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Compensation norms create inequity in clinical trials.

Imagine a patient participating in a clinical trial for a new vaccine. They take a half day of PTO to visit the clinic, which is a short 15-minute drive from their home. After an hour visit, they are given $50 as compensation – a reasonable amount which they spend on a nice dinner. This describes a typical experience for a certain kind of patient.

What happens when some of those details change? Instead of taking PTO, the patient misses a shift at work and subsequently loses income to visit the clinic. They may have to ride the bus for an hour to get there. This patient is given the same $50 as before, but for them, that doesn't even come close to replacing the lost income.

For a voluntary activity like a clinical trial, $50 per visit doesn't begin to cover the burdens that some patients face in order to participate.

Nothing stirs up anxiety in the clinical trial industry like the topic of patient compensation, but this apprehension adds to the burden of participating patients. There are legitimate concerns around undue influence through compensation, but it's not difficult to avoid. There are robust safeguards in place for compensation, with Institutional Review Boards (IRBs) providing guidance and the FDA outlining permissive guardrails.

Patients, as healthcare consumers, make a choice about the care they receive, meaning compensation is already part of that decision. Good, thoughtful compensation respects the patient and offsets the burden of participation, while not pushing participation. The clinical trial industry misses the opportunity to respect the patient due to this fear of undue influence.

The Patient Perspective

Patients evaluate participation in terms of the value they receive versus the burden of participating. Every patient calculates that value versus burden equation for themselves as an individual or family decision. And each participant weighs their own transportation, healthcare, and economic needs. Value can come in many forms, including:

Altruism: The desire to be part of something positive and groundbreaking like clinical trials shouldn't be discounted. When surveyed, we found that 52% of respondents cited helping future patients as a reason to participate.

Treatment: Patients with chronic conditions look for better treatments to manage their condition. 36% of surveyed patients noted treatment as a major motivator for participation.

Compensation: In the absence of value from altruism or new treatment, compensation acts as a major incentive for participation. 34% of our surveyed patients cited compensation as a motivator.

What is the regulatory framework for talking to patients about the value of a clinical study? IRBs are well versed in the value of compensation for patients, and we've collaborated with Advarra, a provider of IRB and Institutional Biosafety Committee (IBC) solutions to advance clinical trial research, to paint a clearer picture of these challenges and opportunities for clinical study participants.

The Regulatory Framework of Participation

IRBs are required to review protocols following criteria outlined by the FDA, which include obtaining **informed consent** from the patient. The regulatory criteria read (in part):

> ...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**. The information that is given to the subject or the representative shall be in **language understandable to the subject** or the representative.

James Riddle, Vice President of Research Services and Strategic Consulting at Advarra, explains how those criteria are incorporated into the review process:

> IRBs spend a lot of time confirming that language is understandable to the patient, changing consent language to make the reading level more accessible or clarify key terms. But IRBs spend just as much time looking at the whole consent process. Participation should be an informed and free choice, and while compensation is an important topic, there are other matters that influence potential coercion or undue influence.
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> What is the **threat of coercion?** The threat of harm or loss to elicit an action. In consent terms, it's more relevant to an employer demanding employees enroll in

research or face termination — or other threats and intimidation. It's nearly impossible to coerce someone with money alone.

And what does it mean to **'unduly influence'** a patient? A person can be unduly influenced with an offer of so much in money and gifts that the compensation is all that matters. Of course, figuring out 'how much is too much' depends on the circumstances of each participant. A $100 payment for an hour-long survey about homelessness and drug use may be unduly influential to someone experiencing homelessness, but not to a physician treating someone at a homeless shelter."

James also notes that "regulations don't say to eliminate undue influence, just to minimize the possibility." IRBs carefully consider the protocol, procedures, study population (including locations), and payment plans when determining if the amount of money offered to participants represents an undue influence. "In Advarra's experience, we rarely need to significantly modify a participant compensation plan, which might imply either sponsors are good at setting an appropriate amount, or that the sponsors could offer participants' more without reaching the level of 'undue influence.'"

Balancing Out the Burden

With IRBs rarely disapproving payment plans proposed by the sponsor or site, and with patients highly motivated by compensation when participating, we have an opportunity to offer more value to patients.

When a patient weighs the value of a study against the burden of participation, that value needs to offset the burden or risk the patient walking away. Consider some patient burdens:

Patient Time
Office visits, at-home journal entry, transportation, and any activity required by the study.

Out-of-Pocket Expenses
The cost of gas, public transportation, lost wages from missing work, parking, childcare and more.

Physical Demands
Invasive procedures and side effects of treatment.

Medical Tradeoffs
The potential for a placebo and washing out of existing medications.

By looking at patient compensation through this lens of value and burden, the industry acknowledges the strain placed on the patient instead of framing compensation as a misunderstood attempt at bribery.

Compensation will need to be adjusted by study. For example, SubjectWell saw an increase of over 400% in randomization rates when a meningitis study offered compensation, but compensation barely affected recruitment for a cosmetic enhancement trial because patients found value in the treatment itself. Many diabetes trials also see no impact on recruitment from compensation for a variety of reasons. In general, compensation improves randomization rates across the board, increasing participation and offsetting patient burdens.

The burdens of clinical study participation also disproportionately impact patients of color, young patients, and low-income patients. These burdens help result in patient populations that are older (30%) and skew white (75%), compared to the national population (17% and 60%, respectively) – patients who can typically afford to miss work and cover more expenses.

The FDA recognized the lack of diversity in clinical studies, and recently published new guidance to encourage more diverse patients to participate in a trial.

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Designing Better Patient Compensation

There are a wide variety of factors to consider when designing the patient compensation component for a study. Luke Gelinas, Senior Chair Co-Director at Advarra, explains the differences and permissibility of reimbursement and direct payments like remuneration:

> "**Reimbursement** for direct expenses allows for more flexibility within FDA guidance than direct payments, or remuneration. Reimbursing lodging, airfare, parking, and other associated costs with participation are all fine and have no cap.
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> **Remuneration**, or direct payments, are what IRBs care about most. This is the difference between reimbursing the actual cost of a hotel stay vs. estimating a flat $300 per participant for a hotel stay and paying each patient that amount for lodging. Reimbursement involves more administrative work, but allows for a greater deal of flexibility when it comes to patient compensation in study design."

Payments are fine if they don't represent an undue influence, Luke explains, "And as long as they don't hold people in the study when they'd otherwise withdraw." FDA guidance states that IRBs should watch out for bonus payments or holdbacks that would cause a person to stay enrolled to get the payout at the end.

In other words, the patient should see participation more as a **want** than a **need**. IRBs will be most comfortable with payments that match the visit schedule, number of procedures, etc. "IRBs likely won't approve a payment where a patient **only** receives a payout at the end of the study."

"Designing better compensation also means addressing patients' nontraditional needs," states Nancy Sacco, PhD, Head of Clinical and Site Development Operations at SiteBridge. "I remember a study with a population of mostly retirees who were 65 or older. While determining compensation, the sponsor removed compensation for lost work time, yet patients still had expenses like transportation, meals, and other costs from that period which increased the patient burden. It was a bit short-sighted as not everyone over 60 years of age is retired."

She also described an oncology study with sites in rural Iowa: "Patients were asked

to fill out online questionnaires, but Internet access was difficult or unavailable in that area. Many patients had to visit local libraries just for access to Wi-Fi, when study organizers expected them to finish the questionnaires from home." Time spent traveling to the library and finishing the questionnaire was all valuable time spent away from their work and farms, again increasing the burden on the patient.

> "Better patient compensation won't be a simple one-size-fits-all stipend, nor will all sites be able to accommodate a complex patient reimbursement plan.

"Compensation plans need to allow sites some degree of flexibility," added Johanne Laboy, PhD, MBA, SiteBridge's Head of Community Engagement. "That flexibility needs to include allocations for non-traditional forms of services that may be unique to racial, ethnic, rural, or other populations."

Better patient compensation won't be a simple one-size-fits-all stipend, nor will all sites be able to accommodate a complex patient reimbursement plan. This is a conversation worth having – the value is clear for patients and medical research will benefit from increased randomization rates.

Moving Toward a Patient-Centered Solution

Our industry already has a full set of tools and options to increase the value of a study for patients, thanks to clear guidelines from the FDA and recommendations from IRBs, like the guidance from Advarra above.

Sponsors should become a leading voice in this discussion. With IRB regulations broadly supporting patient compensation, sponsors don't need to fear undue influence. Sponsors can design compensation for their studies and confidently message the plan to patients. By leveraging this incentive, studies will recruit more interested and more diverse patients. Compensation is a leading motivator across demographics, and even more valuable to diverse patients. With sponsor-designed plans, sites will have clearly defined benefits to aid patient recruiting and retention.

IRBs are incredibly helpful in this process, but they can't design a study's compensation scheme for a sponsor. It's their job to let the sponsor know when compensation is off course...but as Advarra noted, it's currently rare for IRBs to deny study designs due to compensation, leaving room to explore the boundaries of more reasonable compensation.

In an article published in the June 2022 issue of JAMA Oncology, top researchers suggested that every patient receive reimbursement for out-of-pocket expenses from clinical trial participation: "The common reason given for not reimbursing patients for their participation in trials is the desire to avoid undue influence on patients' decision-making about treatment choices." But this reasoning, intent aside, has created an income disparity in clinical trial participation. They argue that "the **greater ethical challenge** is increasing participation among these patients."

As an industry, we have a moral imperative to evolve patient compensation. Our current participation populations are overwhelmingly whiter, wealthier, and older than the general population. If we want to have more diverse and representative patient populations, then we need to use compensation as a method to ensure we don't end up with studies filled only by people who can afford to join.

Have any questions for our marketplace? Reach out by emailing sales@subjectwell.com.