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The Importance of Participant Tracking When Conducting Clinical Pharmacology Drug Trials

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On behalf of the ACCP Public Policy Committee

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The American College of Clinical Pharmacology (ACCP) strongly recommends the use of research participant databases, registries, or independent monitoring organizations to oversee the recruitment and enrollment of participants in clinical pharmacology trials. All clinical research trials involve a level of risk. It is the ethical responsibility of sponsors, ethical review boards, and researchers for these trials to ensure that this risk is minimized, and participant safety maximized, to the extent possible based on the available data at that time. Trial risk mitigation is primarily managed through trial design, conduct, and independent ethical review. An important aspect of trial conduct is participant recruitment and enrollment. It is therefore paramount that those participating in the trial fully meet the inclusion and exclusion criteria set forth in the protocol and be truthful regarding previous trial experience during the screening phase of the trial.

Clinical pharmacology trials, also termed phase I development trials, play a pivotal role in the initial safety investigation, regulatory approval, and continued lifecycle management of all pharmaceutical therapies. These trials rely on the ability to recruit and enroll participants of different ages, races, ethnicities, sex, weight, and health status to best characterize the pharmacokinetics, pharmacodynamics, and initial tolerability of medicinal products. Among the various types of trials conducted, phase I trials typically include those that assess the administration of single and multiple doses of a novel compound for the first time in humans. They may also include, but are not limited to, assessing the effects of renal and/or hepatic impairment, differences in drug absorption, cardiac function, concomitant drug interactions, and different formulations. These studies play a critical role in the development of safe and effective new therapies. As such, the demand for these trials and the competitive nature of medical research create an environment of consistent demand for clinic resources and healthy volunteers, rapid timelines, and the potential for high financial gain for those involved.

While some individuals participate in clinical trials for altruistic or socially based reasons, compensation for time and travel motivates the participation of many others, thus creating an environment where participants may rely on this compensation as either supplemental to or as their sole or main source of income. These "occupational" or "professional" research individuals will seek out and enroll in numerous types of trials throughout a calendar year, at times in quick succession, and may even attempt to participate in more than 1 trial simultaneously.[1] Current literature has indicated that approximately one-third of those participating in clinical pharmacology studies fall into this "occupational" category.[1] Unfortunately, some participants take an indifferent attitude toward the risks inherent in participating in multiple trials over short periods of time or enrolling in trials sequentially, even though they are well informed and repeatedly warned of the risks by the researchers conducting these trials. Concerningly, to maximize their clinical trial compensation over time, participants have been known to deceive trial

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researchers for entry in a study and justify any risk with financial gain.[2–4]

The scale of participant deception is not insignificant. Publications by Devine et al[5,6] describe the results of a survey in which 100 "experienced research subjects" were recruited from both newsprint and online postings to help quantify this level of potential deception. From this survey, 75% of those who participated reported concealing some type of information from researchers when screening for a study.[5] While these acts of deception varied, a significant number were found to likely prevent the enrollment of the individuals if they truthfully disclosed these potential issues. For example, 43% of individuals reported they enrolled in more than 1 study concurrently, 32% provided false or unreported health conditions, 28% did not disclose the use of concomitant medications, 20% admitted to current recreational drug use, and 20% consumed alcohol.[5,6]

A more recent analysis by Pinho et al[7] analyzed data from a private research subject database called Verified Clinical Trials. The investigators assessed an aggregated collection of phase II and III psychiatric clinical trial data to identify the various attempts by "professional" research subjects to enroll in these trials. Although the data set encompassed later-phase clinical trials, the types of deceptions can be found across all types of clinical research and are therefore relevant to this discussion. The types of deceptions/violations included reenrollment attempts, dual enrollment attempts, washout period violations, prior experimental drug exposure, dual screening attempts, rescreening attempts, and exclusionary health conditions and compound use, to identify a few.[7] While the frequency of each violation is not provided, the variety of the different violations is concerning and makes the need for additional modalities to support and improve clinical trial oversight evident.

While a "washout period" between clinical trial enrollments is a de facto requirement for virtually all interventional trials, not all washout periods are the same due to the unique absorption, distribution, metabolism, and excretion properties of investigational drugs. This behavior becomes concerning when individuals, ignoring these washout periods and risks of sequential enrollment, do not fully disclose or purposely misinform researchers to gain entry.[5–7] Specifically, for these scenarios, the risk of the participant may significantly increase due to unknown drug-drug interactions between investigational products and/or latent or unknown pharmacodynamic effects from the prior investigational product that was not adequately cleared from the participant's body. Inaccurate or misleading safety information could also result due to the carryover of effects from the prior study test product. Invalidation of the subsequent study or unnecessary secondary safety monitoring in future studies may result.

The adoption of a system to track participant enrollment will also help prevent the exploitation of both vulnerable and clinically unique populations that often participate in these types of clinical trials. Deceptive practices can be a significant issue in vulnerable populations like the elderly, infants and children, and undocumented immigrants. Studies that rely on assent from the individual and informed consent from a caregiver or a relative can create an unforeseen abusive scenario where these individuals are essentially "used" by their caregivers, guardians, or family members as a source of income. Without proper monitoring, these individuals may be coerced or even forced into participating without the knowledge of the research team.

Additionally, considering that a majority of the specialized phase I trial participants (ie, those renally impaired/on dialysis, hepatically impaired, experienced in nasogastric tube feeding, and drug abusers) are specifically sought out and are in high demand across multiple sponsor-supported trials, care needs to be taken to ensure that enrollment abuses are kept in check. While it is the hope of both the sponsors and investigators that these trial participants are not enrolling in multiple trials simultaneously or sequentially, many times the demand for these patient types far exceeds the actual number of participants available, creating an environment of participant fraud and abuse.

It is not the purpose of this policy statement to discuss the morality of paid medical research or the recruitment of "occupational" research participants (albeit both are important topics) but to signal the potential safety risk and consequences involved when individuals ignore, misunderstand, or take an indifferent attitude toward participating serially in clinical trials without being fully transparent about previous research participation or hiding underlying medical conditions that may place their overall health at risk. While obtaining informed consent is a critical component of all clinical research and supports the autonomy of those participating, such a tool used in isolation may not ensure that the risks of the trial are truly minimized for all those enrolled. Therefore, there is a need for balance between respecting the participant's autonomy and the clinical paternalism needed to ensure that the patient's safety is maximized.

There have been previous calls for the creation of a centralized system of participant tracking.[8] While this would be ideal, until such a system is created, the use of research participant databases, registries, or independent monitoring organizations to oversee the recruitment and enrollment of participants in these trials should be adopted. Finally, the costs of these participant deceptions extend beyond just the safety of

those involved to include the overall validity of these trials and the future regulatory approval or rejection of the therapy.[9] Enrollment of individuals who do not properly disclose prior trial participation or are purposely deceptive during the screening and enrollment periods can create a complex scenario impacting the identification and accurate reporting of safety events and kinetic and dynamic interactions.

American College of Clinical Pharmacology Call to Action

The ACCP strongly advocates for the need of a harmonized method or system to track participant enrollment in clinical pharmacology research studies. The use of such a method or system would support the current efforts of clinical researchers to ensure safe participation, help mitigate participant exploitation, prevent abuse of the enrollment process, and maximize the scientific integrity of these studies. In the absence of a federally established modality, the ACCP recommends the use of independent research subject databases, registries, or organizations when conducting these studies to oversee the proper enrollment of its participants. The ACCP also stresses the need for improved participant awareness concerning the potential safety risks when volunteers enroll in multiple research studies simultaneously or concurrently.

Conflicts of Interest

K.T.M., an employee and shareholder of Janssen Pharmaceuticals, declares no conflicts of interest.

Disclaimer

The opinions expressed in this article are those of the authors on behalf of the American College of Clinical Pharmacology and should not be interpreted as the position of the entities or institutions at which the authors are employed.

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