Wrongful Termination: Lessons From the Geron Clinical Trial

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SUMMARY

Geron Corporation is a publically traded company that launched a phase I clinical trial of a human embryonic stem cell-based therapy for spinal cord injury. The company enrolled the first patient in October 2010 and stopped the trial 1 year later. The fifth patient had been enrolled but not transplanted when the company announced the trial’s end. After discussions with clinical staff and family, an agreement was reached to add her to the cohort and proceed with the transplant. Two and half years later, the research is still waiting to restart. With this background in mind, we discuss the major ethical and social questions raised by the Geron case. We offer recommendations for institutional review boards and clinical sites as they deliberate approvals of early-phase trials in frontier medicine.

THE GERON SPINAL CORD INJURY CLINICAL TRIAL

Geron Corporation is a publically traded company that launched a phase I clinical trial of a human embryonic stem cell (hESC)-based therapy for spinal cord injury (SCI). The company enrolled the first patient in October 2010 and stopped the trial just a year later after transplanting only 4 of the planned 10 patients. Geron announced that it was discontinuing all of its stem cell research programs—neural, cardiac, and pancreatic. Geron’s president justified the decision by stating that the change would save the company at least $25 million per year over the next few years [1]. The CEO stated that remaining resources would be used for its cancer programs. The company laid off 66 workers, or approximately 38% of its workforce [2]. Geron announced that it would commit $8 million to wind down the SCI study, follow the transplanted patients with periodic assessments for 15 years, and report the results to the U.S. Food and Drug Administration (FDA) and medical community [2, 3].

From a feasibility perspective, the clinical protocol was complex. It involved several teams of surgeons, treating clinicians, study personnel, and physical therapists spread within the same site and across institutions nationwide. Surgeons and sites were required to undergo specialized training to familiarize themselves with the cells, reagents, and cell delivery devices. The informed consents were long and involved, adding to worries that patients would not fully understand the risks. Critics feared the potential for therapeutic misconception—in which patients conflated the early-phase research with a treatment or cure—was very high [4].

The first patient at Atlanta’s Shepherd Center was transplanted with two million oligodendrocytes made from H9, an hESC line derived by the University of Wisconsin’s James Thomson, who had been funded by Geron more than a decade earlier [5]. The fifth patient had been enrolled but not transplanted when the company announced the trial’s end. After discussions with clinical staff and family, an agreement was reached to add her to the cohort and proceed with the transplant [6]. Whether the risk/benefit ratio for this patient (who received the transplant after it was known that the trial was to be discontinued) was reasonable and whether consent was sufficient basis for enrolling in a trial that is known in advance to “fail” is one of the many significant questions raised by the termination of the trial.

In January 2013, BioTime, a blood plasma company headquartered in Alameda, California, acquired Geron’s stem cell assets—including more than 400 patents and the phase I SCI trial—for a stock swap. It raised $10 million and created an hESC-based subsidiary, Asterias [7]. Asterias, led by former Geron executives, announced the unpublished results of the first five transplanted patients at a scientific meeting in May 2014. After 3 years of clinical follow up with the subjects, Asterias announced that no serious adverse events associated with the cells or the associated immunosuppression had been identified [8]. This report was later followed with news that the California Institute for Regenerative Medicine (CIRM) had approved a $14.3 million award to Asterias, which would support the company’s planned phase I/II dose-escalation trial in cervical spinal cord injury [9]. Two and half years after the Geron SCI trial ended, this research has still not been restarted.

With this background in mind, we discuss the prominent ethical and social questions raised by the Geron trial. We offer recommendations for institutional review boards (IRBs) and clinical sites as they deliberate approvals of early-phase trials in frontier medicine.

VULNERABLE PATIENTS

The Declaration of Helsinki states: “the well-being of the individual research subject must take precedence over all other interests.” With respect to vulnerable populations such as in this case, research is only justified if it is responsive to the health needs and...
priorities of the vulnerable and “if there is a reasonable likelihood that this population or community stands to benefit from the results of the research” [10].

The five patients enrolled in the Geron trial were especially vulnerable because of (a) the severity of the injury and complications related to management of pain and stabilization surgery, which raises the question of whether patients themselves had full capacity to understand the risks and benefits of the procedure; (b) the narrow time window required to give informed consent (7–14 days post injury); and (c) the emotional state of patients and families during the acute phase of the injury [11–14]. The acute phase of the injury raised ethical concern. Bretzner et al. [15] stated “[T]hat recently diagnosed complete SCI patients—as compared with chronic complete SCI patients or patients with primary progressive MS with spinal lesions—may be more vulnerable to undue influence and possibly exploitation (where exploitation involves taking unfair advantage of another).” Considering the potential for therapeutic misconception, Miller and Rosenstein [16] remark, “Insofar as patient-subjects confuse research with therapy, they do not accurately comprehend what they are doing and thus may be vulnerable to exploitation.” These vulnerabilities are highlighted when considering the charged social context surrounding the trial. Following dramatic depictions of SCI animal research, expectations had been high. CIRM, too, had announced its support, loaning the company $25 million.

In addition, quality of life studies of long-term SCI patients show that although initially many people with these injuries may see nothing but a low quality of life, given time and adjustments in lifestyle they eventually report a life of acceptable quality [17]. Acute, traumatic cases such as this with compressed means in lifestyle they eventually report a life of acceptable quality [17]. Acute, traumatic cases such as this with compressed, emotional and physical context of a severe, acute injury with a shortening window of enrollment, while reconsenting she again might change the calculus of a person during the consent process. Indeed, the only other FDA-approved trial for SCI, a phase I study sponsored by Neuralstem, Inc., will transplant fetal neural stem cells into the lumbar regions of eight chronic SCI volunteers [18]. Obtaining fully informed and voluntary consent from these participants, we believe, is less problematic than in an acute setting.

Finally, the vulnerability question is called into sharp relief when considering the fifth patient in the Geron trial. After her initial consent, she learned the trial had been discontinued. In the emotional and physical context of a severe, acute injury with a shortening window of enrollment, while reconsenting she again had to weigh the risks and benefits with her family, knowing the trial would be stopped and the research halted after her transplant.

**THE COSTS OF PREMATURELY ENDED TRIALS**

One of the primary benefits of a clinical trial is its ability to add to generalizable knowledge. Current U.S. regulations require that the decision to approve clinical research should depend upon the risks of the trial weighed against the potential benefits, not just to the individual, but the benefit of the knowledge to be gained. When an IRB calculates the risk/benefit ratio of a clinical trial, it does so on the assumption that a good faith effort will be made to complete the proposed trial. If unanticipated adverse events occur, there is a process for re-evaluating the protocol. Similarly, if a data safety monitoring board has reason to believe that a trial is no longer in equipoise, there is a process for IRB review and reassessment of the risk/benefit ratio. At these critical points, it may be appropriate for the IRB, the investigators, or the trial sponsors to reassess whether it is reasonable to continue the trial. Because of the dynamic nature of research, the risk/benefit ratio may change as a result of new findings, and this provides good reason for any of the stakeholders involved in the research (including the research subjects) to reassess their commitment to continuing a trial. In general, as the safety, efficacy, or feasibility of a trial is called into question, it is appropriate to consider discontinuing a trial. In contrast, discontinuing a trial for purely financial or economic motives has the potential to significantly alter the risk/benefit ratio that was the basis of approval, without any prior change in the risk/benefit ratio to justify its discontinuation [19].

For first-in-human, frontier research like the Geron trial, there were many significant scientific and financial risks. There was potential that tumor formation further upstream could worsen a patient’s functional outcome. Although investigators and subjects doubtless hoped for dramatic improvement, given the large gap between human and murine models (such as the vastly greater axonal distance that would need to be covered in neuronal growth), the primary value of this research was likely to be the generalizable knowledge produced [20]. Geron and the FDA agreed to two clinical holds on the investigational new drug application, whereas more animal data were collected to satisfy concerns of tumor growth from the transplanted cells. The 22,500 page document cost $45 million and reportedly was the largest the FDA had ever received [21]. It was clear that the company was stretched financially, returning to the capital markets 24 times for funds [22]. Thus, ending the trial prematurely likely altered the risk/benefit ratio in a way that might have produced different results from the IRB deliberation, and it did so with no evidence that there was prior alteration of the ratio to justify the trials’ discontinuation.

**COMPROMISING THE CONTRACT BETWEEN PARTICIPANT AND SPONSOR**

Informed consent forms do not usually mention the potential that business considerations may lead to the premature discontinuation of a trial. In fact, there is an implicit agreement that investigators and sponsors will see a trial through to completion unless there is a good reason to discontinue. It is a safe assumption that vulnerable patients enrolled in risky, first-in-human trials do not discern the particular financial risks involved. It is likely that patients believe that the sponsor is committed to the trial and that it will proceed to completion. When subjects lack such an understanding, they have no reason to inquire whether the sponsor is sufficiently funded to finish the trial so that they can appropriately weigh this risk. Unless an informed consent reveals this risk and the subsequent possible consequences, the requirement for fully informed consent will not be met, violating the research contract with participants. When commerce stops a trial midstream, the possibility of benefits such as generalizable knowledge are in jeopardy, which are important justifications for altruistic acts. In sum, once the potential benefits disappear, so too do the grounds on which human subjects have given their consent [23].

Loss of trust in clinical research may also result. Subjects are typically informed that their welfare was the primary concern of the researcher, and IRBs exist to ensure that this is the case.
When companies stop trials midstream, subjects can conclude that the corporate bottom line was the real concern. These factors can result in an erosion of trust, the consequences of which include reluctance of subjects to volunteer, which undermines the social utility of clinical research [14, 24, 25].

**RECOMMENDATIONS**

The most obvious solution that springs from the Geron case is that internally, sponsors should budget adequate resources to finish trials they start. Geron argued that continued funding of its stem cell program might ultimately delay the translation of life-saving cancer therapies. Although it is true that allocating scarce resources is sometimes part of the calculus for companies seeking to successfully translate therapies, ethical issues arise when an individual trial is ended prematurely and when thinly funded frontier science programs wither. Therefore, we suggest that sponsors give assurances to IRBs that they have the financial wherewithal to responsibly complete the protocol under review and that IRBs considering early-phase trials ask for this information as a contingency of reviewing the protocol. We note that this requirement may be difficult to negotiate successfully, especially for highly visible, first-in-human trials at medical centers that want to lead in promising areas of science. However, many small companies enter into early-phase clinical trials on a wing and a prayer, with high product-development burn rates and no clear pathway for financial stability, either from capital markets or from pharmaceutical partners. As investors demand increasingly shorter time-to-market development milestones and fast exits for their startups, biotechnology companies find themselves under increasing pressure to show efficacy in trials designed ostensibly for safety. This home-run strategy means that underfunded programs will fail more often than not. The ethical and social consequences are similar for trials that stop as Geron’s did or for trials that run to completion and then are abandoned for other reasons. Much longer and deeper commitments from founders are needed to bring stem cell and other frontier therapies to market.

Should informed consent forms contain information that would help participants gauge whether a trial is sustainable or warn them about early termination for financial reasons? Established concepts of informed consent require participants to be informed about the specific details of each proposed research project [26]. We maintain that it is better to reveal the risks in informed consent documents than not; however, historically the effectiveness of informed consents has been challenged, with the hype and promise attached to stem cell treatments further complicating whether participants truly understand the risks associated with a particular trial [27, 28].

Current regulations allow sponsors to discontinue their support of clinical research regardless of the reasons. Given the profound impact early discontinuation for reasons unrelated to safety, efficacy, or feasibility can have on the risk-benefit ratio, as well as the potential to undermine consent and the covenant between subject and researchers, IRBs should perhaps do at least some evaluation of the likelihood that a trial will not be ended early except on the basis of safety, efficacy, or feasibility. The most obvious way of predicting that is past behavior by a company. That Geron stopped a highly visible clinical trial midstream for business reasons ought to give pause to any IRB considering approving any clinical research they sponsor. Ethically, it is possible for institutions to hold sponsors accountable for meeting ethical standards of fidelity. If a company has demonstrated ethically problematic behavior in this regard in the past, IRBs should take that into consideration in assessing the risk/benefit ratio of future trials and possibly should include language in the consent forms indicating their past poor performance.

**CONCLUSION**

When reviewing a trial, IRBs base their decisions on the information they receive from the investigators and sponsors. Potential participants evaluate whether to enroll in a trial based on this information, too. The investigators also agree to commit their time and effort also based upon the information provided by sponsors. Early-phase trials make their case based upon a goal of producing a novel intervention into clinical practice. It is (or should be) understood that each step in the research can be halted for reasons of safety, efficacy, or feasibility. However, halting a trial for financial reasons when there are no unanticipated problems (or launching a phase I trial with no intention to proceed to a later phase regardless of outcome) is problematic if it would alter the risk/benefit ratio of the decisions of the stakeholders (the decisions of the IRB to approve the trial, of the participants to enroll, and of the investigators to carry out the research). Companies should be held accountable for their actions, and we hope that future trials sponsored by firms with records of early termination of trials for financial reasons will be carefully scrutinized.

**ACKNOWLEDGMENTS**

We thank Margaret Eaton, Brian Kwon, and Judy Illes for their conceptual contributions. We acknowledge support from the Clinical Translational Science Award (SPECTRUM) grant (NIH 2U54TR000123) and the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

**AUTHOR CONTRIBUTIONS**

C.T.S. and D.M.: conception and design, data analysis and interpretation, manuscript writing.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

The authors indicate no potential conflicts of interest.

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