Non-homologous use of adipose-derived cell and tissue therapies: Osteoarthritis as a case study

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\begin{abstract}
Adipose tissue is widely recognized as an abundant and accessible human tissue that serves as a source of cells and extracellular matrix scaffolds for regenerative surgical applications. Increasingly, orthopedic surgeons are turning to adipose tissue as a resource in their treatment of osteoarthritis and related conditions. In the U.S., the regulatory landscape governing the orthopedic surgical utilization of autologous and allogeneic adipose tissue remains complex. This manuscript reviews the Food and Drug Administration’s nomenclature and guidance regarding adipose tissue products. Additionally, it surveys recent pre-clinical and clinical trial literature relating to the application of adipose-derived cells and tissues in the treatment of osteoarthritis.
\end{abstract}

1. Introduction

The Food and Drug Administration (FDA) regulates both biological products and devices developed by the emerging regenerative medicine community in the US. Within the FDA, the Center for Biologics Evaluation and Research (CBER) has the requisite expertise to evaluate the science, safety, and efficacy of potential cell-, genetic-, or tissue-based therapies. Rapid advancements in tissue engineering and regenerative medicine and their clinical translation have made this regulatory landscape complex and costly to navigate for biotech companies, physicians/surgeons, academic researchers and patients, all united by a desire to attain improved outcomes for historically unmet medical needs. This situation contrasts with the better-defined pathway for traditional drug development where the pharmaceutical industry and the FDA have established a standardized set of assays, toxicology testing, and therapeutic metrics to assess and validate small molecules as future drugs. As the audience of Bone Reports is well aware, orthopedic practitioners worldwide have embraced the infusion of adipose-derived stromal vascular fraction (SVF) cells, culture-expanded adipose stromal/stem cells (ASC), or micronized fat as a potential therapy for osteoarthritis. Nevertheless, these treatments’ scientific basis, safety, and efficacy remain to be demonstrated via trials providing evidence adequate to support FDA approval. Several rulings from Congress and the FDA are of particular relevance to these matters. In 2016, the U.S. Congress passed the 21st Century Cures Act specifying that companies could request a Regenerative Medicine Advanced Therapy (RMAT) designation for their cell or tissue engineered therapy if it addressed a serious or life-threatening disease or illness and displayed preliminary clinical evidence (21st Century Cures Act, 2020). In November 2017, the FDA issued a Guidance to Industry and the Food and Drug Administration Staff entitled “Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use” which was further updated in May 2021 (Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-based Products: Minimal Manipulation and Homologous Use, 2020). The original document called for clinical practitioners currently administering cell based therapies to comply with FDA regulations and provided a 3 year moratorium to do so. Shortly thereafter, the FDA in August 2018

\textbf{Abbreviations:} CBER, Center for Biologics Evaluation and Research; ASC, Adipose Stromal/Stem Cells; SVF, Stromal Vascular Fraction Cells; MFAT, Micro-Fragmented Adipose Tissue; HCT/P, Human Cells, Tissues, and Cell/Tissue related Products; OA, Osteoarthritis.

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issued a related Guidance to Industry entitled “Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment” which acknowledged that there was a need for better metrics correlating structural features with meaningful patient oriented beneficial outcomes in OA and invited industry stakeholders to help address this issue (Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry, 2018). Additionally, this document identified OA as “serious disease with an unmet medical need for therapies that modify the underlying pathophysiology of the disease and potentially change its natural course to prevent long-term disability”, thereby making cell-based OA therapies eligible for RMAT designation (Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry, 2018). After their three year moratorium, the FDA began taking legal actions to curtail clinical application of non-approved adipose-derived cell therapies to OA patients (Bruder, 2021). While the verdict on some of these cases has favored the authority of the FDA, others remain pending in court (Circuit U.S.C.O.A.F.T.E., 2021; Hilfick, 2022). In part due to these ongoing controversies, the current review article has focused on adipose-derived biologic products as a potential therapy for osteoarthritis, using it as a case study for understanding the current status of FDA regulation in the regenerative medicine arena. The authors have focused particular attention to the English language literature published since 2018 using the following keywords in Pubmed: adipose,stromal/stem cell, osteoarthritis.

2. FDA nomenclature, definitions, and regulations

The following Centers within the FDA have the greatest relevance to regenerative medical (Table 1):

| Center for Biologics Evaluation and Research (CBER) |
| Center for Devices and Radiological Health (CDRH) |
| Center for Drug Evaluation and Research (CDER) |
| Center for Veterinary Medicine (CVM) |

Each Center holds primary control over a specific therapeutic or diagnostic domain as their name implies. Within each Center, specific Offices have expertise focused on targeted subjects. Of note, the CBER Offices of Compliance and Biologics Quality and Tissues & Advanced Therapies hold particular relevance to the regenerative medical arena with respect to cell and decellularized tissue products (Table 1). Nevertheless, it is essential to be aware of the related Offices as they may play a co-regulatory role if there is a “combination product” that adds drug or other non-biological elements to a cell construct. In such cases, the resulting combination product must fulfill the regulatory safety and efficacy requirements of both its biologic and drug-related elements.

When investigators are ready to begin clinical studies using a novel biologic or drug therapy, the culmination of their initial approach to the FDA comes in the form of an Investigational New Drug (IND) application (Table 2) or an Investigational Device Exemption (IDE) application. The approval of an IND or IDE permits the principal investigator and sponsor to administer the therapy to patients in a defined and mutually agreed upon manner that, first and foremost, protects the safety and authority of the participants. The IND or IDE must be registered in a national clinical trial database as part of the approval process. Detailed information relating to each trial, including the existence of the IND or IDE authorization, is kept confidential by the FDA unless disclosed to the public directly by the company. Eventually, the FDA’s final approval of a biologic therapy will result in the approval of a Biologic License Application (BLA), permitting the sponsoring company or entity to use the product in interstate commerce. Clinical trials initiate as safety studies under Phase I and advance to safety and efficacy analyses in larger cohorts of test subjects in Phase II and III. In the realm of biologics, Phase I or pilot trials may focus on a single concentration or dose, or may provide for an escalating dose in small cohorts of the test article to focus on safety in subjects with the disease of interest. Phase II and III or pivotal trials typically will evaluate single or multiple concentrations of the test article in a randomized, controlled, and, often, blinded clinical trial format. Institutions conducting clinical trials will frequently register them online with www.clinicaltrials.gov, an online data repository maintained by the National Library of Medicine. In addition to a registration number, this searchable database includes the site(s) of the clinical trial, the sponsor, the number of subjects to be enrolled, a brief description of the study design, its primary and secondary endpoints, and current status with respect to enrollment. Studies registered on www.clinicaltrials.gov are just as likely to be ongoing anywhere in the world and are not exclusively those underway in the U.S. and North America. Thus, it does not accurately or effectively identify studies conducted with full authorization by the US FDA.

Many devices are handled distinctly from drugs under the CDRH, while selected devices that primarily function to obtain cellular material are regulated via IDE submissions handled through CBER. A subset of devices is eligible for classification as “Preamendment”. These are devices manufactured and marketed prior to 1976 and are “grandfathered” as exempt from further FDA approval; however, such devices are an exception and are not relevant to this discussion. Instead, most devices are categorized into three distinct Classes based on the degree of risk they present to the patient or user (Fig. 1 and Table 2). Forty-seven percent (47 %) of devices fall into Class I with low to moderate risk to patients; an example of a representative Class I device is an elastic bandage. Indeed, the vast majority of Class I devices are exempt from regulatory restrictions. Manufacturers can file a 510 K premarket document indicating that the device is substantially equivalent to an existing device actively being marketed with an FDA allowance. Substantial equivalence indicates that the device serves the same purpose as a currently approved device (known as a predicate) using the same or different technologies where these claims are supported by satisfactory evidence of safety and efficacy. Forty-three percent (43 %) of devices are classified as Class II with moderate to high risk; a Class II device example is a diagnostic test kit for pregnancy. The remaining 10 % of devices are classified as Class III with high risk. These are generally implanted into patients, necessary to sustain or maintain life, or present risk of disease or illness. Examples include breast implants, pacemakers, and blood collection apparatus. Class III devices are subjected to a Premarket Approval (PMA) process prior to marketing to ensure safety and efficacy by the FDA. Part of this process may include an Investigational Device Exemption (IDE) from the FDA, authorizing the manufacturer to perform interstate transportation and use of the device in clinical trials designed to assess safety and efficacy in a clinical trial.
FDA Definitions of relevant terminology as quoted from Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-based Products: Minimal Manipulation and Homologous Use (2020).

| BLA | Investigational New Drug Application |
|-----|--------------------------------------|
| IND | Investigational Device Exemption     |
| IDE | Devices are categorized based on risk to patient or user: Class I (low to moderate risk); Class II (moderate to high risk); Class III (high risk) |
| HCT/P | Human cells, tissues, and cellular and tissue-based product, i.e., bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue |

Non-HCT/P

1. Vascularized human organs for transplantation;
2. Whole Blood or blood components or blood derivative products;
3. Secreted or extracted human products, such as milk, collagen, and cell factors, except semen, are considered an HCT/P;
4. Minimal manipulation bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow);
5. Ancillary products used in the manufacture of HCT/P;
6. Cells, tissues, and organs derived from animals other than humans;
7. In vitro diagnostic products; and
8. Blood vessels recovered with an organ, as defined in 42 CFR 121.2 that are intended for use in organ transplantation and labeled “For use in organ transplantation only” (21 CFR 1271.3(d))

Processing of HCT/P

Any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage (21 CFR 1271.3(c)). Processing also includes cutting, grinding, shaping, culturing, enzymatic digestion, and decellularization.

Homologous use

The repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor:

a. Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor; or,
b. Recipient cells or tissues that may not be identical to the donor's cells or tissues but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor.

Structural tissue

Tissues that physically support or serve as a barrier or conduit, or connect, cover, or cushion in the donor, i.e., adipose tissue, amniotic membrane and umbilical cord, articular cartilage, blood vessel, bone, non-articular cartilage, skin, tendon or ligament

Non-structural tissue

Tissues that serve predominantly metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions, i.e., hematopoietic stem/progenitor cells (e.g., cord blood), lymph nodes and thymus, reproductive cells or tissues (e.g., oocytes).

Minimal manipulation (structural tissue)

The processing of the HCT/P does not alter the original relevant characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement

Minimal manipulation (non-structural tissue)

The processing of the HCT/P does not alter the relevant biological characteristics of cells or tissues

3. Human cells, tissues, and cell/tissue related products

Many of the products under development for osteoarthritis (OA) treatment are classified by the FDA as Human Cells, Tissues, and Cell/Tissue related Products (HCT/P) (Fig. 1). These include cells or cell-derived products from musculoskeletal tissues such as primary mesenchymal stromal/stem cells (MSC) and primary autologous chondrocytes as well as ligaments, tendons, and isolated hematopoietic stem cells. While not yet in clinical trials, this category may eventually include embryonic stem cell (ESC) and induced pluripotent stem cell (iPSC) therapeutics. In contrast, non-HCT/P products are categorized as blood-derived products such as erythrocytes and platelets, blood vessels or whole organs designed for transplant, secreted bodily fluids (except for semen), or solutions used in the processing or sterilization of cells or tissues.

From a regulatory perspective, the FDA subdivides body tissues into two categories: Structural and Non-Structural. Structural tissues are considered primarily those that serve as physical support, cushion or conduit. Examples include adipose tissue, amniotic, bone, cartilage, ligament, skin, and umbilical cord. For structural tissues, the definition of homologous use is restricted to the use of the tissue or cells exclusively for supportive or cushioning functions; any activity relating to the inherent endocrine, immune or metabolic activity of the cells or structures would be characterized as non-homologous use, thereby subjecting them to greater regulatory scrutiny and evaluation. In contrast, Non-Structural tissues are those that the FDA views primarily as serving a metabolic role and examples include endocrine, hematopoietic, lymphoid, and reproductive tissues. In these cases, homologous use relates directly to the cells’ endocrine, immune, and metabolic functionality. These distinctions are independent of the autologous or allogeneic origin of the tissue and have critical implications for regulation based on the meaning of minimal manipulation. For Non-Structural tissues, minimal manipulation is defined as any process that does not alter the biological properties of the cells or tissue. In contrast, for Structural tissues, minimal manipulation is defined as any process that does not alter the properties of the tissue for reconstruction, repair, or replacement purposes. While these may appear to be semantic distinctions, they have a profound impact at the level of manufacture and production. Without taking this into account, newcomers to the field may be puzzled by apparent incongruities in the FDA’s rationale for their differential categorization of cells or tissues from, for example, adipose tissue vs. pancreas where the use of collagenase is treated with different levels of regulatory scrutiny depending on the tissue classification. When a pancreas is digested with type I collagenase to isolate beta islets for transplantation to an allogeneic diabetic patient, this is classified as “minimal manipulation”. In contrast, when autologous adipose tissue is digested with type I collagenase for cosmetic fat grafting, this is considered “more than minimal manipulation”. Distinctions based on the definition of what constitutes a structural vs. metabolic tissue and, by extension, minimal manipulation have served as the basis of ongoing discussions in the literature regarding the categorization of adipose tissue exclusively as a structural tissue (Rodriguez et al., 2020; Marks, 2020). Thus, the research and manufacturing communities need to share a full appreciation of these FDA distinctions based on tissue of origin and their impact on the regulatory control of subsequent cell and tissue products.

4. Case study — use of adipose-derived cells and tissues for treatment of osteoarthritis

Due to its relative abundance and accessibility, adipose tissue has attracted considerable attention in the past decade as a source of cells, tissues, and scaffolds for OA treatment. Adipose tissue can be processed by enzyme digestion with collagenase and/or dispase to yield a heterogeneous Stromal Vascular Fraction (SVF) cell population including fibroblasts, adipose-derived stromal/stem cells (ASC), pericytes, as well...
employed non-invasive imaging analytical methods such as MRI to disrupt the tissue (Tremolada et al., 2016a; Tremolada et al., 2016b). Additionally, intact adipose tissue can be decellularized using a combination of detergents, solvents, and mechanical processing steps to yield an extracellular matrix (ECM)-rich hydrogel (Mohiuddin et al., 2020; Flynn, 2010; Kokai et al., 2019). Finally, the adipose cell-derived secretome (ASC-S) harvested from adipose cells or tissues holds promise as a biologically derived therapeutic in multiple indications, including osteoarthritis (Wei et al., 2009; Ellis et al., 2021; Niada et al., 2019; Amodeo et al., 2021).

The exosomes serve as delivery vehicles for anti-inflammatory growth factors and signal transductive microRNAs (Ni et al., 2020). Currently, pre-clinical and/or clinical level evaluations are underway for each biologic reagent as injectable therapy for osteoarthritis. Indeed, since 2019, at least 19 reviews from authors in 17 countries have been published on this topic; nearly half of these articles self-identify as meta-analyses or systematic reviews (Table 3). To avoid making the current article more repetitive than necessary, readers are referred directly to this previously published collection of eloquent reviews.

Likewise, since 2019, there has been an abundance of peer-reviewed published literature reporting clinical trial results using adipose-derived biological therapeutics for OA (Tables 4–7). The vast majority of these studies have monitored the quantitative response of OA patients based on measurements made with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Visual Analogue Scale (VAS) metrics for pain, stiffness and activity, or the Knee Injury Osteoarthritis Outcome Score (KOOS) (Tables 4–6). Additionally, a subset of studies employed non-invasive imaging analytical methods such as MRI to monitor cartilage repair, with or without enhancement agents (Zhao et al., 2019). In a single trial comparing cohorts of ten subjects each treated with microfracture alone or in combination with hyaluronic acid injection with or without autologous ASC, outcomes were further monitored using a histological evaluation of a cartilage biopsy obtained under arthroscopic examination; however, this level of post-operative invasive assessment was the exception, and only four of the sixty enrolled subjects consented to the biopsy procedure (Qiao et al., 2020). Only a single study reported a serious adverse event involving infection of an injected joint; however, this event occurred in a patient enrolled in the control arm (hyaluronic injection) study cohort and did not involve adipose-derived cells (Lu et al., 2019). Multiple studies reported adverse events, and these were frequently bruising or pain at the adipose harvest site or swelling following the joint injection.

Overall, these clinical trials enrolled a total of n = 939 subjects. The studies can be sub-divided based on their level of evidence. The least rigorous were case reports, case series and retrospective reviews that primarily benchmarked treatment outcomes using the pre-operative self-reported patient metrics as baseline control (Table 4). These appeared in a total of six publications with authors enrolling subjects in five separate countries; three of the studies included at least one US-based author. One of the studies evaluated SVF cell therapy, two evaluated ASC therapy, and three examined microfragmented adipose tissue (MFAT). Only 16% (1/6) of these publications reported a national clinical trial registration. Altogether, these trials represent findings from a total of n = 235 patients.

The next level of rigor included prospective, non-randomized clinical trials (Table 5). These appeared in a total of thirteen publications, with authors enrolling subjects in ten separate countries; one of the studies was conducted in the US. One of the trials evaluated SVF cell therapy, two examined ASC treatment, and nine focused on MFAT. Nearly half (46%) of these publications reported a national clinical trial registration. Altogether, these trials represent findings from a total of n = 410 patients.

The most rigorous studies reported were prospective, randomized controlled clinical trials (Table 6). These appeared in a total of nine...

![FDA Classification of Products Under Development for Osteoarthritis Treatment](image_url)
Table 3
Recent reviews focused on biologic therapy for osteoarthritis.

| Author (country) | Journal (ref) | Title |
|------------------|---------------|-------|
| Agarwal N et al. (UK) | Cells 2021, 10:1365 (Agarwal et al., 2021) | Meta-Analysis of Adipose Tissue-Derived Cell-Based Therapy for the Treatment of Knee Osteoarthritis |
| Biazzo A et al. (Italy) | The Physician and Sportsmedicine 2020, 48: 392–399 (Biazzo et al., 2020) | Autologous adipose stem cell therapy for knee osteoarthritis: where are we now? |
| Buzazo N & Alshammary S (Bahrain) | Stem Cells and Cloning: Advances and Applications 2020, 13: 117–136 (Buzazo and Alshammary, 2020) | Clinical Applicability of Adult Human Mesenchymal Stem Cell Therapy in the Treatment of Knee Osteoarthritis |
| De Francesco F et al. (Italy) | International Journal of Molecular Sciences 2021, 22:10197 (De Francesco et al., 2021) | Stem Cells in Autologous Microfragmented Adipose Tissue: Current Perspectives in Osteoarthritis Disease and Therapies for the Treatment of Knee Osteoarthritis |
| Delanois RE et al. (US) | Journal of Arthroplasty 2019, 34:801–813 (Delanois et al., 2019) | Systematic Review: Allogeneic Use of Stromal Vascular Fraction (SVF) and Decellularized Extracellular Matrices (ECM) as Advanced Therapy Medicinal Products (ATMP) in Tissue Regeneration |
| Gentile P et al. (Italy & Greece) | International Journal of Molecular Sciences 2020, 21:4982 (Gentile et al., 2020) | Expanding Clinical Indications of Mechanically Isolated Stromal Vascular Fraction: A Systematic Review of Intra-Articular Injections of Hyaluronic Acid or Steroids Associated With Better Outcomes Than Platelet-Rich Plasma, Adipose Mesenchymal Stromal Cells, or Placebo in Knee Osteoarthritis: A Network Meta-analysis |
| Ghaslooo M et al. (Belgium) | Aesthetic Surgery Journal 2020, 40: NP546–NP560 (Ghaslooo et al., 2020) | Meta-Analysis of the Use of Stromal Vascular Fraction (SVF), platelet rich plasma (PRP) and stem cells in the treatment of osteoarthritis: an overview of clinical trials improved outcomes after mesenchymal stem cells injections for knee osteoarthritis: results at 12-months follow-up: a systematic review of the literature |
| Han SB et al. (Republic of Korea) | Arthroscopy 2021, 37:292–306 (Han et al., 2021) | The use of stromal vascular fraction (SVF), platelet rich plasma (PRP) and stem cells in the treatment of osteoarthritis: An overview of clinical trials improved outcomes after mesenchymal stem cell injections for knee osteoarthritis: results at 12-months follow-up: a systematic review of the literature |
| Keeling LE et al. (USA) | Am J Sports Med In Press (Keeling et al., 2021) | Bone Marrow Aspirate Concentrate for the Treatment of Knee Osteoarthritis: A Meta-Analysis of the Efficacy and Safety of Stem Cell Therapy for Intra-Articular Injection of Stromal Vascular Fraction for the Treatment of Knee Osteoarthritis—A Systematic Review and Network Meta-analysis |
| Mehranfar S et al. (Iran) | Artificial Cells, Nanomedicine, and Biotechnology 2019, 47:882–890 (Mehranfar et al., 2019) | The use of stromal vascular fraction (SVF), platelet rich plasma (PRP) and stem cells in the treatment of osteoarthritis: An overview of clinical trials improved outcomes after mesenchymal stem cell injections for knee osteoarthritis: results at 12-months follow-up: a systematic review of the literature |
| Migliorini F et al. (Germany) | Archives of Orthopaedic and Trauma Surgery 2020, 140:853–868 (Migliorini et al., 2020) | Knee Osteoarthritis: A Systematic Review of the Literature |
| Primorac D et al. (Croatia) | Genes 2020, 11:854 (Primorac et al., 2020) | Non-Operative Therapeutic Considerations of Knee Osteoarthritis: A Systematic Review |
| Shanmagusundaram S et al. (India, Oman, UAE, US) | International Orthopaedics 2021, 45:615–625 (Shanmagusundaram et al., 2021) | Assessment of safety and efficacy of intra-articular injection of stromal vascular fraction for the treatment of knee osteoarthritis: a systematic review and meta-analysis |

Table 3 (continued)

| Author (country) | Journal (ref) | Title |
|------------------|---------------|-------|
| Shariatzadeh M et al. (UK) | Cell and Tissue Research 2019, 378:399–410 (Shariatzadeh et al., 2019) | The efficacy of different sources of mesenchymal stem cells for the treatment of knee osteoarthritis |
| Tan SHS et al. (Singapore) | Am J Sports Med 2021, 49: 3113–3124 (Tan et al., 2021) | Intra-articular Injections of Mesenchymal Stem Cells Without Adjuvant Therapies for Knee Osteoarthritis: A Systematic Review and Meta-analysis |
| Vahedi P et al. (Iran, Turkey) | International Journal of Molecular Sciences 2021, 22:9215 (Vahedi et al., 2021) | The Use of Infrapatellar Fat Pad-Derived Mesenchymal Stem Cells in Articular Cartilage Regeneration: A Review of Administration of mesenchymal stem cells from adipose tissue at the hip joint of dogs with osteoarthritis: A systematic review |
| Zhao D et al. (China) | Journal of Arthroscopic and Related Surgery 2021, 37:2298–2314 (Zhao et al., 2021) | Intra-Articular Injections of Platelet-Rich Plasma, Adipose Mesenchymal Stem Cells, and Bone Marrow Mesenchymal Stem Cells Associated With Better Outcomes Than Hyaluronic Acid and Saline in Knee Osteoarthritis: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials |
| Xiang XN et al. (China) | Stem Cell Research & Therapy 2022, 13:14 (Xiang et al., 2022) | Mesenchymal stromal cell-based therapy for cartilage regeneration in knee osteoarthritis |

publications with authors enrolling subjects in seven countries; one of the studies was conducted in the US. Two trials evaluated SVF cell therapy, six examined ASC treatments, and one employed MFAT. Two-thirds (66 %) of these publications reported a national clinical trial registration, either with the FDA or another national regulatory agency. Altogether, these trials represent findings from a total of n = 294 patients.

While FDA clinical trials often include international patients, the agency frequently requires that a sizable percentage of patients be recruited from US to represent the nation’s unique demographics. There is a single FDA registered Phase IIB clinical trial that was performed exclusively in the US using SVF cells to treat OA which merits further evaluation (Garza et al., 2020). This double-blinded, randomized controlled study was conducted at three sites (Camber NJ, Philadelphia PA, San Antonio TX) and enrolled 39 subjects. All patients, regardless of randomization, underwent liposarplation and both patients and healthcare providers were blinded to the therapy. The adipose tissue was processed with a single closed system device (GID-SVF2 tissue processing device, GID Group, Louisville CO) to recover isolated autologous SVF cells. Subjects were randomized to receive knee joint injections under ultrasound guidance. Under the dose escalation protocol, the first 15 consecutive participants were randomized to either the low dose (1.5 × 10^7) of autologous SVF cells or the placebo group (Lactated Ringer’s Solution) and followed for 6 weeks with a safety and adverse events analysis. The remaining 24 patients were randomly assigned to the high dose (3 × 10^7), the low dose or the placebo group. Patients were
monitored by WOMAC questionnaire prior to surgery and 6 weeks, 3, 6, and 12 months after surgery and by MRI exam prior to surgery and 12 months afterward. At the 6-month time point, the control or placebo group showed a mean change of 25.0 % relative to baseline in outcome scores, while the low dose and high dose SVF cell treatment groups showed clinically significant improvements of 51.5 % and 83.9 % relative to baseline. Despite a rigorous clinical design, the study faces several limitations. First, the study was unblinded after 6 months, so that the persistence of the therapeutic outcomes beyond that timepoint is not known. Second, the enrolled population was 82 % Caucasian, 15.4 % Hispanic, and 2.6 % African-American which does not adequately reflect the US demographic. Third, patients with body mass indices >35 and/or co-morbidities were excluded from the study resulting in a mean subject BMI of 27.8 (range 19–34.9). Thus, extensions of this work will need to address these potential shortcomings by enrolling a more representative cohort with respect to racial and ethnic minorities in the OA population, displaying BMIs of morbid obesity, and with co-morbidities. Despite these limitations, the report by Garza et al. represents the most comprehensive FDA-approved randomized controlled clinical

| Table 4 | Case reports, case series and retrospective studies. |
|---------|--------------------------------------------------|
| Authors/Reference | Study type/therapy/device | Subject # | Metrics, outcomes & serious adverse events (adverse events) |
| Freitag et al. (Freitag et al., 2020a) (Australia) | Ankle OA CR/ Auto ASC (20 to 50 × 10^9 ASC at 0, 6, 12 mo) | 1 | FADI, MRI; Improvement vs baseline up to 24 mo; No SAE |
| Freitag et al. (Freitag et al., 2020b) (Australia) | OA Knee CS NR Pro/Auto ASC (50 × 10^6 per knee at 0 and 6 mo) | 8 | KOOS, MRI, WOMAC; Improvements with 24 mo follow up; No SAE |
| Gobbi et al. (Gobbi et al., 2021) (Italy, United Arab Emirates, USA) | Knee OA NR Retro/Auto MFAT (Lipogems) | 75 | KOOS; Significant improvement vs baseline up to 24 mo follow up; No SAE (49 % pain at lipo site, 37 % bruising at lipo site, 13 % knee swelling); Serum Cytokines, Ultra, VAS, WOMAC; Significant improvement vs baseline at 12 mo follow up; No SAE (Emory QLF, KOOS); VAS, Significant improvement pre vs post with >1 yr follow up; No SAE (DASH, Rad, VAS), Significant improvement vs baseline at 12 mo follow up; No SAE (VAS, KOOS, ICF, MOCART, VAS, WOMAC) |
| Laguente et al. (Laguente et al., 2020) (Spain) | Knee OA NR Retro/Auto SVF | 50 | Serum Cytokines, Ultra, VAS, WOMAC; Significant improvement vs baseline at 12 mo follow up; No SAE (Emory QLF, KOOS); VAS, Significant improvement pre vs post with >1 yr follow up; No SAE (DASH, Rad, VAS), Significant improvement vs baseline at 12 mo follow up; No SAE (VAS, KOOS, ICF, MOCART, VAS, WOMAC) |
| Mautner et al. (Mautner et al., 2019) (USA) | OA Knee NR Retro/Auto BMAC or MFAT/ Lipogems | 76 | VAS, Significant improvement pre vs post with >1 yr follow up; No SAE (DASH, Rad, VAS), Significant improvement vs baseline at 12 mo follow up; No SAE (VAS, KOOS, ICF, MOCART, VAS, WOMAC) |
| Vinet-Jones & Harr (Vinet-Jones and Harr, 2020) (USA) | OA Shoulder CS NR Pro/Auto MFAT (Lipogems) | 25 | Significant improvement vs baseline at 12 mo follow up; No SAE (VAS, KOOS, ICF, MOCART, VAS, WOMAC) |

Table 5 | Non-randomized prospective clinical trials. |
|---------|--------------------------------------------------|
| Authors/Reference | Subject | Metrics, outcomes & serious adverse events (adverse events) |
| Bakowski et al. (Bakowski et al., 2021) (Poland) | Knee OA NR Pro/ auto liposaripate | 37 | IDK2000, KOOS, NPRS, WOMAC; Satisfaction in Stage II but not Stage IV; 27 mo follow up; No SAE |
| Barfod & Blond (Barfod and Blond, 2019) (Denmark) | Knee OA NR Pro/ Auto MFAT (Lipogems) | 20 | KOOS, VAS; Significant improvement vs baseline up to 12 mo; No SAE (FJS, KOOS, KSS, LS, NRS); Significant improvement vs baseline av. 23.5 mo follow up; No SAE (knee swelling, minor venous thrombosis) |
| Bistolfi et al. (Bistolfi et al., 2021) (Italy) | Knee OA NR Retro/ Auto MFAT (Lipogems or Lipocells) | 78 | 4GEMBRIC, VAS; Significant improvement vs baseline up to 24 mo |
| Boric et al. (Boric et al., 2019) (Croatia) | Knee OA NR Pro/ Auto MFAT (Lipogems) | 10 | IKDC 2000, KOOS, MOCART, VAS, WOMAC; Significant improvement vs baseline up to 11 mo follow up; No SAE (hip, WOAMC, VAS, Improvement vs baseline; 6 mo follow up; No SAE (one hematoma @ lipo site) KOOS, MRI, MOCART, NPRS, PGIC, WOMAC; Significant improvement vs baseline up to 36 mo follow up; No SAE (MHQ); Significant improvement vs baseline at 12 mo follow up; No SAE KOOS, VAS; WOMAC; Significant improvement vs baseline up to 12 mo; No SAE KOOS, NPRS; Significant improvement vs baseline up to 12 mo follow up; No SAE (swelling/ bruising at lipo site) (Nia et al., 2019) or injection site (Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry, 2018) |
| Dall'Occo et al. (Dall'Occo et al., 2019) (Italy) | Hip OA NR Pro/Auto MFAT (Lipogems) | 6 | IHS, WOAMC, VAS; Improvement vs baseline; 6 mo follow up; No SAE (one hematoma @ lipo site) KOOS, MRI, MOCART, NPRS, PGIC, WOMAC; Significant improvement vs baseline up to 12 mo; No SAE (MHQ); Significant improvement vs baseline at 12 mo follow up; No SAE KOOS, VAS; WOMAC; Significant improvement vs baseline up to 12 mo; No SAE KOOS, NPRS; Significant improvement vs baseline up to 12 mo follow up; No SAE (swelling/ bruising at lipo site) (Nia et al., 2019) or injection site (Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry, 2018) |
| Freitag et al. (Freitag et al., 2020c) (Australia) | OA Knee CT NR Pro/ Auto ASC (50 × 10^6 per knee at 0 and 6 mo) | 27 | IHS, WOAMC, VAS; Improvement vs baseline; 6 mo follow up; No SAE (one hematoma @ lipo site) KOOS, MRI, MOCART, NPRS, PGIC, WOMAC; Significant improvement vs baseline up to 12 mo; No SAE (MHQ); Significant improvement vs baseline at 12 mo follow up; No SAE KOOS, VAS; WOMAC; Significant improvement vs baseline up to 12 mo; No SAE KOOS, NPRS; Significant improvement vs baseline up to 12 mo follow up; No SAE (swelling/ bruising at lipo site) (Nia et al., 2019) or injection site (Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry, 2018) |
| Haas et al. (Haas et al., 2020) (Germany) | Thumb Carpometacarpal OA NR Pro/Auto MFAT (Luer Lock) | 89 | 4GEMBRIC, VAS; Significant improvement vs baseline up to 24 mo follow up; No SAE KOOS, VAS; WOMAC; Significant improvement vs baseline up to 12 mo; No SAE KOOS, NPRS; Significant improvement vs baseline up to 12 mo follow up; No SAE (swelling/ bruising at lipo site) (Nia et al., 2019) or injection site (Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry, 2018) |
| Hudetz et al. (Hudetz et al., 2019) (Croatia) | Knee OA NR Pro/ Auto MFAT (Lipogems) | 20 | DASH, PRWE, VAS; Significant improvement vs baseline up to 12 mo; No SAE KOOS, NPRS; Significant improvement vs baseline up to 12 mo follow up; No SAE (swelling/ bruising at lipo site) (Nia et al., 2019) or injection site (Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry, 2018) |
| Malanga et al. (Malanga et al., 2021) (USA) | Knee OA NR Pro/ Auto MFAT (Lipogems) | 20 | DASH, PRWE, VAS; Significant improvement vs baseline up to 12 mo; No SAE KOOS, NPRS; Significant improvement vs baseline up to 12 mo follow up; No SAE (swelling/ bruising at lipo site) (Nia et al., 2019) or injection site (Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry, 2018) |
| Mayoly et al. (Mayoly et al., 2019) (France) | Wrist OA NR Pro/ Auto MFAT (Hapifat) + PRP | 3 | DASH, PRWE, VAS; Significant improvement vs baseline up to 12 mo; No SAE KOOS, NPRS; Significant improvement vs baseline up to 12 mo follow up; No SAE (swelling/ bruising at lipo site) (Nia et al., 2019) or injection site (Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry, 2018) |

Abbreviations: Allo, Allogeneic; ASC, Adipose-derived Stromal/stem Cells; Auto, Autologous; B, Blinded; BMAC, Bone Marrow Aspirate Concentrate; CR, Case Report; CS, Case Series; CT, Controlled Trial; DASH, Disabilities of the Arm, Shoulder and Hand; Emory QLF, Emory Quality of Life; FADI, Foot and Ankle Disability Index; HA, Hyaluronate; KOOS, Knee Injury and Osteoarthritis Outcome Score; MFAT, Microfragmented Adipose Tissue; MRI, Magnetic Resonance Imaging; NR, Not Randomized; Pro, Prospective; PRP, Platelet Rich Plasma; R, Randomized; Rad, Radiography; Retro, Retrospective; SAE, Serious Adverse Event; SVF, Stromal Vascular Fraction Cells; TBCR, To Be Conducted/Reported; Ultra, Ultrasound; VAS, Visual Analog Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
5. Clinical translation of adipose-derived products in the treatment of osteoarthritis: future directions and needs

While the literature review indicates substantial international interest in applying adipose-derived products in OA therapy, it also highlights a series of questions that must be addressed.

5.1. Do we need more US-based clinical trials?

Clinical trials remain an absolute and necessary requirement for a transparent, evidence-based assessment of new biological therapies. While a single-arm, unblinded study is sufficient for a Phase I (IND) or pilot (IDE) safety trial, an FDA-approved Phase II/III (IND) or pivotal (IDE) efficacy trial is likely to be required to include at least one “standard of care” arm to serve as a baseline control to compare against any experimental modality. From a regulatory perspective, the “gold standard” remains the randomized controlled trial (RCT) and future studies must incorporate this design. Recently, alternative approaches have been suggested, such as Practice Based Evidence or “pragmatic” clinical trials (https://www.nejm.org/do/full/10.1056/NEJMra1510059), where large community-based populations are enrolled with minimal exclusion criteria into studies using detailed clinical monitoring metrics over extended periods. While PBE trials have proven helpful in discovering new therapies in broad patient populations, this methodology is at best likely to be viewed as only a complement to RCT by regulatory authorities in the U.S. (Horn et al., 2012; Henry et al., 2017). Therefore, it can be expected that an approved RCT study designed to enroll US-based patients, with positive outcomes and acceptable cellular product characterization, will be necessary before the FDA will approve

### Table 5 (continued)

| Study (Date) | Study Design | NCT Number | OA Mode | Baseline Improvement |
|--------------|--------------|------------|---------|----------------------|
| Natali et al. (Natali et al., 2021) (Italy) | Ankle OA NR Pro/Auto MFAT (Lipogems) | NCT03164122/EudraCT #2016-002648-18 | baseline up to 12 mo; No SAE (pain reported at adipose harvest site) | AOFAS, FAHI, VAS; Significant improvement vs baseline up to 24 mo follow up; No SAE |
| Tsubosaka et al. (Tsubosaka et al., 2020) (Japan) | Knee OA NR Pro/Auto SVF (Cytori) (25 × 10^6 at 0 mo) | NCT02726945 | baseline av. 13.4 mo; No SAE | KOOS, MRI, VAS, WOMAC; Improvement vs baseline av. 13.4 mo; No SAE |

### Table 6

| Study (Date) | Study Design | NCT Number | OA Mode | Baseline Improvement |
|--------------|--------------|------------|---------|----------------------|
| Freitag et al. (Freitag et al., 2019) (Australia) | OA Knee RCT Pro/Auto ASC (100 × 10^6 per knee at 0 ± 6 mo) | NCT03164122/EudraCT #2016-002648-18 | Significant improvement with 1 or 2 injections vs saline at 12 mo follow up; No SAE (mild to moderate injection site pain) | MRI, WOMAC; Dose dependent significant improvement vs placebo control; 12 mo follow up; No SAE |

Abbreviations: Allo, Allogeneic; AOFAS, American Orthopaedic Foot and Ankle Society (AOFAS) scale; ASC, Adipose-derived Stromal/stem Cells; Auto, Autologous; B, Blinded; BMAC, Bone Marrow Aspirate Concentrate; CR, Case Report; CS, Case Series; CT, Controlled Trial; DASH, Disabilities of the Arm, Shoulder, and Elbow; dGEMRIC, Delayed Gadolinium Enhanced MRI of Cartilage; FJS, Forgotten Joint Scale; HA, Hyaluronate; HHS, Harris Hip Score; IKDC 2000, International Knee Documentation Committee 2000; KOOS, Knee Injury and Osteoarthritis Outcome Score; LS, Lysholm Score; MFAT, Microfragmented Adipose Tissue; MHPQ, Michigan Hand Outcomes Questionnaire; MOCART, MRI Observation of Cartilage Repair Tissue; NPRS, Numeric Pain Rating Scale; NR, Not Randomized; NRS, Noise Reporting Scale; PGIC, Patient Global Impression of Change; Pro, Prospective; PRP, Platelet Rich Plasma; PRWE, Patient-Related Wrist Evaluation; R, Randomized; Retro, Retrospective; SAE, Serious Adverse Event; SVF, Stromal Vascular Fraction Cells; TBCR, To Be Conducted/Reported, VAS, Visual Analog Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

evaluation of an adipose cell-derived therapy for OA completed in the US to date (Garza et al., 2020). Indeed, the GID Group is pursuing its promising findings by recruiting subjects at twelve sites within the US for a Phase III clinical trial. While clinical trial designs with comparable levels of rigor are being proposed in the literature (Table 7), all of these will be conducted exclusively outside the US in either the EU or China.

5. Clinical translation of adipose-derived products in the treatment of osteoarthritis: future directions and needs

While the literature review indicates substantial international interest in applying adipose-derived products in OA therapy, it also highlights a series of questions that must be addressed.
evaluate their OA patients with respect to mobility, pain, and quality of life. This requires collaboration among device companies, and the pharmaceutical industry. Additionally, a seamless integration of therapies for OA includes partners from academia, biotech ventures, and performance metrics. The industry developing adipose-derived biologic therapies for OA now has a standard for adipose-derived cell and tissue therapeutics in concert with the FDA. With the advent of sophisticated statistical tools now available, this approach may allow investigators to combine data from multiple individual studies. With the support of regulatory authorities (Bourin et al., 2013; Galipeau et al., 2016; Dominici et al., 2006), this field is advancing rapidly.

5.2. Can there be mechanisms for industry to establish and certify adipose-derived biologic therapies for OA?

The biomanufacturing and regulatory landscapes are evolving as basic research is translated into clinical practice. This offers an opportunity to coordinate and standardize product safety, efficacy, potency, and performance metrics. The industry developing adipose-derived therapies for OA includes partners from academia, biotech ventures, device companies, and the pharmaceutical industry. Additionally, a number of public and private organizations, institutions, and partnerships are stakeholders. These include the Advanced Regenerative Manufacturing Institute (ARMI/BioFabUSA), American Association of Orthopedic Surgeons (AAOS), Foundation for Accreditation of Cellular Therapy (FACT), International Federation of Adipose Therapeutics and Science (IFATS), International Society for Cell and Gene Therapy (ISCT), and National Institute for Standards and Technology (NIST), to name a few. If there can be industry-wide coordination between these entities, it will be feasible to standardize and harmonize international metrics for critical elements in the biomanufacturing process with respect to product safety and efficacy. These standards would include definitions based on quantifiable assays associated with each cell type (SVF, ASC), biologic product (hydrogels and scaffolds from decellularized adipose tissue) and devices (point of care adipose cell isolation). Industry-wide acceptance of a standard set of assays related to functionality (differentiation, immunomodulation), composition, and/or performance could accelerate product development if appropriately coordinated with regulatory authorities (Bourin et al., 2013; Galipeau et al., 2016; Dominici et al., 2006). Similarly, the identification of a common set of questionnaires and clinical evaluation tools could benefit the field. As shown in Tables 3–7, clinicians have used a wide range of questionnaires to evaluate their OA patients with respect to mobility, pain, and quality of life. Standardizing these protocols may set the stage for future investigators to combine data from multiple individual studies. With the sophisticated statistical tools now available, this approach may allow regulators to evaluate the safety and efficacy of cell or biologic OA therapies in larger populations more accurately and quantifiably without enrollment of an entirely new patient cohort.

5.3. Can there be mechanisms for patients and caregivers to identify FDA authorized clinical trials moving forward?

Currently, patients and their caregivers rely heavily on word of mouth and the website of the clinical trials.gov to access ongoing adipose-derived therapeutic trials enrolling OA patients. Importantly, this mechanism is flawed, since FDA approval is not included as a criterion for determining whether or not a trial can be registered on the website. Steps are underway to address this challenge: a number of private sector partners are working together to develop an initiative known as TrueTrials, a 501c3 not-for-profit organization, with the website www.truetailors.org. This website will only list clinical trials authorized by the FDA to enroll patients, generally via IND or IDE; it provides a patient-directed interface with a searchable table of trials along with a linked map of trial sites (see Fig. 2). By allowing reliable access to this clinical trial website, patients and caregivers will have greater confidence in enrolling in clinical trials which have received FDA authorization, and with an appropriately reduced risk of safety, ethical or economic concerns. It will also assist in accelerating the rate of trial recruitment.

5.4. Is there a continued need for basic science research into the mechanism of action of adipose-derived products in OA treatment?

Bad scientists are actively pursuing the fundamental mechanisms of the action exerted by adipose-derived biological products relevant to OA. While this body of work extends beyond the scope of the present review, one study merits comment since the majority of clinical trials have reported improvement in OA pain scores based on blinded patient-generated questionnaires (Tables 4–6). Pre-clinical studies in a murine subcutaneous adipose tissue regenerative model have demonstrated that opioid receptors and resident macrophages contribute to the wound healing and scarring processes (Rabiller et al., 2021; Berthezene et al., 2021; Labit et al., 2018). By blocking nociceptive pain receptors with naloxone, genetic knockout, or supplementation with the neuromodulator Calcitonin-Gene Related Peptide (CRGP), the authors were able to reduce scarring and enhance wound healing in the subcutaneous adipose resection model (Berthezene et al., 2021; Labit et al., 2018). These novel findings indicate that cells within adipose tissue can actively direct regeneration by modulating the pain response. They suggest a possible mechanism(s) of action for adipose-derived products that merit additional investigation in the context of OA treatment. Clearly, this is just one example of how basic research in pre-clinical animal models has identified novel cellular mechanisms for OA therapies. There remains a need for further investigations into adipose cell paracrine- and secrectome-based mechanisms can be utilized to modulate the underlying etiology of OA and ultimately to benefit patient care, quality of life, and overall outcomes.

Abbreviations: Allo, Allogeneic; ASC, Adipose-derived Stromal/stem Cells; Auto, Autologous; B, Blinded; BMAC, Bone Marrow Aspirate Concentrate; CR, Case Report; CS, Case Series; CT, Controlled Trial; HA, Hyaluronate; MFAT, Micro-fragmented Adipose Tissue; NR, Not Randomized; Pro, Prospective; PRP, Platelet Rich Plasma; R, Randomized; Retro, Retrospective; SVF, Stromal Vascular Fraction Cells; TBCR, To Be Conducted.

| Study Design / Study, Reports et al., 2020 (Poland) | Knee OA RCT Pro/ (Lipogems) vs PRP | Not reported | KOOS, IKDC | 2000, WOMAC; TBC, 12 mo follow up |
|---|---|---|---|---|
| Krzesniak et al. (Krzesniak et al., 2021) (Poland) | Knee OA RCT Pro/ (Lipogems) | 100 | KOOS, MRI; TBC, 12 mo follow up |
| NCT04675359 (06 Jan 2021) | OA Knee B RCT Pro/ (Lipogems) | 120 | KOOS, Tegner |
| Mikkelson et al. (Mikkelson et al., 2021) (Denmark) | Phase II Efficacy/ Auto MFAT (5 ml per knee)/Lipogems | Activity Scale; TBC, 24 mo follow up |
| NCT03771989 | Registered on Dec. 13th 2018. | |
| Nasb et al. (Nasb et al., 2020) (China) | Knee OA B RCT Pro/ ± Auto ASC ± Ultrasound Rx | 96 | MRI, WOMAC; TBC, 6 mo follow up |
| ChiCTR1900025907 | |

Table 7
Study designs for to be conducted-randomized controlled prospective clinical trials.

Currently, patients and their caregivers rely heavily on word of mouth and the www.ClinicalTrials.gov website to access ongoing adipose-derived therapeutic trials enrolling OA patients. Importantly, this mechanism is flawed, since FDA approval is not included as a criterion for determining whether or not a trial can be registered on the website. Steps are underway to address this challenge: a number of private sector partners are working together to develop an initiative known as TrueTrials, a 501c3 not-for-profit organization, with the website www.truetailors.org. This website will only list clinical trials authorized by the FDA to enroll patients, generally via IND or IDE; it provides a patient-directed interface with a searchable table of trials along with a linked map of trial sites (see Fig. 2). By allowing reliable access to this clinical trial website, patients and caregivers will have greater confidence in enrolling in clinical trials which have received FDA authorization, and with an appropriately reduced risk of safety, ethical or economic concerns. It will also assist in accelerating the rate of trial recruitment.

CRediT authorship contribution statement
Conceptualization; TF, JRG, JMG. Project administration; JMG. Software; KH. Visualization; KH, KM. Roles/Writing - original draft; TF, JMG. Writing - review & editing BAB, JRG, KFD, KM, ER.

Declaration of competing interest
T. Frazier and J.M. Gimble are co-founders, co-owners, and employees of Obatala Sciences, a for-profit biotechnology company focused on the development of adipose-derived cell and biomaterial products for research and clinical translational applications. They are co-inventors on patents relating to such products. Likewise, K. Hamel and E. Rogers are employees of Obatala Sciences. K. Darr is a co-owner and employee
of Covington Orthopedics Sports Medicine Institute. K. March is actively involved as a developer and founder of TrueTrials.org, a 501c3 non-profit entity. J.R. Garza has received funding from the GID Group and InGeneron for the conduct of clinical trials and funding as a Medical Monitor/DSMB member for an FDA trial with 3D Bio. B.A. Bunnell, J.M. Gimble and K. March are former presidents and active board members of the International Federation of Adipose Therapeutics and Sciences (IFATS), a non-profit organization promoting research and clinical translation of adipose tissue products.

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