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Patient-Funded Trials: Opportunity or Liability?

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Summary: Patient-funded trials (PFTs) are gaining traction as a means of accelerating clinical translation. However, such trials sidestep mechanisms that promote rigor, relevance, efficiency, and fairness. We recommend that funding bodies or research institutions establish mechanisms for merit review of patient-funded trials, and offer some basic criteria for evaluating PFT protocols.

Introduction

A new funding model that claims to empower patients and expand the resources available for cutting-edge research is picking up steam and garnering particular attention in cell-based intervention research. Studies funded by patients have been conducted in conditions ranging from Parkinson's disease (Fikes, 2013) to Multiple Sclerosis (Cree et al., 2010) to ALS (Sipp, 2012), and have begun to attract mainstream media attention. Models of patient funding can take many forms, from crowd-funding campaigns to support academic researchers, to studies in which participants pay for access to investigational interventions in for-profit clinics. In addition, the U.S. FDA permits drug companies to recover costs from subjects for trial participation in certain circumstances (U.S. Department of Health and Human Services, 2009). Our focus is on patient funded trials (PFTs), a term we use to refer to studies funded directly by patients seeking to enroll in trials as participants.

Supporters of PFTs hope for better-informed patient engagement in clinical research, as well as greater opportunities to pursue research lines that lack public funding or industry support. They contend that worries about patient autonomy and the potential for exploitation are overblown and manageable via existing oversight and review mechanisms (Vayena and Tasiolas, 2013a, Vayena and Tasiolas, 2013b). Concerns about conflicts of interest between patient payers and sound trial design have been dismissed as no different than those encountered in industry-sponsored research (Morreim, 1991).

Whatever progress this model might bring to cutting edge research, it is subject to several liabilities that have not yet been adequately considered. PFTs change relationships between research stakeholders – patients, researchers, and sponsors in particular – in ways that undermine the ability of oversight systems to protect patients, ensure the production of reliable medical

evidence, and preserve confidence in the research enterprise itself. Without adequate corrective measures, this reconfiguration of research relationships leaves the PFT model prone to inefficiencies, including exploitation by those seeking to use the cachet of cutting-edge science to market unproven, ineffective, and perhaps even dangerous interventions to patients desperate for a cure.

The Vulnerabilities of PFTs

Although research stakeholders share a common interest in promoting health through the production of reliable medical evidence, they are also each motivated by strong parochial interests. Drug companies are driven by commercial considerations, patients seek access to promising new treatments, and scientists hope to advance their careers through successful research and publication. Left unchecked, these interests can threaten the ability of research to advance biomedical progress. The goal of oversight and regulation is to align these myriad interests with the social objectives of advancing science and improving health. Existing oversight mechanisms promote this alignment by focusing on the long-term interests of traditional study sponsors and researchers. They are not geared towards aligning the near-term objectives of patient funders and PFT clinics with the broader goal of efficient and reliable medical evidence production.

First, consider how existing oversight mechanisms promote research efficiency. Requirements for market access attempt to align the profit motive of private sponsors with the demands of sound science. Sponsors must produce adequate evidence regarding safety, toxicity, and efficacy before submitting a marketing application. Since trials are expensive, sponsors generally prefer to minimize the number and duration of studies necessary to generate that

evidence. This provides an incentive to conduct research quickly while minimizing sample sizes and, therefore, patient exposure to unproven interventions.

In PFTs, patient sponsors are strongly motivated by the short-term goal of access to new interventions and the profit motive shifts from the sponsor to PFT clinics, which generate revenue directly from the enrollment of participants. Clinics offering PFTs often charge substantial fees for trial access; for example, according to a recent report, Novastem, the exclusive distributor in Mexico of stem-cell products of the US company Stemedica, conducts research at Clinica Santa Clarita where it costs US $30,000 to participate in a trial of the use of neural stem cells for the treatment of stroke-related brain damage (Bouffard, 2015). This funding model effectively reverses incentives to minimize sample size and encourages sponsors to enroll large cohorts. In doing so, it also increases patient exposure to the risks of unproven interventions. And, because clinic revenues derive directly from research rather than a product's commercialization, the downstream desire for profit from marketed interventions no longer exerts pressure to quickly and efficiently distinguish promising interventions from ineffective or harmful ones. Instead, trials are launched such as one recent Phase I/II study planning to enroll 500 participants to test autologous adipose-derived stromal cells on patient funders for the treatment of erectile dysfunction (Ageless Regenerative Institute, 2014) – a sample size far greater than typical early-phase explorations.

Second, consider how current systems try to ensure that studies are founded on solid scientific rationales and that patients are not exposed to risks without first establishing the potential for the generation of important data. Publicly funded studies are screened via peer review. Although imperfect, this mechanism uses the scientific community's standards of evidential support to weed out studies that lack sufficient grounding before patients are put at

risk in a trial. Because industry sponsors can only recoup research investments after licensure, they have strong incentives to pursue platforms or interventions that have the most compelling evidential support.

As stated above, however, investigators pursuing PFTs can market their investigative products directly to patients. The initiation of a trial doesn't depend on peer review committees or a concern for downstream marketing approval. Rather, the "gatekeepers" for trial launch are patients, often with debilitating or life-threatening diseases. Although some such patients may have the acumen and emotional reserve to properly vet PFT clinics and review the preclinical evidence, many will lack the requisite knowledge or motivation to do so. The result is the ability of unscrupulous clinics to co-opt the "therapeutic hope" (Hyun, 2013) of desperate patients to sell them access to "trials" of interventions with little or no scientific foundation. This may be of particular concern in new stem cell modalities, where high-profile media reports of "miracle cures" like the stem cell treatments that purportedly restored strength to Denver quarterback Peyton Manning's throwing arm or aided hockey legend Gordon Howe's post-stroke recovery are likely to breed unrealistic expectations about the outcomes associated with investigational treatments.

Third, consider how existing incentive mechanisms promote the production of high-quality evidence. The threat of regulatory disapproval is leveraged to encourage industry sponsors to utilize 'gold standard' methodologies such as blinding and randomization. Peer review plays a similar function for publicly-funded studies. Although these mechanisms are imperfect, there is no comparable means to encourage study quality in the PFT model. Patient funders primarily seeking access to new interventions are unlikely to fund studies that might randomize them to something other than the investigational intervention, exclude them based on

eligibility criteria, or involve burdensome research procedures for monitoring effect. Indeed, many PFTs utilize open-label and case series designs (Baker, 2005), which are notoriously unreliable and in numerous instances have suggested clinical utility that was later decisively refuted in randomized trials. In some instances, the research element in PFTs is even presented as secondary to treatment access. For instance, one clinic advertises that patient funders are "strongly encourage[d]… to participate in longitudinal patient data collection to demonstrate… that these therapies offer fundamental improvement" in health status (Arbitrage Medical, 2014). The upshot is that absent constraints on methodology, the PFT model invites the production of low-quality evidence.

Moreover, unless the shortcomings canvassed here can be addressed, the proliferation of PFTs could also create liabilities that reach beyond this particular funding model. If such trials recruit large numbers of patients in areas that compete with studies grounded in strong scientific rationales, the net effect could be to stymie rigorous evaluations of new strategies in the very areas where they are needed most. This is of particular concern in rare diseases, which are also the areas in which the PFT model may be most attractive to investigators and patients.

Finally, even if patient funders understand and freely accept the risks associated with this funding model, high-profile events occurring in one study can alter beliefs and activities surrounding other, related research (London et al., 2010). A debacle involving patient injury, for example, or even a string of negative findings, can deter investment in what might otherwise be a promising line of research. This occurred in gene therapy after the high-profile death of Jesse Gelsinger in 1999. This is a concern in PFTs, where patients' desires for access to new treatment options and dosages with directly observable outcomes may encourage unusually aggressive study designs, such as rapid dose escalation or the early enrollment of recent-onset patients.

Recommendations

Key aspirations of the patient-funded model are to provide participants with greater control while also enabling research in areas that are currently unfunded or under-funded. If PFTs are to achieve these goals, policies must be designed to align participant and investigator interests with the imperatives of socially valuable research. At a minimum, this means that policies and mechanisms are needed to encourage the use of research methods that minimize bias, promote the vetting of preclinical evidence before the launching of PFTs, and ensure that potential patient funders are in a position to assess the scientific value and rigor of the trials they might fund.

The creation of such mechanisms is likely to be difficult in the absence of centralized rule making, and may require coordinated efforts on the parts of multiple parties. Ethics review might play a role in this process, but will likely be insufficient for at least two reasons. First, in countries such as the U.S., private clinics may not always be required to submit protocols for ethical review, as when they do not receive federal funds or pursue Investigational New Drug applications. Second, ethics review committees often have limited capacity as well as an ambiguous mandate for vetting the preclinical evidence and scientific quality of the studies they review.

Instead, we suggest three broad directions for possible reform, with the recognition that any such reforms would require careful study and may be difficult to implement. First, policy makers could create a mechanism for providing scientific and ethical oversight of PFTs. This could take many forms, some of the more ambitious of which would require large-scale policy changes. For example, steps could be taken to empower public research agencies – such as the NIH or the California Institute of Regenerative Medicine in the U.S. – to provide external review and ethical oversight of PFTs. This might be modeled loosely on the Recombinant DNA

Advisory Committee's public reviews of novel gene transfer trials. In the near-term, clinics offering PFTs should establish credible and fully independent scientific panels to review pre-clinical data and methodological features of proposed trials. For this approach to successfully avoid the vulnerabilities canvassed above, however, the establishment of mechanisms to ensure the credibility and independence of such panels would be crucial.

Second, to encourage the use of such mechanisms in the absence of larger legal or policy mandates, academic medical centers, professional organizations, and licensing boards should discourage their members from participating in studies not approved via such review. For example, academic medical centers could make credible, independent scientific review of PFTs a requirement for study approval. National and international professional organizations could amend codes of conduct to clearly signal that such review is required to remain within accepted professional norms and licensing boards can signal that it is a requirement for acceptable professional practice.

Finally, policy makers should consider whether accreditation requirements for health care facilities could be used to encourage entities conducting PFTs to utilize an appropriate mechanism for scientific review and ethical oversight.

Although incomplete, these suggestions attempt to balance the legitimate goals of PFTs with the social mandate to ensure that research is scientifically sound, ethically conducted, and worthy of continued support. Yet any such incomplete approach has downsides. First, without comprehensive policies that apply to all researchers or health facilities, incremental reforms may shift the demand for PFTs to those investigators and clinics without significant credentials to protect. This may not eliminate dubious clinics, but with mechanisms in place to clearly signal which clinics are performing valuable research and which are not, their impacts might be

minimized. Second, merely reducing the number of dubious PFTs may be insufficient to prevent the stigma associated with PFTs that promote low-quality research or harbor unethical researchers from spilling over into public perceptions of legitimate PFTs or the broader clinical research enterprise. Finally, even if the PFT market could be more transparently segmented into those studies that have markers of scientific quality and those that do not, ethical concerns about the latter market would remain. In particular, limited research resources absorbed by low-quality studies impose opportunity costs on legitimate research, and PFTs may involve significant financial burdens for participants and their families that go unredeemed by the prospect of either individual benefit or social value.

The goals of PFTs to empower patients, expand available research resources, and accelerate the pace of translation are worthy and important objectives. Because the current system lacks regulations or incentives that constructively channel the desires of patients, the ardor of investigators, and the profit motives of host clinics, this funding model harbors important liabilities for both patients and the broader clinical research enterprise. Building institutional mechanisms to ensure that PFTs promote high scientific and ethical standards will help ensure that this new model advances not only the interests of patient payers, but of science and society as well.

Web Resources

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