Phase1 Healthy

Optimize Your Phase I Healthy Trial Design

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Quorum REVIEW IRB

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As the essential first step in bringing a new product to market, phase 1 trials may be the first time the investigational product is introduced into humans. Per regulation, these studies are designed to determine the metabolism and pharmacologic actions of the drug in humans and the side effects associated with increasing doses and, if possible, to gain early evidence on effectiveness.[1]

According to the NIH, a "healthy volunteer" is a subject with no known significant health problems who participates in research to test a new drug or intervention.[2] The choice to enroll healthy volunteers in research should be justified. The choice depends on the expected risks, recognizing that there will be considerable uncertainty about those expectations. Expected risks may be estimated from the nonclinical data, an understanding of the biological mechanisms, and any previous relevant human experience, but the clinical significance of those risks can depend on the study population. The objective is to select an equitable trial population with an acceptable ratio of risk to reward. For example, safety considerations may preclude the use of healthy volunteers for certain drug classes, such as cytotoxic anticancer drugs, because exposure may lead to unacceptable long-term morbidities.

There are many reasons why a healthy individual may choose to enroll in a phase 1 trial. Yet, a participant's motivation may not necessarily align with the IRB's mandate in assessing the benefits that may be considered in evaluating whether a Phase 1 Healthy (P1H) trial should be approved. A participant may appreciate the medical exams they receive in association with the study, expenses paid (such as travel to the clinic) are covered, or free lodging and meals during a confinement period. Also, perhaps, one of the biggest perceived motivators is payment. However, an IRB will not consider payment for participation in the study, or any of these incentives, to be a "benefit" of participation, in weighing the risk/benefit ratio. Rather, an IRB will likely consider payment as a risk and a factor that may either lead to inequitable subject selection or compromise the voluntariness of the consent process.

1% of adverse events that occur in Phase I Healthy research are characterized as severe

As for risk associated with the investigational intervention itself, history is replete with much publicized, P1H trial outcomes that arguably, in hindsight, should have been avoided, such as the result of the "Elephant Man" trial.[3] There is evidence, however, that P1H trials may not be so pervasively problematic. A 2015 meta-analysis of Pfizer P1H trials from 2004 – 2011 found that nearly one third of participants did not experience an adverse event (AE).[4] Of the remaining two thirds, 85% experienced mild AEs. Prior to unblinding, 76% of all AEs were attributed to the test product; that percentage fell

to 64% after unblinding. For both small molecules and biologics, approximately 1% of participants experienced a severe AE, defined as interfering in a major way with a participant's basic daily functioning.

The only true benefit that can be attained from P1H trials, from a regulatory and IRB perspective, is the gain in scientific knowledge. It is important to realize that reward in P1H research does not inure to the benefit of the participant. There are no direct benefits. While it may be true that some volunteers are primarily motivated by altruism when deciding to participate, the IRB must be very critical of the study design in order to ensure that the resulting data is useful in moving drug development into the patient population it is intended to serve.

Sound Design

Typical study design involves dose escalation to establish expected and unexpected toxicities and to define the acceptable maximally tolerated dose (MTD). This design is the most prevalent of P1H trials, but there are many other types that may be necessary to address particular issues, such as food effect on pharmacokinetics (PK). Food effect studies are usually crossover trials, with volunteers being given two identical doses of the drug, once while fasted and once after having eaten.

Regulatory and IRB delays typically result from the identification of a safety concern or insufficient data to make an evaluation of safety.[5] The sponsor should identify whether either the drug substance or the drug product presents any signals of potential human risk. If so, these signals of potential risk should be discussed, and the steps proposed to monitor for such risk should be described in the protocol.

Dosing regimens must be scrutinized for clearly identified procedures. It is advisable to use a safety factor to provide a margin for protection of human subjects receiving the initial dose. For example, a default safety factor of 10 might be considered. Sentinel dosing should be considered. This entails administration of the test article to a limited number of subjects, followed after a time by the remainder of the cohort. Also, multiple–dose schedules could be explored in late phase 1 (or phase 1b), after basic data on toxicity, peak levels, clearance, distribution, and biologic effects are available from single–dose studies (or phase 1a).

The information necessary, the procedures for review of the data, and the level of follow-up before each dose escalation and new participant dosing should be detailed in the protocol. Similarly, defined criteria and procedures for stopping the intervention in case of an adverse reaction should be clearly identified. For example, in crossover designs, a sufficient observation period between crossover arms to

detect and interpret any adverse reactions should be utilized.

Study designs that leverage pharmacogenomics (PGx) can maximize the utility of data and minimize participant risk. In phase 1 studies designed to characterize the MTD, it would be important, for example, to understand whether excess exposures are restricted to subjects with certain genotypes so that that these subjects do not inappropriately cause a generally suboptimal dose to be selected as the MTD—a critical consideration for determining which doses to carry forward to subsequent trials.[6] Likewise, when nonclinical studies suggest that an investigational product is metabolized or converted to an active metabolite through a polymorphic pathway, PGx analyses should be conducted in single- and/or multiple-dose PK studies in healthy subjects to evaluate common gene variants with known phenotypic effects, in order to determine the extent of variability and the maximal differences in systemic exposure between genotypes.[7]

While increasing their complexity, it is recommended to consider the design of phase 1 trials in the context of the objectives of the overall development program.[8] For example, some phase 1 studies include selected features of phase 2 study design in order to gather preliminary evidence of effectiveness, for example including a patient cohort. Although the FDA has indicated that for most Cellular and Gene Therapy (CGT) trials, the benefit-risk profile is not acceptable for healthy volunteers due to the possibility of extended effects and a high potential for immunogenicity, it would be prudent to design early-phase CGT trials to identify and characterize any technical or logistic issues with manufacturing and administering the CGT product.[9]

Other Study Considerations

Not only is the sound design of study procedures integral, but there are considerations for other study activities in P1H trials, as well.

Screening

Screening is of paramount importance. It is not considered ethical—and, indeed, would likely be considered exploitative—to include an individual who is not capable of understanding the associated risks, and who, therefore, is unable to provide consent to participate in P1H research without an LAR.[10]

43% of participants fail to disclose concurrent enrollment in other studies during screening

Less readily identifiable are those prospective participants who may be competent but may yet be motivated by payment, without regard for safety or science. According to a 2004 study, monetary payments appeared to influence respondents' propensity to neglect to tell researchers about restricted activities engaged in either before or during a study.[11] In fact, a 2015 article, reported that 43% of participants who had participated in more than one clinical trial in the recent past failed to disclose

concurrent enrollment.[12] Yet, according to the aforementioned 2015 meta-analysis, the majority of participants had not previously participated in a P1H trial.[13] Also, the 2004 study found that, while certainly an incentive for participation, payments did not blind subjects to risk.[14] Illustratively, the riskier the research, the less likely respondents were to neglect to tell.[15] Also notable, the severity of AEs during the seven years of Pfizer phase 1 trials did not differ significantly between healthy volunteers who participated in only one study and those who had previously participated in other studies.[16] These data paint a complex picture and present numerous challenges in the context of P1H research.

As a general rule, enrollment should be proscribed within 30 days or within a certain drug half-life of a prior study. Various methods can be implemented to help ensure participant compliance. These include registries, background-check services, fingerprinting, comprehensive laboratory tests, positive reinforcements for honesty, and, if necessary, exclusion.[17]

Recruitment

While the therapeutic misconception is diminished in healthy individuals, as a healthy volunteer is obviously less likely to attribute a curative intent to the intervention, the term "treatment" should generally be avoided in participant materials, to the extent it connotes that the intervention is nonetheless safe and effective rather than investigational. Payment should not be set apart, for example with bolded or larger text. Also, any general testimonials should not be overly reassuring.

While "free medical treatment" should not be advertised when the intent is only to convey that subjects will not be charged for taking part in the investigation, advertisements may call out a "no-cost health examination" as a benefit for recruiting purposes.[17] Advertising free health exams should be done with caution, however, in the P1H context, as it is likely only acceptable when the intent includes the return of useful health information to the participant.

As for enumerating benefits, care should be taken to not emphasize a prospective participant's assistance in aiding medical research or improving future healthcare. This is because, from phase 1, it is more likely than not that the test product will not result in an approved treatment. Any such representations to the contrary are potentially misleading or overly optimistic about the impact of participation.

Due to the need to recruit healthy volunteers quickly, some P1H facilities utilize a "generic" or "general" screening process and consent, to build a database of potential participants. It is important to remember

that OHRP considers construction of a database for this purpose to constitute research. Also, the FDA considers any research-specific intervention, including screening, to require IRB oversight and informed consent.[18] If a site is in this situation and looking to speed recruitment, an IRB may consider a waiver of documentation of informed consent and a phone script to verbally consent individuals before they arrive at the clinic for screening procedures, in order to facilitate fasting in preparation of a blood draw or wash out from any other medications.

Consent

Consent can be obtained as in any other study, except P1H subjects should be clearly told both that one of the aims is to produce drug toxicity, which can cause pain or discomfort and pose significant medical risk, and that no direct medical benefits will result. In addition to the eight required elements of informed consent, the identification of unforeseeable risks is critical in P1H trials.[19] It should be explained that some toxicities identified in nonclinical studies may translate into AEs in healthy humans, while others may not, and also that as-of-yet unidentified risks may arise.

While P1H trials will generally be completed quickly, data may arise that would necessitate that a participant be informed. As such, the consent form should have a statement that significant new findings will be shared. The relevant standard for such disclosures asks whether the new information would impact a participant's continued willingness to partake.[20] If this sharing of new information becomes necessary, it may not require full re-consent due to the short duration of most phase 1 trials, but it may require that special effort is taken to make past participants aware of a previously unknown risk.

Compensation

Payment is considered a recruitment incentive. As a guiding axiom, the amount paid to participants should not be so much that it incentivizes subjects to remain in the study, against their better judgment, when they might otherwise withdraw. This is a fact-specific determination informed by the participant population and the wider local context, so as not to be exploitative. Payment should also correlate to the amount anticipated to effectively recruit the study. As such, a participant might be reimbursed for transportation expenses and compensated for time and inconvenience, including confinement, opportunity cost, and restriction from certain activities (such as smoking cessation or dietary limitations). However, payment should not be based on the risk associated with study procedures.

Finally, the FDA has advised that payment should accrue as the study progresses and should not be contingent upon the participant completing the entire study.[21] However, it is possible to hold a small portion of the entire payment as an incentive for completion. The IRB is required to determine that the amount paid as a bonus for completion is reasonable and not so large as to be unduly influential. As a general rule, not more than 40% of the total compensation amount should be contingent upon completion.

Phase 1 Healthy trials are integral to and ethically justifiable in drug development. Ultimately, direct benefits to participants are not required, if P1H risks are reasonable in relation to the anticipated benefit to society as a whole. Important knowledge may be learned that helps to ensure that future participants and patients, who might not be as healthy, are nonetheless protected from unnecessary harm.

A completion incentive bonus should not exceed 40% of the total compensation amount

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About Quorum Review IRB

In 1992, Quorum's founders saw a need for an IRB that protected human participants while providing high-touch customer service. That's exactly what Quorum delivers. Each member of our team brings a wealth of experience in clinical research human participant protection—as well as the knowledge, reliability, accuracy, and speed that matters when getting products to market.

With a focus on performance, these are the core values that comprise Quorum's foundation:

- Ethical protection of human research subjects
- Customer service
- Continuous quality improvement
- Promotion of organizational capability

Quorum Review IRB has been fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) since 2006. AAHRPP's "Full Accreditation" emblem signifies that Quorum Review consistently demonstrates excellence in comprehensive protections for research participants while facilitating the highest quality research processes.

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