



Helping Patients Navigate Regenerative Medicine and Cell and Tissue-Based Therapies (RMCTs)

March 24, 2022



Advancing Regenerative Medicine and Cell Therapies for Patients in Need



Executive Summary

More than 900 active clinical studies are now underway in the United States that explore the use of regenerative medicine and cell and tissue-based therapies (RMCTs) for a whole range of conditions, including cancer, musculoskeletal conditions, neurological conditions, COVID-19, and wound healing. Most (95 percent) are Phase 1 or Phase 2 clinical trials. As of December 31, 2021, at least 67 RMCTs had been approved worldwide, 29 in the United States. Federal funding for large-scale, randomized, controlled clinical trials will help move a greater number of RMCTs through the Food and Drug Administration (FDA) evaluation and approval process.

There is great interest in these therapies among patients, given their role in repairing, replacing, restoring function, and in some cases, reversing disease, in organs or tissues that have been damaged or are functioning poorly. Unfortunately, advances in regenerative medicine and cell therapies have coincided with an increase in private clinics that market RMCTs outside of clinical trials with unproven claims of safety and efficacy. Recent reports have shown an increase in unlicensed clinics operating outside of the law.

The independent, non-profit organizations Alliance for Cell Therapy Now and the Alliance for Cell Therapy Foundation have teamed up with the non-profit National Football League Alumni Association (NFLA) to educate patients about RMCTs, giving individuals the tools they need to assess whether treatments being offered to them—either through clinical practice or through clinical trials—are trustworthy, safe, effective, and suitable for human use.

This “patient primer” offers answers to questions frequently asked by patients, including:

- How do I know whether RMCTs are approved for use?
- How do I know if a therapy is trustworthy?
- Is off-label use of RMCTs safe and legal?
- Where can I find information about RMCT clinical trials?

It also provides questions that patients should be asking their health care providers before seeking treatment, such as:

- Does the therapy I’m exploring require FDA approval?
- If so, can the treating provider provide evidence of approval?
- Is the treating clinician licensed and certified in the intended area of treatment?
- Is the treating clinician licensed or trained to use these therapies?

The primer also offers a series of questions that patients should be asking before participating in a clinical trial, such as:

- Has the FDA evaluated the clinical trial design and authorized the study through approval of an investigational new drug application or investigation device exemption?
- Has the clinical trial received institutional review board (IRB) approval?
- Have I received a valid informed consent? What are the qualifications of the team conducting the clinical trial?
- What are the qualifications of the team conducting the clinical trial?

Additional information is offered in the Appendix, including details about the regulatory aspects of RMCTs and additional information about some of the technical requirements associated with clinical trials.

Introduction

Regenerative medicine and cell and tissue-based therapies (RMCTs) focus on repairing, replacing, restoring function, and in some cases, reversing disease, in organs or tissues that have been damaged or are functioning poorly, due to disease, trauma, or congenital conditions. Thousands of clinical trials have been conducted both in the United States and abroad that explore the use of RMCTs for a range of conditions, including cancer, cardiovascular disease, musculoskeletal conditions, neurological (brain) conditions, diabetes and kidney disease, COVID-19, wound healing, and a full range of other conditions affecting patients.

Alliance for Cell Therapy Now and the Alliance for Cell Therapy Foundation—independent, non-profit organizations (together referred to as the Alliance) guided by leaders representing academic and medical institutions, industry innovators, and patients, and the National Football League (NFL) Alumni Association (NFLA)—a non-profit organization representing former NFL players and other NFL alumni—are collaborating on efforts to educate patients on RMCTs. Nationally recognized leaders in the field—who serve on the [Advisory Board of the Alliance](#) and the [NFLA Regenerative Medicine and Cell Therapy Advisory Committee](#) and who are listed in the Appendix—lent their expertise and guidance to the development of this report.

Results of a [recent survey](#) of former NFL players and other NFL Alumni—conducted by NFLA in collaboration with the Alliance and Sanford Health—indicated that nearly half have considered RMCT trials or treatments and more than 80 percent are interested in learning more about these therapies. Similarly, many Americans are also interested in learning more about these therapies, but unfortunately, there are few, plain language, easily accessible resources that are available to patients who are trying to navigate this rapidly growing, complex field.

This report serves as a “patient primer” on RMCTs, offering answers to frequently asked questions, as well as questions that patients should be asking before undergoing treatment or participating in clinical trials. The goal of this report is to help patients assess whether treatments being offered to them—either through clinical practice or clinical trials—are authorized by the FDA and are trustworthy, safe, effective, and suitable for human use.



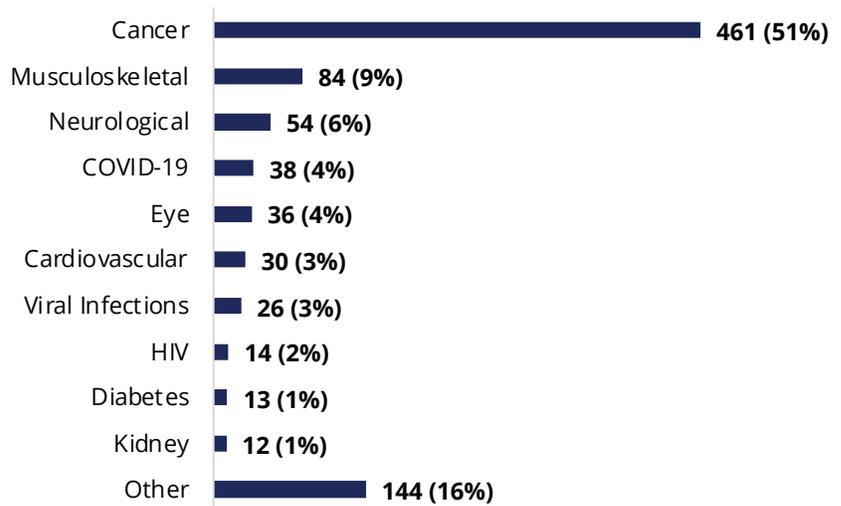
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Key Facts About RMCTs

As of December 31, 2021, there were more than 900 active clinical studies in the United States exploring the use of various types of RMCTs (regenerative medicine and cell and tissue-based therapies), including cell-based immunotherapies (54 percent), cell therapies (28 percent), and gene therapies (18 percent). As summarized in Figure 1, cancer is the most prevalent condition being studied (51 percent), followed by musculoskeletal conditions (9 percent), neurological conditions (6 percent), COVID-19 (4 percent), and eye-related conditions (4 percent).

Figure 1. Active U.S. Clinical Studies by Condition (n=912)

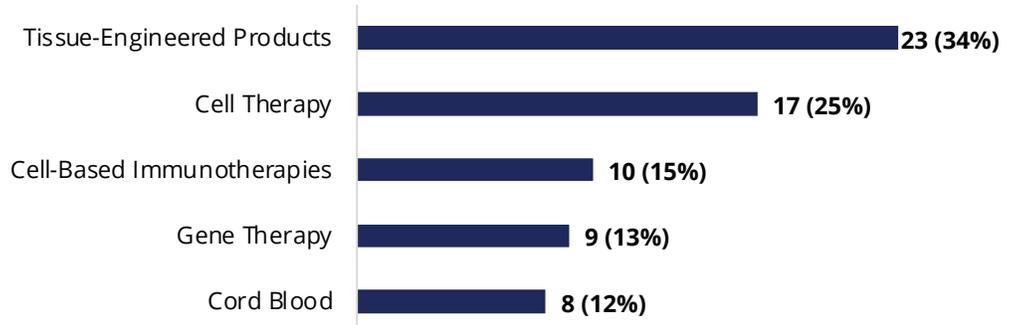


More than 900 clinical studies are now underway in the U.S. exploring the use of RMCTs for a range of conditions, including cancer, musculoskeletal conditions, and neurological conditions.

The vast majority (95 percent) of clinical studies are Phase 1 or Phase 2 clinical trials. Many have promising results, but large-scale, randomized, placebo-controlled trials are needed to confirm early results to bring these therapies to patients. The lack of federal funding serves as the primary barrier to conducting these large-scale trials.

According to a recent [analysis](#) conducted by the Alliance, to date, 67 RMCT products have been approved for use in various countries across the globe. As noted in Figure 2, tissue-engineered products (34%) and cell therapies (25%) make up nearly 60% of products approved across the globe, followed by cell-based immunotherapies (15%), gene therapies (13%), and cord blood products (12%).

Figure 2. RMCT Products Approved Worldwide (n=67)



Key Facts About RMCTs

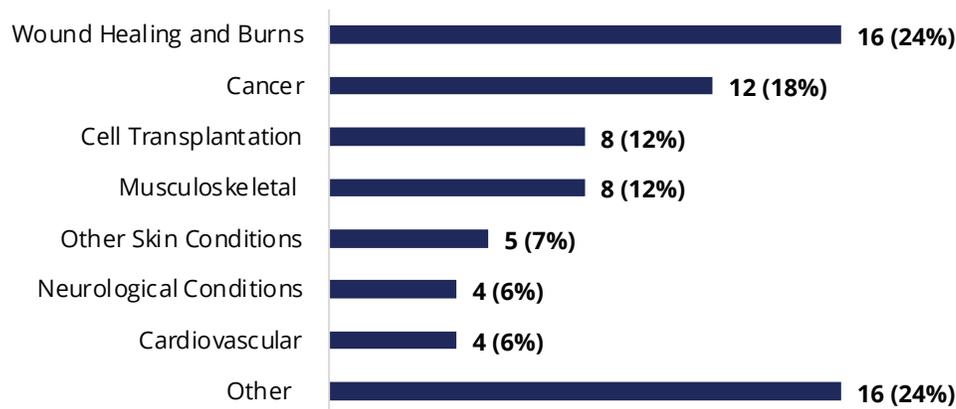
As of December 31, 2021, 29 of the 67 RMCT (regenerative medicine and cell and tissue-based therapy) products worldwide have been approved by the Food and Drug Administration (FDA) within the United States.

The FDA has made considerable progress in advancing RMCTs—primarily due to new authorities granted by Congress in the 21st Century Cures Act—which was passed nearly unanimously and on a bipartisan basis, a little more than five years ago. In response to the Act, the FDA implemented a new regenerative medicine regulatory framework, helping promising researchers and innovative biotechnology companies bring safe and effective therapies to patients in need.

FDA has approved a range of RMCTs, including tissue-engineered products (38 percent), cord blood products (28 percent), cell-based immunotherapies (21 percent), gene therapies (10 percent), and cell therapies (3 percent).

As noted in Figure 3, most products approved in the U.S. by the FDA are focused on wound healing and burns (24 percent), followed by cancer (18 percent), cell transplantation (12 percent), and musculoskeletal conditions (12 percent).

Figure 3. Products Approved in the U.S. by Condition (n=67)



Unfortunately, advances in regenerative medicine and cell therapies have coincided with an increase in private clinics that market RMCTs outside of clinical trials with unproven claims of safety and efficacy. Recent reports have shown an increase in unlicensed clinics operating outside of the law.

In response, as part of its regenerative medicine framework, FDA has taken regulatory and compliance action against a number of companies and individuals over the last several years for marketing products without FDA approval and for significant deviations from good manufacturing practice requirements—both of which put patients at risk. This has included issuance of hundreds of warning letters to stem cell marketers, clinics, and health care providers.

For patients considering RMCTs, Dr. Peter Marks, Director of the FDA's Center for Biologics Evaluation and Research (CBER) has [stated](#), "It is critical to only seek treatment using legally marketed products, or, for unapproved products, to enroll in clinical trials under FDA oversight."

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*Peter Marks, MD
Director, Center for Biologics
Evaluation and Research
Food and Drug Administration*

Answers to Frequently Asked Questions

The Alliance and NFLA have compiled a list of questions commonly asked by patients—drawing from a series of virtual, interactive panel discussions hosted by both organizations in 2021. Answers to those questions—which were developed with the guidance of nationally recognized experts who comprise the [Alliance Advisory Board](#) and [NFL Alumni Advisory Committee](#)—are summarized below.

1. How Do I Know Whether RMCTs are Approved for Use?

- To date, only a small number (29) of RMCTs (regenerative medicine and cell and tissue-based therapies) have been approved by the FDA as safe and effective. The list of products approved by the FDA are located on the FDA website, here, <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>
- Unproven RMCTs may only be used as a treatment in an FDA-authorized clinical trial.



RMCTs offered: (1) without regulatory approval or (2) outside of an FDA-authorized and registered clinical trial may be harmful to patients.

2. Does an RMCT Treatment That Consists of My Own Stem Cells Need FDA Approval?

- RMCTs that are exempt from FDA requirements include cells and tissues that are transplanted as part of a fertility treatment or are harvested and reimplanted in the same original form within the same patient during the same surgical procedure, known as the “same surgical procedure exemption” (21 CFR §1271.15(b)(e)).
- Cells and tissues removed for further processing and culturing with media and growth factors, such as MSC-based therapies, are considered investigational RMCT products that must be licensed and approved by the FDA or administered only through FDA-authorized clinical trials.

Answers to Frequently Asked Questions

3. How Do I Know if a Treatment is Trustworthy?

Recognizing the potential harms that unproven RMCTs (regenerative medicine and cell and tissue-based therapies) pose to patients, in a [recent article](#), the California Institute for Regenerative Medicine (CIRM) describes the policy framework it has adopted to support the responsible delivery of stem cell treatments.

1. Regulated. Adherence to Regulatory Standards (Product Level)

- **Manufacturing and Processing.** Products should conform to the FDA (or equivalent) and state standards for manufacturing, processing, and facility registration.
- **Product Authorization.** The administration of any product should be authorized or approved by the FDA.

2. Reliable. Administered by Reliable and Qualified Teams of Practitioners (Practitioner Level)

- **Certified Clinicians.** Administration of products should be directed by a doctor with certification in the particular specialty area for that disease or condition.

3. Reputable. Delivered at Reputable Medical Centers (Organizational Level)

- **Patient Disclosure and Consent.** The medical standard of care for providing stem cell treatments outside a formal clinical trial should include disclosure of essential information consistent with standards for voluntary informed.
- **Claims of Clinical Effectiveness.** Any claims of efficacy should be supported by clinical data published in peer-reviewed journals.
- **Follow-up and Adverse Event Reporting.** Clinics providing stem cell or regenerative medicine products should provide ongoing support and follow-up of patients including monitoring for safety and efficacy. Patients and or provider reported outcome data should be compiled and available for ongoing evaluation of safety and efficacy.
- **Patient Autonomy.** Patients should not be restricted in their right to talk about a medical practice or stem cell treatments.

A full description of the CIRM policy framework can be found in the article cited below:

Lomax, G.P., Torres, A., and Millan, Maria T. (2020). Regulated, reliable, and reputable: Protect patients with uniform standards for stem cell treatments. *STEM CELLS Translational Medicine*, 2020;9:547-553. Available at: <https://academic.oup.com/stcltm/article/9/5/547/6406811>

RMCTs should: (1) adhere to regulatory standards; (2) be administered by reliable and qualified teams of practitioners, and (3) be delivered at reputable medical centers

(CIRM, 2020)

Answers to Frequently Asked Questions

4. Is an “Off-Label” RMCT Treatment Safe and Legal?

- Drugs, biologics, or medical devices that have been **approved by the FDA as safe and effective for a specific indication**, or “on-label” use, may be legally prescribed by a licensed physician for any other purpose (off-label use) as a practice of medicine.



The safety and efficacy for “off-label” use of an FDA-approved RMCT has not been evaluated by the FDA and may not be covered by insurance.

5. Where Can I Go to Find Information About RMCT Clinical Trials?

- Search [ClinicalTrials.gov](https://clinicaltrials.gov), which is a database maintained by the National Library of Medicine at the National Institutes of Health (NIH) that lists privately and publicly funded clinical studies. Study site locations are provided for all studies listed. Listing a study does not mean that the study has been evaluated by the U.S. Federal Government.
- Patient and disease advocacy groups may have referral services to help find clinical trials.
- Confirm with the study sponsor or principal investigator that the investigational RMCT for clinical use in humans has an Investigational New Drug (IND) or an Investigational Device Exemption (IDE) in effect as specified by FDA regulations.

Avoid clinics that offer the same RMCT for a wide variety of injuries, conditions, or diseases if the claims cannot be supported by publicly available clinical trial results (e.g., published in scientific/medical journals and not “patient testimonials” or clinic commercials) or are FDA-approved for a specific indication.

Questions to Ask Your Health Care Provider Before Treatment

Patients who are offered an RMCT (regenerative medicine and cell and tissue-based therapies) as a treatment option are advised to ask the following questions of their health care provider offering the treatment regarding safety and effectiveness of the RMCT for their specific condition.

Table 1. Checklist of Questions to Ask Your Health Care Provider Before Treatment with RMCTs

1	Does the therapy require FDA approval?
2	If “yes” for item #1, is the therapy approved by the FDA and can the clinician provide the FDA-approved drug labeling information?
3	If the treatment does not require FDA approval, what studies have been done to show safety and effectiveness? Can you share the results of individual studies and where they have been published?
4	If the treatment is part of a clinical trial, is there an active IND or IDE or an exemption from the FDA?*
5	If the treatment is part of a clinical trial, has an IRB approved the study?*
6	Was the product manufactured according to cGMP in a facility that is registered with the FDA?
7	Is the treating clinician licensed and certified in the intended area of treatment?
8	Is the treating clinician licensed (or trained) to use these therapies?
9	Is treating clinician promising to cure a full range of conditions with RMCTs (e.g., knee problems, hair loss, traumatic brain injury, Alzheimer’s, etc.)?
10	If there is a charge for participation in a clinical trial, is the charge approved by the FDA as reasonable “cost-recovery”?
11	What is the safety profile of this therapy? Have there been adverse events?
12	What follow-up procedures will be done?
13	How will health care provider measure benefit?
14	What happens if there are any complications?
15	Is there an informed consent form and does it include all of the essential elements for the consent process?*

*See “Questions to Ask Before Participating in a Clinical Trial on page 10 for more

Patients considering RMCT treatment options should assure that therapies have been approved or authorized by the FDA.

Questions to Ask Before Participating in a Clinical Trial

Patients who are considering participating in a clinical trial are advised to ask the following questions of the sponsor or principal investigator conducting the clinical trial.

Table 2. Checklist of Questions to Ask Before Participating in a Clinical Trial

1	Has the FDA evaluated the clinical trial design and authorized the study through approval of an IND or IDE?
	<p>The FDA does not release any public information regarding an investigational new drug (IND) or investigational device exemption (IDE) application as this is confidential information between the Agency and the sponsor. The only way to know whether an IND or IDE is active/approved for an RMCT used in a clinical trial is to ask the study sponsor or clinical investigator or contact the director of the institutional review board (IRB) that approved the clinical trial. Contact information for each of these individuals should be provided on the informed consent form.</p>
2	Has the clinical trial received IRB approval?
	<p>An IRB is a group comprised of scientists and non-scientists that is formally designated under the US Government’s Code of Federal Regulations [45 CFR §46, 21 CFR §50 and 21 CFR §56] to review and monitor biomedical research involving human subjects.</p> <p>The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of people who participate in clinical trials that are regulated by the FDA.</p> <p>The FDA is responsible for determining whether an IND or IDE application is required for a drug, biologic or medical device study to proceed, but it is IRB approval that is required before a clinical trial may begin to consent and enroll subjects.</p> <p>For more information about IRB approval, see Appendix.</p>
3	Have I received a valid informed consent?
	<p>Before enrolling in a clinical trial, all prospective subjects should be provided an informed consent form (ICF) written in a language that is understandable by the prospective subject that must be carefully read, signed, and witnessed.</p> <p>The informed consent process involves three key features: (1) disclosing to the prospective clinical trial participant information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether to participate in the research.</p> <p>To be valid, the consent process must provide several basic elements within the informed consent form, which are outlined in the Appendix.</p>

Patients considering participation in a clinical trial should determine whether an FDA-authorized IND or IDE has been granted, whether it has received approval by an IRB, and whether a valid informed consent has been received.

Questions to Ask Before Participating in a Clinical Trial

The following is a continued list of questions that patients ask when considering participation in a clinical trial.

Table 2. Checklist of Questions to Ask Before Participating in a Clinical Trial

4	What are the qualifications of the team conducting the clinical trial?
	<p>During the consent process, potential subjects may ask about the training, licensure and prior experience the clinical investigator and study team members have in conducting clinical trials. Potential subjects should ask the clinical investigator to describe how the clinical trial will be monitored for adverse events and whether study data and results will be reported (e.g., to the FDA, at ClinicalTrials.gov, in a scientific publication). Some clinical trials that are potentially high risk may require an independent data safety monitoring board (DSMB), which meets periodically to review study data and recommends to the clinical investigator whether a study may continue.</p> <p>If a health care provider promotes the use of an investigational medical product, including many RMCTs, but declines to provide evidence of training or qualification to use RMCTs, lacks licensure, certification, or training in the intended area of treatment, and/or fails to describe the clinical trial monitoring, then patients are encouraged to seek a healthcare provider who does have the education, training, and experience in the use of RMCTs and the appropriate credentials for treatment.</p>
5	Does the team have experience in conducting clinical trials?
	<p>Clinical trials are costly and labor intensive to run and often involve additional procedures, documentation and monitoring that go beyond the standard practice of care. Most academic medical centers have specially trained clinical teams or entire departments dedicated to conducting clinical trials in compliance with FDA regulations. Clinical trials conducted at academic medical centers may be sponsored either by in-house experienced clinical investigators or by private biopharmaceutical and medical device companies, and patients treated at these academic medical centers have easy access to information regarding specific studies and study team qualifications. In addition to an IRB-of-record, a local IRB at an academic medical center may also provide monitoring and oversight of clinical trials.</p> <p>Assessing the clinical trial experience of the team at a private clinic not affiliated with a large academic medical center may require more effort on the part of the potential patient. A list of items that patients should confirm before participating in a clinical trial is provided in the Appendix.</p>
6	Where are the trials being carried out?
	<p>Clinical trials should be conducted in a clinical setting appropriate to the study design and under Good Clinical Practices (GCP) in compliance with applicable statutory and regulatory requirements.</p> <p>FDA-regulated clinical trials are required to be registered at ClinicalTrials.gov, which is a database maintained by the National Library of Medicine at NIH that lists privately and publicly funded clinical studies. Study site locations are provided for all studies listed. Listing a study does not mean that the study has been evaluated by the U.S. Federal Government.</p>

Patients considering participation in a clinical trial should review the qualifications of the team conducting the trial.

Looking Ahead

RMCTs hold great hope for patients in need, yet patients must be armed with the most current and reliable information to navigate this growing, complex field.

RMCTs (regenerative medicine and cell and tissue-based therapies) hold great hope for patients in need. A handful of these therapies have been approved and many more are under development.

Several actions are needed to help bring safe and effective RMCTs to patients in need. They include increased federal funding of clinical trials, optimization and scaling of manufacturing, and continued advancements at the FDA to provide clarification, education, and regulatory innovation, to help advance the field.

Navigating the field can be confusing for patients due to the complexity of FDA regulations, the lack of publicly available information to determine whether a clinical trial has been authorized by the FDA, and the false or misleading claims that some clinics and product developers have made.

Patients researching RMCTs should use this report to verify that products that they are considering are either (1) approved for specific disease(s) or condition(s) by the FDA, (2) if unapproved, then being conducted under an FDA-authorized clinical trial, or (3) do not require FDA approval and fall under the practice of medicine.

From a health care perspective, RMCTs may present less costly, more effective, and potentially more durable treatments for some of the most expensive and devastating conditions, contributing to vastly improved health outcomes.

The Alliance and NFLA will continue to monitor RMCTs and provide information useful to patients as they navigate this rapidly growing, complex, and promising field.

Appendix: Navigating the Regulatory Aspects of RMCTs

Understanding Which RMCTs are Authorized for Use

Very few RMCTs are approved by the FDA for use outside of a clinical trial. FDA's oversight of RMCTs is dictated, in part, by the extent of manipulation of cells and tissues before the final product is used in patients; however, the distinction is not always clear.

RMCTs that do not meet the "[same surgical procedure exemption](#)" are generally regulated according to two different paths constructed by the FDA's Office of Cellular, Tissue, and Gene Therapies within the Center for Biologics Evaluation and Research (CBER) to reflect what the agency considers to be "relative risk." Based on Sections 351 and 361 of the Public Health Service Act (PHSA), these pathways are commonly called "351" and "361" products and are described in greater detail in the following sections.

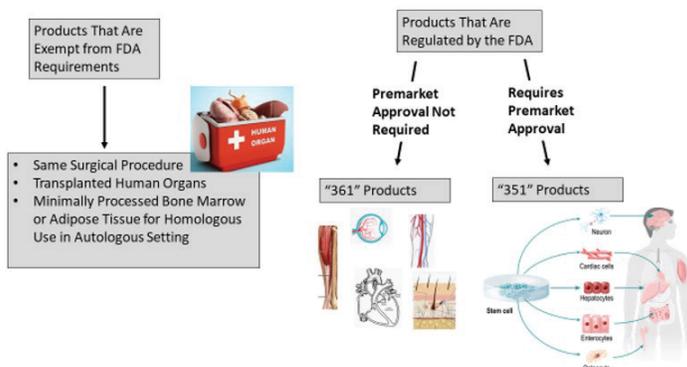
The "351" regulatory pathway closely resembles that of a traditional drug product. "351" products are more than minimally manipulated (i.e., undergo further processing or manufacturing) or products that are intended for non-homologous use and present a higher risk with respect to both manufacturing and clinical testing. "351" products are regulated as biologics that [require clinical investigations under an Investigational New Drug \(IND\) application and obtaining premarket approval of a Biological License Application \(BLA\) from the FDA](#). "351" products include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products, see Table 3.

RMCTs that are regulated under the "361" pathway are those products that present a lower risk due to minimal manipulation (i.e., they are not expanded in a flask or culture dish with media that would change gene expression or function) and are intended for homologous use, not combined with any other material, and rely on the metabolic activity of the living cells as a primary function if used in the same patient. Requirements for "361" products focus only on the prevention of communicable diseases and [no FDA premarket approval of a BLA](#).

No efficacy or potency claims may be made for 361 products because they lack rigorous clinical trial results and quality testing that would ensure consistency of the RMCT product from lot to lot. More detail is provided below regarding the full criteria for an RMCT to be regulated as a "361" product, and examples of 361 products are listed in Table 3.

The FDA has attempted to clarify how certain RMCTs will be regulated in a [recent guidance document](#). Regulation of human cells and tissues is illustrated in Figure 4.

Figure 4. Regulation of Human Cells and Tissue Products



Very few RMCTs are approved by the FDA for use outside of a clinical trial.

Appendix: Navigating the Regulatory Aspects of RMCTs

Products exempt from FDA requirements includes cell and tissues transplanted as part of a fertility treatment or harvested and re-implanted within the same patients during the same surgical procedure.

The two pathways for nonexempt products differ significantly with respect to the time, effort, and expense to market the product in the U.S. There are very few 351 products approved by the FDA; however, 351 products that have not yet been approved can be offered to patients under a clinical trial that has been authorized by the FDA.

Patients can receive RMCTs in the following scenarios:

1. Products That Are Exempt from FDA Requirements
2. Products That Are Regulated by the FDA
 - a. “361” Products That Do Not Require FDA Premarket Approval of BLA
 - b. “351” Products That Require FDA Premarket Approval of BLA
 - i. approved by the FDA for patient use for certain indications;
 - ii. off-label uses; and
 - iii. offered under an [FDA-authorized clinical trial](#).

Patients should not use RMCTs under any other circumstances. These categories are also described below in greater detail.

Products That are Exempt from FDA Requirements

RMCTs that are exempt from FDA requirements include cells and tissues that are transplanted as part of a fertility treatment or are harvested and reimplanted within the same patient during the same surgical procedure, known as the “same surgical procedure exemption” (21 CFR §1271.15(b)(e)). There are three requirements for same surgical procedure:

1. Applies only to autologous use –that is, cells/tissues come from the same patient.
2. Treatment is considered a single surgical procedure.
3. Cells/tissues must remain in original form –processing and manipulation may only include sizing, shaping, cleaning, and rinsing.

Products That are Regulated by the FDA

The following section describes the two different pathways that the FDA regulates RMCTs (termed “361” and “351” products), which are listed in Table 3. The two pathways differ significantly with respect to the time, effort, and expense to market the product in the U.S.

Table 3. 361, 351, and Combination Products

“361” Products	
Bone (includes demineralized bone)	Amniotic membrane (when used alone –without added cells- for ocular repair)
Ligaments	Dura mater
Tendons	Heart valve allografts
Fascia	Hematopoietic stem cells derived from peripheral or umbilical cord blood
Cartilage	Semen
Ocular tissues (corneas & sclera)	Oocytes
Skin	Embryos
Vascular grafts (veins & arteries, except preserved umbilical cord veins)	
Pericardium	

Appendix: Navigating the Regulatory Aspects of RMCTs

“351” Products (IND/IDE Required for Clinical Trial)

- Cultured cartilage cells
- Cultured nerve cells
- Lymphocyte immune therapy
- Gene therapy products
- Human cells used in therapy involving the transfer of genetic material (cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material contained in a genetic donor)
- Unrelated allogeneic hematopoietic stem cells
- Unrelated donor lymphocytes for infusion
- Cultured cartilage cells

Combination Products

- Demineralized bone combined with handling agents (glycerol, sodium hyaluronate, calcium sulfate, gelatin, collagen) –regulated as medical devices
- Bone-suture-tendon allografts –regulated as medical devices
- Cultured cells (fibroblasts/keratinocytes/nerves/ligament/bone marrow) on synthetic membranes or combined with collagen may be regulated as medical devices or biological products (these products are currently under review and may be regulated by CBER under either device authorities or §351 of the PHSA)

“361” Products That Do Not Require FDA Premarket Approval of a BLA

Briefly, §361 of the Public Health Services Act (PHSA) authorizes FDA to issue regulations aimed at preventing the spread of communicable disease. Under this authority, FDA has relied upon Title 21 of the Code of Federal Regulations (CFR) part 1271 as the basis for regulation for cell and tissue products. “361” products that meet all the requirements of part 1271 are not required to be licensed or approved by the FDA. Manufacturers of 361 products must ensure that appropriate donor eligibility measures are in place and current Good Tissue Practices are followed. Additional requirements for reporting, labeling, inspections, importation, and enforcement are described in part 1271 that apply to “361” products.

Looking at RMCTs, FDA will consider whether the product meets **all four criteria** below to be considered a “361” product.

1. It is minimally manipulated.

Examples of minimal manipulation include:

- Cutting, grinding, shaping, soaking in antibiotic solution, sterilization by gamma irradiation, lyophilization, freezing, and demineralization of bone
- Density-gradient separation, cell selection, centrifugation, and cryopreservation of cells

2. It is intended for homologous use (performs the same basic function in recipient as in donor, but it does not have to be used in same location).
3. It is not combined with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent.
4. It does not have a systemic effect, and it is not dependent upon the metabolic activity of living cells for its primary function or, if it has such an effect, it is intended for autologous use in close relatives or for reproductive use.

Appendix: Navigating the Regulatory Aspects of RMCTs

RMCTs that meet the criteria of a 361 product are required to be labeled and advertised only for homologous use, which is defined in 21 CFR §1271.3(c) as “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.” FDA clarified in the preamble to the regulation that homologous use of a structural tissue does not require use of tissue in the same location as it occurred in the donor; however, it must perform the same basic function or functions in the recipient as it did in the donor. The FDA stated, “We intend to interpret ‘nonhomologous’ narrowly.”

Application of the definitions of “minimal manipulation” and “homologous use” by some clinicians have created a “gray area” when it comes to determining the regulatory status of a cell-based therapy. The FDA has attempted to improve stakeholders’ understanding of these terms with the issuance of a guidance document [Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use, \(July 2020\)](#) that specifically addresses the FDA’s thinking on the criteria under 21 CFR part 1271 regarding minimal manipulation and homologous use.

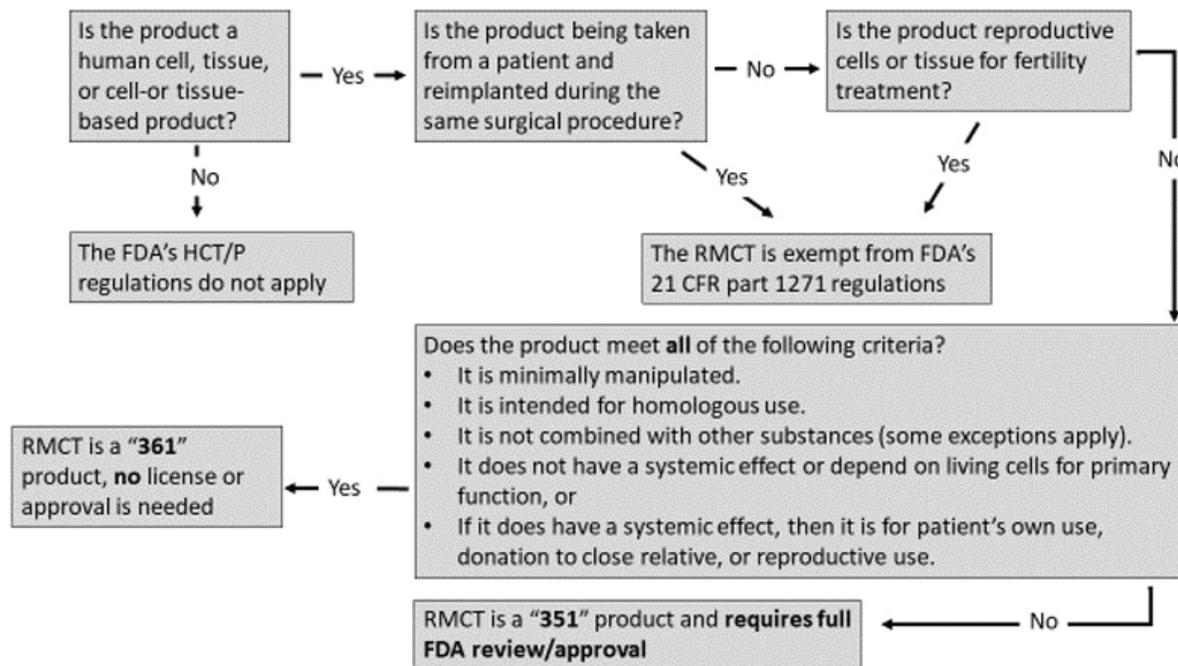
“351” Products That Require FDA Premarket Approval of a BLA

RMCTs that do not meet all the criteria outlined in 21 CFR §1271.10 will be regulated as a “drug, device, or biological product” under the Federal Food, Drug, and Cosmetic Act (FDCA) and §351 of the PHS Act. Federal law requires that a drug or biologic, which includes RMCTs, has an approved marketing application before it is transported or distributed across state lines for use in a clinical trial.

These “351” products require clinical trials to demonstrate safety, purity, potency, and effectiveness and FDA approval of a BLA. An investigational new drug application (IND) or investigational device exemption (IDE) if a medical device) is required before a clinical trial of an unapproved “351” RMCT product may begin. Once the IND or IDE is active, then an IRB will need to review and approve the clinical trial and subjects can begin to be enrolled.

Figure 5 summarizes the scenarios under which patients can access RMCTs.

Figure 5. Navigating RMCTs



Appendix: Navigating the Regulatory Aspects of RMCTs

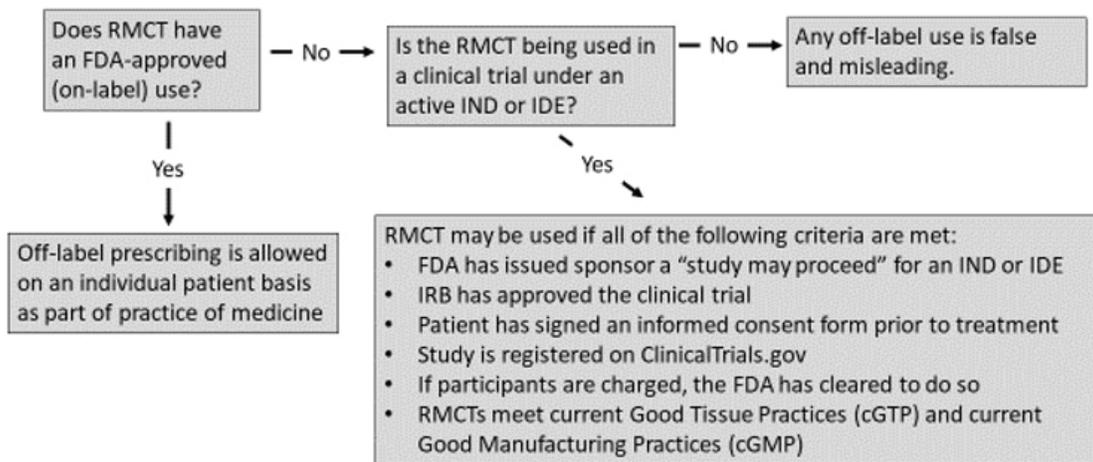
“351” Products That Have Been FDA-Approved

The current and complete list of FDA-approved cellular and gene therapy products can be found on FDA’s website <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>. RMCTs that enter the marketplace via the 351 regulatory pathway have undergone FDA’s rigorous regulatory approval process and demonstrate safety and efficacy that is backed by robust clinical trial data.

Off-Label Use of FDA-Approved Products

Off-label prescribing of FDA-approved drugs and medical devices is legal and commonplace in almost every field of medicine when the practice is supported by expert consensus or practice guidelines. FDA approval is granted for a drug, biologic, or medical device as safe and effective for a specific indication (i.e., “on-label,” use). Once approved and available on the market, the FDA does not limit or control how a medication is prescribed, and physicians may legally prescribe it for an indication, or dispense a dosage or dosage form, that has not been approved through the FDA process (i.e., off-label use), see Figure 3. Manufacturers of such drugs, biologics or medical devices are only legally able to educate and inform physicians about the on-label use and are prohibited from commercially marketing off-label uses.

Figure 6. Off-Label Use of RMCTs



The FDA prohibits “misbranding” of medications, which includes labeling a medication with misleading information, including off-label uses. Although barred from promoting off-label uses, manufacturers are allowed to respond to unsolicited questions from health care professionals about off-label use. The responses must be documented by the manufacturer. By definition, studies of new drugs or studies involving expanded use of an existing drug are “off-label” indications until FDA approval is obtained. If an off-label use of an FDA-approved product is offered as a treatment option, the FDA recommends patients ask the health care provider the questions in Table 4.

FDA has recently (August 2021) issued a [Final Rule](#), clarifying off-label marketing of a prescription drug, biologic, or medical device for a use that FDA has not approved.

Off-label use of RMCTs is allowable under certain circumstances.

Appendix: Navigating the Regulatory Aspects of RMCTs

Table 4. Questions to Ask Your Provider Regarding Off-Label Use of FDA-Approved Products

1	What is the drug approved for?
2	Are there other drugs or therapies that are approved to treat my disease or medical condition?
3	What scientific studies are available to support the use of this drug to treat my disease or medical condition?
4	Is it likely that this drug will work better to treat my disease or medical condition than using an approved treatment?
5	What are the potential benefits and risks of treating my disease or medical condition with this drug?
6	Will my health insurance cover treatment of my disease or medical condition with this drug?
7	Are there any clinical trials studying the use of this drug for my disease or medical condition that I could enroll in?

“351” Products That are Available Under an Active IND or IDE

Promising research in the field of regenerative medicine and cell-based therapies has given rise to steady growth of clinical trials that are expected to lead to full approval of many more therapies to help patients in need.

RMCTs undergo extensive preclinical evaluation before clinical studies involving patients begin. Preclinical testing includes in vitro studies to understand the product characteristics, in vivo studies to evaluate safety and mechanism of action, and pivotal animal studies that adhere to Good Laboratory Practices. RMCTs must demonstrate that the potential benefit of the treatment outweighs any potential safety risks found in the preclinical testing.

Patients can access investigational RMCTs (e.g., RMCTs being evaluated under clinical trials) so long as such trials are authorized by the FDA. A sponsor (usually the manufacturer or potential marketer) will submit an Investigational New Drug (IND) application to the FDA that includes results of preclinical studies of the new RMCT (i.e., animal pharmacology and toxicology studies), manufacturing information, investigator information, and detailed clinical protocols.

The sponsor cannot begin a clinical trial using an unapproved RMCT until the FDA has completed a 30-day review to assess whether the initial-phase trials will expose subjects to unnecessary risks. The FDA issues a “study may proceed” letter that is signed and dated by the Agency representative, and the sponsor must commit to (1) obtain informed consent from subjects, (2) obtain review of the study by an IRB, and (3) adhere to the IND regulations.

An RMCT that is an investigational medical device, which could include combination products, may be used in a clinical trial to collect safety and effectiveness data if a sponsor obtains an IDE from the FDA's Center for Devices and Radiologic Health before the study is initiated. An approved IDE permits a device to be shipped for the purpose of conducting clinical trials of the device.

Appendix: Additional Information About Clinical Trials

Additional Information about IRB Approval

An institutional review board (IRB) is a group comprised of scientists and non-scientists that is formally designated under the U.S. Government's Code of Federal Regulations [45 CFR §46, 21 CFR §50 and 21 CFR §56] to review and monitor biomedical research involving human subjects.

The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of people who participate in clinical trials that are regulated by the FDA. An IRB has the authority to approve, require modifications in, or disapprove research including clinical trials that will be used to support applications to the FDA to market drugs, biologics, and medical devices for human use.

The FDA is responsible for determining whether an IND or an IDE application is required for a drug, biologic or medical device study to proceed, but it is IRB approval that is required before a clinical trial may begin to consent and enroll subjects.

The IRB uses a group process to review research protocols and related materials (e.g., informed consent forms, study protocols, confirmation of IND/IDE "study may proceed" if required by FDA, patient-facing materials, qualifications of the study team members, conflicts of interest, and reimbursement).

The IRB-of-record for the clinical trial should be registered with the Office of Human Research Protections (OHRP), which provides oversight of human subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS). The OHRP website provides resources for the public regarding volunteer participation in a clinical trial. Many IRBs have earned accreditation from the Association for the Accreditation of Human Research Protection Programs, Inc., which is considered the "gold seal" for human research protection programs.

Essential Elements of an Informed Consent

Before enrolling in a clinical trial, all prospective subjects should be provided an informed consent form (ICF) written in a language that is understandable by the prospective subject that must be carefully read, signed, and witnessed.

The informed consent process involves three key features: (1) disclosing to the prospective clinical trial participant information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether to participate in the research.

Informed consent is more than just a signature on a form. It is a critical communication link between the prospective subject and an investigator, beginning with the initial approach of an investigator and continuing through the completion of the clinical trial. The study team should allow prospective subjects sufficient time to review the ICF when considering whether to participate and minimize the possibility of coercion or undue influence. Orders for research tests and procedures should not be finalized until after informed consent has been obtained.

The ICF is a legal document, and its main purpose is to protect the patient. No consent form should contain language that would waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the clinic or institution, or its agents from liability for negligence.

IRB approval is required
before a clinical trial can
commence.

Appendix: Additional Information About Clinical Trials

To be valid, the consent process must provide the following basic elements in an ICF (defined in 21 CFR §50.25):

1. A statement that the study involves research;
2. Purpose of the study;
3. Expected duration of a subject's participation;
4. A description of the study procedures and identification of any procedures that are experimental (e.g., procedures that are not standard care for disease or condition being treated);
5. Explanation of any known risks or discomforts to subjects who participate in the study;
6. Any anticipated benefits to subjects who participate in the study;
7. Disclosure of alternative procedures or treatments other than participation in the study;
8. A statement describing how records identifying a subject will be kept confidential and who may have access to those records (e.g., the FDA);
9. Explanation as to whether any compensation and medical treatments are available if injury occurs, and if so, what they consist of, or where further information may be obtained;
10. Contact information for answers to questions about the research and research subjects' rights, and whom to contact if a research-related injury occurs; and,
11. A statement that participation is voluntary, and refusal to participate or discontinue participation will not involve any penalty or loss of benefits to which the subject is otherwise entitled.

Additional elements of an ICF may include:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable;
- The circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- Any additional costs to the subject that may result from participation in the research;
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- A statement that new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject; and,
- The expected number of subjects involved in the study.

The FDA requires a statement in the ICF to certify registration of clinical trials that are conducted under an IND that will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank. The statement is: "A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. "Informed consent must be documented by the use of a written consent form approved by the IRB-of-record and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The person obtaining consent will also sign the consent form. A copy of the signed and dated consent form must be given to the person signing the form, and the investigator should retain the signed original in the research records.

These informed consent requirements are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed for informed consent to be legally effective.

Appendix: Additional Information About Clinical Trials

Considerations for Qualifications of the Team

As part of the FDA and IRB review process, a curriculum vitae or other statement of qualifications and prior research experience of the principal or lead investigators, as well as study team members who make treatment decisions, will be evaluated to ensure that they are qualified by training and experience in the intended area of treatment to investigate the drug, biologic, or medical device for the use under investigation.

During the consent process, potential subjects may ask about the training, licensure and prior experience the clinical investigator and study team members have in conducting clinical trials. Potential subjects should ask the clinical investigator to describe how the clinical trial will be monitored for adverse events (e.g., IRB, FDA) and whether study data and results will be reported (e.g., to the FDA, at [ClinicalTrials.gov](https://www.clinicaltrials.gov), in a scientific publication). Some clinical trials that are potentially high risk may require an independent data safety monitoring board (DSMB), which meets periodically to review study data and recommends to the clinical investigator whether a study may continue.

If a health care provider promotes the use of an investigational medical product, including many RMCTs, but declines to provide evidence of training or qualification to use RMCTs, lacks licensure, certification, or training in the intended area of treatment, and fails to describe the clinical trial monitoring, then patients are encouraged to seek a healthcare provider who does have the education, training, and experience in the use of RMCTs and the appropriate credentials for treatment.

Assessing the Team's Experience in Conducting Clinical Trials

Clinical trials are costly and labor intensive to run and often involve additional procedures, documentation and monitoring that go beyond the standard practice of care. Most academic medical centers have specially trained clinical teams or entire departments dedicated to conducting clinical trials in compliance with FDA regulations. Clinical trials conducted at academic medical centers may be sponsored either by in-house experienced clinical investigators or by private biopharmaceutical and medical device companies, and patients treated at these academic medical centers have easy access to information regarding specific studies and study team qualifications. In addition to an IRB-of-record, a local IRB at an academic medical center may also provide monitoring and oversight of clinical trials.

Assessing the clinical trial experience of the team at a private clinic not affiliated with a large academic medical center may require more effort on the part of the potential patient.

Patients should confirm the following before participation:

1. The clinical trial has IRB approval;
2. FDA has evaluated the clinical trial and issued an IND or IDE study may proceed;
3. The lead clinical investigator is licensed and certified in the area of treatment;
4. The team has successfully conducted other FDA-regulated clinical trials, or if not,
5. The team will be working with an experienced Contract Research Organization (CRO) to conduct the trial; and
6. A signed ICF will be obtained prior to any investigational treatment.

Patients should carefully consider the clinical team performing the clinical trial before participation.

Glossary

BLA	Biological License Application
CAR-T	Chimeric Antigen Receptor T-Cell
CBER	Center for Biologics Evaluation and Research
CDER	Center for Devices and Radiologic Health
CFR	Code of Federal Regulations
CIRM	California Institute of Regenerative Medicine
CRO	Contract Research Organization
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMP or cGMP	Good Manufacturing Practices or current Good Manufacturing Practices
GTP or cGTP	Good Tissue Practices or current Good Tissue Practices
HCT/P	Human Cells, Tissues, and Cellular and Tissue-Based Products
HHS	U.S. Department of Health and Human Services
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
NFL	National Football League
OTC	Over the Counter
MSCs	Mesenchymal Stromal Cells
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
PHSA	Public Health Services Act
RMCTs	Regenerative Medicine and Cell and Tissue-Based Therapies

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Scott Boden, MD

Professor of Orthopedic Surgery, Emory University School of Medicine and Director, Emory Orthopedics and Spine

Arnold Caplan, PhD

Professor of Biology, Director of the Skeletal Research Center, Case Western Reserve University

George Christ, PhD

Professor of Biomedical Engineering and Orthopaedic Surgery, Director of Basic and Translational Research in Orthopaedic Surgery; University of Virginia School of Engineering and Applied Sciences

Billy Davis

Co-Director, Healthcare Initiatives, NFL Alumni; Former NFL Player

Colleen Delaney, MD, M.S.c.

Founder, Chief Scientific Officer and Executive Vice President of Research and Development, Deverra Therapeutics and Professor, Department of Pediatrics, Division of Pediatric Hematology/Oncology, University of Washington

Joe GN "Skip" Garcia, MD

Dr. Merlin K. DuVal Professor of Medicine, University of Arizona Health Sciences

Jaime R. Garza, MD, DDS, FACS

Professor of Orthopedic Surgery, Professor of Otolaryngology, and Director of Human Regenerative Cell Trials at Tulane University School of Medicine; Professor of Surgery and Professor of Otolaryngology, University of Texas – San Antonio; Former NFL Player; Member, NFL Alumni Association

Steven R. Goodman, PhD, Vice Chancellor for Research, Professor, Departments of Pediatrics and Physiology, College of Medicine, University of Tennessee Health Science Center; President and CEO, Clinical Trials Network of TN; Memphis Institute of Regenerative Medicine

Geoffrey Green

Chief Executive Officer, Longeveron

Joshua G. Hackel, MD

Primary Care Sports Medicine Physician, Andrews Institute for Orthopedics and Sports Medicine; Director, University of South Alabama/Andrews Institute Primary Care Sports Medicine Fellowship; Director, Sports Medicine Outreach Program, Baptist Healthcare; Associate Professor, Florida State School of Medicine; Medical Advisory Board Member, Ladies Professional Golf Association (LPGA)

Joshua M. Hare, MD, FACC, FAHA

Louis Lemberg Professor of Medicine, Founding Director, Interdisciplinary Stem Cell Institute, University of Miami, Miller School of Medicine

James Kovach, MD

Chief Innovation Officer, Aggie Square (UC-Davis Sacramento Innovation Center) and Director of Translational Entrepreneurship and Industry Research Relationships, University of California – Davis; Former NFL Player; Member, NFL Alumni Association

Joanne Kurtzberg, MD

Jerome Harris Distinguished Professor of Pediatrics; Professor of Pathology; Director, Marcus Center for Cellular Cures; Director, Pediatric Blood and Marrow Transplant Program; Director, Carolinas Cord Blood Bank; Co-Director, Stem Cell Transplant Laboratory; Duke University Medical Center

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Janet M. Marchibroda
President, Alliance for Cell Therapy Now; Vice President and Executive Director, NFL Alumni

Maria T. Millan, M.D.
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President, NFL Alumni Association

J. Marc Overhage, MD, PhD
Principal Investigator, Alliance for Cell Therapy Research Evidence Development Collaboration, Alliance for Cell Therapy Foundation; Chief Medical Informatics Officer, Anthem

David A. Pearce, PhD
President of Innovation, Research, and World Clinic, Sanford Health; Senior Scientist, Sanford Children's Health Research Center; Professor of Pediatrics, University of South Dakota Sanford School of Medicine

Wenchun Qu, MD, PhD
Associate Professor of Anesthesiology; Associate Professor of Physical Medicine and Rehabilitation; Physiatrist and Pain Specialist, Mayo Clinic

Kyle Richardson
Vice-Chair of the Board, President of Chapters, Co-Director of Healthcare Initiatives, NFL Alumni

Camillo Ricordi, MD
Stacy Joy Goodman Professor of Surgery, Distinguished Professor of Medicine, Professor of Biomedical Engineering, and Microbiology and Immunology, Director of the Diabetes Research Institute and the Cell Transplant Program, University of Miami

Ricardo L. Rodriguez, MD
Medical Director, Cosmeticsurg.net; Member, Regenerative Medicine Task Force, American Society of Plastic Surgeons; Former President, International Federation for Adipose Therapeutics and Science

Krishnendu Roy, Ph.D.
Robert A. Milton Chair; Director, NSF Engineering Research Center for Cell Manufacturing Technologies; Director, Marcus Center for Cell-Therapy Characterization and Manufacturing; Technical Lead, National Cell Manufacturing Consortium; Director, Center for ImmunoEngineering, Georgia Institute of Technology

Fred Sanfilippo, MD, PhD
Professor, Pathology and Laboratory Medicine, School of Medicine, and Health Policy and Management, Rollins School of Public Health, Emory University; Director, Emory-Georgia Tech Healthcare Innovation Program; Former CEO, Woodruff Health Science Center, Emory University; Former CEO and Executive Dean, Ohio State Medical Center

Beth Shaz, MD
Professor in Pathology, Deputy Director of the Marcus Center for Cellular Cures, Duke University School of Medicine; Former Chief Medical and Scientific Officer and Senior Vice President, New York Blood Center

Bernard Siegel, JD
Executive Director, Regenerative Medicine Foundation; Founder and Chair, World Stem Cell Summit

Robin L. Smith, MD, MBA
President and Chair, Stem for Life and Cura Foundation

Mark L. Weiss, PhD
Professor, Director, Midwest Institute for Comparative Stem Cell Biotechnology, Coordinator of the Stem Cell Certificate program, Member Terry C. Johnson Center for Basic Cancer Research, Kansas State University

Piotr P. Witkowski, MD PhD
Associate Professor of Surgery, Biological Sciences Division, University of Chicago

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About Alliance for Cell Therapy Now and Alliance for Cell Therapy Foundation

Alliance for Cell Therapy Now and Alliance for Cell Therapy Foundation are independent, non-profit organizations guided by leaders representing academic and medical institutions, industry innovators, and patients, that are working to advance safe and effective regenerative medicine, including cell and tissue-based therapies, for patients in need. For more information, go to <http://allianceforcelltherapynow.org/>

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