Money and Morals

Ending Clinical Trials for Financial Reasons

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Abstract Too often, biopharmaceutical companies stop their clinical trials solely for financial reasons. In this chapter, we discuss this phenomenon against the backdrop of a 2011 decision by Geron Corporation to abandon its stem cell clinical trial for spinal cord injury (SCI), the preliminary results of which were released in May 2014. We argue that the resultant harms are widespread and are different in nature from the consequences of stopping trials for scientific or medical reasons. We examine the ethical and social effects that arise from such decisions and discuss them in light of ethical frameworks, including duties of individual stakeholders and corporate sponsors. We offer ways that sponsors and clinical sites can ensure that trials are responsibly started, and once started adequately protect the interests of participants. We conclude with recommendations that industry sponsors of clinical trials should adopt in order to advance a collective and patient-centered research ethic.

Keywords Neuroscience · Neurons · Stem cells · Human embryonic stem cells · Ethics · Informed consent · Clinical trials · Spinal cord injury · Biotechnology · Geron Corporation

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1 Introduction

We believe, along with other commentators, that any company that stops a clinical trial for financial reasons creates a unique set of negative and potentially harmful consequences that raise ethical concerns (Malmqvist et al. 2011; Iltis 2004; Lièvre et al. 2001; Evans and Pocock 2001). What is missing from the literature is a discussion of this two-part question: What are companies expected to do to minimize the risk of stopping trials for financial reasons, and what are their obligations after they abandon such trials? Here, we discuss halting trials for financial reasons against the backdrop of the 2011 decision by Geron Corporation to abandon its stem cell clinical trial for spinal cord injury (SCI). We examine the social impact and harms that arise from such decisions and discuss them in light of the duties that corporate sponsors assume when initiating such trials. We further discuss ways that sponsors and clinical sites should ensure that trials are responsibly started, and once started adequately protect the interests of human participants. We conclude with recommendations that sponsors of clinical trials and their collaborators should adopt in order to advance a collective and patient-centered ethic.

2 Definition

This topic requires an explanation of what we mean by *stopping a corporate-sponsored clinical trial for financial reasons*. We address situations where trials are abandoned solely or primarily for economic and business reasons unrelated to safety, efficacy, or feasibility. We exclude from discussion trials that are stopped for other reasons, such as the emergence of unacceptable rates of toxicity,

discoveries that alter the understanding of the therapeutic intervention, or problems with research execution. Though trials stopped in this fashion may have financial consequences, we do not include them in our definition. We recognize that there may be mixed reasons to abandon a trial but address instances where money is the primary, driving motivation for a sponsor to stop a trial.

3 Examples of Corporations that Stopped Clinical Trials for Financial Reasons

There is little information about the prevalence of this phenomenon, most probably because corporations are not required to reveal the details of their research failures. While it was not possible to discover prevalence data, we did locate cases that illustrate the range of circumstances that exist when clinical trials are stopped by corporations for financial reasons.

In 1996, Hoechst AG shut down the European trials of Pimagedine (under study to slow the progression of renal disease in diabetics) 2 years after recruitment had begun. The clinical investigators strongly objected to the decision on ethical grounds since the decision was based primarily on financial considerations (Keen et al. 1997). In 1997, Hoechst Marion Roussel drew fire when the company stopped a trial after treating 500 subjects with Cardizem, a drug being tested to prevent myocardial re-infarction. The reason given for the decision was that Cardizem faced competition from a generic product. That same year, the Liposome Company halted a study of doxorubicin in metastatic breast cancer, citing strategic reasons (Langer 1997; Hopf 1997). In 2000, after enrolling nearly 1,500 patients, Novartis stopped a placebo-controlled trial of fluvastatin intended to prevent hypercholesterolemia in individuals aged 70–85 years. Novartis feared that a competitor's clinical trial of a similar drug would end sooner and stated that this decision was necessary "to reallocate resources…to the newer growth assets" and cited "the competition entering the elderly segment" (Lièvre et al. 2001).

In another case, Pharmacia stopped a large-scale trial for hypertension in 2003 for financial reasons and criticisms about study design (Black et al. 2003; Psaty and Rennie 2003). The trial aimed to enroll over 15,000 patients to compare the ability of three drugs to reduce the incidence of myocardial infarction, stoke, and cardiovascular death. In 2006, Antigenics lacked sufficient funds to conduct a confirmatory trial to verify preliminary data showing that its vaccine was safe and effective in preventing recurrence of intermediate-stage renal cell carcinoma (Goldman and DeFrancesco 2009). Renal cell cancer patients spoke out about their disappointment that a potentially effective and demonstrably safe cancer vaccine might never become available (Anand 1986).

More recently, ReVision Therapeutics, Inc., stopped the development of its drug fenretinide because it lacked the funds to complete its clinical trials. The drug had been under clinical study for over four years to treat dry age-related macular

degeneration, a leading cause of blindness in the elderly for which there are no FDA-approved treatments (PR Newswire 2011; Roberts 2012). Most recently, in October 2012, Aveo Pharmaceuticals, Inc., stopped two clinical trials midstream and announced a cost-cutting layoff and restructuring plan to focus the business on its more promising renal cell carcinoma drug (Aveo 2012; Bonanos 2012).

To better illustrate the consequences and concerns about corporate abandonment of clinical research for financial reasons, we take an in-depth look at Geron Corporation's SCI stem cell clinical trial.

4 The Geron SCI Clinical Trial

Geron Corporation (Menlo Park, CA) is a publicly traded company that garnered international headlines for initiating the first ever phase 1 clinical trial of a human embryonic stem cell (hESC)-based therapy for SCI. The highly publicized trial began with the enrollment of their first patient in October 2010 and came to an abrupt halt on November 14, 2011 after enrolling only 4 out of the planned 10 patients. The CEO, John Scarlett, cited the cost of the research and "capital scarcity" as the reasons (Loftus 2011). The company was abandoning its stem cell programs to focus on its cancer programs, which would produce quicker profits and issued the statement:

> we anticipate having sufficient financial resources to reach these important near-term value inflection points for shareholders without the necessity of raising additional capital. This would not be possible if we continue to fund the stem cell programs at the current levels (Geron 2011a).

Geron then laid off 66 workers, representing 38 % of its workforce.

Public expectations in this trial had been high and Geron was central in maintaining that expectation.[1] In advance of the phase 1 trial, the company had raised significant amounts of venture capital funding and, after going public, had returned to the capital market 24 times to support its programs. Geron had also obtained a $25 million loan from the state's granting agency, the California Institute for Regenerative Medicine (CIRM), to fund hESC research (Scott and Huggett 2012). Geron spent $45 million alone submitting its 22,500 page Investigational New Drug Application to the FDA, the largest application the FDA had ever received (Gawrylewski 2008). All told, Geron had spent $250 million and had taken 12 years to get to the start of this first-in-human study of hESCs (Scott and Huggett 2012). This study involved seven research centers and investigator teams that Geron trained to perform the treatment. Informed consents were long and involved, adding to worries that patients would not fully understand the risks and conflate an experimental

[1] Geron funded both the initial derivation of hESCs in 1998 and the research that produced videos in 2002 of spinal cord injured rats walking after being transplanted with cells made from hESC-derived oligodendrocyte precursors.

procedure with a treatment or cure (Kimmelman et al. 2006). After the trial commenced, some patients contacted the investigators, offering a million dollars and more to receive the cells. Another patient, a jockey paralyzed in a fall, recruited his doctor to move "heaven and earth" to get him into a trial and commenced a letter writing campaign by other paralyzed patients on his behalf (Regalado 2011).

One year after the study started, only four out of an anticipated ten subjects had been recruited and transplanted; and this was only the first of a series of studies required to merely assess safety. The fifth patient had been enrolled, but not transplanted, when the company announced its termination of the trial. After discussions with clinical staff and family, an agreement was reached to add her to the cohort and proceed with the transplant (Conger 2011).

Geron's announcement that it was discontinuing all of its cell therapy research programs—neural, cardiac, and pancreatic—was seen as a blow to the nascent field of regenerative medicine (Salahi 2011). Geron's president, David Greenwood, justified the decision by stating that the change would save the company at least $25 million per year over the next few years (Moran 2011). It announced that it would commit $8 million to wind down the SCI study and follow the patients with periodic assessments for 15 years (Geron 2011b). It refunded $6.5 million it had used from state coffers. All told, these moves allowed Geron to retain about $151 million in cash reserves.

In January 2013, BioTime, a blood plasma company, acquired Geron's stem cell assets including its stem cell intellectual property. BioTime's subsidiary, Asterias Biotherapeutics, now owns multiple lots of the hESC-derived oligodendrocytes used in the Geron trial, which were starting materials to manufacture additional lots of the cells for cancer immunotherapy, chondrocytes for cartilage and disc repair, and cardiomyocytes for heart disease. The deal transferred all of the clinical and regulatory documents pertaining to the SCI clinical trials (Brown 2013; Businesswire 2013). After two–three years of clinical follow-up with the five subjects, Asterias announced the trial was successful and that no serious adverse events associated with the cells or the associated immunosuppression had been identified (Asterias 2014). This report was followed just weeks later with news that CIRM had approved a $14.3 million award to Asterias, which would support the company's planned Phase 1/2 dose escalation trial in cervical spinal cord injury (CIRM 2014). Two and half years since the Geron trail ended, the clinical research is still waiting to restart.

Using the examples cited above, we will examine the consequences of trials prematurely stopped for financial reasons.

5 Harms to Enrolled Subjects

Stopping a trial for financial reasons may cause physical and emotional harm to human subjects, especially for those in medical need and where decision-making is compromised. In the examples cited above, the human subjects were elderly

(70–85 years of age) or were enrolling in studies of drugs to treat severe illness (cancer, diabetic renal disease, heart attack, and impending blindness). Stopping trials mid-stream on these patients most likely resulted in some emotional (if not physical) harm. In the Geron trial, the human subjects were particularly vulnerable going in since, to qualify for the study, they had to have recently experienced complete paralysis from a life-altering traumatic injury. This vulnerability is underscored by (1) the severity of injury (complete and likely permanent paraplegia); (2) post injury and surgical pain; (3) the charged emotional atmosphere of concerned family members; and importantly, (4) the brief window of time (7–14 days) in which the patient had to decide to undergo the transplant (Scott 2008; Bretzner et al. 2012; Illes et al. 2011).

The last and fifth patient to receive the stem cell transplant was particularly complex. At age 23, she was suddenly paraplegic and the decision to enroll in the study was emotionally trying. Eventually, she signed the consent but then learned that Geron had stopped the study. She did not know if the transplant would take place. She also recalls worrying about getting proper care and monitoring after the procedure. Would another company step forward and continue the research? Eventually, she was re-consented and elected to undergo the procedure after being informed of the status of the trial (Conger 2011). By her own account, she believes her decision was the right one. But she admits to being disappointed upon learning that Geron was stopping the study and she remains concerned about whether another company will take the research forward (personal communication).

Geron's subjects were warned in the consent form of the risk that the transplanted cells might cause tumor growth within the spinal cord, the consequences of which are unknown. They were also warned of the risk of developing neuropathic pain (Siddall et al. 2003).[2] The development of these adverse events would require medical care, and the subjects were not assured that Geron would cover the costs of care or other costs associated with these adverse effects after termination of the trial. Finally, patients would likely be precluded from participating in future research studies of novel SCI treatments because of the potentially confounding effects of the transplants.

Whether or not physical harm results, trials that end in this fashion can make patients feel like that they have been treated merely as means to an end, and denied opportunities to fulfill an altruistic act (Murdoch and Scott 2010). One scholar commented that Geron's human subjects had been left stranded "in a kind of twilight zone between patient and research participant" (Baylis 2011). One volunteer, Ryan Neslund, highlighted this complicated dynamic when he told a reporter about his thoughts going into the study, "Whatever the dangers are, I don't care. I just want to do something rather than nothing," adding that he was glad he participated because he hoped the cell transplant would eventually lead to something positive. But after learning that the trial had been stopped, Neslund

[2] Since this pain is quite common in SCI patients, it is unclear in such cases how the role of transplanted cells would be adjudicated.

said, "You have these things shot in your back and then they tell you that they ran out of money. It just doesn't seem right to me" Dizikes (2011).

Before the Geron trial ended, another patient, TJ Atchison, wrote that though he feared the development of tumors at the injection site, he had acted altruistically:

> I realized that I had a great responsibility to fulfill. I'd be the one to help doctors and researchers learn how these cells actually work in humans. I'd be able to encourage continued research in this controversial field from the perspective of someone who had been through the type of injury the researchers hope to treat (Atchison and Minus 2011).

6 Harms to Patient Communities

Patients and patient advocates follow the progress of clinical trials to learn about their failures and successes, and relay this information through websites, meetings, and advocacy efforts. Prior to Geron's SCI clinical trial, patients had been expressing their frustration about the legal, funding, and religious roadblocks that had hindered progress in the development of hESC treatments. One SCI patient expressed this frustration to a reporter:

> Imagine being paralyzed by a SCI in your teens, watching for decades as medical treatment progresses but not quite fast enough, and knowing that it could have been faster (Kinsley 2000).

Expectations for the Geron trial were especially high. The paralyzed movie actor Christopher Reeve lobbied for aggressive approaches to SCI, and spinal injured patients testified ardently in support of California's stem cell research bond initiative. Sabrina Cohen, who was paralyzed in a car accident and runs a stem cell research foundation based in Florida, summed up her dismay at the news that Geron had terminated its trial: "It was like someone ripped my heart out" (Brown 2011). Daniel Heumann, who is paralyzed and is a board member of the Christopher and Dana Reeve Foundation, said, "To get people's hopes up and then do this for financial reasons is despicable. They're treating us like lab rats" (Stein 2011). These comments illustrate the tenuous trust that exists between patient volunteers and sponsors of clinical research. Patients can likewise lose trust in the physician who recruited them for a study that was terminated. Newspaper and blog reports of these dissatisfactions can dissuade others from volunteering as human subjects.

7 Harm to Researchers and Their Institutions

When trials stop for financial reasons, researchers will certainly lose the money they would have been paid if the trial continued and may have invested time, money, and personnel in the trial that cannot be recouped. Clinicians and their trainees may be

disappointed to have lost opportunities to help their patients and publish the results. The lead clinical investigator of the Geron trial at Northwestern University, Richard Fessler, said this about the Geron trial's premature end: "It is both disturbing and annoying and atypical when compared to other areas of research" (Dizikes 2011).

However, residual benefits may result. Fessler points out the advantages of learning how to purify, store, and administer the stem cell derived products. He added that the trial "keeps us thinking about (paralysis) and trying to figure out ways to treat it effectively, and it advances our knowledge of stem cell biology" (Dizikes 2011). And, the opportunity to conduct a high-profile clinical research may give an institution needed expertise and exposure required to raise funds and further develop its clinical programs.

8 Loss of Knowledge and Delay

One of the primary benefits of a clinical trial is its ability to add to generalizable knowledge. When a trial is terminated early, important scientific information often remains concealed. For industry-sponsored trials, preclinical research and information that led to federal approvals is confidential and protected to preserve corporate trade secrets (Code of Federal of Regulations[3]). If a company abandons a trial or an area of research altogether and does nothing to publish, sell or otherwise transfer the technology, then the data may be lost to the scientific community and thus to society. Also lost are opportunities to learn from past mistakes. This failed social obligation undermines trust between sponsors of research, human volunteers, medical scientists, and future stakeholders that stand to benefit. To its credit, Geron did announce that, as part of its commitment to follow the five human subjects for 15 years, it would report the results to the FDA and medical community (Geron 2011a). Asterias, the current owner of Geron's hESC technologies, did present the results of following the five patients at the 2014 American Society for Gene and Cell Therapy (ASGCT) Annual Meeting in Washington, DC (Asterias 2014).

If a trial is stopped before a reasonable judgment can be made about the safety or effectiveness of an intervention, then opportunities for continued research and the inertia required to complete the study are also lost. If a company does attempt to sell the technology, a lag will occur during efforts to find a buyer, and another lag in know-how will ensue once the transfer is made. The acquiring party may buy the technology defensively and do nothing with it, protecting its own competing products.

As noted above, a company, BioTime, did buy Geron's stem cell assets and its subsidiary, Asterias, has plans to develop the hESC technology. However, in the face of this, raising cash for a new clinical trial and filing approvals with the federal government would remain enormous obstacles for any company attempting to

[3] 21 Code of Federal Regulations, Subchapter F, Part 601.

resume Geron's research. Geron was able to overcome these tall hurdles but whether Asterias can do the same is uncertain.

9 Relevant Ethical and Social Considerations

When analyzing the ethical ramifications of these events, the magnitude of the problem matters primarily within a utilitarian construct. The fewer instances of research abandonment and the fewer people harmed, the more inconsequential the problem becomes. However, within the ethical frameworks of rights and justice, the prevalence of harm is less relevant. Violations of rights and occurrences of injustice are legitimate concerns no matter how often they occur. Below, we discuss the major ethical and social consequences that arise from these decisions.

9.1 Corporate Duty

For decades a debate has existed about the social responsibilities of business beyond maximizing shareholder value. Regardless of opinions on this question in general, many believe that bio-pharmaceutical companies should be held to a higher social responsibility standard given how fundamentally their products affect people's lives (Dresser 2006). Others have agreed that the social importance of medical products requires companies to adopt ethical obligations more in line with the medical professions (Relman and Angell 2000; Psaty et al. 2004). Especially when these companies engage in human research, their activity spills outside of the corporate realm and comes within the purview of the Declaration of Helsinki and other ethical standards that require primary emphasis on the well being of the human subject, informed and voluntary consent, and recognition that human subject research is justified because of its usefulness to society. When companies sponsor and control so many aspects of this kind of research, they have responsibilities along with the actual investigators to abide by these principal duties, to respect these rights, and to preserve the social utility of their research. The industry trade associations acknowledge these corporate duties (PhRMA 2011). These duties are derived from several ethical concepts. The stakeholder theory of business ethics requires companies to consider the consequences to the many research partners and participants impacted by corporate actions. Principles of distributive justice require that the burdens born by human subjects impose duties on sponsors that benefit from such research (The Belmont Report 1978). Fairness requires that a company mitigate the harm caused by its research, since the company initiates and controls the research and is often better positioned, financially and otherwise, to mitigate any resulting harm (National Bioethics Advisory Commission 2001).

9.2 Compromising the Risk-Benefit Contract

Researcher Steven N. Goodman, a physician and biostatistician at Johns Hopkins University, has said that when a research subject's sacrifice and altruism are for naught,

> In the ethical world, two things need to be considered—harms and wrongs. People in unnecessary trials are sometimes harmed, but I would say they are always wronged. And in the world of clinical research, wrongs are almost worse than harms (Brown 2006).

We believe that the lack of disclosure about the risk that the company will shut down the research for business reasons alone constitutes one such wrong.

In consent documents, sponsors typically state that they reserve the right to discontinue trials at any time. We call this the "reservation clause." Malmqvist and colleagues have argued that this disclosure is sufficient to fully inform subjects about this risk:

> If subjects consent to participation knowing that a trial may be stopped and why, there is no commitment, and no violation [of the consent agreement] occurs. This is so regardless of whether the trial is terminated for financial or other reasons (Malmqvist et al. 2011)

The use of the reservation clause, at least as it is usually written, does not meet Malmqvist's requirement since the typical reservation clause does not say "why" a trial may stop. Also, we believe that more is required. Without revealing the risk that the trial may be stopped for financial reasons and the subsequent consequences to the subjects, the requirement for fully informed consent will not be met and a violation of the research contract with subjects will occur.

To understand our opinion, we can compare the typical disclosure of the reservation clause to the disclosure of other risks in the consent document. For instance, subjects are informed of the *specific* risks of bodily harm and the risk of death from participation in a study. It is reasonable to assume that this kind of disclosure is sufficient to apprise the potential subject of some of the immediate downstream consequences of these risks, such as additional morbidity, the need for further medical care, or even death. However, when the consent document states that the sponsor reserves the right to terminate the trial at any time for any reason (the typical disclosure), the possibility and consequences of this risk are not so readily apparent.

The clause is likely to be discounted as boilerplate legal cover and is so non-specific that it conveys no information. Without information, subjects have no reason to inquire whether, for example, the sponsor is sufficiently funded to finish the trial so that the subject's participation can matter in determining the safety or efficacy of the technology. The ability of patients to delve this deeply into the circumstances of any trial is not as far-fetched as it once was, now that patients can research companies and their trials online. Additionally, unlike the risk of bodily harm disclosures, only the savviest of subjects can envision personal consequences if a trial ends prematurely. From our collective experiences with clinical research, we believe that, despite reading the typical reservation clause, most subjects assume that the study will be completed and are naive to any of the harms that may flow from the sponsor abandoning the study.

Further, the contention by Malmqvist et al. that disclosing that a trial may stop means that the sponsor has made "no commitment" to finish the trial requires comment. Recruiting patients with the representation that the clinical trial can advance medical progress and lead to an approved therapeutic implies that the company has made a commitment to complete the trial. We are not arguing that a human subject who recognizes the potential for abandonment of a trial for financial reasons will necessarily weigh this heavily in her decision to participate. But, the requirement that subjects be informed so that they can provide a knowing consent means that sponsors should do more to convey information about this specific risk (if it exists) and its consequences. If the sponsor is aware of this risk, it seems only fair that the human subjects should be as well.

Finally, to avoid the therapeutic misconception, researchers make diligent efforts to convey the fact that subjects may receive no personal medical benefit from enrolling in studies. Subjects are encouraged to believe in the value of participating for the possible benefit only to medical knowledge or to future patients. When commerce and not science stops a trial midstream, the possibility of these benefits diminishes significantly, since the incomplete data set is typically not as instructive as compared to what would have emerged from the finished trial or even a trial stopped for medical reasons. The corporate sponsor thereby nullifies this basis upon which consent was given. Once the potential benefits disappear, so too do the grounds on which human subjects have given their consent (Boyd 2001).

9.3 Compromising the Social Utility of Clinical Research

Unlike when trials are stopped for scientific or clinical reasons, stopping a trial for financial reasons compromises the calculus of risk and benefit that makes such research justifiable. Typically, when trial data show that the risk-benefit ratio of continuing is no longer justifiable, it makes sense to stop in order to prevent harm to human subjects and future patients who are spared further exposure to ineffective or harmful products. Preventing this harm can thus be seen as a benefit. Harm is usually confined to those directly involved in the original research, making medically based decisions to stop generally understandable and acceptable since the net result produces more overall benefit than harm.

When the reasons for stopping are purely financial, the net effect is likely to be just the opposite—the harms outweigh the benefits. If the only reason to stop is financial, the positive risk-benefit ratio of the investigational product that initially justified the trial may still hold and that product may retain the ability to improve future medical care. Yet, it is abandoned. Therefore, when there is a significant risk at the outset that a sponsor will not be able to complete the research, the social requirements that the research has potential utility and be able to contribute to generalizable knowledge are only tenuous at best. It would obviously be preferable to devise a study plan with a higher probability of success. Otherwise, proceeding

with a trial with a significant risk of financial failure undermines the product's potential, exposes subjects to avoidable risk, and wastes resources.

Loss of trust in the research endeavor may also result when companies stop trials for financial reasons. Subjects are typically informed that their welfare was the primary concern of the researcher and that IRBs exist to ensure that this is the case. When companies stop trials for financial reasons, subjects can conclude that the corporate bottom line was the real concern, as illustrated by Ryan Nusland's comments. These factors can result in an erosion of trust in the research, the consequences of which include reluctance of subjects to volunteer and increased difficulty in performing clinical research.

This does not mean that no knowledge accrues from a trial stopped in this fashion. As we explain in the Geron example, some researchers and clinical sites learned a sophisticated methodology for cell delivery into the spinal cord and techniques for expanding and manipulating cell populations. Investigators likely learned a great deal about recruitment challenges and the complications of performing transplants after patients had been stabilized with spinal fusion hardware. Regulatory agencies, too, plowed new ground with the approval process and will surely apply this knowledge to future applications. Institutions and their IRBs gained from reasoned discussions that took place before trials commenced. And though the cohort is very small, we can hope that forthcoming papers will provide the field with information about technique, outcomes (both positive and negative), and challenges for this promising area of regenerative medicine.

But this upside should not sway us from considering the duty to minimize the harms and wrongs described above. We conclude that, as regrettable as it is that clinical trials fail for scientific or medical reasons, prematurely stopping clinical trials solely for financial reasons, from an ethical standpoint, is worse. Therefore, we propose that companies take a number steps to minimize the possibility of having to stop trials for financial reasons and that all engaged in the process of corporate-sponsored trials warn about the risk and minimize the harm from such an event as much as possible.

10 Recommendations

Some commentators suggest that it is unacceptable to terminate a trial early for financial reasons if there is not yet sufficient benefit to be gained from the study to offset the risks to which participants have been exposed (Iltis 2004). Simply stated, if it is unacceptable to stop a trial, the trial should not be stopped. We understand the impetus behind this conviction but the recommendation is not practical. Even the best plans of competent, well-intentioned companies can go awry. We believe that companies have the duty to do as much as reasonably possible to prevent having to stop trials prematurely for financial reasons and, if this is not possible, to mitigate harm. The range of concern should extend beyond the company to patients, researchers, collaborating institutions, and the public at large. We encapsulate this

Table 1 Recommendations summary

Pre-trial obligations	(1) Convene an independent ethics advisory board
	(2) Confirm individual trials are properly funded and devise contingency plans if needed
	(3) Assess how potential financial failure might harm stakeholders outside the company and devise plans to insulate them from the identified harms
Intra-trial obligations	(4) Be vigilant for signs of impending financial problems
	(5) Refrain from hype as an investigational product enters a clinical trial
Obligations if the research has been abandoned for financial reasons	(6) Fulfill obligations to patients and researchers. Transfer data and disseminate results
Obligations of non-corporate stakeholders	(7) Review and approve protocols based on a collective, patient-centered ethic

proposition in seven recommendations that rest on corporate social responsibility with the patient at the center (Table 1).

10.1 Pre-trial Obligations

(*Recommendation* 1)*Convene an independent ethics advisory board.*

Given the novelty and ethical sensitivity surrounding the use of hESC's, it is interesting to note that, while Geron began its hESC program with ethics advice, it is unclear whether such advice was sought when the human research was started or when the research was abandoned (Eaton 2004).[4] Nonetheless, many biomedical companies, understanding the ethical complexity of their work, have incorporated ethics into their decision-making. Geron Bio-Med's Chief Executive Officer Simon Best recognized the need for ethics advice when he said, "We in the industry are not experts in ethics. Forming an ethics advisory board to deal with both scientific discoveries and the conduct of business is therefore a strategic and moral necessity" (Brower 2002). This statement is a recognition that ethics advisory boards (EABs) can play an important role in assisting companies to ensure that safeguards for stakeholders are in place before human trials begin (Eaton 2007). In addition, EABs can expand their usefulness by assisting companies in executing their obligations in the event that a trial ends prematurely.

[4] According to Geron, the groups that provided advice on the SCI human subjects protocol were as follows: Geron's clinical steering committee, an independent data monitoring committee, an embryonic stem cell research oversight committee, investigators, the FDA, 7 independent IRBs, and numerous other committees at the clinical trial sites. If Geron did use ethics advice, the company must have done so confidentially.

Specific to our main concern, EABs should examine whether the financial commitment, resources, and track record exist for a company to complete a planned trial. Financial experts can be appointed to the EAB to assist this deliberation. The language of informed consent should also be clear about the risk of stopping a trial for all reasonably foreseeable causes, including economic. Also, the consent should describe the consequences, plans, and funding for follow-up care if the trial ends prematurely. Any clause signaling the right of the sponsor to discontinue any study for any reasons at any time should be eliminated.

(*Recommendation* 2) *Ensure individual trials are properly funded.*

An objective, good faith analysis of the ability to fund a trial to completion is required. Sponsors certainly plan for financial success and strive to guard against losses from unsuccessful clinical programs, but they should also design trials within the company's means and plan for any reasonably foreseeable financial contingencies that may require abandoning the trial. These include avoiding overly optimistic cost and time projections, lack of sufficient funds, unrealistic faith in the ability to raise money during the trial, emerging competing products that would make this product obsolete or inadequate, and inability to meet milestone requirements of a major funder of the research. If any of these factors pose a significant risk of financial failure, the company should re-consider proceeding and devise contingency plans to better assure successful study completion. We note the likelihood that clinical research will cost more and/or take longer to complete when the therapeutic in question is novel, unique, or associated with ethical or political controversy, thereby increasing the difficulty of making these determinations. We also note that novel therapeutics associated with significant scientific concern that first-in-human research is premature also have a higher likelihood of failure.

(*Recommendation* 3) *Assess how potential financial failure might harm stakeholders outside the company and devise plans to insulate them from the identified harms.*

After an investigation of the likely consequences, informed consents should reveal to subjects and stakeholders any significant risk of abandonment for financial reasons. Patients and researchers should be told not just that the company reserves the right to abandon the trial, but that there is a risk of this particular kind of failure and the consequences that may result. If it is likely that the subjects will have ongoing medical needs after the research has been stopped, the company could consider funding a trust to pay for the costs of that future medical treatment. If these medical needs stem from exposure to a unique or first-in-human therapeutic, the company may want to identify and/or train those physicians best placed to provide competent care for the subjects. These measures can promote confidence in human volunteers and researchers and improve the willingness to participate in clinical trials.

Sponsors should also decide in advance what it would do to preserve the data and the technology if the company steps away, providing that both retain their value to society. Investigating opportunities for sale, transfer, and/or license of the

intellectual property rights should be a component of this obligation. A commitment to publish the results should be made if the trial ends prematurely or if the program is abandoned.

Once the company has assured itself that it has a good faith belief that it can fund the trial to completion and that protective contingencies are in place, managers need to make a commitment to finish the trial in order to prevent the harms discussed here. If the company cannot assure itself of these factors, it should not initiate the trial.

10.2 Intra-trial Obligations

(*Recommendation* 4) *Be vigilant for signs of impending financial problems.*

It is by no means a given that markets have the same optimism in the research progress as does the company conducting it. Neither should the company assume that there is an unending appetite to fund the company's continuing research. Early detection of signs that the funding will run out should lead the company to execute contingency plans in the event that market forces impede trial progress. Such plans may take the form of the identification of better-funded research partners, co-licensing technology, or merger with another company in the same financial sector.

(*Recommendation* 5) *Refrain from hype as a product enters a clinical trial.*

Companies are always motivated to project an optimistic view of their technology, since shareholders, investors, and the marketplace value the start of an approved clinical trial. During product development, companies use optimism to drive shareholder value and raise money. They reason, correctly, that any indication that a research program is in trouble destroys value.

However, overly optimistic statements are unfairly misleading and unethical. Inflating the promise of the investigational product can also induce patients to unwisely volunteer for the research and as such violate moral norms of protecting the vulnerable (Goodin 1998; Hawkins and Emanuel 2008). Even if optimistic statements result in the infusion of capital investments, values will plunge when unembellished research data emerge or studies are abandoned.

10.3 Obligations if the Research Has Been Abandoned for Financial Reasons

(*Recommendation* 6) *Fulfill obligations to patients and researchers. Transfer data and disseminate results.*

If the company has taken reasonable steps in advance to address this possibility, mitigating the resultant harm will be much less problematic. Prior commitments to subjects and researchers can be fulfilled, the protocols can be transferred if

possible, the data disclosed, and the intellectual property made available to others who have the capability of making use of it.

10.4 Obligations of Non-corporate Stakeholders

(*Recommendation* 7) *Review and approve protocols based on a collective, patient-centered ethic*.

Additionally, we propose that institutions and researchers insist that a corporate sponsor commits to completing its clinical trial before a trial begins. If there is reasonable uncertainty, sponsors should be asked by researchers and IRBs to provide evidence that proper resources exist to fund trials to completion and ensure that the findings become available to society. Furthermore, we recommend that the usual reservation clause where the sponsor "reserves the right to discontinue any study for any reasons at any time" (or similar vague language) should no longer be present in clinical trial protocols or informed consents and that IRBs should refuse to approve trials with this language. The language should make clear that the risk of stopping a trial for various reasons, including business reasons, exists and then explains what will happen in these cases. IRBs, on behalf of their clinical researchers and institutions, should ask companies what commitments they are making to take care of abandoned research subjects. Researchers should also ask the company whether they have plans to preserve the utility of the technology if the trial is stopped. This is in many ways similar to the assurances researchers seek from corporate sponsors that they will be eventually free to publish the data regardless of the outcome. Finally, institutions and their investigators should consider carefully whether it is in their and their patients' best interests to participate in future clinical trials from industry sponsors who have previously abandoned clinical trials for financial reasons.

11 Conclusions

Stopping a clinical trial prematurely for reasons related to safety, efficacy, medical unknowns, or feasibility problems is an unavoidable aspect of the endeavor that can be minimized by careful planning but not entirely eliminated. Stopping a trial because the company sponsor has run out of funds or has decided to spend its money more profitably elsewhere is different–both in the harms created and in its social and ethical acceptability. Companies should take steps to minimize the risk of trial abandonment and to protect the interests of all major stakeholders affected by the research decisions of the company but most especially the interests of the human subjects. This ethical stance obligates companies to refrain from starting clinical trials that they cannot reasonably finish, to commit to finish clinical trials that they start, to implement every reasonable strategy to prevent trial cessation for

financial reasons, and to mitigate the harm caused when they cannot abide by these commitments. Research institutions, and clinical sites and their investigators have a reciprocal obligation to engage in this collective ethic and encourage the undertaking of an approach whose successful ethical structure matches a financial one.

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