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EDITORIALS

The secret realm of phase I trials in healthy volunteers

Regulators should demand greater transparency

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Phase I clinical trials in healthy volunteers aim at establishing safety, pharmacokinetics, and dosage for subsequent testing of new drugs. They are a necessary step in building the evidence for new treatments. But many view them with suspicion. Phase I trials expose humans to unproved drugs—often at plasma concentrations needed for detecting toxicity. Because volunteers are healthy, the ratio of medical risk to benefit for them is almost infinite. Another reason for suspicion is that healthy volunteers are paid—a fact that makes it likely that primary motivations for participation are misaligned with those of researchers,[1] and that study participants will be drawn from underemployed people.

A few catastrophic events in phase I testing, including the death of a relatively healthy volunteer in 1999, and the occurrence of life threatening toxicities in six participants in 2006, have also fuelled concerns.[2 3] Finally, there is the problem of opacity. What happens in phase I studies in healthy volunteers is largely hidden from public view.[4 5] Some policies, such as the US Food and Drug Administration Amendments Act of 2007,[6] exempt phase I studies in healthy volunteers from obligatory public registration, and most studies are conducted outside academic medical centres at private facilities run by pharmaceutical companies or contract research organisations. Most drugs put through phase I testing are never licensed, and the majority of trials testing drugs that eventually were abandoned are never published.[7] Phase I studies in healthy volunteers enjoy a peculiar isolation from the norms of transparency and publication that are operative in almost every other realm of medical research.

In this issue, Emanuel and colleagues (doi:10.1136/bmj.h3271) look into the hidden world of risk in phase I studies in healthy volunteers.[8] Using the complete electronic records for all non-oncology trials from Pfizer, the authors estimated the frequency and severity of adverse events. They also probed the demographics of study participation, and correlates of risk. In brief, they reported that a third of subjects never experience study related toxicity; that the frequency of mild to moderate toxicities experienced by subjects receiving investigational drugs is no different from that for subjects receiving placebo; and that no subjects died or developed permanent disability during the period studied. They also observed that many study related events arose from procedures, such as placement of arterial lines, rather than from drug toxicity. Many commentators worry most about the unquantifiable risks associated with administering novel substances, but this finding reminds us that familiar procedures can be more burdensome.

However, phase I studies are not totally benign. Emanuel and colleagues also found that 10 in 1000 participants experience transient severe drug related adverse events (defined as significantly interfering with daily functioning), and that 1.5 in 1000 experience study related, serious adverse events. These included episodes of aseptic meningitis, pan colitis, and headaches after lumbar puncture.

This report is the largest and most detailed analysis so far of risk to healthy volunteers in phase I studies. The study team obtained extraordinary access to a large dataset from a pharmaceutical company, and in contrast with previous reports, tried as far as possible to ensure the impartiality of their analyses. The findings suggest that the risk to subjects in phase I studies is broadly comparable to that associated with participating in other types of medical investigations, such as later phase drug trials or physiological studies of healthy volunteers. They also provide evidence that preclinical toxicology studies, medical monitoring, and oversight do a reasonable job in anticipating and preventing harm.

In common with most research, Emanuel and colleagues' study leaves unresolved questions. The findings are unlikely to satisfy the more dug in critics of phase I studies. For example, it tells us little about the socioeconomic status of participants. Nor are we able to assess whether the mostly modest burdens catalogued here are adequately redeemed by worthy research endeavours: what proportion of these studies tested "me too drugs," for example, rather than treatments directed towards genuinely unmet medical need? It is not clear whether event rates might have been diluted by the inclusion of less aggressive study designs (such as single dosing studies), or by the exclusion of oncology studies (occasionally, cancer drugs are tested in healthy volunteers). Lastly, the data on which this analysis was based came from a single pharmaceutical company. We cannot rule out the possibility that other companies were approached for datasets but declined to cooperate owing to less favourable safety records. Or that the risk profile of phase I studies pursued by large pharmaceutical companies is milder than that for

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biotechnology companies—which often pursue biologics and sponsor development of edgier products like the two leading to the catastrophic phase I episodes mentioned previously.

Phase I studies in healthy volunteers are a necessary step in developing new pharmaceuticals—they are indispensible if we value a vigorous drug development enterprise. Emanuel and colleagues make a good start at generating a reliable evidence base for evaluating ethical conduct in this realm of research. On balance, their findings are reassuring.

Less reassuring are the barriers faced by researchers trying to secure this kind of evidence. Why have other companies not matched Pfizer's courage and opened their filing cabinets to independent investigators? It is surely time for drug regulators to develop policies that would oblige companies to register all phase I studies in healthy volunteers and to deposit results in publicly available databases.

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