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Adverse event reporting for cellular therapy products: Current status and future directions

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BRIEF REPORT

TRANSFUSION

Adverse event reporting for cellular therapy products: Current status and future directions

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Abstract

Adverse event (AE) and adverse reaction (AR) reporting are key components of patient safety and surveillance systems. Review and analysis of this data yields opportunities for process improvement, product information and interventions, and can lead to improved patient outcomes and donor safety overall. AE and AR reporting for cellular therapy products is fragmented and not well characterized in a central reference. This review article, authored by experts from various organizations, serves to summarize the current state of reporting and offers opportunities for streamlining and coordination, as well as key reference for professionals in this field.

1 | INTRODUCTION

The goal of medical intervention is to cure, or mitigate, suffering; however, no treatment is without risks. The Greeks coined the term *iatrogenesis* to describe harm occurring as an inadvertent result of intervention not originating from the disease.[1] Iatrogenic harm ranges from the negative effects of a drug (eg, nausea following chemotherapy), to unnecessary procedures and medication errors. Medical errors are avoidable causes of death, prompting many - including the Institute of Medicine in the United States (U.S.) in 1999 - to call for expanded voluntary adverse event reporting to build a safer health system.[2]

Regulatory organizations consider AE reporting vital for ongoing post-marketing surveillance of initial product

safety; however, challenges exist.[3] The challenges are multifactorial and must be analyzed systematically. Error reporting affects how a given healthcare intervention (eg, drug, device, procedure, etc.) is used, reveals populations at risk for rare events, exposes rare adverse events not seen during the investigational trials, provides targets for process improvement, and can result in the removal of interventions from the market.

2 | MATERIALS AND METHODS

Individuals representing the following professional stakeholder organizations in cellular therapies contributed to this summary: AABB, Alliance for Harmonization of Cell Therapy Accreditation (AHCTA), International Society of Blood Transfusion (ISBT), World Marrow Donor Association (WMDA), European Society for Blood and Marrow Transplantation (EBMT), Joint Accreditation Committee ISCT-Europe & EBMT (JACIE), Worldwide Network for Blood & Marrow Transplantation (WBMT) Donor Issues Committee, and Foundation for the Accreditation of Cellular Therapy (FACT).

In this article, the current status of AE and AR reporting for cellular therapy (CT) products, regarding regulations and requirements in a variety of countries as well as activities of organizations and registries, are described.

2.1 | Donors and recipients of cellular products

Products from donors of human cells, tissues, or cellular or tissue-based products (HCT/Ps) play critical roles in the medical treatment of many patients, including those with hematological cancers. Donors must have a clear understanding of the true risks of donation as part of their consenting process. AE reporting should be collated across organizations as well as by country to obtain information on overall risk.

2.2 | United States federal regulations and oversight

The U.S. regulation of CT products is complex with various pathways contributing to premarket research and approval. The U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) regulates CT products, human gene therapy products, and certain devices related to cell and gene therapy. CBER uses both the Public Health Service (PHS) Act and the Federal Food, Drug, and Cosmetic (FD&C) Act as enabling statutes for oversight. These products can be known as biologics or biologic products. The Center for Drug Evaluation and Research (CDER) within FDA regulates other categories of biologic products mostly produced by biotechnology methods, such as monoclonal antibodies.[4] The Center for Devices and Radiological Health (CDRH) also regulates certain HCT/P products with medical devices.

CT products are commonly referred to as either "361" or "351" products, referencing sections 361 and 351 of the PHS Act. "361" products must meet all criteria in 21 CFR 1271.10(a). Tables 1 and 2 summarize these criteria. If a product does not meet all criteria in 21 CFR 1271.10(a), then it is regulated as a drug and/or a biologic product (PHS Act Section 351 and/or FD&C Act). In general, 361 products must be minimally manipulated, serve the same basic function(s) as the original cell/tissue it is replacing, and fall under FDA's definition of homologous use. The FDA Standard Operating Procedures and Policies (SOPP) 8508: Procedures for Handling AR Reports Related to "361" Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) provides important information on AR reports and describes procedures for receipt and reporting as well as the framework for communication with regulatory agencies. For 361 products, an AR means a reasonable possibility that a noxious and unintended response is a result of an HCT/P [21 CFR 1271.3(y)].[5] Any AR involving a communicable disease related to an HCT/P must be investigated by the manufacturer that made the HCT/P available for distribution [21 CFR 1271.350(a) (1), FDA-2015-D-0309].[6] On 25 May 2005, the FDA implemented regulations governing the manufacture of human products for transplantation and immune modulation, as well as a variety of other cellular- and tissue-based human products. The U.S. regulations are primarily founded on the FDA's responsibility to limit the transmission of infectious diseases through the administration of human or human-derived products, including CT products.[7] Table 3 provides a brief outline of common terms used by U.S. FDA to describe adverse reactions. The flowchart in Figure 1 is taken from the FDA guidance document, "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use."

2.3 | European union requirements

A Serious Adverse Event (SAE) is any untoward occurrence associated with the procurement, testing, processing, storage, and distribution of tissues and cells

TABLE 1 Regulatory pathways

Regulatory pathway	CRITERIA	Example
Section 361 of the PHS Act and CFR Title 21 Part 1271	HCT/P must meet all criteria: 1. Minimally manipulated 2. Intended for homologous use as determined by labeling and advertising 3. Not combined with a device or drug, except for sterilizing, preserving or storage agents that do not raise safety concerns 4. Free of systemic effects and independent of the metabolic activity of living cells for its primary function, unless the HCT/P is for (a) autologous use, (b) allogeneic use in a first- degree or second-degree blood relative, or (c) reproductive use	Related (first or second degree) allogeneic peripheral blood, hematopoietic stem/ progenitor cells
Public health service act section 351	1. Manipulated such that biological or relevant functional characteristics are altered 2. Genetically modified 3. ex vivo expanded 4. Used for other than normal function of the HCT/P (non-homologous use) 5. Combine with a drug, device or biologic that may raise safety concerns 6. Active systemically or dependent on the metabolic activity of the living cells for primary function unless a) autologous b) used in first or second-degree relative or c) reproductive use	Unrelated allogeneic peripheral blood, hematopoietic stem/ progenitor cells

Note: The FDA set the regulatory path for HCT/Ps based relationship between recipient and donor, degree of product manipulation and purpose for which the tissues and/or cells are utilized.

TABLE 2 Regulation of minimally manipulated hematopoietic progenitor cells

Source	Marrow	Peripheral blood	Cord blood
Autologous	No federal regulation	21 CFR 1271 applies, except Subpart C, Donor Eligibility, which is recommended but not required	21 CFR 1271 applies, except Subpart C, Donor Eligibility, which is recommended but not required
Related allogeneic (first-degree or second-degree blood relative)	No federal regulation	All subparts of 21 CFR 1271 are requirements	All subparts of 21 CFR 1271 are requirements
Unrelated allogeneic	Health Resources and Services Administration oversight (contract with the National Marrow Donor Program)	Regulated under both Sections 351 and 361 of the PHS Act and require premarket approval based on safety and effectiveness assessments. All subparts of 21 CFR 1271 are requirements. Be issued under an IND (example- multicenter programs of the National Marrow Donor Program)	Regulated under both Sections 351 and 361 of the PHS Act and require premarket approval based on safety and effectiveness assessments. All subparts of 21 CFR 1271 are requirements, be licensed and thus abide by standards set forth in the Guidance for Industry Minimally Manipulated Placental/ Umbilical Cord Blood or fall under the auspices of an IND

TABLE 3 Adverse reactions associated with infusions of cellular therapy products

Adverse reaction	Typical findings	Temporality to CT administration
Acute hemolytic reaction	Fever, chills, tachycardia, tachypnea, pain, unusual bleeding, hemoglobinuria, shock, positive acute biochemical markers of hemolysis	Within 24 hours
Febrile nonhemolytic reaction	Fever, chills, rigors, tachycardia, tachypnea	Within 2 hours
Allergic/Anaphylactoid/ anaphylactic reaction	Pruritus, urticarial rash, bronchospasm, laryngospasm, dyspnea, tachypnea, nausea, facial or glottal edema, hypotension	Within hours
Transfusion related acute lung injury (TRALI) reaction	Acute respiratory distress, tachypnea, hypoxemia, radiographic evidence of bilateral lung involvement	Within 6 hours
Alloimmunization to antigens	Alloantibody formation to foreign antigens of RBCs, WBCs, platelets, or plasma proteins	Within days to weeks
Delayed hemolytic reaction	Fever, anemia, jaundice, positive DAT/other biochemical markers of hemolysis	Within 1 day to 3 weeks
Graft vs host disease (GVHD)	Spectrum of tissue and organ damage, typically skin, mucous membranes, liver, and gut	Within days to months
DMSO toxicity	Nausea, vomiting, flushing, coughing, wheezing, rash, cardiovascular irritation/instability	During or immediately after infusion
Septic reaction	Fever, chills, abdominal pain, nausea, vomiting, bloody diarrhea, dry/warm skin, hypotension	During or immediately after infusion
Fat emboli	Dyspnea, tachypnea, coughing, hypoxia, petechiae, confusion	Within hours
Transmission of disease agents	Attendant impacts of specific disease agent	Within days to years
Excessive anticoagulation-induced bleeding	Bleeding due to anticoagulants, typically heparin, in CT product	During to hours after infusion
Circulatory overload	Dyspnea, tachypnea, tachycardia, peripheral edema, hypertension	During to hours after infusion
Hypothermia	Decreased temperature, chills, cardiac arrhythmias/arrest	During to immediately after infusion
Nonimmune hemolysis	Similar to acute or delayed hemolytic reactions	During to days after infusion
Cytokine release syndrome	Fever, chills, nausea, dyspnea, tachypnea, hypotension, tachycardia, neurologic abnormalities, kidney injury, cytopenias, coagulopathy, hepatic injury, myalgias, rash	Immediately after to days after infusion

that might lead to the transmission of a communicable disease; to death or life-threatening, disabling, or incapacitating conditions for patients; or which might result in, or prolong, hospitalization or morbidity. Within the EU no centralized reporting of serious AEs and/or ARs that are linked to the procurement, testing, processing, storage, and distribution of human tissues and cells for human application exists. Member States were required to establish a reporting system and usually, regulatory bodies involved in health care oversee these. The EU Commission Directive 2006/86/EC of 24 October 2006 implemented Directive 2004/23/EC of the European Parliament and of the Council for traceability requirements, notification of SARs and SAEs and certain technical requirements for the coding, processing, preservation, storage, and distribution of human tissues and cells. This directive states that suspected SARs, in the donor or in the recipient, and SAEs from donation to distribution of tissues and cells, which may influence the quality and safety of tissues and cells and which may be attributed to procurement (including donor evaluation and selection), testing, processing, preservation, storage, and distribution of human tissues and cells should be reported to the competent authority. SARs should be reported to the

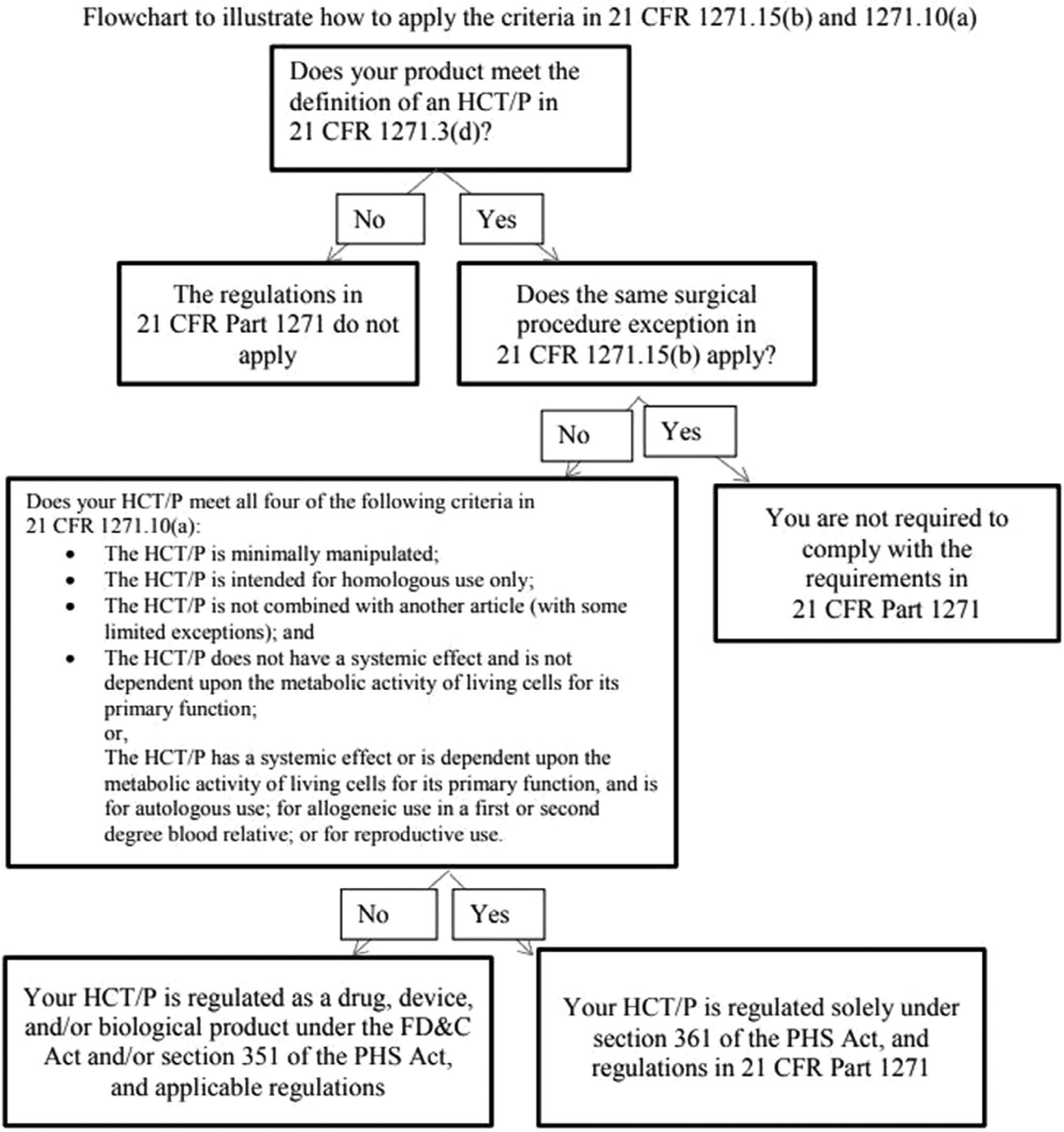

FIGURE 1 Flowchart to illustrate how to apply the criteria in 21 CFR 1271.15(B) and 1271.10(A)

associated tissue establishment for subsequent investigation and notification of the competent authority. This Directive defined the minimum data needed for notification to the competent authority but allows Member States to maintain or introduce more stringent and protective measures which comply with the requirements of the Treaty. The competent person within a tissue bank is responsible for reporting every SAE and/or SAR to the competent authority and must provide a statement on its cause and consequences. If cells are imported from non-EU countries, the importing tissue bank is obligated to report all SAEs and/or SARs to the competent authority. Procurement and application of human blood and blood components including donor lymphocytes are subject of the Directive 2002/98/EC.[8] Of note, both directives make no distinction between source of cells or type of product regarding follow-up and reporting. The two directives were opened for evaluation and comments in 2018 and

were still under review at the time of this publication. Regulation (EC) No 1394/2007 of the European Parliament and of the Council published November 13th, 2007 addresses advanced therapy medicinal products (ATMP) and amended Directive 2001/83/EC and Regulation (EC) No 726/2004. ATMP is defined as any of the following medicinal products for human use: a gene therapy medicinal product, a somatic cell therapy medicinal product, and a tissue engineered product. This regulation emphasizes the importance of follow-up of efficacy and ARs of ATMPs and requests companies seeking marketing authorization to include detailed plans on follow-up measures and establish a suitable risk management system that addresses (to address) risks related to ATMPs for their applications. For chimeric antigen receptor T-cell (CAR-T) therapies the European Medicines Agency (EMA) requests post-marketing reporting of all therapies including SAE reporting that will be performed through the European Blood and Marrow Transplant registry.

2.4 | United Kingdom requirements

The Human Tissue Authority (HTA) is the regulator for human tissue and organs in the U.K. The HTA manages an online system, via the secure web Portal (https://www.hta.gov.uk/hta-portal), for the reporting of any SAEs and/or SARs that are linked to the procurement, testing, processing, storage, and distribution of human tissues and cells for human application.

2.5 | Requirements in Asia

In Asia, regulatory convergence and cooperation via the Regulatory Harmonization Steering Committee is a primary goal. Endorsed by Asia Pacific Economic Cooperation (APEC) leaders in 2011, the aim is to achieve regulatory convergence for medical products by 2020 by the promotion of existing international guidelines.

2.5.1 | Singapore

The finalization of the framework and implementation of Cell, Tissue, and Gene Therapy Product (CTGTP) regulations is expected to be completed mid-2020. A risk-based tiered approach has been applied whereby clinical trials and product license of high-risk cell- and tissue-based therapeutic products (substantially manipulated products, products intended for non-homologous use or combined products) and gene therapy products are regulated under the Health Products Act. There will be requirements for long-term follow up for patient safety and efficacy.

2.5.2 | Japan

Since 25 November 2014, "the Act on the Safety of Regenerative Medicine" has been in effect to ensure the safe and ethical administration of regenerative medical technologies and the safe yet accelerated adoption of specific processed cellular products by establishing a manufacturing permit system. The act divides regenerative medicinal products into three classes depending on the potential risk to human health—Class I: identifying high-risk products including Induced Pluripotent Stem Cell (iPSC), embryonic stem cells, allogeneic, and xenogeneic cells; Class II: referring to medium-risk products covering all autologous somatic stem cells; and Class III: defining low-risk products including autologous somatic cells. The act was issued to promote safe clinical studies and allows an accelerated route to the clinic for regenerative medicine. If the regenerative medical product satisfies specific conditions, the entity may obtain approval from a subcommittee of the Pharmaceutical Affairs and Food Sanitation Council and receive conditional approval for a maximum of 7 years. During this period, measures must be taken to ascertain the proper use of the regenerative medical products; upon reapplication, adequate efficacy and safety must be demonstrated. By treating regenerative medicine products in a similar manner to orphan drugs, the approved product will typically skip a Phase III trial and obtain marketing authorization after demonstration of safety and signs of minimal efficacy following a solid Phase I and II trial.

2.6 | Requirements in South Korea

South Korea requires safety reporting of all AEs related to approved CT products and long-term reporting for those in clinical trials.

2.7 | Requirements in Australia

AE reporting falls within the responsibility of the Therapeutic Goods Administration (TGA) that also adopts a risk-based approach with biologicals categorized into five categories. Reports are submitted to TGA.

2.8 | Registries

Several registries are available that allow for data analysis.

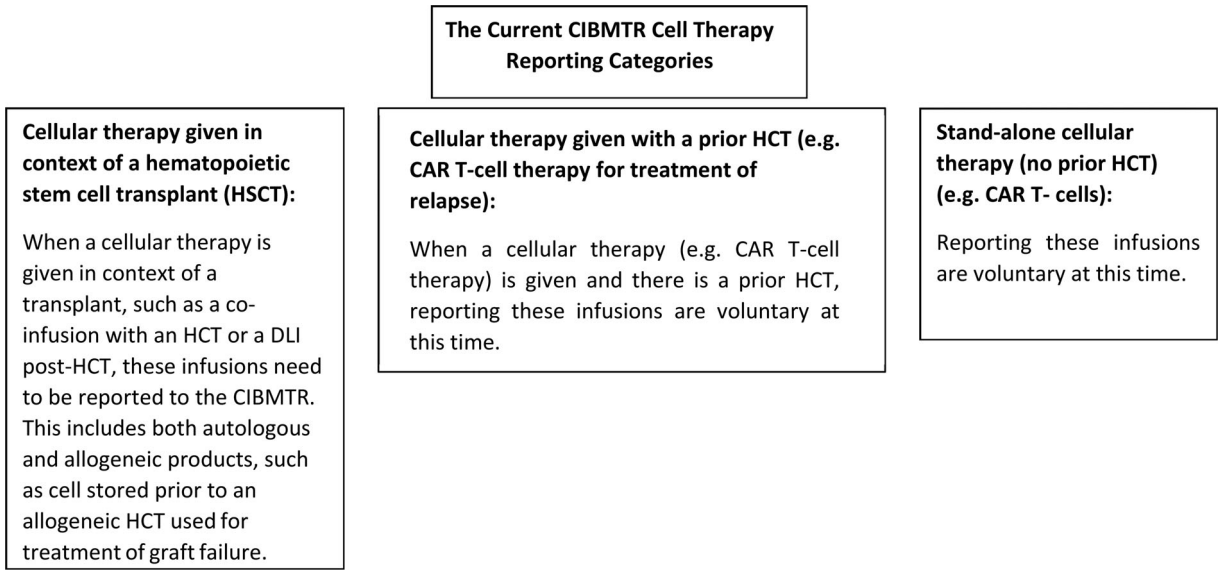

FIGURE 2 Current CIBMTR Reporting Categories

2.8.1 | National Marrow Donor Program/Be The Match (NMDP)

In 1986 the U.S. government appropriated funds to establish the NMDP Registry. In 1988 the U.S. Organ Transplant Amendments Act legislated and mandated collecting outcome data (Recipient Registry). The NMDP collects data related to unrelated donor outcomes from donor centers and maintains a robust donor AE biovigilance program. Donor AEs are reported to the NMDP and are reviewed by NMDP Medical Services. Downstream reports are made to the FDA via the NMDP's Donor and Patient Safety Monitoring group (DPSM) and Institutional Review Board (IRB) when NMDP holds an Institutional New Drug (IND) application. If an IND hold is not in place, NMDP forwards the report to the IND holder. Additional reports may be provided to pharmaceutical manufacturers (eg, mobilization agents), the Health Resources and Service Administration (HRSA) and other U.S. government stakeholders, as applicable. Being a fully accredited member, NMDP is also obliged to report incidents involving unrelated donors to World Marrow Donor Association (WMDA). WBMT submission forms are available on the website.

2.8.2 | Center for International Blood and Marrow Transplant Research (CIBMTR)

The most well-known registry in the setting of hematopoietic cell transplantation (HCT) is the CIBMTR, a research collaboration between the NMDP/Be The Match and the Medical College of Wisconsin (MCW). The CIBMTR collaborates with the global scientific community to advance HCT and CT worldwide to ensure the health and safety of donors and increase survival and enrich quality of life for patients by collecting data on HCT and more recently, from other non-HCTCT. The CIBMTR facilitates observational and interventional research and includes a mechanism for information sharing with contributors. CIBMTR collects donation and outcomes data on every allogeneic transplantation performed in the U.S. (for the Stem Cell Transplant Outcomes Database, as required by U.S. law) and on all HCTs performed with products procured through the Program but performed outside of the U.S. Transplant centers in the U.S. also voluntarily submit autologous transplantation data, and transplant centers worldwide voluntarily submit both autologous and allogeneic transplantation data. As a result, the clinical database now contains information on more than 475 000 patients. Currently, there is no mandatory requirement for autologous CT data to be reported to CIBMTR although this is actively encouraged, especially for the commercial chimeric antigen receptor (CAR-T) products like Yescarta and Kymriah (Figure 2).

2.8.3 | The European Society for Blood and Marrow Transplantation (EBMT) Registry

EMBT established in 1974, is the backbone of the EBMT's research and educational activities. Membership in EBMT requires HCT data submission on all consecutive patients.

TABLE 4 Countries with National Registries

Registry name	Country or origin	Weblink	Notes
Japanese data Center for Hematopoietic Cell Transplantation (JDCHCT)	Japan	http://www.jdchct.or.jp/en/outline/	Collects and analyzes data on outcomes of HCT
The Australasian Bone Marrow Transplant Recipient Registry (ABMTRR)	Australia and New Zealand	http://www.abmtrr.org/	Every year the ABMTRR produces an annual data summary, which describes the latest transplant activity in Australia and New Zealand. Collects and analyzes data on outcomes of HCT
Asian Pacific Band Marrow Transplant Group	Asia	https://www.apbmt.org/research/registry/outcome https://www.apbmt.org/research/registry/survey	Activity survey since 2007 Outcome registry since 2010
Indian Stem Cell Transplant Registry (ISCTR)	India	http://isctreg.net/about-isctr/	Coordinated by the Dept. of hematology, Christian Medical College, Vellore. Activity survey
Canadian Blood and Marrow Transplant Group (CBMTG)	Canada	https://www.cbmtg.org/	The CBMTG registry is a clinical database, containing detailed information on Canadians who have undergone autologous or allogeneic transplant in Canada. Data are available on over 16 000 patients from 15 Canadian transplant centers, going back to 1990, and several research projects are underway. Planning for this project started in 2012 and has progressed quickly from the idea stage to full operations in just over 3 years.
Sociedade Brasileira de Transplante de Medula Óssea (SBTMO)	Brazil	https://sbtmo.org.br/	The National Registry of bone marrow recipients (REREME) is a system created by the National Cancer Institute (INCA) to expedite the search process for donors. The Brazil cord network brings together the Public Banks of Umbilical and Placentary Cord Blood (BSCUP). The goal is to store umbilical cord blood, a material rich in hematopoietic stem cells (capable of producing the fundamental elements of blood), essential for bone marrow transplantation.
Eastern Mediterranean Blood and Marrow Transplantation (EMBMT)	Eastern Mediterranean (EM) countries	http://www.embmt.org/	Eastern Mediterranean Blood and Marrow Transplantation Registry (EMBMT registry). Data reporting is voluntary. More information here: http://www.embmt.org/embmt2/index.php/registry-main

TABLE 4 (Continued)

Registry name	Country or origin	Weblink	Notes
Swiss Transfusion SRC (Swiss red cross)	Switzerland	http://en.blutspende.ch/	In 1997, the Swiss Blood Stem Cell Transplantation Group (SBST) initiated a mandatory national registry for all hematopoietic stem cell transplants (HCTs) in Switzerland. As of 2016, after 20 years, information was available for 7899 patients who had received an HCT (2781 allogeneic [35%] and 5118 autologous [65%]). Data are included in the EBMT Registry.

As of 2017, the Registry has acquired data on 631 000 HCT patients including 243 000 allogeneic and 388 000 autologous HCT. Transplant teams (n = 683) from 60 countries participate in the Registry with the main purpose to provide a pool of data to EBMT members and EBMT Working Parties to perform studies, assess epidemiological trends, and improve patient outcomes.[9] Some European countries have national registries reporting to EBMT.

2.8.4 | Eastern Mediterranean Blood and Marrow Transplantation (EMBMT) group registry

EMBMT established a Registry in 1984. As of 2017 this Registry has collected data on 25 000 HCT patients including 16 300 after allogeneic and 9000 after autologous HCT. Approximately 30% of these patients have also been reported to the EBMT Registry. To date, 28 HCT centers from 13 countries have provided transplant data to this Registry. Data reporting in these countries is voluntary.

2.8.5 | The Asia Pacific Blood and Marrow Transplantation group (APBMT)

APBMT is an international organization involved in HCT, sharing its information and cooperating with research in Asia-Pacific countries. In 2009, APBMT established bylaws and was a founding member of the WBMT, which does not have a separate registry. APBMT is now comprised of 21 countries that have national registries or centers and submit data to APBMT with forms identical to CIBMTR. For countries/regions with difficulty reporting, a simplified version "Least Minimum Dataset (LMD)" form is available. Table 4 provides a summary of other registries with similar data collection systems and sharing components. Other countries with national registries include Australia, New Zealand, India, Japan, Korea, and Taiwan.

TABLE 5 Organizations that address adverse effects of cellular therapy products

Organization
AABB
Centers for Disease Control and Prevention (CDC)
Center for International Blood and Marrow Transplant Research (CIBMTR)
Council of Europe (CE)
European Society for Blood and Marrow Transplantation (EBMT)
Food and Drug Administration (FDA)
Foundation for the Accreditation of Cellular Therapy (FACT)
International Society of Blood Transfusion (ISBT)
International Society for Cell and Gene Therapy (ISCT)
Joint Accreditation Committee ISCT-Europe & EBMT (JACIE) National Marrow Donor Program (NMDP)/ Be The Match
World Marrow Donor Association (WMDA)
Worldwide Network for Blood & Marrow Transplantation (WBMT)

2.9 | Additional Organizations and Government Efforts

Other organizations are involved in gathering information on AE. Table 5 lists some of the prominent organizations that address AE for CT products.

2.9.1 | Vigilance and surveillance of Substances Of Human Origin project (SOHO V&S)

SOHO V&S was an EU-funded project (2009-2012) that developed guidance documents for vigilance and

surveillance of tissues and cells for transplantation and for assisted reproduction. The Bologna Initiative for Global Vigilance and Surveillance (BIG V&S) initiative resulted from the Notify Project, which was coordinated by the World Health Organization (WHO) and the Italian National Transplant Centre (CNT); with the collaboration of the EU funded project SOHO V&S. Global experts gathered didactic information on documented types of adverse outcomes in transplantation and assisted reproduction and reviewed cases to identify general principles supporting detection and investigation. The open website, www.notifylibrary.org, hosts the database of vigilance information collected by the Notify Project. The library is maintained and updated on this platform and is intended as a communication hub for institutions and organizations worldwide collaborating in facilitation of access to vigilance and surveillance information.

2.9.2 | World Marrow Donor Association (WMDA)

The WMDA is an international association that oversees global standards for unrelated HPC donations and the international exchange of HPC products. Approximately half of HPC collected from unrelated donors are transported across international borders. WMDA-accredited registries, including NMDP's Be The Match, contain 75% of donors listed worldwide. Participation in WMDA is open to all unrelated registries. Accredited registries are responsible for reporting SARs and must have a process implemented for reporting SAEs affecting a product to the WMDA. Members must also comply with governmental regulations including requirements to report such ARs to a regulatory agency. The WMDA definitions for SAE and SAR are identical to the EU regulations.[10] A severe adverse reaction or SEAR, defined in a donor during or after a donation procedure and Serious Product Events and Adverse Reactions or SPEAR, defined as events or reactions in a recipient as well as product related to processing, labelling, handling and transport errors/problems[11] are examples of data also shared with Notify. The S(P)EAR committee is responsible for review of all events/reactions reported to WMDA as potential SARs or SAE and evaluation of the events/reactions' immutability and impact. If the S(P)EAR committee judges the impact of the report to be high, it will prepare a communication to be sent to the WMDA member organizations and relevant members of the international community involved in allogeneic donor and patient care.

Currently, WMDA is introducing a web-based reporting system that adapts the EU definitions including the distinction between AEs and ARs. What was formerly called 'SEAR' is now defined as "Harm to Donor," while former SPEAR is classified as either "Harm to a Recipient" or "Risk of Harm." Any AE as per EU criteria should be reported as 'Risk of Harm.' Reporting includes donors and recipients, including cord blood, and is mandatory for all registry members.

2.10 | Accrediting organizations

Numerous voluntary accrediting organizations which include AABB, FACT, JACIE and College of American Pathologists (CAP) have requirements for reporting donor and recipient AEs. Their terms and definitions (may) also vary.

2.11 | Clinical-trial specific reporting

Clinical-trial related injury and SAE are of major concern. The investigator is ethically bound to report the event to all stakeholders. In the U.S., unanticipated events, including certain AE reports, must be reported to the IRB under Title 21 of the Code of Federal Regulations (21 CFR) part 56 (Institutional Review Boards), part 312 (Investigational New Drug Application), and part 812 (Investigational Device Exemptions).[12] These must be reported to the manufacturer and the institutional review board. In Europe, SAEs must be reported to local/national Ethics committees. The manufacturer (trial sponsor) has obligations to report to the FDA through their biologic license application or to EMA in Europe. Additionally, gene therapy products have specific requirements for outcomes reporting. For example, CAR-T trials and clinical use of commercial CAR-T-cell products requires a 15 year follow up in the US and Europe.

3 | RESULTS

3.1 | Gaps, redundancies, and a path forward

Much work has been done globally to collect, analyze, and learn from donor and recipient AEs and ARs. Regulatory agencies and professional organizations have laid a solid foundation to promote safety and sharing of data and best practices. The development of new and novel therapies makes it challenging for regulatory agencies to keep pace. In October 2009, the Public Health Service Biovigilance Working Group published a review of the gaps remaining in the United States biovigilance system

related to blood, organs, and tissues.[13] The list of gaps identified in the U.S. mirrors global challenges.[14] The lack of precise definitions, real time reporting and analysis of reported data, and the lack of mature regulations concerning AR reporting extending to the level of the healthcare facility or provider are just a few of the gaps identified that are still relevant today.

3.2 | Changes outpacing current regulatory infrastructure

The FDA maintains a website of approved stem cell products (https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products). FDA oversight of CT focuses on overall patient safety and product efficacy through the regulatory framework for HCT/P approval. Such oversight is designed to protect patients that may be vulnerable to unproven, dishonestly marketed, illegal, and potentially harmful products and claims.[15] Recently, stem cell clinics globally have come under increased scrutiny following serious AEs. Despite these concerns, the public's interest in the use of unproven therapies continues to increase.[16] Cellular therapies are moving away from bone, tissue, and organ transplantation towards cell-specific and tissue-based engineered products. The focus is to minimize surgical intervention and use more cell and cell-based products to encourage the body's own healing processes, often referred to as regenerative therapies. This challenges traditional terms such as "minimally manipulated" and "homologous use," and can result in a protracted approval timeline and potentially delay treatment. Inadequate investigator familiarity with current regulatory product approval pathways contributes to this delay. The US 21st Century Cures Act, signed into Law December 13, 2016, modified the FDA approval process with the intent to expedite the approval of new drugs and devices to bring innovative therapies to trial sooner. Other countries have enacted similar legislation.

3.3 | Correlation of outcomes

A key part of any surveillance system is the ability to turn data into actionable process improvement practices. CT surveillance is complicated by the lack of standardization between groups in preparatory regimens, procurement, manufacturing, testing, storage conditions, transportation, infusion, and stability metrics. Much of the product characterization in CT (eg, CD34+ and colony forming units [CFU]enumeration, viability testing, and stability assays), while helpful to predict donor readiness and document product quality, is a poor overall predictor of donor and recipient risk. Moreover, while reporting systems for HCT are in place, there is no organized outcome reporting for therapies in other related disciplines (eg, adipose tissue in the plastic surgery setting or any myriad of biological products in orthopedic therapies). Further compounding the problem, some specialties may have numerous practice-specific databases which lack uniformity and standardization.

4 | DISCUSSION

4.1 | Use of harmonized terminology

As previously described, the U.S. FDA defines a SAR as one that results in death, is life-threatening, requires hospitalization, results in or permanent damage, congenital anomaly, or requires intervention to prevent permanent impairment or damage.[17] While the EU definitions are similar, words like mild, moderate, and severe are vague and variably defined; so too are the words "life-threatening" and "disability."[18] Fortunately, several groups are working towards harmonization. Efforts such as the National Cancer Institute's common terminology criteria for adverse events (CTCAE) dictionary are attempting to provide practical guides and consistency for treatment related toxicities, for example.[19] International transportation further necessitates a global dictionary of AE terms.

4.2 | Use of central analysis and automated data collection

Data reporting can vary. Few donors and their recipients are seen at any one facility; therefore, data from many sources must be analyzed to understand donor risk.[20] Documentation and transmission of AEs often relies on manual techniques, limiting the information collected, especially outside the highly structured nature of a clinical trial. Currently only SAEs and SARs are required to be reported; although organizations such as CIBMTR ask members to report less severe events as well. Some professionals report the current reporting forms are long, tedious and include multiple areas for free text and are one of the major barriers to reporting all but the most significant AEs. While such forms are necessary to gather information for infrequent or novel AEs, they are resource-intensive to complete. Expanded use of automated data collection and use of standardized forms (with standardized terminology) across the cell therapy supply chain is necessary for improving data collection and analysis. Currently, healthcare providers find it difficult to share recipient (and donor) data both inside and

outside their facility due to lack of access to data sharing systems, concerns about data privacy and security, and lack of interoperability of record systems, among others.[21]

4.3 | Barriers to reporting

Underreporting of SAE/SAR is near universal across healthcare, with some suggesting that only 10% of all healthcare AEs are reported to the FDA annually.[22] A study focused on understanding why AEs are underreported found that in addition to concerns about cultures that avoid reporting, whether due to fear of litigation, the resulting "blame and retrain" response, or the inherently difficult task to objectively report anything that might cast oneself or one's team in a negative light - other reasons for underreporting exist. The medical specialty of the provider, poor knowledge of what and how to use reporting systems, lack of confidence/fear of ridicule in reporting, conflicts of interest, complacency, lack of time, and uncertainty of causality were also identified as barriers.[23] Even if policies and procedures are in place to update staff immediately after a new AE is published, there is still a lag between the report of a new AE and its accessibility to professionals in the literature.[24] One study found a median of 4 years lapse from a drug's initial launch and subsequent report of AEs appearing in peer-reviewed literature.[23]

4.4 | Moving forward with increasing cooperation and transparency

Continued cooperation between international organizations and regulatory agencies is critical to the future success in CT and its surveillance. Regulatory organizations have worked together or at least in parallel with sponsors during the early development and approval of new therapies.[25] With increasing human mobility, multiple therapeutic rounds, and the increasing diversity of cellular and gene therapy based treatment options, we must work together to share clear and complete surveillance data. Fortunately, regulatory agencies and organizations are aware of this reality and increasingly work together to insure interoperability. It is the authors' hope that this review will serve as a platform for increased harmonization and collaboration.

CONFLICT OF INTEREST

Professional: One author is a member of the American Society of Apheresis (ASFA) board of directors and the Foundation for the Accreditation of Cellular Therapy (FACT) board of directors.

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