Cytotherapy 23 (2021) 886–893

Contents lists available at ScienceDirect

CYTOTHERAPY

journal homepage: www.isct-cytotherapy.org

International Society ISCT Cell & Gene Therapy®

Short Report

Standardization, workforce development and advocacy in cell and gene therapies: a summary of the 2020 Regenerative Medicine InterCHANGE

Ian K. McNiece[1,6,*], Kara K. Wacker[2,6], Joanne Kurtzberg[3,6], Phyllis I. Warkentin[2,4,5,6]

[1] CellMED Consulting, Coral Gables, Florida, USA
[2] Foundation for the Accreditation of Cellular Therapy at the University of Nebraska Medical Center, Omaha, Nebraska, USA
[3] Marcus Center for Cellular Cures, Duke University School of Medicine, Durham, North Carolina, USA
[4] Departments of Pathology/Microbiology and Pediatrics, University of Nebraska Medical Center, Omaha, Nebraska, USA
[5] Board of Directors, Foundation for the Accreditation of Cellular Therapy at the University of Nebraska Medical Center, Omaha, Nebraska, USA
[6] Regenerative Medicine Task Force, Foundation for the Accreditation of Cellular Therapy at the University of Nebraska Medical Center, Omaha, Nebraska, USA

ARTICLE INFO

Article History:
Received 16 December 2020
Accepted 7 February 2021

Key Words:
advocacy
cellular therapy
collaboration
regenerative medicine
standardization
workforce

ABSTRACT

Cell and gene therapy is a promising and disruptive new field of medicine for diseases lacking effective treatments. Collaboration among stakeholders has become critically important as investigators, health care providers, manufacturers, couriers, data registries, regulators and payers all become more invested in the success of this field. Many organizations have collaborated with each other to increase clarity, advocate for improvements and share lessons learned. These efforts appear to be making an impact, although the potential for duplicative efforts could slow progress. The second Regenerative Medicine InterCHANGE, hosted by the Foundation for the Accreditation of Cellular Therapy, took place at the Phacilitate Leaders World/World Stem Cell Summit conference in Miami, Florida, on January 24, 2020. Participants from several organizations outlined needs to advance cell and gene therapies. Efforts to address these include standardization, workforce development and advocacy. This article summarizes the major challenges and opportunities discussed during the InterCHANGE.

Introduction

Cell and gene therapy is a promising and disruptive new field of medicine for diseases lacking effective treatments. As illustrated by commercialization of these therapies in recent years, several elements of the health care system must be prepared to accommodate paradigm-shifting treatment methodologies before they can be widely accessible to patients. This includes new and shared responsibilities among many different stakeholders, such as investigators, health care providers, manufacturers, couriers and data registries. Collaboration among these stakeholders, regulators and payers has become critically important as all become more invested in the success of this field.

Many organizations have collaborated with each other to increase clarity, advocate for improvements and share lessons learned. As described later in this article, these efforts appear to be making an impact, although the potential for duplicative efforts could slow progress. The Foundation for the Accreditation of Cellular Therapy (FACT) determined that linking the needs of all involved in the advancement of novel cell and gene therapies is key to proactive change management. Lessons learned can be applied to any cell and gene therapy to minimize the disruptions, barriers and time frames between regulatory approval and patient delivery. This is the purpose of the Regenerative Medicine InterCHANGE.

The second Regenerative Medicine InterCHANGE, hosted by FACT,[1] took place at the Phacilitate Leaders World/World Stem Cell Summit conference in Miami, Florida, on January 24, 2020. Several organizations accepted FACT's invitation to participate and selected one to two representatives to attend. A description of each of these organizations is provided as a supplement to this article.

Efforts to Advance Cell and Gene Therapies

The first hurdles in the development of cellular therapy for regenerative medicine are well known and require continued attention: scientific advancement, product development and manufacturing processes. These can lead to regulatory approval; however, this is no

* Correspondence: Ian K. McNiece, PhD, CellMED Consulting, 438 Minorca Ave, Coral Gables, Florida 33134, USA.
E-mail address: aussiflier@aol.com (I.K. McNiece).

[1] The first InterCHANGE took place at the Cord Blood Connect international congress in Miami Beach, Florida, on September 17, 2018. The genesis of this meeting was the initial experience of implementing novel cellular therapies within FACT-accredited blood and marrow transplant programs. The second InterCHANGE broadened the scope of participants.

https://doi.org/10.1016/j.jcyt.2021.02.004
1465-3249/

guarantee that the product will or can be used. Downstream stakeholders must also be prepared, including health care providers and payers and the intermediary quality and legal professionals that coordinate the two.

Participants in the InterCHANGE outlined several needs to advance cell and gene therapies, and efforts to address them include standardization, workforce development and advocacy (Figure 1). Many organizations represented at the InterCHANGE are already participating collaboratively in these efforts.

This article summarizes the major challenges and opportunities discussed during the InterCHANGE but is not an exhaustive list of all issues or initiatives. The summary includes the content that was presented and discussed during the InterCHANGE but does not necessarily indicate agreement on each initiative by all participating organizations.

Apheresis Collection

Standardization

Apheresis facilities have collected cells for hematopoietic stem cell transplantation for decades, and many are accredited and expert in the use of collection equipment, development of and compliance with validated collection protocols, patient and adverse event management, labeling and release. Clinical trial sponsors and commercial manufacturers (both hereafter referred to as commercial manufacturers) have also created their own collection protocols and procedures as part of their trial design and manufacturing processes.

The combination of facilities' own validated procedures and specific procedures mandated by individual companies led to wide variability within and across facilities, challenging apheresis professionals to follow the correct protocol for the correct product using resources that are further limited by additional required training and implementation. The associated regulatory burden also increases costs. The result is decreased efficiency and increased risk of noncompliance.

- The Standards Coordinating Body (SCB) formed a working group to establish standard cell collection requirements that ensure consistency, safety and comparability in final products and reduced loss of cell material. This working group aims to evaluate cell collection protocols to determine what standards could be adopted by investigators and companies as they develop their research and commercial protocols. The group is currently developing surveys for industry and apheresis centers to clearly identify areas of variability. Future trials and commercial processes could use any resulting standards to reduce efforts for developing collection processes and to reduce variability within apheresis facilities. The reduction in effort and increase in consistency would be of benefit for both industry and apheresis facilities.
- The American Society for Apheresis (ASFA) serves a membership primarily comprised of apheresis professionals and therefore offers many resources for this field. Its Apheresis Standard Operating Procedures Manual [1] provides a collection of sample procedures that could be used as a basis for standardized processes.

Workforce development

As demand for cell and gene therapies increases, a natural consequence is that there will be an increase in demand for apheresis services. Many apheresis facilities also provide other services, such as therapeutic apheresis and collection of convalescent plasma for the worldwide coronavirus disease 2019 pandemic. Growth in demand, though, is not the only source of increased need. Apheresis professionals are in demand by a variety of stakeholders, with responsibilities for designing, implementing and overseeing the provision of cellular starting material. The increased competition increases the costs of recruiting and retaining personnel. The lack of standardization of mandated collection procedures and parameters and the additional regulatory burden are creating increased needs for full-time equivalent personnel.

- ASFA's Principles of Apheresis Technology [2] provides a basic overview of the theory and applications of apheresis with a self-study guide and can be used to develop training programs for new apheresis personnel. ASFA offers a Qualification in Apheresis [3] in partnership with the American Society for Clinical Pathology Board of Certification, which promotes professional development and retention. ASFA also hosts an Apheresis Awareness Day, an annual meeting, online webinars and other member resources to support and advance apheresis.

Advocacy

Apheresis facilities are at the frontline of the growth in demand for cellular therapies, with peripheral blood being a common source of cells for many investigational and licensed products. Given the large number of apheresis facilities and commercial manufacturers, these stakeholders have sought systemic improvements.

- The International Society for Cell & Gene Therapy (ISCT) hosts Cell Therapy Liaison Meetings that allow 20 invited stakeholder organizations and industry to present in person to the US Food and Drug Administration (FDA) or Health Canada's Biologics and Genetic Therapies Directorate specific concerns, challenges and

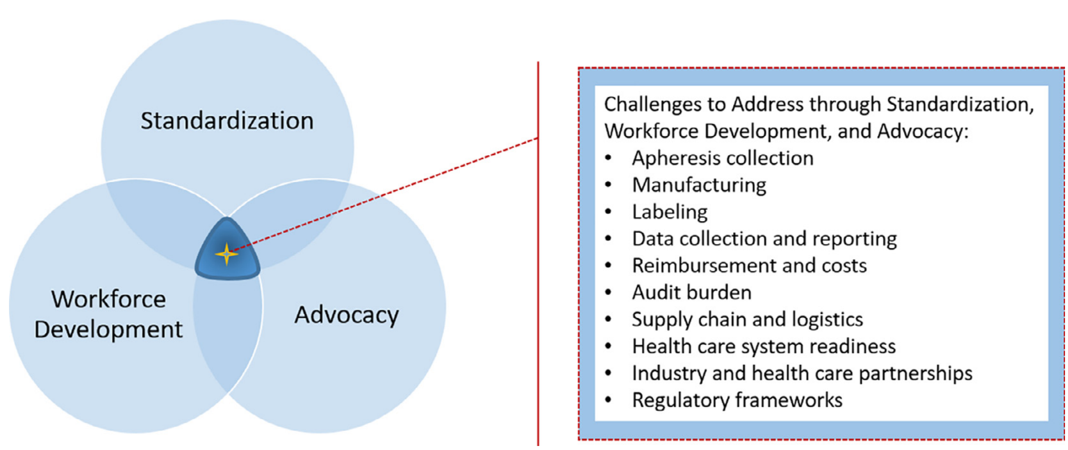

Figure 1. Efforts to enable access to novel cell and gene therapies. (Color version of figure is available online).

recent developments in cell and gene therapy. During the FDA Cell Therapy Liaison Meeting on March 5, 2019 [4], Jay Raval on behalf of ASFA presented regarding the collection of mononuclear cells for immune effector cellular therapy products, stating that a desired outcome is that specific goals for collection of cells be a requirement for immune effector cell products. This would reduce variability in starting material, optimize the quality of collections, enhance donor safety by eliminating unproductive or unnecessarily long collections and allow collection with optimal target cell counts and low presence of contaminating cells. Suggested means by which solutions could be designed were professional meetings, data sharing among manufacturers, investigational new drug reports or a white paper.
- One of the priorities of the Cord Blood Association (CBA) is to expand the market for cord blood and enhance consumer access to banking services and cellular therapies. Cord blood has the potential to be a readily available source of cells for cell and gene therapy and could add to the health care system's capacity for cell procurement and, most importantly, increase patient access to cellular therapies. For example, Gamida Cell uses its technology platform to enhance the number and functionality of allogeneic cord blood units for its investigational drug, omidubicel [5].

Manufacturing

Standardization

Manufacturing consistency could not only promote and expedite regulatory approval but would also lessen the burdens of personnel training, validation and trial and error. Standardization of laboratory manufacturing may be difficult given proprietary platforms, but some common processes could be achieved. Furthermore, the early adoption of an underlying quality system will allow procedures, documents and training to be systematically updated as more details specific to a disease, indication or manufacturing method emerge.

- Standards of AABB [6] and FACT [7–9] that serve as the basis of voluntary accreditation require, and are based on, quality management systems.
- Celltrials.org is a compilation of clinical trials in cell and gene therapy worldwide that uses 15 clinical trial registries to view global trends. The compilation allows a review of manufacturing methods and can identify variability in manufacturing. For example, Couto *et al.* [10] reported the number of passages used in the manufacture of umbilical cord-derived mesenchymal stromal cells and also noted that 48% of 98 publications did not report the number of passages.

Workforce development

- AABB created an online module, Bringing Flow Cytometry to Life, that covers the basics of flow cytometer operation and application of flow cytometry in cellular therapies. The module includes exercises that demonstrate gating strategies and analyses of a variety of cell types [11].
- The Alliance for Regenerative Medicine (ARM) is developing books of knowledge titled *A-Gene* and *A-Cell* for best practices in cell and gene therapy manufacturing using a quality by design approach. The books are being written by a broad base of experienced contributors, including 50 ARM member companies, and in collaboration with the National Institute for Innovation in Manufacturing Biopharmaceuticals, SCB and United States Pharmacopeia. The books are anticipated to be released as open source online and possibly as print publications, with continued maintenance and updates.
- ASFA annual meetings, webinars, journal clubs and online resources provide many learning and training tools for apheresis professionals.

Advocacy

- The Florida Organization for Regenerative Medicine convenes the state's many clinical and research groups and industry in Florida to direct efforts to educate policymakers on the importance of regenerative medicine and leverage state, federal and philanthropic funding to accelerate regenerative medicine in the state of Florida.
- ASFA has initiated an Apheresis Awareness Day to increase awareness of apheresis professionals.

Labeling

Standardization

Labeling of both the starting cellular material and the final biologic product is critical to maintaining chains of identity and custody. Labels are typically proposed by a commercial manufacturer as part of its application for regulatory approval. With hundreds of manufacturers proposing their own labels, this is quickly becoming an unsustainable process for the decentralized apheresis facilities labeling the starting cellular material. The increasing variety of labels has put undue pressure on resources, from training personnel to identifying counter space for required hardware. The potential for product mix-ups from labeling errors and inadequate identifiers poses an unacceptable risk to patients.

- The Deloitte NexGen Industry Working Group identified labeling as a key challenge. It coordinates a label focus group with the SCB that consists of clinicians, industry quality and regulatory advisors, accrediting organizations, technical solution providers and leading pharmaceutical companies. The label focus group determined ways in which the commonly used ISBT 128 international coding and labeling standard, administered by the International Council for Commonality in Blood Banking Automation, could be used to accommodate cell and gene therapies. A draft document with example label templates titled *Standard Labeling for Apheresis Collection Products for Sponsor Cellular Therapy Manufacturing* [12] was available for public review and comment from February to May 2020. Comments are currently under review.
- The use of an ISBT 128-compliant label reduces manual transcription errors and promotes chain of identity, including for autologous cells. Furthermore, the use of ISBT 128 for these collections allows the use of processes, labels, equipment and software compatible with those already in use for other types of cellular therapy products collected by apheresis facilities for clinical application.

Data Collection and Reporting

Standardization

Regulatory authorities require long-term (e.g., 15 years) patient follow-up for gene-modified therapies to determine possible latent effects, such as secondary malignancies. Data collection and reporting are the ultimate responsibility of the commercial manufacturer; however, clinical sites are tasked with collating the information and submitting it. Industry has understood the importance of a positive data submission experience for clinical sites, and the focus is beginning to transition from individual company data portals to a standardized method.

- The Cellular Therapy Registry Initiative of the Center for International Blood and Marrow Transplant Research (CIBMTR) provides a data submission and repository to study cellular therapies for indications other than hematopoietic replacement or recovery. This includes immunotherapy and regenerative medicine indications (e.g., neurology and cardiovascular). It provides an infrastructure to allow long-term follow-up of patients treated with genetically manipulated cell therapy products. The registry is already in use for the two licensed chimeric antigen receptor (CAR) T-cell products, Yescarta (Kite) and Kymriah (Novartis), as of the time of this writing. It is also used by the National Cancer Institute Cellular Immunotherapy Data Resource. To further promote international submission, it harmonized forms with the European Blood and Marrow Transplant registry and developed a Japanese platform to capture data. As of 2019, over 2000 CAR T-cell administrations have been entered into the Cellular Immunotherapy Data Resource for nearly as many patients. The number of clients, cell administrations and patients that can already be accommodated by the CIBMTR Cellular Therapy Registry demonstrates its ability to be an industry-wide solution.
- The Cell and Gene Therapy Catapult, as part of its partnership with the Advanced Therapy Treatment Center (ATTC) network, is designing digital solutions that will utilize integrated National Health System (NHS) data in the UK and allow for universal data integration and exchange.

Advocacy

- The Alliance for Cellular Therapy Now (ACT Now) advocated for support in the fiscal year 2020 spending bill in the USA to include funding for the National Institutes of Health, FDA and Health Resources and Services Administration to explore the feasibility and utility of an outcomes database for adult cellular therapies by engaging experts and stakeholders to define data types and necessary standards.

Reimbursement and Costs

Standardization

The high cost of goods during cellular manufacturing does not have an effect on what the market will bear. Standardizing cost of goods has the potential to decrease the final cost of a cell and gene product and increase the potential for adequate reimbursement. Ancillary materials affect the purity, integrity and potency of cellular therapy products and must undergo qualification prior to use—a major driver of time and cost constraints in cellular therapy product development.

- ISCT's Commercialization Committee is charged with describing manufacturing and production cost drivers. It created a roadmap for cost of goods planning [13].
- The SCB has a working group on ancillary materials used in cellular therapy production and partnered with the International Organization for Standardization to develop a three-part series of documentary standards [14–16]. The SCB is now coordinating the effort in the US to combine these three parts into a single document for publication as an international standard.

Advocacy

Cell and gene therapies could use a new reimbursement model and new coding structures because the costs of product acquisition and clinical care are incurred in a short amount of time, rather than over the course of traditionally long-term, chronic-based treatments. Payers cannot pay the high price tag of the product plus the potential for acute, intensive clinical care and remain solvent under the current model. However, without reimbursement, providing these therapies is not sustainable for health care entities.

- The American Society for Transplantation and Cellular Therapy (ASTCT) has been leading multi-organizational efforts to create value assessments and developing new frameworks for coding and reimbursement in the USA. Examples include participation in the Massachusetts Institute of Technology Financing and Reimbursement of Cures in the US consortium, engagement with the Institute for Clinical and Economic Review and partnerships with key organizations, including clinical professional societies, ARM and CIBMTR.
- ARM has engaged with the Centers for Medicare & Medicaid Services (CMS) and successfully advocated for a new drug resource group for CAR T-cell products, paving the way for increased patient access.
- ASTCT advocates for proper reimbursement at the US federal level via congressional visits and with CMS. Key successes include passage of the PACT ACT [17] and a New Technology Add-On Payment increase.
- ACT Now, in conjunction with the Bipartisan Policy Center, has recommended that CMS launch demonstration projects focused on the use of real-world evidence to support value-based payment models.
- ISCT provides education to industry regarding pre-commercialization reimbursement considerations.
- Gamida Cell provides direct support for prior authorizations, claims appeals and assistance for the uninsured or underinsured. This helps not only patients and their families but also health care providers with increasing responsibilities.
- ASFA has been publishing apheresis-related guidelines, including a reimbursement guide, and actively engaging in dialogue with regulatory agencies such as the FDA and CMS on issues related to cell collection.

Audit Burden

Standardization

Health care entities providing cell collection or processing services for commercial manufacturers and subsequently utilizing the final drug products are subject to multiple layers of audits: site qualification and routine oversight audits by commercial manufacturers for both clinical trial and commercial products, regulatory inspections and voluntary accreditation inspections. Many of the requirements included in these audits are duplicative, creating an unnecessary burden on health care personnel and finances and conflicting citations that need correction.

- FACT updates its standards every 3 years to evolve with the cellular therapy field. In its most recent draft eighth edition, anticipated to be published in May 2021, it proposes revisions to more explicitly state requirements to align with commercial manufacturers' audit obligations. The standards also reflect new developments in the field, such as the use of cells collected by apheresis as "starting material" for further manufacturing and direct distribution of final products from a manufacturer to a clinical unit.
- Be the Match BioTherapies implemented its Quality System Audit Program, through which it conducts audits of cell collection facilities and licenses the audit report, closure letter and findings response to manufacturers. The intent is to perform one audit that can satisfy the requirements for multiple manufacturers to reduce the burden on collection facilities. Be the Match BioTherapies has also initiated efforts to narrow the scope of its Quality System Audit Program audits when AABB or FACT accreditation is in place to further reduce duplicative audit requirements.

- Dendreon developed a response to streamline its onboarding activities for Provenge (sipuleucel-T) for FACT-accredited centers to reduce audit duplication.
- Other manufacturers are leveraging FACT accreditation to allow accredited sites the option of an abbreviated site audit to reduce duplicative audits of quality systems.

Advocacy

The blending of the pharmaceutical industry and health care provider-directed therapies has resulted in a convergence of different perspectives and experiences. Identifying synergies is a critical component of maximizing the benefits of audits with the most efficient and least burdensome approach. Two-way discussions between commercial manufacturers and accrediting organizations often reveal that necessary requirements are already in place.

- FACT has focused on creating awareness of existing FACT requirements and how FACT accreditation can be used to meet manufacturer audit requirements. It works with other standards-setting organizations by participating in a variety of conferences (e.g., Be the Match ONE Forum, Phacilitate Leaders World/World Stem Cell Summit) and working groups (e.g., SCB). It also communicates directly with interested commercial manufacturers and, with cellular therapy program permission, has allowed manufacturer observations of its on-site inspections to gain insight into the rigor of its accreditation process.

Supply Chain and Logistics

Standardization

Many cell and gene therapy products are patient-directed—either autologous or with a directed recipient of an allogeneic donation. To maintain chains of identity and custody, robust supply chain management and logistics are required. When commercial manufacturers design their own supply chains, apheresis facilities, cell processing facilities and clinical sites are expected to use multiple information system platforms, forms, couriers and more. The variation can be counterproductive and overly burdensome.

- Be the Match BioTherapies was created as a subsidiary of the Be the Match program to leverage its extensive experience with supply chain logistics and required infrastructure, which includes 30 years of experience and 36 000 cell and blood shipments annually across an international network. Commercial manufacturers can utilize Be the Match BioTherapies' services for cell collection, supply chain and collection network management, among other services. Use of its services would streamline the ordering, distribution and tracking processes among many different manufacturers and products.
- The Cell and Gene Therapy Catapult, as part of the ATTC network, is developing and delivering systems for the routine supply delivery of cell and gene therapies and will disseminate lessons learned and systems from the initial centers to enable widespread adoption across the NHS.
- The international ISBT 128 standardized terminology and product codes support traceability of products and improve data transfer accuracy. Furthermore, ISBT 128 is maintained with the guidance of an international committee with representation from standards-setting organizations and professional societies to promote harmonization with other requirements. ISBT 128 is applicable to products at multiple stages of development, including standard of care, clinical trials and commercial licensing.
- The CBA is evaluating ways to harmonize international requirements for donor testing and transporting products across borders given the global use of cord blood units as a cell source.

Health Care System Readiness

Standardization

To grow the capacity of the health care system to accommodate disruptive cell and gene therapies, there is benefit to sharing steps facilities have taken to implement them. A collaborative spirit will reduce both trial and error and variability.

- The Cell and Gene Therapy Catapult developed an organizational readiness toolkit for cell and gene therapies, which is a platform with guidance, checklists and standard operating procedures. It was launched to the ATTC network in January 2020.
- ISCT provides BEACON, an online suite of navigational tools, to its membership. It is a database of research, regulatory and accreditation documents; standard operating procedures, forms and templates; and other tools.

Workforce development

The field has a lot of learn. New scientific discoveries, new supply chain participants and new clinical applications are all expanding the day-to-day duties of the current health care workforce. Additionally, the workforce needs to grow exponentially if the health care benefits are to be realized by the substantial number of patients who could benefit from them.

- The AABB Cellular Therapies Certificate Program [18], administered in partnership with the George Washington University, offers biomedical/health care professionals a certificate program in cellular therapies. It consists of 12 professionally narrated online modules developed by faculty experts.
- The Cell and Gene Therapy Catapult and ATTC have initiatives to provide coordinated, multidisciplinary training in the UK. They created a single platform to host NHS Advanced Therapy Medicinal Product (ATMP) education and collaborated with the University of Manchester on the development of a Master of Science degree in ATMPs, a postgraduate master's course designed to educate candidates on the challenges of ATMP development and clinical delivery [19].
- The ISCT Laboratory Life Line online forum is an online community of laboratory professionals and is a resource for colleagues who wish to ask questions, share ideas and solve problems [20].
- Sanford Research provides internal education and integrates professional development with its clinical care resources to ready its workforce for new cell and gene therapies.

Advocacy

- ACT Now is advocating for significantly expanded workforce development initiatives, including at technical and community colleges, to build capacity and develop a skilled technical workforce for the field.
- Sanford Health frequently interacts and collaborates with industry to provide practical, real-world experiences applying novel cellular therapies in the clinic. It accepts speaking engagements both nationally and internationally, during which it describes challenges and solutions, from clinical space to coding for reimbursement.

Industry and Health Care Partnerships

Standardization

The dichotomy between industry regulatory submissions and health care operations is that industry, as the sponsor of cell and gene therapies, is the stakeholder that submits proposals (via commercial applications such as biological license applications and ATMP applications), but health care providers also apply them. To avoid conflicting guidelines and allow real-world applicability of commercial manufacturers' requirements, partnerships between the two are necessary.

- ASTCT hosts consensus meetings to harmonize clinical applications of cell and gene therapies among industry, providers and related stakeholders. For example, a single patient could be assigned different grades of cytokine release syndrome by three different published criteria plus additional clinical trial and after-market reporting requirements. In 2018, ASTCT hosted meetings to create consensus grading criteria for cytokine release syndrome and neurotoxicity that included investigators, industry, payers and governmental agencies. The result was published consensus grading criteria [21] that are applicable to both clinical trials and commercial use and can be used at the bedside by any provider. A similar effort is underway for consensus patient management of these toxicities.
- The SCB publishes and updates two reports that provide a summary of standards already in existence, including *The Regenerative Medicine Landscape* [22] and *Needed Standards in Regenerative Medicine* [23].

Workforce development

Industry and health care entities can align their needs to efficiently use the limited personnel resources in cell and gene therapies. By focusing on each other's strengths, the synergies achieved can improve patient access and reduce the costs of doing business.

- The efforts undertaken by commercial manufacturers, FACT and Be the Match BioTherapies to streamline audits (described earlier) can reduce manufacturers' needs for auditing personnel, sustain an adequate workforce for apheresis facilities and leverage the professional experience of cellular therapy professionals to conduct quality inspections.

Advocacy

The relationship between industry and academia is mutually beneficial: industry benefits from academia's scientific expertise and clinical infrastructure, and academia benefits from industry's financial resources and regulatory expertise.

- ASTCT's Corporate Council allows candid exchanges between members of society, industry and other subject matter experts to discuss critical issues of mutual concern, find solutions to pressing challenges, share knowledge on best practices and advise ASTCT on its major initiatives.
- Dendreon has actively participated in multi-stakeholder standardization efforts, such as SCB working groups, to create industry awareness around similar existing standards.
- FACT has connected health care providers administering cellular therapies with industry to find a balance between information needed by clinicians to adequately manage patients and the burden on manufacturers (e.g., cell dose in a CAR T-cell product).

Regulatory Frameworks

Standardization

The use of peer-developed standards and voluntary accreditation could alleviate the burden of oversight on regulatory agencies, providing them with a reassurance of quality and allowing them to focus on bad actors promoting unproven therapies.

- The CBA is working with the FDA to streamline approval mechanisms for directed cell therapy products. It is promoting the standardization of release specifications rather than specific manufacturing endpoints, such as the approach taken for public bank licensure, so that the millions of cord blood units already stored around the world could be used as a cell source for new therapies.
- The CBA is determining how to strengthen the role of accreditation in the field of cellular therapies.

Advocacy

Novel cellular therapies are currently regulated in some countries using the same frameworks as drugs. Many organizations are advocating for new regulatory structures that are designed specifically for these new biologics.

- ACT Now is encouraging increased capacity within the FDA Center for Biologics Evaluation and Research to support additional education, dialogue and technical assistance for health care entities, industry and providers to support understanding of and compliance with new FDA regulations [24].
- The CBA is proposing that the FDA redefine "homologous use" to allow for cellular therapies to be more appropriately regulated without the unnecessary burdens expected of mass-produced, traditional pharmaceuticals.
- ARM has engaged with the FDA on key issues related to cell and gene manufacturing and is also advocating for the limited growth and use of hospital exemption and other regulatory carve-outs that threaten patient safety.

Going Forward

As this article describes, there has been meaningful progress in standardization, workforce development and advocacy for cell and gene therapy. To strengthen and spread the impact of these efforts, all stakeholders are encouraged to participate in or support them. Appendix A outlines the efforts described in this article, including the lead organizations. The organizations welcome feedback and will work to incorporate the needs of all. By focusing on progress already being made, less duplication of effort will occur.

The participants in the InterCHANGE also discussed several new ideas to facilitate the uptake of novel cell and gene therapies. The organizations plan to build upon the current momentum and determine steps needed to advance these ideas via regular communication and continued annual meetings.

Collaboration and support among organizations with missions related to cell and gene therapies will benefit the entire field. Proactive change management will expedite the ability of patients and their health care providers to realize the benefits of this promising field of medicine.

Funding

No funding was received.

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

Author Contributions

Conception and design of the study: . Acquisition of data: . Analysis and interpretation of data: . Drafting or revising the manuscript: . All authors have approved the final article.

Acknowledgments

FACT thanks the participants of the Regenerative Medicine InterCHANGE for their contributions to the fields of cellular therapy and regenerative medicine, for their collaborative spirit in increasing access to patients and for participating in the InterCHANGE. A full list of participating organizations and a description of each can be found in the supplementary material.

Appendix A. Outline of resources and initiatives

Effort	Resource or initiative	Organization
Apheresis collection		
Standardization	Cell Collection Working Group	SCB
	Apheresis Standard Operating Procedures Manual	ASFA
Workforce development	*Principles of Apheresis Technology*	ASFA
	Apheresis workshop, annual meeting, webinar and online resources	ASFA
	QIA	ASFA in partnership with ASCP
Advocacy	Presentation to the FDA during CTLM	ISCT
	Promote use of cord blood as another source of cells	CBA
	Apheresis Awareness Day	ASFA
Manufacturing		
Standardization	Quality-based standards	AABB FACT
	Global review of manufacturing methods	Celltrials.org
Workforce development	Bringing Flow Cytometry to Life online training module	AABB
	Best practices in cell and gene therapy manufacturing using Quality by Design approach	ARM
Advocacy	Convene Florida's clinical and research groups and industry to direct efforts related to policy and funding	FORM
Labeling		
Standardization	*Standard Labeling for Apheresis Collection Products for Sponsor Cellular Therapy Manufacturing*	Deloitte NexGen Industry Working Group SCB ICCBBA
	ISBT 128 Standard coding and labeling technology	ICCBBA
Data collection and reporting		
Standardization	Cell Therapy Registry for cell and gene therapies	CIBMTR
	Integration of NHS data in the UK	Cell and Gene Therapy Catapult in partnership with ATTC
Advocacy	Request support in US spending bill for outcomes database	ACT Now
Reimbursement and costs		
Standardization	"A roadmap for cost-of-goods planning to guide economic production of cell therapy products" [13]	ISCT
	Three-part documentary standards on ancillary materials	SCB in conjunction with ISO
Advocacy	Multi-organizational efforts to create value assessments and develop new frameworks for coding and reimbursement	ASTCT ARM
	New drug resource group for CAR-T products from CMS	ARM
	Visits to congressional offices and CMS	ASTCT ARM
	Recommendations that CMS launch demonstration projects focused on the use of RWE	ACT Now and BPC
	Industry education on pre-commercialization reimbursement considerations	ISCT
	Direct support for prior authorizations, claims appeals and assistance for uninsured or underinsured	Gamida Cell
	Apheresis reimbursement guide	ASFA
Audit burden		
Standardization	Incorporate commercial manufacturers' feedback into updated accreditation standards	FACT
	QSAP to license audit results to multiple manufacturers	Be the Match BioTherapies
	Streamline onboarding activities for FACT-accredited centers	Dendreon
	Leveraging FACT accreditation to allow centers the option of an abbreviated site audit	Industry
Advocacy	Creating awareness of existing standards and on-site inspections among multiple stakeholders	FACT
Supply chain and logistics		
Standardization	Provide cell collection, supply chain and collection network management to multiple commercial manufacturers	Be the Match BioTherapies
	Development of systems for the routine supply delivery of cell and gene therapies in the UK	Cell and Gene Therapy Catapult and ATTC
	ISBT 128 standardized terminology and product codes to support international traceability and data transfer	ICCBBA
	Evaluating means to harmonize international requirements for donor testing and transporting cell products across borders	CBA
Health care system readiness		
Standardization	Organizational readiness toolkit for cell and gene therapies	Cell and Gene Therapy Catapult and ATTC
	BEACON, an online suite of tools	ISCT
Workforce development	Cellular Therapies Certificate Program	AABB in partnership with the George Washington University

(*continued*)

(*Continued*)

Effort	Resource or initiative	Organization
	Single platform for NHS ATMP education	Cell and Gene Therapy Catapult and ATTC
	Development of Master of Science degree in ATMPs	Cell and Gene Therapy Catapult and ATTC in collaboration with University of Manchester
	Lab Practices Committee Forum	ISCT
	Integration of professional development with its clinical care resources	Sanford Research
Advocacy	Recommending expanded workforce development initiatives, including at technical and community colleges	ACT Now
	Share practical, real-world experiences with applying novel cellular therapies in the clinic with industry	Sanford Research
Industry and health care partnerships		
Standardization	Consensus guideline development (e.g., grading criteria for cytokine release syndrome and neurotoxicity and patient management of these toxicities)	ASTCT
	The Regenerative Medicine Landscape and *Needed Standards in Regenerative Medicine* reports	SCB
Workforce development	Efforts to streamline audits to reduce needs for auditing personnel and sustain an adequate workforce for apheresis	FACT Be the Match BioTherapies Commercial manufacturers
Advocacy	Corporate Council among health care providers, industry and other subject matter experts	ASTCT
	Industry participation in multi-stakeholder standardization efforts	Dendreon
	Connect health care providers administering cellular therapies with commercial manufacturers	FACT
Regulatory frameworks		
Standardization	Work with FDA to streamline approval mechanisms for directed cell therapy products	CBA
	Determine how to strengthen the role of accreditation in the field of cellular therapies	CBA
Advocacy	Encourage increased capacity within FDA to support additional education, dialogue and technical assistance	ACT Now
	Propose redefining the term “homologous use”	CBA
	Engage with FDA on key issues related to cell and gene manufacturing	ARM
	Recommend limiting the growth and use of hospital exemption and other regulatory carve-outs	ARM

ASCP, American Society for Clinical Pathology; BPC, Bipartisan Policy Center; CTLM, Cell Therapy Liaison Meeting; DRG, drug resource group; FORM, Florida Organization for Regenerative Medicine; ICCBBA, International Council for Commonality in Blood Banking Automation; ISO, International Organization for Standardization; QIA, Qualification in Apheresis; QSAP, Quality System Audit Program; RWE, real-world evidence.

References

[1] Wu Y, et al. (2019). *Apheresis Standard Operating Procedures Manual*. First edition.

[2] Linz W, et al. (2017). *Principles of Apheresis Technology*. Sixth edition.

[3] American Society for Apheresis. *Qualification in Apheresis*. Available: https://www.apheresis.org/page/QIA.

[4] International Society Cell & Gene Therapy (ISCT, 2019). FINAL Meeting Summary of the 15th Cell Therapy/FDA Liaison Meeting. Available: http://www.factwebsite.org/uploadedFiles/Education_and_Resources/FDA_Liaisons_Meetings/CTLM%20Meeting%20Summary%2003.05.19%20FINAL.pdf.

[5] Mehta RS, et al. Cord Blood Expansion: A Clinical Advance. Journal of Clinical Oncology 2018;37(5):363. 2017.

[6] AABB. (2019). *Standards for Cellular Therapy Services*. 9th edition. Available: https://www.aabb.org/standards-accreditation/standards.

[7] Foundation for the Accreditation of Cellular Therapy. (2018). *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration*. Edition 7.0. Available: http://www.factweb.org/forms/store/CommercePlusFormPublic/search?action=Publications.

[8] Foundation for the Accreditation of Cellular Therapy. (2018). *FACT Standards for Immune Effector Cells*. Edition 1.1. Available: http://www.factweb.org/forms/store/CommercePlusFormPublic/search?action=Publications.

[9] Foundation for the Accreditation of Cellular Therapy. (2019). *FACT Common Standards for Cellular Therapies*. Edition 2.0. Available: http://www.factweb.org/forms/store/CommercePlusFormPublic/search?action=Publications.

[10] Couto PS, et al. First Decade of Clinical trials and Published Studies with Mesenchymal Stromal Cells From Umbilical Cord Tissue. Regenerative Medicine 2019;14(4):309–19. 2019.

[11] AABB. (Accessed 2020). *Bringing Flow Cytometry to Life*. Available: https://education.aabb.org/aabb/lessons/18.

[12] ICCBBA (2020). *ISBT 128 Standard Labeling of Collection Products for Cellular Therapy Manufacturing*. Available: https://www.iccbba.org/tech-library/iccbba-documents/standards-documents/st-018-isbt-128-standard-labeling-of-collection-products-for-cellular-therapy-manufacturing.

[13] Lipsitz YY, et al. A roadmap for cost-of-goods planning to guide economic production of cell therapy products. Cyotherapy 2017;2017(19):1383–91.

[14] International Organization for Standardization. (2018). *Biotechnology—Ancillary materials present during the production of cellular therapeutic products—Part 1: General requirements*(ISO/TS 20399-1:2018). Available: https://www.iso.org/standard/67897.html.

[15] International Organization for Standardization. (2018). *Biotechnology—Ancillary materials present during the production of cellular therapeutic products—Part 2: Best practice guidance for ancillary material suppliers*(ISO/TS 20399-2:2018). Available: https://www.iso.org/standard/70982.html.

[16] International Organization for Standardization. (2018). *Biotechnology—Ancillary materials present during the production of cellular therapeutic products—Part 3: Best practice guidance for ancillary material users*(ISO/TS 20399-3:2018). Available: https://www.iso.org/standard/70983.html.

[17] *Patient Access to Cellular Transplant Act*. S. 1268. 116th Congress. (2019). NMDP publication of US House of Representatives ACT (HR 2498).

[18] AABB. (Accessed 2020). *Cellular Therapies Certificate Program*. Available: http://www.aabb.org/aabbcct/certificate/Pages/default.aspx.

[19] The University of Manchester. (Accessed 2020). *MSc Advanced Therapy Medicinal Products*. Available: https://www.manchester.ac.uk/study/masters/courses/list/12672/msc-advanced-therapy-medicinal-products/course-details/.

[20] International Society Cell & Gene Therapy. (Accessed 2020). *Laboratory Life Line*. Available: https://isctglobal.org/forums/Default.aspx.

[21] Lee DW, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated With Immune Effector Cells. Biology of Blood and Marrow Transplantation 2019;24(4):625–38. 2019.

[22] Standards Coordinating Body and Nexight Group. (2019). *The Regenerative Medicine Landscape*. Available: https://static1.squarespace.com/static/58a331b0db29d63c7fb64528/t/5ec4187751b9d87ac1a79718/1589909649116/LandscapeReportFall2019.pdf.

[23] Standards Coordinating Body and Nexight Group. (2020). *Community Perspectives: Needed Standards in Regenerative Medicine.*Available: https://www.standardscoordinatingbody.org/landscape.

[24] Alliance for Cell Therapy Now. (2019). *Regenerative Cell Therapies: Making Safe and Effective Treatments Available to Patients*. Available: http://allianceforcelltherapynow.org/wp-content/uploads/2019/12/Regenerative-Cell-Therapies-Alliance-for-Cell-Therapy-Capitol-Hill-Briefing-Sept-2019-1.pdf.