Perspective

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Regenerative Medicine

ClinicalTrials.gov, stem cells and 'pay-to-participate' clinical studies

Numerous US businesses that engage in direct-to-consumer advertising of stem cell interventions that are not US FDA-approved also recruit clients by listing 'pay-to-participate' studies listed on ClinicalTrials.gov. Individuals considering enrolling in such studies and NIH officials responsible for overseeing the database need to be aware that some businesses are using the registry to promote unapproved stem cell interventions that study subjects are charged to receive. Inclusion of such studies in ClinicalTrials.gov reveals that the database needs better screening tools. In particular, screening should evaluate whether studies submitted to the registry have been reviewed and permitted to proceed by the FDA in the case of clinical studies requiring FDA clearance in addition to institutional review board approval.

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Numerous US businesses that engage in direct-to-consumer advertising of purported stem cell treatments recruit clients by registering clinical studies on ClinicalTrials.gov. Some studies registered by businesses selling putative 'stem cell therapies' disclose that study subjects are charged. The studies are explicitly described as being 'patient-funded', 'patient sponsored' or 'self-funded' [1,2]. However, other studies registered on ClinicalTrials.gov by businesses selling stem cell interventions do not reveal that study subjects are charged to participate in clinical research [3]. It is only when interested individuals contact sponsors, investigators or clinic employees and inquire about enrolling in the studies that they are then informed they must pay to participate.

Listing studies on ClinicialTrials.gov is an effective way for businesses selling stem cell interventions to solicit prospective clients. One such company was recently the subject of considerable news media scrutiny after clinicians independent from the business published a study documenting that three of its patients suffered severe vision loss after paying $5000 per person for stem cell interventions that were supposed to treat their age-related macular degeneration [4–8]. At least one of the women who were blinded reportedly contacted the stem cell clinic after learning about the one of the clinical studies this business had registered on ClinicalTrials.gov [9].

There are no reliable estimates of how many individuals pay for stem cell interventions advertised by businesses that use ClinicalTrials.gov listings and other marketing tools to solicit individuals searching for treatments. Nonetheless, such listings play an important role in promoting particular companies and clinics. The studies they register on ClinicalTrials.gov help confer legitimacy on their promotional claims and commercial activities.

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ClinicalTrials.gov

Established by the US FDA Modernization Act of 1997, ClinicalTrials.gov is a registry and searchable database of clinical trials [10,11]. Administered by the NIH, the website is used by patients and their advocates, clinicians, researchers, journalists and other parties. The database is intended to increase transparency in clinical research, facilitate registration of clinical trials in a public database, help prospective study participants identify trials for which they might be eligible to enroll and make results of studies publicly available [12].

Information about whether clinical studies have been approved by institutional review boards (IRBs) must be submitted during the process of registering trials in ClinicalTrials.gov. However, before being registered on ClinicalTrials.gov, clinical studies are not screened and scrutinized to determine whether they are subject to review and clearance or approval by the FDA or other national regulatory bodies in addition to IRB review [13]. Registration works on an 'honor system' basis. According to a disclaimer on the ClinicalTrials.gov website, "*Information on ClinicalTrials.gov is provided by study sponsors and investigators, and they are responsible for ensuring that the studies follow all applicable laws and regulations*" [14]. This failure to scrutinize whether submitted studies comply with applicable regulations has created a situation in which sponsors and investigators can register clinical studies and deposit them in the database without careful screening by NIH employees responsible for maintaining the database.

To improve the quality, integrity and public value of ClinicalTrials.gov, the failure of NIH officials to properly screen studies submitted to the registry needs to be addressed. In particular, screening needs to determine whether clinical studies submitted for registration in ClinicalTrials.gov have been reviewed and permitted to proceed by the FDA and IRBs, where both FDA review and IRB review are required by federal regulations. In the case of trials requiring Investigational New Drug (IND) or Investigational Device Exemption (IDE) applications reviewed and cleared by the FDA, screening must also establish whether sponsors or investigators are authorized by the FDA to charge individuals participating in clinical studies. This legal requirement for IND studies is addressed in federal regulations and explored in detail in FDA guidance document [15–17]. Absent evidence that the FDA has reviewed such studies, approved all charges to research subjects and permitted clinical research to proceed, such studies should not be accepted for inclusion and public listing in the ClinicalTrials.gov registry. Regrettably, these issues were not adequately addressed in Section 801 of the Food and Drug Amendments Act and in 42 CFR Part 11, the final rule for Clinical Trials Registration and Results Information Submission [18,19].

As of January 18, 2017, the protocol registration process for ClinicalTrials.gov requires providing a 'Yes/No' response to the question of whether a clinical study is evaluating an FDA-regulated drug product or other FDA-regulated intervention [20]. Similarly, the existence of an IND or IDE and IND or IDE numbers must be disclosed, though this requirement is optional for observational studies. However, screening mechanisms are not in place to identify cases in which parties submitting data to the registry inaccurately claim that interventions are not FDA regulated and do not require INDs. Similarly, no screening mechanisms are in place to identify cases in which study subjects are charged to participate in clinical studies that should be conducted under INDs in which the FDA has permitted study sponsors to recover costs of conducting research from research subjects or their insurers.

Sponsors and investigators listing studies that administer stem cells products which appear to require FDA oversight are not required to provide documentation that their studies were reviewed by the relevant FDA Center and cleared to proceed. Likewise, there is no requirement to furnish evidence that the FDA has approved charging research subjects. ClinicalTrials.gov's failure to require such documentation from sponsors and investigators submitting clinical studies constitutes a significant flaw in the registration process because many studies involving administration of stem cells to research subjects require FDA review and clearance in addition to IRB approval. In such studies, the FDA must also approve any charges to research participants.

'Pay-to-participate' clinical studies

In most clinical trials, study subjects are not charged fees to participate. In contrast, individuals enrolled in what are often called 'pay-to-participate' studies are charged thousands or tens of thousands of dollars. The fees individuals are charged to participate in such studies are distinct from the living and travel expenses that sometimes accompany participating in clinical studies. For example, individuals who must travel to visit a clinical trial site often have to pay for airline tickets, local accommodations, meals and ground transportation. In the latter case, study subjects are not charged to participate in clinical research. There are no fees to access whatever intervention is being tested or to become a participant in a clinical study. In contrast, in 'pay-to-participate' studies, study subjects must pay to enroll in clinical research. They are typically told that the fees they

pay are to cover the costs associated with whatever interventions are administered in particular studies. Sometimes they are informed that the interventions being tested are provided free of charge but they must nonetheless pay for the related costs associated with conducting clinical research [21].

Whether charges to participate in studies are disclosed or concealed, the stem cell interventions advertised by these companies and provided in the clinical studies they promote are not approved by the FDA as new drugs or licensed as biological products. Many such studies have not been submitted to the FDA in the form of IND or IDE applications, reviewed by the relevant FDA center, and cleared to proceed before being registered on ClinicalTrials.gov. Individuals considering enrolling in such studies, advocates for patients and research subjects, health researchers and officials at both the NIH and the FDA need to be aware that some businesses are using the ClinicalTrials.gov registry to promote stem cell interventions that study subjects are charged to receive.

Why 'pay-to-participate' studies listed on ClinicalTrials.gov frequently involve the administration of autologous stem cells rather than other interventions is unclear, and has not yet been the subject of scholarly analysis. While two registered studies charge study subjects seeking to undergo fecal microbiota transplantation for recurrent *C. difficile*-associated diarrhea, and one registered study charges study subjects who receive 'young donor plasma transfusions', the most common studies in which research subjects are charged appear to be ones in which autologous stem cells are administered as interventions or their effects are observed, in the case of observational studies [22–24].

'Pay-to-participate' autologous stem cells studies registered in ClinicalTrials.Gov

US businesses that engage in direct-to-consumer advertising of stem cell therapies have registered with ClinicalTrials.gov 'pay-to-participate' clinical studies in which study subjects receive autologous stem cells obtained from adipose tissue, bone marrow or peripheral blood. Limiting searches to studies with at least one listed US location, and using the search terms 'patient-sponsored', 'patient-funded' and 'self-funded' resulted in the identification of seven registered stem cells studies that explicitly state research subjects are charged to participate. Six studies were found by using the search terms. The seventh listing was found by reviewing additional studies registered by one of the businesses.

Ageless Regenerative Institute lists on ClinicalTrials.gov five US-based 'patient sponsored' studies in which 'autologous adipose-derived stem cells' or 'autologous adipose-derived stromal cells' are administered to study subjects with, respectively, Type II diabetes, osteoarthritis, erectile dysfunction, critical limb ischemia and chronic obstructive pulmonary disease (COPD) [25–29]. In all five studies, liposuction is first performed to obtain 'the patient's' adipose-derived tissue. According to the studies, adipose tissue is then transferred to a laboratory setting, and stem cells are obtained from the adipose tissue. Autologous adipose-derived stem cells are then administered using study-specific delivery methods. The clinical site location for these five studies, all reportedly conducted with IRB approval, is the Ageless Institute in Florida. Table 1 provides additional information concerning the five patient-sponsored studies registered by the Ageless Regenerative Institute. While eleven additional Ageless Regenerative Institute studies are registered with ClinicalTrials.gov, not all of the listed studies specify that they are 'patient-sponsored' and some of them are restricted to clinical sites in Tijuana, Mexico. These latter studies are not listed in Table 1.

Another business, the Lung Institute, has registered two studies in which 'autologous stem cell treatment' or 'autologous cell therapy' is administered to 'self-funded patients'. One study is listed as an 'Observational Outcomes Study for Autologous Cell Therapy Among Patients with COPD and Interstitial Lung Disease' [30]. In this study, "*the patient's cells and platelet-rich plasma are collected through venous or bone marrow harvesting techniques*" and then administered to individuals with chronic lung disease. In the second Lung Institute study, 'self-funded patients' receive 'cell therapy' consisting of "*stem cells harvested either from peripheral blood or from bone marrow plus peripheral blood*" [31]. There is no mention in the listing of whether the study was approved by an IRB. The location for the clinical study is listed as the Lung Institute in Dallas, TX, USA. A different Lung Institute facility, one based in Tampa, FL, USA, is currently the subject of a class action lawsuit brought by a former patient [32]. The Lung Institute is contesting this plaintiff's claims in court. Table 1 contains additional information concerning the two 'self-funded' studies registered by the Lung Institute.

Registered stem cells studies that do not explicitly mention payments by study subjects

In addition to registered clinical studies that make explicit reference to charging study subjects, a number of businesses have registered clinical studies that do not mention charges to study participants but appear to nonetheless involve payments from individuals

Table 1. ClinicalTrials.gov registered 'patient-sponsored', 'patient-funded', or 'self-funded' studies involving administration of autologous stem cells.

Sponsor	Study title	ClinicalTrials.gov identifier	Type of study	Intervention	Disease or injury	Estimated enrollment
Ageless Regenerative Institute	An open-label, non-randomized, multi-center study to assess the safety and effects of autologous ADSCs delivered intravenously in patients with Type II DM	NCT01453751	Interventional	Harvesting & implantation of AD-SVF	Type II DM	100
Ageless Regenerative Institute	An open-label, non-randomized, multi-center study to assess the safety and effects of autologous ADSCs delivered intra-articularly in patients with OA	NCT01739504	Interventional	Liposuction with local anesthesia; intra-articular infusion of AD-SVF	OA	100
Ageless Regenerative Institute	An open-label, non-randomized, multi-center study to assess the safety and effects of autologous ADSCs delivered into the corpus cavernous in patients with erectile dysfunction	NCT02087397	Interventional	Liposuction; AD-SVF cell injection	Erectile dysfunction	100
Ageless Regenerative Institute	An open-label, non-randomized, patient funded, multi-center study to assess the safety and effects of autologous ADSCs via intramuscular injections for the treatment of critical limb ischemia	NCT02099500	Interventional	Liposuction, stem cell injection	Critical limb ischemia	200
Ageless Regenerative Institute	An open-label, non-randomized, multi-center study to assess the safety and effects of intra-venous and inhalation implantation of autologous AD-SVF cells in patients with COPD	NCT01559051	Interventional	Lipo-aspiration with local anesthesia	COPD	100
Lung Institute	An observational outcomes study for autologous cell therapy among patients with COPD and interstitial lung disease	NCT03040674	Observational	Cell therapy: stem cells harvested from peripheral blood or from bone marrow plus peripheral blood	COPD, interstitial lung disease	200
Lung Institute	Autologous stem cell treatment for chronic lung disease study	NCT03044431	Observational	Cell therapy: stem cells harvested from peripheral blood or from bone marrow plus peripheral blood	COPD, interstitial lung disease	214

ADSC: Adipose-derived stromal cell; AD-SVF: Adipose-derived stromal vascular fraction; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; OA: Osteoarthritis.

undergoing stem cell interventions. Some businesses do not mention charging research subjects in their ClinicalTrials.gov listings but elsewhere acknowledge that subjects in their studies pay fees to participate. Other companies with studies registered on ClinicalTrials.gov deny that research subjects are charged to participate in their clinical studies but acknowledge that their clients must pay for the 'stem cell therapies' evaluated by the studies they have listed on ClinicalTrials.gov. These latter responses reflect the objections some companies have to claims that they are conducting 'pay-to-participate' clinical studies.

A recently published analysis containing a database of US businesses involved in direct-to-consumer marketing of stem cell treatments was used to investigate whether any companies listed in the database have registered with ClinicalTrials.gov studies involving administration of stem cells [33]. In total, five such businesses were found to have registered a total of 11 clinical studies on ClinicalTrials.gov. Additional information about these studies is provided in Table 2.

Cell Surgical Network, an organization that serves as an umbrella for a network of over 50 US clinics that engage in direct-to-consumer marketing of autologous adipose-derived 'stem cell treatments' for a wide range of indications, provides one example of how a US business that sells stem cell interventions has listed a clinical study on ClinicalTrials.gov without disclosing in the study listing that study participants must pay to participate. In 2013, one of the founders of this business registered a 'Safety and Clinical Outcomes Study' involving administration of autologous adipose-derived stromal vascular fraction (SVF) to individuals suffering from "*select orthopedic, neurologic, urologic and cardio-pulmonary conditions*" [34]. This clinical study will reportedly enroll 3000 subjects with such diseases as amyotrophic lateral sclerosis, Parkinson's disease, neuropathy, arthritis, autoimmune disease, COPD, cardiomyopathy, Peyronies disease, interstitial cystitis or erectile dysfunction. The ClinicalTrials.gov listing of this study does not mention that research subjects are charged USD$6000 or more to participate. Elsewhere, however, the sponsor and investigators acknowledge that research subjects pay to participate in this study [35]. Cell Surgical Network uses its registered ClinicalTrials.gov study as a powerful marketing device. Press releases and the websites of the clinics that are part of this network emphasize that the study is registered on ClinicalTrials.gov [36,37].

Kimera Society Inc. has listed a study that is reportedly evaluating the safety and efficacy of autologous adipose-derived stem cells administered intravenously to individuals with COPD [38]. While the listing on ClinicalTrials.gov does not mention that study subjects are charged to participate, the organization's website states that the 'treatment' provided in the COPD study is not publicly funded, not covered by health insurance and 'not free' [39]. The ClinicalTrials.gov listing identifies clinical study site locations in Florida, Illinois, Nevada, New York and Texas.

Two additional businesses, Retina Associates of South Florida and MD Stem Cells, are sponsor and collaborator for two clinical studies in which autologous bone marrow-derived stem cells (BMSC) are administered to paying study subjects. One study involves administering autologous bone marrow-derived stem cells to individuals diagnosed with retinal or optic nerve damage or disease [40]. Specific diseases and injuries mentioned in the 'conditions' section of the listing include retinal disease, macular degeneration, hereditary retinal dystrophy, optic nerve disease and glaucoma [41]. 'Keywords' provided in the listing suggest that individuals with other diseases or injuries of the eye are also eligible to participate in this study. The clinical sites for this study are in Florida and Dubai.

Another study listed by these two businesses involves intravenous and intranasal administration of autologous bone marrow-derived stem cells to individuals with neurologic disorders, nervous system diseases and neurodegenerative diseases [42]. Keywords in the study listing include neurologic disease, cerebral vascular accident, stroke, traumatic brain injury, multiple sclerosis, Parkinson's disease, neuropathy, neurodegeneration, diabetic neuropathy and cerebral ischemia. Two clinical sites are mentioned, with one in Florida and one in Dubai. The ClinicalTrials.gov listing does not mention whether the study has IRB approval.

A study listed by just one of the two previously mentioned businesses, MD Stem Cells, is reportedly evaluating the efficacy of autologous bone marrow-derived stem cells in women suffering from premature ovarian failure [43]. The clinical site for this study is in Augusta, Georgia. Another study listed by MD Stem Cells involves administering bone marrow-derived stem cells to individuals with such conditions as retinal disease, age-related macular degeneration, retinitis pigmentosa, Stargardt disease, optic neuropathy, nonarteritic ischemic optic neuropathy, optic atrophy, optic nerve disease, glaucoma or Leber hereditary optic neuropathy [44]. The clinical sites listed for this study are in Florida and Dubai. Neither study listing provides information concerning IRB oversight.

StemGenex®, a business that advertises 'stem cell therapies' for a wide range of indications, lists on ClinicalTrials.gov five observational studies that involve research subjects who have received autologous

Table 2. Clinical studies in which study participants must pay to participate or are charged for prior access to stem cell interventions.

Sponsor	Study title	ClinicalTrials.gov identifier	Type	Intervention/evaluation	Condition	Estimated enrollment
Cell Surgical Network	Safety and clinical outcomes study: SVF deployment for orthopedic, neurologic, urologic, and cardiopulmonary conditions	NCT0195323	Interventional	Procedure: administration of autologous adipose derived SVF (AD-SVF)	Neuro-degenerative diseases, OA, Erectile dysfunction, Autoimmune diseases, Cardio-myopathies, Emphysema, COPD, Peyronies disease, Interstitial cystitis, Parkinsons, ALS, Neuropathy	3000
Kimera Society Inc.	Safety and efficacy of ADSCs for COPD/an open-label, non randomized, multi-center study to assess the safety and effects of intravenous implantation of liposuction derived autologous ADSCs in subjects with COPD	NCT02216630	Interventional	Drug: ADSC therapy; liposuction followed by isolation and intravenous injection of ADSCs	COPD	200
MD Stem Cells	Bone marrow-derived stem cell ophthalmology treatment study II (SCOTS2)	NCT03011541	Interventional	Autologous BMSCs provided retrobulbar, subtenon, and intravenous for one or both eyes; BMSC provided retrobulbar, subtenon, intravitreal, and intravenous for one or both eyes; BMSC provided either intraoptic nerve or subretinal for eye with worse vision with fellow eye receiving either retrobulbar and subtenon or retrobulbar, subtenon, and intravitreal, followed by intravenous	Retinal disease, age-related macular degeneration, retinitis pigmentosa, Stargardt disease, optic neuropathy, nonarteritic Ischemic optic neuropathy, optic atrophy, optic nerve disease, glaucoma, leber hereditary optic neuropathy	500
MD Stem Cells	Autologous stem cell therapy for premature ovarian failure	NCT02696889	Interventional	Laparoscopy, injection of BMSCs into the right ovary	Premature ovarian failure	33
Retina Associates of South Florida/MD Stem Cells	Bone marrow-derived SCOTS	NCT01920867	Interventional	Procedure: retrobulbar, subtenon, intravenous, intravitreal, intraocular injection of autologous BMSCs	Retinal disease, macular degeneration, hereditary retinal dystrophy, optic nerve disease, glaucoma	300

ADSC: Adipose-derived stem cells; BMSC: Bone marrow derived stem cells; COPD: Chronic obstructive pulmonary disease; MS: Multiple sclerosis; OA: Osteoarthritis; RA: Rheumatoid arthritis; SVF: Stromal vascular fraction.

Table 2 (cont.). Clinical studies in which study participants must pay to participate or are charged for prior access to stem cell interventions.

Sponsor	Study title	ClinicalTrials.gov identifier	Type	Intervention/evaluation	Condition	Estimated enrollment
Retina Associates of South Florida/MD Stem Cells	Neurologic BMSC treatment study	NCT02795052	Interventional	Procedure: intravenous administration of autologous BMSCs, intranasal administration of BMSCs	Neurologic disorders, nervous system diseases, neuro-degenerative diseases, neurological disorders	300
StemGenex	Outcomes data of adipose stem cells to treat Parkinson's disease	NCT02184546	Observational	*"Evaluate quality of life changes in individuals with Parkinson's disease for up to 12 months following SVF treatment"*	Parkinson's disease	75
StemGenex	Outcomes data of adipose stem cells to treat MS	NCT02157064	Observational	*"Evaluate quality of life changes in individuals with MS for up to 12 months following SVF treatment"*	MS	100
StemGenex	Outcomes data of adipose stem cells to treat COPD	NCT02348060	Observational	*"Evaluate quality of life changes in individuals with COPD for up to 12 months following SVF treatment"*	COPD	75
StemGenex	Outcomes data of adipose stem cells to treat OA	NCT02241408	Observational	*"Evaluate join pain and functionality changes in individuals with OA for up to 12 months following SVF treatment"*	OA	50
StemGenex	Outcomes data of adipose stem cells to treat RA	NCT02348086	Observational	*"Evaluate changes in pain and functionality in individuals with RA for up to 12 months following SVF treatment"*	RA	50

ADSC: Adipose-derived stem cells; BMSC: Bone marrow derived stem cells; COPD: Chronic obstructive pulmonary disease; MS: Multiple sclerosis; OA: Osteoarthritis; RA: Rheumatoid arthritis; SVF: Stromal vascular fraction.

SVF. In one study, autologous adipose-derived stem cells are administered to individuals with Parkinson's disease [45]. A second study administers SVF to persons with multiple sclerosis [46]. A third study provides SVF to study subjects with COPD [47]. Two additional studies assess pain and functionality by gathering 'outcomes' data following administration of SVF to study subjects with, respectively, osteoarthritis and rheumatoid arthritis [48,49]. The clinical site for these five studies is listed as being in California.

StemGenex uses the five studies it has registered with ClinicalTrials.gov as a marketing tool intended to confer legitimacy on its business practices [50,51]. A company press release states, "*By providing access to registered clinical studies through the NIH, we are providing patients with the ability to choose a stem cell treatment center with the highest standard of care*" [52]. Not all of StemGenex's former clients agree with this assessment. StemGenex is currently the subject of a class action lawsuit brought by three former patients who allege they were defrauded as a result of the representations the company makes about patients' assessments of its stem cell treatments [53]. StemGenex denies these allegations and is contesting plaintiffs' claims in court.

At least two additional US businesses involved in direct-to-consumer marketing of purported stem cell therapies appear to have listed multiple clinical studies on ClinicalTrials.gov. With few publicly available details concerning the exact relationships between the two businesses marketing stem cell interventions and the numerous studies they have listed on ClinicalTrials.gov, their studies are not reviewed or summarized in Table 2. Nonetheless, there is evidence that additional US companies involved in direct-to-consumer advertising of stem cell 'treatments' are registering studies on ClinicalTrials.gov. These studies appear to require payments from study subjects, even though the listings in ClinicalTrials.gov do not disclose that study participants are charged.

Ethical & scientific problems with 'pay-to-participate' clinical studies

Critiques of 'pay-to-participate' clinical studies have identified serious scientific and ethical problems associated with charging individuals to participate in studies conducted on an apparent for-profit basis [54–56]. In such studies, research subjects are charged before the safety and efficacy of investigational agents have been established and the interventions in question have received premarketing authorization from the FDA. It is common to find no public record of peer-reviewed preclinical research by the investigators leading these studies. The absence of any record of peer-reviewed preclinical research generates concerns about whether the sponsors and investigators responsible for such studies have sufficient safety and efficacy data to justify making the transition from preclinical research to clinical studies involving human subjects.

'Pay-to-participate' studies often are open-label and, therefore, do not 'blind' investigators, study subjects or anyone else involved in clinical research to the intervention being tested, do not use placebos or sham procedures to control for placebo effects, and do not randomize subjects to different study arms.

Many businesses conducting 'pay-to-participate' studies in which stem cells are administered risk promoting the therapeutic misconception by describing investigational stem cell interventions as safe, efficacious and innovative treatments. Misrepresentations on the part of businesses conducting such studies and substantial misunderstandings on the part of research participants are particular concerns in such 'pay-to-participate studies'. 'Pay-to-participate' studies also risk amplifying placebo effects as a result of the sizable fees companies often charge research participants and the hyperbole sometimes used to promote such studies.

It is common for 'pay-to-participate' studies in which stem cells are administered to use research methodologies and designs that are unlikely to generate meaningful evidence of safety and efficacy. For example, numerous 'pay-to-participate' studies that administer stem cells have expansive inclusion criteria and include study subjects with a wide range of disparate diagnoses rather than focusing on a well-defined study population of individuals suffering from a particular medical condition.

'Pay-to-participate' studies raise troubling questions about justice and fairness in the selection of research subjects because usually only individuals who can afford to pay thousands or tens of thousands of dollars can become research participants. Investigators and sponsors typically do not take into account how the ability to pay substantial fees might confound whatever results emerge from such studies.

Finally, another significant problem with such 'pay-to-participate' studies is that many businesses publish individual case studies while never publishing in credible peer-reviewed journals data obtained from all study subjects. This publication strategy can be used to promote purported 'clinical successes' while withholding from public scrutiny data documenting instances in which study subjects were injured by the interventions they received or paid hefty fees while experiencing no improvements to their health.

US federal regulations & 'pay-to-participate' stem cells studies

Ethical and scientific shortcomings with 'pay-to-participate' clinical studies in which stem cells or other interventions are administered have been reviewed in some detail by research ethicists and other scholars. In contrast, the regulatory status of 'pay-to-participate' clinical studies in which autologous stem cells are administered to study participants has attracted less scrutiny. From a legal perspective, in numerous cases such studies prompt questions about whether they are in compliance with all applicable federal regulations. In many cases, these clinical studies appear to require FDA oversight in the form of IND applications or IDE applications that have been reviewed and cleared by the FDA.

Businesses that engage in direct-to-consumer advertising of putative stem cell 'treatments' typically deny that the stem cell interventions they market are subject to FDA premarketing review and authorization. Representatives of such businesses claim that the cellular products they promote do not require approved Biologics License Applications or New Drug Applications (NDAs). They also claim that they do not require FDA-reviewed and cleared IND applications for studies in which they administer stem cells to research participants. These claims – while made by many US businesses marketing 'stem cell treatments' – often appear to conflict with how the FDA interprets federal legislation and regulations. Despite this apparent conflict, there is no public record of any of the businesses listed in Tables 1 or 2 receiving a warning letter from the FDA or otherwise being subject to regulatory action by the FDA.

IRBs & US FDA oversight

US IRBs have reportedly approved clinical studies in which autologous stem cells obtained from adipose tissue, bone marrow, or peripheral blood are administered to paying research subjects [57]. However, these studies were not reviewed and permitted to proceed by the FDA even though the studies in question involve the administration of cellular products that appear to require cleared IND applications or approved IDEs. When cleared INDs or approved IDEs are required, clinical studies must be submitted to the FDA for review and clearance to proceed before they can commence. Federal regulations also stipulate that the FDA is responsible for determining whether research subjects can be charged any fees to participate in such clinical trials. When FDA oversight is required, for the purpose of regulatory compliance, it is insufficient for such studies to be reviewed and approved only by IRBs. Furthermore, IRBs lack the legal authority required to allow sponsors or investigators to charge research subjects enrolled in such studies.

It is possible that in some cases the IRB members approving such studies do not have an adequate understanding of federal regulations related to human subjects research and the administration of human cells and tissues. Perhaps some IRBs are allowing such studies to proceed without IRB members being aware that they are approving clinical research that requires FDA clearance and approval for charging research participants. In such instances, improved education of such IRB members might help them better identify instances where IRB approval should be conditional on studies being reviewed and cleared by the FDA, and otherwise complying with all applicable federal regulations. It is also conceivable that such IRBs sometimes approve 'pay-to-participate' studies because sponsor and investigators have not disclosed that study participants will be charged, and IRB members have failed to investigate before approving studies conducted by businesses that charge their clients to participate in research.

Another possibility is that some US IRBs are deliberately approving 'pay-to-participate' stem cell studies that they know have not been reviewed and cleared by the FDA, and have also not received permission from the FDA to charge study participants. In such cases, efforts to help IRB members better understand how to interpret and apply federal regulations related to stem cells and human subjects research might not lead to adequate reform of IRB practices. Rather, FDA investigators should conduct site inspections of IRBs engaged in such conduct. Depending on what FDA investigators conducting such inspections find, in some cases regulatory action might be warranted.

The 'global patchwork' of laws related to stem cells & human subjects research

US businesses marketing putative stem cell therapies are not alone in using ClinicalTrials.gov to register studies in which stem cells are the investigational agents and research subjects are charged to participate [58,59]. Businesses and clinics that sell 'stem cell treatments' and are located in such countries as China, India, Russia and the Philippines have also registered such studies with ClinicalTrials.gov.

As legal scholars note, there is a global 'patchwork' of laws and regulations related to oversight of clinical studies in which stem cells are administered to humans [60,61]. Not all countries require oversight of clinical studies administering stem cells by both IRBs and national or regional regulatory authorities. Furthermore, many countries make legal distinctions

among different types of cell-based interventions, requiring varying levels of regulatory oversight depending upon the particular types of cells administered in specific studies [62]. There are also national variations in the oversight of human subjects research and whether sponsors and investigators can charge research subjects fees. These country-specific differences in regulations create practical challenges for the development of screening tools for registries and databases of clinical trials. Addressing the challenges posed by regulatory heterogeneity is going to increase in significance as registries and databases of clinical studies become ever more international in scope.

US businesses marketing stem cell therapies & US federal laws & regulations

Acknowledging national variations in the laws and regulations applicable to the use of stem cells in humans and the conduct of human subjects research, US-based sponsors and investigators conducting studies at US sites and registering their studies on ClinicalTrials.gov are clearly subject to US federal laws and regulations. It is therefore possible to consider whether they are complying with how the FDA interprets relevant US federal regulations governing the administration of human cells, tissues and cell- and tissue-based products (HCT/Ps) in clinical studies as well as regulations governing clinical research conducted under INDs.

Autologous stem cell products: same surgical procedure exception, minimal manipulation & homologous use

Various documents provide insight into how the FDA distinguishes autologous stem cell interventions requiring premarketing review and approval from autologous cells and tissues that do not require premarketing approval and need not be evaluated for evidence of safety and efficacy in FDA reviewed and cleared clinical studies. 21 Code of Federal Regulations Part 1271 [63], a 2006 FDA guidance document [64], four draft guidance documents [65–68] relevant to clinical studies in which stem cells are administered, the Center for Biologics Evaluation and Research's Tissue Reference Group's responses [69,70] to questions about the regulatory status of various autologous stem cell products, and publications by FDA officials [71] all address how the FDA makes such distinctions. Warning letters sent by the FDA to such businesses as Young Medical Spa [72], IntelliCell Biosciences [73], Celltex Therapeutics [74] and Irvine Stem Cell Treatment Center [75] provide practical examples of how the FDA interprets and enforces federal regulations related to the administration of autologous stem cell products when it determines that businesses have failed to comply with applicable regulatory standards.

Autologous stem cell interventions that do not comply with the minimal manipulation, homologous use and combination product standards described in 21 CFR 1271, and do not fall within the same surgical procedure exception, are classified as biological products or drugs subject to FDA premarketing approval [76]. Evidence of safety and efficacy must be established in clinical trials before the FDA will consider approving a biologics license or NDA or grant premarketing approval for a medical device used to produce such biologics. Such studies can only be conducted after submitting IND or IDE applications to the FDA for review. Following FDA review, studies are either allowed to proceed or the FDA imposes a clinical hold. When a study is placed on a clinical hold, it is usually because the FDA has concerns about safety that need to be addressed before research can commence.

According to the FDA's current interpretation of applicable federal laws and regulations, the process of enzymatically digesting autologous adipose tissue, using ultrasonic cavitation, or otherwise processing fat tissue to obtain adipose-derived stem cells in SVF does not fall within 21 CFR 1271's same surgical procedure exception [77]. 21 CFR 1271.15(b) states, "*You are not required to comply with the requirements of this part if you are an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure*" [78]. According to the FDA, processing of autologous cells or tissues within the confines of the same surgical procedure exception is limited to such steps as rinsing, cleansing, sizing and shaping. The FDA states that these steps "*raise no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery*". In contrast, the FDA generally considers enzymatic digestion, ultrasonic cavitation and similar methods used to process fat tissue, isolate stem cells and produce SVF as manufacturing steps that fall outside the scope of the same surgical procedure exception.

The FDA is also on record stating that processing fat tissue to produce SVF does not meet the definition of minimal manipulation that is also used to determine whether autologous biologics require premarketing approval [79–83]. Rather, the FDA presumptively classifies autologous adipose-derived SVF as a more than minimally manipulated autologous stem cell product that requires premarketing approval. SVF contains a heterogeneous mixture of cell types, including adipocytes, fibroblasts, endothelial progenitor cells and adipose-derived mesenchymal stromal cells [84]. According to the FDA, this 'soup'

or 'slurry' of cells differs from the fat tissue that exists before any processing steps occur.

With regard to the distinction between homologous and nonhomologous uses of autologous stem cells, the FDA currently interprets federal legislation and regulations to mean that administration of autologous SVF for treatment of neurological diseases, cardiac diseases and disorders, orthopedic diseases and injuries, immunological conditions and numerous other indications will generally require premarketing approval on grounds of nonhomologous use [85]. Autologous stem cells derived from bone marrow are also subject to the homologous use standard.

INDs & charging research subjects to participate in clinical studies

When testing INDs in clinical trials, sponsors and investigators are not permitted to charge research subjects on a for-profit basis [86–88]. While they can in some cases engage in cost-recovery, charging research subjects to recoup expenses associated with conducting clinical studies can only occur under well-defined conditions and with the approval of the FDA. Absent explicit permission from the FDA, sponsors and investigators are not permitted to charge research participants for costs associated with conducting clinical research.

The FDA, NIH & 'pay-to-participate' clinical studies involving the administration of autologous stem cells to study subjects

Given the FDA's determination that autologous SVF, when marketed and administered to treat diseases, injuries and other conditions, is a drug and biological product, companies wishing to market and provide such a product must first obtain approval for a NDA or Biologics License Application. Before seeking premarketing authorization, companies must conduct clinical studies and generate needed safety and efficacy data. To conduct such studies, sponsors and investigators require FDA-cleared IND applications or IDEs in addition to IRB approval. Likewise, nonhomologous uses of autologous bone marrow derived cells are supposed to be tested in IND clinical studies that have been reviewed and cleared by the FDA. Plans to charge research subjects to participate in such studies must also be reviewed and approved by the FDA.

Given how the FDA interprets federal legislation and 21 CFR 1271, the FDA needs to publicly and promptly address instances in which clinical studies of autologous adipose-derived stem cells, autologous bone marrow-derived stem cells, or autologous stem cells reportedly obtained from peripheral blood are being conducted without FDA reviewed and cleared INDs. Since the FDA is responsible for determining whether sponsors or investigators can charge study participants in IND studies, it is also imperative for the FDA to publicly address the regulatory status of ClinicialTrials.gov registered studies in which research subjects are paying to participate in clinical studies where the FDA has not approved the fees charged study subjects. Finally, NIH officials need to publicly address whether such studies should be listed in ClinicalTrials.gov or whether more effective screening of studies prior to registration is required.

Addressing the need for better screening of studies submitted to ClinicalTrials.gov

The development of robust screening tools that review whether submitted studies are compliant with regulatory standards concerning oversight of human subjects research and the administration of stem cells is necessary to prevent ClinicalTrials.gov from being used as a marketing platform by companies using clinical studies to sell access to their putative 'stem cell treatments'. Before clinical studies are registered with the database and made available for public viewing, screening should determine whether IRB approval is sufficient or whether particular studies must have also undergone review and clearance by the FDA or a comparable national regulatory body. In particular, screening should evaluate whether studies submitted to the registry have been reviewed and permitted to proceed by the FDA in the case of clinical studies requiring IND or IDE applications. Before studies are registered and deposited in the database, screening should also determine whether sponsors and investigators have been authorized by the FDA to charge study subjects fees to participate in clinical research. Such screening should be applied to studies that are already registered and to future submissions.

Conclusion

Listing studies in ClinicalTrials.gov without first conducting meaningful scientific, ethical and regulatory review risks promoting confusion and uncertainty among prospective study participants rather than serving the website's intended goal of increasing transparency in clinical research. It also increases the likelihood that study subjects are exposed to unjustifiable risks, such as when studies are listed before adequate preclinical research has taken place, when investigators lack the necessary training and expertise required to fulfill their legal, ethical and clinical obligations to research subjects, and when studies suffer from serious methodological problems that expose research subjects to unacceptable risk/benefit ratios. While a disclaimer on the ClinicalTrials.gov website states that 'listing of a study on this site does not reflect endorsement by the NIH', lack of meaningful screening creates a 'buyer beware' ethos for a clinical trials database that, notwithstanding

the NIH's disclaimer, is regarded by many of its users as a reliable and trustworthy source of information [89].

Future perspective

Proper scientific, ethical and regulatory review of studies submitted to ClinicalTrials.gov will require providing the NIH with the financial resources and staff members required to perform this important task. Increased funding needs to be tied to the anticipated costs associated with providing meaningful screening of studies submitted to ClinicalTrials.gov. Since the current Trump Administration appears focused on reducing funding to federal agencies such as the FDA and NIH, in the current political climate it will doubtless be very difficult to obtain the additional funding the NIH needs to effectively review studies submitted to ClinicalTrials.gov [90]. Nonetheless, this is an example of where a modest increase in federal funding could generate substantial returns in improving the integrity of the registry and increasing the quality of information provided to prospective research participants.

Greater awareness that some US businesses and international companies and clinics are using ClinicalTrials.gov to recruit individuals who are then charged to access unapproved stem cell interventions administered in clinical studies should prompt increased understanding of the need to conduct meaningful screening of clinical studies before they are registered and deposited in the database. The ClinicalTrials.gov database is vulnerable to being used by businesses seeking to solicit prospective clients by claiming that they are conducting studies registered with the NIH. Other clinical studies registries have demonstrated their vulnerability to the same tactics and are also being used as marketing tools by businesses engaged in direct-to-consumer advertising of putative stem cell interventions. Like ClinicalTrials.gov, such registries need to put better review mechanisms in place if they wish to avoid having their value diminished. As the number of 'pay-to-participate' studies registered by US companies engaged in direct-to-consumer marketing of 'stem cell therapies increases, even though these studies were not reviewed and cleared to proceed by the FDA or screened by the NIH, the integrity of the ClinicalTrials.gov database is further compromised and its value declines. Absent meaningful changes, it seems likely that there will be more reports of patients harmed after paying for unapproved stem cell interventions that first came to their attention on ClinicalTrials.gov. Patients, patient advocates, clinicians, researchers, policy-makers, NIH and FDA officials, and other parties should all dedicate themselves to addressing and resolving this serious problem before more individuals are injured.

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The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

- The NIH website, ClinicalTrials.gov, is a registry and database of clinical studies. The registry is intended to promote transparency in clinical research.
- Patients and their advocates, health researchers, and many other parties use ClinicalTrials.gov for a variety of purposes. Many individuals trying to find clinical studies for which they are eligible to participate regard ClinicalTrials.gov as a trustworthy, reliable source of information.
- Carefully designed and properly conducted clinical studies are valuable tools for generating meaningful safety and efficacy data while minimizing risks to research subjects and promoting informed decision-making by prospective research participants. However, clinical studies, including studies that are poorly designed and suffer from numerous scientific, ethical and regulatory shortcomings, can also be used as marketing devices to recruit clients.
- Numerous US businesses that engage in direct-to-consumer advertising of purported stem cell treatments also charge individuals to participate in clinical studies in which stem cells are administered. Some of these companies use clinical studies listed in ClinicalTrials.Gov to sell stem cell interventions provided in the context of 'patient-funded', 'patient-sponsored' or 'self-funded' studies.
- Inclusion in ClinicalTrials.gov of 'pay-to-participate' studies that have not been subject to US FDA oversight and careful screening by NIH officials risks compromising the integrity and utility of the database.
- Listing 'pay-to-paticipate' studies in the database also risks confusing prospective study participants by blurring important distinctions between commercialized medical treatments and clinical research evaluating interventions for which conclusive evidence of safety and efficacy is lacking.
- There is an urgent need for careful screening of clinical studies before they are registered with ClinicalTrials.gov.

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