	Probability	Units	$/Unit	Value	Assumptions
B1	Receive experimental medication that is more effective than S.O.C. drug	15.000%	1	$5,000	$750	50% chance of receiving study drug with 30% chance that it is more effective than S.O.C. comparator.
B2	Receive effective medication at no cost	65.000%	1	$1,000	$650	Subject has insurance for S.O.C. drug with copayment requirement
B3	Discover undiagnosed health problem that can be treated	2.000%	1	$1,000	$20	Study includes tests that subject would not ordinarily receive.
B4	Learn more about medical condition	50.000%	1	$100	$50	Primary care physician provides limited information.
B5	Receive physical exams, treatments, lab tests, and extra attention at no cost	100.000%	2	$20	$40	Subject has insurance for S.O.C. with $20 copayment requirement. Two regular visits are avoided
B6	Receive compensation	100.000%	5	$50	$250	Five visits
B7	Advance medical science, community, etc. (altruism)	60.000%	1	$200	$120	Potential benefit from a new treatment; advancement of knowledge
B8	Enjoy social contact (visits)	100.000%	5	$20	$100	Subject has an adequate social life, but enjoys interacting with study personnel.
	Total Benefits				$1,980	

	Costs	Probability	Units	$/Unit	Dollars	Assumptions
C1	Receive experimental medication that is less effective than S.O.C. drug	35.000%	1	$1,000	$350	50% chance of receiving study drug with 70% chance that it is less effective than S.O.C. comparator.
C2	Experience minor pain or discomfort (not adverse event)	80.000%	3	$50	$120	e.g., blood draws at 3 visits
C3	Experience minor adverse event	20.000%	1	$100	$20	e.g., chills
C4	Experience moderate adverse event	2.000%	1	$1,000	$20	e.g., headache

C5	Experience severe adverse event	0.100%	1	$500,000	$500	e.g., stroke
C6	Experience death	0.010%	1	$6,900,000	$690	Caused by participation in study
C7	Expend funds (transportation, child care, etc.)	100.000%	5	$15	$75	Taxi
C8	Take off time from work (hours)	100.000%	5	$30	$150	$30/hr wage
C9	Consume personal time (hours)	100.000%	0	$30	$0	Value of leisure time
C10	Expend mental & physical energy	100.000%	0	$0	$0	Not an issue for this subject.
	Total Costs				$1,925	
	Net Benefit or Cost				$55	

It is evident from this model that compensation is just one of many factors for a subject to consider. In this example, it is the sixth most important factor of 18 and shifts the balance from net cost to net benefit. However, if the costs in the example were to substantially exceed the benefits, no ethical level of compensation could balance the books. Such a study would probably be exploitative and therefore unethical.

Determining the probability and value of rare events is very difficult. In real life, of course, subjects (and everyone else) will disagree on the value of most rare benefits and costs. Nevertheless, these values are implicit in every study. One use of the model is thus to estimate the unstated assumptions underlying IRB approval of a study. If there is no plausible set of assumptions to support a positive or neutral impact on the subjects, perhaps the study should not be conducted.

A consensus range of values and methods for determining these values is achievable. Exact numbers are not as important as the ability to compare across studies. The model can be used as a framework to help people think about subject benefits and costs in a systematic and sensible way. For example, if an investigator proposes high compensation for a study, he/she should be able to point to the parameters that support the recommendation. Study sponsors can provide estimates of the key parameters that are supported by previous studies and the literature. These estimates should not deviate too far from previous estimates. The absence of such estimates would be a red flag. Actual results can be used to test and refine the assumptions over time.

Putting a monetary value on a life is unpleasant work, but it is done all the time. For example, the U.S. Environmental Protection Agency (EPA) recently adjusted its valuation of human life to $6.9 million.[5] It uses this number in evaluating environment protection measures. Medicare uses a $50,000-per-year value of life to determine reimbursement of medical treatments.[6] It adjusts the number down based on diminished quality of life (QoL). To match the EPA number, a person would need to live a full life for 138 years. However, Medicare's number is not actually its valuation of life; it uses the number only as a guideline to prioritize and manage its expenditures. For example, Stanford researchers have estimated Medicare's cost of dialysis at $129,000 per year.[6]

Wide variations in subject compensation suggest that many investigators and IRBs are not qualified – or do not have adequate tools – to estimate the benefits and costs of a study for the typical subject, much less a specific subject. However, they have the ethical obligation

to make a determined effort. They also have the ethical obligation to help subjects make informed cost/benefit assessments for themselves. Each subject has the right to value his/her life as he/she wishes. A subject with a relatively high fear of death and low fear of pain will make different decisions than a subject with the opposite fears. This model, once populated with reasonably accurate estimates, can help them make informed decisions.

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