Achieving Informed Consent for Cellular Therapies: A Preclinical Translational Research Perspective on Regulations versus a Dose of Reality

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Introduction

On December 7, 2010, Swissmedic authorized a clinical trial testing StemCell Inc.'s human central nervous system derived stem cells (HuCNS-SC) in 12 patients with thoracic spinal cord injury (SCI) (see clinicaltrials.gov: NCT01321333). SCI is a devastating neurological condition, affecting about 226,000 to 500,000 individuals worldwide each year.[1] The incidence of SCI in the US may be as much as five-fold higher than previously estimated.[2] The average age at the time of injury is 34, resulting in a lifetime of paralysis that is associated with a host of medical complications. Moreover, the economic impact of SCI is highly disproportionate to its incidence. The lifetime cost of a thoracic SCI to an individual 25 years of age at the time of injury is estimated to be $2,310,104; someone with a cervical injury faces lifetime costs of $4,724,181.[3] The Swissmedic thoracic SCI trial represented one of the first attempts to treat a neurological condition using neural stem cell transplantation. Neural stem cells have the capacity to generate the three cell types found in the brain and thus restore the functional circuitry disrupted by a SCI. Critically, neural stem cells must be grown and maintained in a laboratory before they can be tested via transplantation. Biological variation between individual cells, and biological changes across a population of cells as they are grown, expanded, and split across time in the laboratory, are unavoidable.

As the neuroscientists who had conducted the preclinical animal SCI research supporting the human thoracic SCI trial, we enthusiastically supported this move to test the potential for this cell-therapy approach. The first thoracic SCI patient was transplanted with HuCNS-SC on September 21, 2011 at Balgrist University Hospital in Zurich, Switzerland. We were deeply satisfied when our colleagues informed us that the procedure in the first patient went well and eagerly awaited the formal report of the one-year follow-up from the first 12 patients. While a peer-reviewed report of the thoracic SCI trial has not been published (as of July 1, 2016), nor have the results been published at clinicaltrials.gov as required, interim safety and preliminary efficacy data were reported at the 4th Joint International Spinal Cord Society and American Spinal Injury Association meeting in Montreal on May 14, 2015. Twelve patients received transplantation of HuCNS-SC in the early

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chronic stage of recovery from thoracic SCI. Seven AIS A patients (those with no motor control and no sensation below the level of their injury) and five AIS B patients (those with no motor control but some sensation below the level of injury) were transplanted with 20 million HuCNS-SC injected directly into their spinal cord. Follow up assessments one year after transplant demonstrated that there were no significant adverse events (that is, the cells and procedure were safe by the measures conducted within the trial). Three of the seven AIS A patients and four of the five AIS B patients showed signs of sensory improvement over the one-year course of follow-up examinations; two patients who were classified as AIS A "converted" to an improved injury grade of AIS B.[4]

More than 50 percent of individuals with SCI have a cervical, or neck level, injury, and the complications and medical costs of cervical SCI are much higher than those for thoracic SCI.[5] However, from a regulatory point of view, thoracic SCI and cervical SCI are often considered separate indications requiring additional review. Thus, following the initiation of the thoracic trial in Zurich and Canada, StemCells Inc. pursued approval for a trial of HuCNS-SC in cervical SCI. In June of 2014, the Food and Drug Administration (FDA) authorized a clinical trial of HuCNS-SC for the treatment of cervical SCI in the United States and Canada (NCT02163876), called the "Pathway Study." In contrast to our strong support for the thoracic trial begun in Zurich, we strenuously objected to proceeding with HuCNS-SC for cervical SCI in the Pathway trial, despite the promising animal model and human subject data already obtained using HuCNS-SC in thoracic SCI. How is it possible that the basic scientists behind the preclinical research supported one advance into the clinical arena and opposed the other?

Prior to the approval of the thoracic trial in man, we had conducted nearly a decade of preclinical tests of multiple different lines of HuCNS-SC in animals. All cell lines we tested demonstrated in vivo efficacy in either rat or mouse tests by experimenters blinded to treatment condition and animals randomly assigned to treatment group, and we published multiple peer reviewed papers of this collaborative work with our colleagues at StemCells Inc.[6]

However, in contrast to both this work and positive preliminary results in cervical SCI with a cell line used in the thoracic studies, a new HuCNS-SC cell line, intended for use in the cervical Pathway Study™, failed to demonstrate efficacy in a large in vivo preclinical cervical SCI experiment. Despite our concerns with the lack of in vivo efficacy data in this study,[7] which was performed under contract with StemCells, Inc., the first patient in the Pathway Study™ was transplanted on December 18, 2014.

A layperson, even a basic scientist, might conclude that plans for clinical testing in man should be halted until this discrepancy could be resolved. However, someone more familiar with the standards and guidelines of the FDA might view a plan to proceed to clinical testing through a different lens. Which approach is ultimately correct is a complex and multifaceted equation. Clearly, the type and focus of scientific data generated and evaluated in gaining FDA authorization for a clinical trial is a key issue. An additional issue, however, is how individuals in the community, who are potential participants in a clinical trial, get their information about preclinical data and gain an understanding of the basis for a trial — in others words, where science and informed consent meet. In this article, we: (1) discuss the similarities and differences between pharmaceutical and cell products; (2) review the FDA's approach to regulating cell products, including defining cell identity and potency; (3) review the role and boundaries of Institutional Review Boards in informed consent for clinical trials of cell products; (4) summarize our view of whether current practice for FDA authorization of, and the process of gaining informed consent for, cell products is adequate.

1. Similarities and Differences between Pharmaceutical and Cell Products

A patient might reasonably assume that the pre-clinical data underlying a trial is from the same cell line they will receive if they give consent to participate in the trial. Are these assumptions correct, and if not, have the patients really given "informed consent"? What is the process for gaining FDA authorization of a clinical trial for a cell product, and is this process adequate? Furthermore, one can reasonably infer that the product administered for in vivo preclinical testing of a pharmaceutical agent is the same product as that planned for a clinical trial, based on a specific chemical composition and reference standards for chemical analysis. Is this assumption equally valid for a cell product? Clearly, there must be unique ethical concerns for cell products where a precise chemical composition is unknown, different cell lines and/or lots may be employed as a part of a single clinical trial, and where administration cannot be reversed or discontinued once the product has been injected.

A drug, or pharmaceutical agent, is a specific compound with definable physical characteristics (chemical formula, molecular weight, method of manufacture via specific raw materials, level of impurities). Accordingly, the FDA's regulation of drugs is fairly straightforward. Consequently, a patient's understanding that

s/he is getting exactly the same compound/drug as that which generated all the preclinical data or phase I trials elsewhere is straightforward as well. When giving informed consent to participate in a FDA authorized clinical trial, patients and their families are focused on the details of the procedure and possible side effects or adverse events of the trial. They are probably not thinking about how the drug they will receive was manufactured, shipped, or prepared for delivery. The situation is further complicated with cell therapies, as cells are living organisms. Even if all preclinical data were generated with the same initial stem cell line (e.g., hypothetical embryonic stem cell line "X1"), and the patient will receive a stem cell therapy derived from X1, subtle changes may occur between the initial derivation of the X1 line and the manufacture of a cell product derived from X1.[8]

Furthermore, administration of a drug during a trial can be stopped if there are adverse events, but once a cell therapy is administered, there is generally no way to "stop" the trial. Indeed, a cell product may be expected to survive within its recipient for many years, and long-term interaction may be required for a cell product to produce the desired clinical effect; consequently, there may be no feasible way to remove the cells should an adverse event occur.

The situation is even more complex when "adult" stem cell lines are used. Embryonic stem cells, in theory, can be expanded indefinitely from a single starting cell line, that is, a single donor. Thus, X1 could, in theory, produce all the doses of the final cellular product ever needed, not just for one clinical trial, but for future use in other trials or as an approved therapy. In contrast, while highly expandable, fetal and adult stem cell lines cannot be expanded indefinitely. As a result, multiple stem cell lines, each from a different donor and each with potentially different characteristics, might be necessary to support preclinical testing, as well as production scale up for human clinical trials.

Furthermore, to achieve expansion for clinical use, embryonic, fetal, and adult stem cell lines are all generally divided and propagated as parallel lots, creating a necessary but additional source of variation. Adding to this range of biological variation, unless initial cell lines are derived from single clones — that is, single cells are used to generate all subsequent cells — each cell line and lot represent a mix of subpopulations that have propagated from different starting cells. Finally, the production of small batches of "research" or "process development" cells for preclinical testing may be different from the production of large batches of the final intended clinical cell line or product.

2. FDA Regulation of Cell Products

2.1 Authority and Guidance

The FDA derives the authority to regulate stem cell therapeutics from the Public Health Service (PHS) and Federal Food, Drug and Cosmetic (FDC) Acts. Broadly, this is conducted under the Center for Biologics Evaluation and Research (CBER). CBER's mission is to "ensure the safety, purity, potency, and effectiveness of biological products including vaccines, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury," with the goal of advancing public health. In this regard, CBER[9] provides academics and industry alike with guidance to promote the safe and appropriate use of biological products.

Critically, the guidance documents issued by CBER and the FDA represent recommendations, not requirements, and are not legally enforceable documents. Ideally, this is to facilitate the Investigational New Drug (IND) application process, enabling an individualized set of milestones to be used in assessing each biological product submitted to the FDA for authorization for use in a human clinical trial. Practically, this is associated with significant variations in the development process for cellular products, as well as in the type of safety, efficacy, identity, and potency preclinical data reviewed by the FDA in the process of evaluating a cellular product as a part of gaining authorization for testing in a clinical trial; this process, of necessity, is significantly different than that applied to a pharmaceutical agent.

Guidance documents from CBER/FDA and the CBER Office of Cellular, Tissue and Gene Therapies (OCTGT)[10] include regulations as defined by the Code of Federal Regulations (CFR) for the IND application process and good manufacturing practices,[11] as well as documents developed by CBER/OCTGT to reflect current thinking and expectations regarding the development of investigational products. Critical elements for cell investigational product development addressed in current documentation are reviewed in Fink and Bauer[12]; these begin with control of source materials, and address the stages of investigational product development, including cell and manufacturing issues pertaining to stem cell products, testing of stem cell products for safety, identity, purity, and potency, expectations for control of the manufacturing process and preclinical evaluation, and proof-of-concept and toxicological assessment. Below, we focus on establishing product identity and potency in the context of preclinical data, and consideration of these issues in the context of achieving informed consent in early and late stage clinical trials.

2.2 Cell Product Identity, Comparability, and Potency
Product identity and potency are unavoidably linked, in that the ability to identify the features of a product that underlie its efficacy represent a clear target around which to build assays to monitor the manufacturing process. Product identity recognizes that cell products may have inherent variability in starting material (e.g., cell lines, and different lots or production runs of the same line), with limited stability, lack of reference standards as available for pharmaceutical agents, and the potential for synergy between multiple active components/ingredients within a cell product. Potency, as defined in the Code of Federal Regulations (21 CFR §600.3[s]), is the "specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result."[13] It is logical, therefore, that potency in turn be linked to mechanism of action.

However, the FDA authorization process for cell therapeutics is faced with a challenging issue in that the mechanism of action for a cell product may be unknown, or may be complex and/or multimodal. Additionally, the FDA recognizes the likelihood that a cell product will encounter specific conditions in the transplantation microenvironment that will affect its activity, including factors modulating its final migration, localization, fate, differentiation, integration, secretion profile, and so on, making direct measurement of potency even more difficult.

As a result, per FDA guidance, product potency testing can be based on establishing a correlation between a measured property and a desired clinical effect, and utilize either in vitro or in vivo assays.[14] Accordingly, in order to facilitate the initiation of first in man clinical trials, FDA guidance for potency test development includes both the potential for significant flexibility and staging, and potency test adequacy is evaluated on a case-by-case basis. For early stage clinical trials (phase 1/2), surrogate biomarkers — that is, activities that provide an estimate of potency — may be sufficient. For later stage clinical trials (phase 3), a validated potency assay is expected. For final FDA licensure, development of a valid potency test, along with tests for safety and purity, is required.

One might imagine that a validation process would include demonstration that the proposed potency assay can distinguish a cell product that produces the desired clinical effect from a cell product that does not, and can thus be definitively linked to mechanism of action. However, this is not necessarily the case. First, a potency assay is not necessarily required for a phase 1 trial (or even a phase 2 trial). Second, validation of a potency assay during the final phases of product development (e.g., for a phase 3 trial) focuses on establishing and documenting "the accuracy, sensitivity, specificity and reproducibility of the test methods employed,"[15] as opposed to rigorous testing of whether the in vitro or in vivo assay selected can be definitively linked to efficacy.

Furthermore, because in vivo testing is more difficult, time consuming, and expensive than conducting an in vitro assay, there are significant pressures to establish an assay that focuses on a surrogate in vitro endpoint. In addition, in many cases, in vivo animal models of disease and injury have been criticized as uninformative for clinical translation. In this regard, there is a significant body of clinical trial data suggesting that achieving a desired clinical endpoint in an animal model (e.g., improvement in behavioral recovery following stroke) does not necessarily transfer to human clinical trial success. For all of these reasons, in vitro assays are often preferred to in vivo assessments.

Importantly, information about presumed mechanism of action and pathophysiology of disease is secondary to the process underlying an IND application to the FDA. In this regard, the FDA's regulatory process has been characterized as 'subsidiary to the fundamental questions' of safety and efficacy.[16] In many regards, reliance on safety and efficacy measures is a positive, as existing biases regarding disease pathophysiology are superseded by the simple question of whether a defined outcome (e.g., a measure of locomotor function) is improved by a given treatment or not.

However, in the case of cell product development, we may expect significant sources of variation specific to scale up and production due to biological variation between cell lots and lines. Accordingly, reliance on in vitro assays for cell product parameters (e.g., migration, differentiation, or biochemical activity), with only correlative relationships to in vivo outcome, may present a very limited dataset to define either the identity or the biological activity of a given cell after in vivo transplantation. Moreover, the inclusion of the potential for correlative associations in potency assay development leaves open a wide range for erroneous conclusions because establishing mechanism of action is not a priori required.

For example, inconsistencies in scale up and production of cell lots and lines for stem cell products, failure to develop potency/comparability assays that are based on demonstrable clinically significant activity rather than simplicity, and failure of potency/comparability assays to offer adequate analysis of clinically significant endpoints, are all issues that have been addressed extensively in the context of mesenchymal stem cell products (MSC). MSCs represent one

example in which the failure of pivotal clinical trials has been linked to these factors.[17] Critically, failure to conduct in vivo testing of all cell product lots and lines used for clinical transplantation is an issue for not only efficacy, but safety. This is particularly relevant as the in vivo factors controlling donor differentiation, cell division, and tumorigenesis remain poorly defined, and a focus on in vitro assays that are poorly linked to efficacy may fail to detect critical variations that result in an altered risk profile.

Given that establishing a definitive mechanism of action may be a complex and difficult hurdle for clinical translation of cell therapeutics, is it truly impossible? If a defined property of a therapeutic cell population cannot be ablated, knocked-down, or empirically tested to block the efficacy of that cell population, how can the capacity to repeat that erroneous assay accurately yield face validity in human testing? Lastly, we want to emphasize that the disparity between preclinical research and clinical findings supports the need for conducting sufficient basic research to understand the mechanism of action of a particular stem cell therapy and enable proper potency/comparability assay design.

The position that mechanism of action should not be required in order to proceed with testing a drug or cell therapy in man posits that, were we to wait until every aspect of a particular cell product were understood, we would never be ready to test in man. In contrast, we suggest that the failure (or disincentive) to understand mechanism of action is a key reason for failure in translational medicine and clinical trials, and that in the case of cell therapeutics, this heightens the risk associated with clinical testing. Moreover, if the mechanism of action of a cell product is not known, then establishing an in vivo potency test that is based upon measurement of a desired outcome, e.g., motor or cognitive improvement, and can be used as a part of release testing for each cell lot and line, may be all the more imperative.

Finally, it should be further noted that, under FDA guidelines, preclinical proof of concept experiments for cell therapeutics need not be conducted using final clinical cell products, and may reflect, in fact, data obtained using analogous cells.[18] In contrast, there is, by definition, always a reference standard for pharmacological agents entering product development for clinical testing. If preclinical testing is not conducted with the final clinical cell product, should this added aspect of risk, which encompasses both the failure to achieve the desired outcome, and an incomplete safety profile, not be disclosed as a part of the informed consent process?

Cell therapeutics have enormous potential to reshape modern medicine, and both basic and translational science have progressed rapidly in the last decade. However, the FDA and local IRBs are grappling with how to regulate and responsibly implement clinical trials of cell products, and how to adapt to the complexities presented by this therapeutic approach.

3. Institutional Review Boards in Informed Consent for Clinical Trials of Cell Products

Clinical trials are subject to local Institutional Review Board (IRB) review and approval in order for each institution to participate in enrolling subjects in an FDA authorized clinical trial. The IRB is the institutional guardian of ethical behavior. It makes the determination that the applicant (or trial sponsor) is qualified to conduct the study, that all institutional and governmental requirements have been met, and that the Informed Consent documents are appropriate. IRBs conduct their business according to federal regulations, specifically DHHS (Department of Health and Human Services) 45 CFR part 46 and FDA regulations 21 CFR Part 50 and Part 56. These regulations define the duties and composition of the IRB. IRBs are required to have expertise in the general area of the proposed study, as well as a non-scientist, non-physician community representative. The IRB reviews all elements of the proposed study, including those conducting it, the scientific rationale for the study, its design, any possible conflicts of interest, and the informed consent process for participants. Despite these strictures regarding IRB composition, there is no specific requirement for the sponsor of a clinical trial involving a cell therapeutic to disclose in the consent document that multiple cell lots and/or lines may be employed in the study protocol.

4. Is the Current Review and Consent Process Adequate?

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ence have progressed rapidly in the last decade. However, the FDA and local IRBs are grappling with how to regulate and responsibly implement clinical trials of cell products, and how to adapt to the complexities presented by this therapeutic approach. If a potential patient consults "Dr. Google," then s/he will come to the conclusion that the HuCNS-SC used in the Zurich thoracic trial and the HuCNS-SC used in the Pathway cervical trial are the same cell. This is rational, logical, and untrue. In this present example, the key issue is that there is no route available in the public domain, nor in the consent form for the Pathway cervical SCI trial, for a patient or the referring clinician to determine whether the cell lot and line employed is the same as that published in peer reviewed journals, or used in the thoracic SCI trial, even if it carries the same cell product name.

Even a willing medical consultant is unlikely to be able to assist a potential clinical trial subject in evaluating a proposed therapy, as not only may key primary preclinical data be unavailable for review, but consent documents are not available in the public domain. For example, when we learned that the Pathway trial was to begin, we contacted the research staff at clinical trial to request a blank copy of the consent documents. We wanted to know if the consent forms that patients were required to sign indicated (A) which cell line they were receiving, (B) clearly indicated that the cells they were to receive were not those used in the peer reviewed publications referenced on StemCell Inc.'s website, and (C) clarified that the patients were not going to receive the same cell line used in the much publicized thoracic SCI trial. Research staff at multiple institutions refused to release blank copies of the consent documents. Moreover, this is common practice as calls to other sites testing other neural stem cells from other companies for SCI or ALS in FDA authorized trials also resulted in a refusal to release blank consent forms to a practicing neuroscientist.[19]

Posing as a patient, we subsequently contacted one of the clinical sites for the Pathway trial, and answered their screening questions. As a potential "subject," we were emailed a copy of the consent document, whereby we learned that the cells being tested carried only the product name "HuCNS-SC," with no cell line or cell lot identifiers and no indication that there existed different cell lines or lots. In a callback to the study nurse for this site, we asked if these were the same cells as used in the Switzerland thoracic trial. The nurse answered yes.[20] Although this most likely simply represents a lack of knowledge on the part of the clinical sites, the answer is clearly a misrepresentation of the reality. Thus, the central question becomes, in our view, does this represent adequate informed consent for subjects that are evaluating whether to not to participate in a clinical trial for a cell product? We suggest that even though FDA requirements for cell manufacture, identity, comparability and potency requirements have been met, and IRB requirements for review and approval of the consent documents (and trial) have been met, there has still been a failure to achieve an ethical minimum standard for informed consent. Accordingly, we suggest that there is a need for the field and regulatory bodies to reconsider this issue, and make the following recommendations:

1) The standard should be to make greater information available to the public, scientific, and clinical community at the onset of a clinical trial.

It is often, perhaps nearly always the case, that one does not know the mechanism of action of a drug, and especially a cell therapeutic. Potency/comparability assays add an additional layer of imprecision in that surrogate markers may not only be used, but are encouraged as measures of biological activity. In many cases, a causal link between biological activity and mechanism of action are not definitively established prior to a clinical trial. Therefore, potency/comparability assays are inadequate to define cell lots and lines. Transparency about the primary data used to validate potency and comparability assays may undermine, in some cases, the potential of companies to maintain/obtain patents. Yet, in return for experimenting on live humans, the standard should be to make more information available to the public, scientific, and clinical communities at the onset of a clinical trial. This transparency should include publication of the supporting preclinical data, with specific identification of cell lots and lines employed, as well as a description of the assays and results used to establish potency/comparability between cell lots and lines, and in release testing for cell lots and lines. Asterias Biotherapeutics Inc. (formerly Geron) release tested each new cell lot of their OPC1 product in vivo, demonstrating efficacy in SCI via in vivo animal testing prior to use in man.[21] Unless definitive mechanism of action assays that are linked to in vivo efficacy are available, release testing each new line/lot in vivo, with assessment of an endpoint that parallels the desired clinical effect, should be the standard for a cell therapeutics.

2) There should be transparency and open-access consent documents, which should include details regarding cell lots and lines the clinical protocol.

Without transparency, clinical trial enrollment is subject to the Dr. Google paradox, whereby patients or

their families attempt to verify background information without the benefit of knowing the fine details and based on biased search results. True ethical informed consent requires transparency regarding cell lines, variability within and between cell lines, and parallel clinical trials. Without this, subjects enrolling in clinical trials might gather informal incorrect information and thereby be unduly influenced in terms of their enrollment.

3) Details about cell lots and lines included in preclinical testing should be accessible via open-access for review by subject experts.
Publications of preclinical data and all supporting studies should include cell line designations, descriptions of all cell lots and lines tested, and descriptions of the stage of cell manufacture from which they derived (production versus final clinical product). Confidentiality agreements with academic investigators should not prohibit disclosure of these experimental details.

The failure to publish timely, peer reviewed updates and summaries of completed clinical trials has been a growing concern. In Europe, this failure has led to a coalition of groups demanding that the methods and results from all clinical trials, successful or not, be published.

4) Dissemination of trial results to the patients and public should be made in a timely manner.
The failure to publish timely, peer reviewed updates and summaries of completed clinical trials has been a growing concern. In Europe, this failure has led to a coalition of groups demanding that the methods and results from all clinical trials, successful or not, be published.[22] With the approval to conduct experiments on willing volunteers comes the obligation to publish the results, including the raw data, so that the participants, the public, and other scientists can learn from the results of human experimentation. Recently, the US added the requirement that study sponsors publish the results of clinical trials within one year of the closure of the trial; however, this requirement can be met by "publishing" summary results on the clinicaltrials.gov website. There is no requirement that the methods and full results be published, or that the results must be published in a peer-reviewed journal. Nor is there a requirement to publish the informed consent documents from each trial site.

Conclusions

Advances in clinical therapies are dependent upon basic science discoveries. The pipeline from bench to bedside therefore necessarily requires breaking new ground in terms of methods, experimental models, clinical models, clinical characterization of disease, and ethical as well as regulatory frameworks. Progress is also dependent on the two-way exchange of information between basic scientists, drug companies, and clinicians. The existence and properties of neural stem cells in the central nervous system were only beginning to be established in the late 1980s, and the presence of these cells in the human brain was only confirmed in 1998.[23] Yet, by 2006, the first clinical trial testing treatment of a brain disorder, neuronal ceroid lipofuscinosis (NCT00337636), with neural stem cells had been initiated, followed closely by clinical trials for Pelizaeus-Merzbacher disease (NCT01005004) in 2009, spinal cord injury (NCT01321333) in 2010, and amyotrophic lateral sclerosis (NCT01348451) in 2011.[24] This rapid advance represents the best of basic science and medical research, and offers the potential for a revolution in medicine. However, it also represents a challenge for developing the necessary framework under which to conduct these efforts, and highlights the need to iteratively reexamine these frameworks. Indeed, the development of new interventions that aim to improve retention and understanding of clinical trial participants have been proposed and are being developed for the stem cell field.[25]

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