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ISCT Committee Paper

International Society for Cell & Gene Therapy Position Paper: Key considerations to support evidence-based cell and gene therapies and oppose marketing of unproven products

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ABSTRACT

The field of regenerative medicine, including cellular immunotherapies, is on a remarkable growth trajectory. Dozens of cell-, tissue- and gene-based products have received marketing authorization worldwide while hundreds-to-thousands are either in preclinical development or under clinical investigation in phased clinical trials. However, the promise of regenerative therapies has also given rise to a global industry of direct-to-consumer offerings of prematurely commercialized cell and cell-based products with unknown safety and efficacy profiles. Since its inception, the International Society for Cell & Gene Therapy Committee on the Ethics of Cell and Gene Therapy has opposed the premature commercialization of unproven cell- and gene-based interventions and supported the development of evidence-based advanced therapy products. In the present Guide, targeted at International Society for Cell & Gene Therapy members, we analyze this industry, focusing in particular on distinctive features of unproven cell and cell-based products and the use of tokens of scientific legitimacy as persuasive marketing devices. We also provide an overview of reporting mechanisms for patients who believe they have been harmed by administration of unapproved and unproven

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products and suggest practical strategies to address the direct-to-consumer marketing of such products. Development of this Guide epitomizes our continued support for the ethical and rigorous development of cell and cell-based products with patient safety and therapeutic benefit as guiding principles.

Introduction

Two decades ago, businesses began advertising purported stem cell treatments on a direct-to-consumer basis for myriad indications. More recently, similar advertisements for purported gene therapy or extracellular vesicle treatments have also arisen. This phenomenon persists today, with a global marketplace of clinics selling putative advanced medicinal therapies without substantive evidence of safety and/or efficacy. This occurs under a number of different guises. Some clinics claim that the supposed advanced products they are selling are indeed safe and effective. Other businesses acknowledge the investigational nature of what they are selling but charge patients to access advanced products in pay-to-participate studies. These purported studies are generally poorly designed, unblinded, unrandomized and uncontrolled; typically, they have not been reviewed and authorized by national regulators. The International Society for Cell & Gene Therapy (ISCT), along with peer scientific organizations and patient advocacy groups, has played an important role in opposing the premature commercialization of unproven cell- and gene-based interventions and supporting the development of evidence-based, safe, and efficacious advanced medicinal products. The ISCT and other groups have also worked toward better regulation of cell and gene therapy investigations to assist the US Food & Drug Administration (FDA) and other regulatory bodies crack down on businesses offering unproven cell and gene therapies. The goal of ISCT and peer scientific organizations is to advocate for patient safety and access to new therapies by supporting clinical translational processes and corresponding regulatory paths developed to generate robust safety and efficacy data before products are commercialized. In particular, rigorous evaluation by national regulators of the benefit-to-risk balance for each individual product increases the likelihood that only safe and effective cell- and gene-based products enter the commercial marketplace.

In this guide for ISCT members, the ISCT Committee on the Ethics of Cell and Gene Therapy provides background and suggested strategies to counteract the direct-to-consumer marketing of unproven and unapproved cell-based, cell-derived and gene-based interventions. For the purposes of the Members Guide, cell-based, cell-derived and gene-based therapies/interventions will herein be consolidated under the term “CGT.” The purpose of this document is to address in an accessible manner the problematic scientific, ethical and legal concerns inherent in direct-to-consumer promotion of prematurely commercialized CGTs. The Guide also identifies additional resources that ISCT members might wish to consult to explore this subject in greater detail, including the 2015 ISCT comprehensive reference guide “Talking about Unproven Cell-Based Interventions” [1]. The Guide begins by identifying common and recognizable features of unproven CGTs. Although there are variations in how such products reach the marketplace and are commercialized, it is common for them to be advertised and administered without a clear scientific rationale, sufficient pre-clinical data to support their use in patients, convincing safety and efficacy data generated in properly controlled clinical trials and/or standardized and reliable methods to confirm product quality and consistency.

The Guide further identifies other common characteristics of unproven CGTs. These include various strategies that businesses use to make unproven CGTs appear scientific and evidence-based. One prominent strategy is the use of “tokens of legitimacy” to make unproven products seem science-based, subject to appropriate oversight and ready for clinical deployment (Table 1) [2–4]. ISCT members, patients, families, caregivers, research participants and other relevant parties must be educated on how to identify such tokens of legitimacy and how they are often used to convince patients that CGT products are safe and effective in the absence of sufficient safety and efficacy data [5].

Next, the Guide provides insight into what constitutes evidence-based CGT products. There are cell- or gene-therapy based products that have been carefully tested in rigorously designed and conducted clinical trials and that subsequently have received pre-marketing authorization by national regulatory bodies. It is thus critically important to distinguish such evidence-based and approved therapies from products lacking evidence and regulatory approval. The Guide helps readers differentiate such products from one another and better understand why some products have obtained pre-marketing authorization. In brief, convincing, or substantial, evidence of safety and efficacy is typically required by regulatory bodies responsible for reviewing CGT products submitted for pre-marketing authorization. The Guide reviews what levels of evidence typically are required to obtain marketing approval and addresses how to determine when such evidence is absent or deficient.

Many patients and their caregivers, as well as clinicians and scientists, do not have framework for what to do if a business is advertising potentially risky unproven CGTs or when there is reason to think that a recipient of an unproven CGT product has been harmed as a result of being administered such an intervention. The Guide identifies reporting mechanisms for ISCT members, patients and other parties to report possible adverse events associated with such products or what may be problematic marketing practices or clinical activities. Although reporting mechanisms differ across jurisdictions, many national regulatory bodies offer online tools that patients and clinicians can use to report adverse events or concerning marketing activities associated with the sale and administration of unproven CGT products. Resources that enable such reporting may be provided from various regulatory and professional bodies. Regulatory bodies responsible for enforcing laws requiring honest advertising practices and consumer protection agencies may provide recourse for deceptive advertising claims. Medical boards and colleges are responsible for regulating the practice of physicians and other licensed health care professionals and may provide tools for reporting physician practices related to unproven CGTs. Drug regulatory agencies also provide mechanisms to report provision of unlicensed cell- or gene-based interventions and/or resulting adverse effects. The Guide provides insight into how to find and use a variety of such reporting tools. Finally, the Guide describes additional steps ISCT members and other concerned parties can take to contest direct-to-consumer

Table 1
Tokens of scientific legitimacy.

Reference to the websites of academic or industry researchers at reputable research institutions to suggest these scientists or their research support the unproven cell-based treatment
Reference to articles from other research groups presenting pre-clinical or clinical research that appears related but do not directly address the marketed unproven intervention [2]
Claims of institutional ethics committee review and approval (e.g., institutional review board approval in the United States) for so-called experimental “studies”
Registering research on the US federal database ClinicalTrials.gov [3,4], or applying for patent protection of unproven “treatment approaches”
Use of scientific advisory boards

marketing of unproven cell and gene interventions and support careful and rigorous evidence-based clinical translation of proven CGTs.

The Guide is not intended to serve as an exhaustive analysis of the various topics it covers. Rather, it is meant to provide an accessible overview that ISCT members can then supplement with additional resources identified in the Guide. This Guide embodies ISCT's continued support for developing CGT products in a rigorous and evidence-based manner that complies with ethical, legal and scientific standards for research and clinical translation of cell-based products and gene therapies.

Features of Unproven Interventions (Including Tokens of Legitimacy)

CGT products may fall into various categories depending on their regulatory status and level of evidence supporting their use. First, some CGT-based interventions are evidence-based and licensed for use. Other interventions are evidence-based and do not require premarketing authorization. Yet, there is a large direct-to-consumer marketplace in which a wide variety of unproven CGT products are currently marketed and promoted without the appropriate regulatory authorization and oversight. Several types of CGTs that are currently offered commercially are unsupported by convincing evidence of safety and efficacy and can justifiably be described as unproven interventions. This means that they are potentially unsafe and there is little or no evidence to support claims that they will have meaningful therapeutic effects. In some cases, these interventions may be based on pre-clinical data that may show promise but is yet to be evaluated in well-designed and properly conducted clinical studies. Instead, these interventions are prematurely marketed directly to patients and requiring patients to pay for these interventions, rather than being offered through clinical trials or judicious use of non-trial preapproval access pathways (such as expanded access). This practice puts patients at risk and limits the opportunity to gather useful data on these interventions. In other cases, CGT-based interventions are offered directly to patients in the absence of even appropriate pre-clinical data, risking patients' health and their financial resources with little-to-no reason to expect benefit from the intervention.

Examples of such interventions unsupported by data include cell-based products, cell-derived products such as extracellular vesicles and perinatal tissue products and rarely gene-based therapies including gene-modified cell therapies. These products continue to be promoted as purported treatments for a number of conditions, ranging from musculoskeletal diseases and injuries to neurological disorders (Parkinson's and Alzheimer's disease, cerebral palsy) and respiratory diseases (pulmonary fibrosis, chronic obstructive pulmonary disease).

The ISCT has previously defined the hallmarks of unproven cell-based therapies that can be readily applied to other types of cell-based or cell-derived or gene therapy products or services [6,7]. Unproven cell-based interventions typically meet some or all of the following criteria:

- unclear scientific rationale to suggest potential efficacy;
- lack of understanding on the mechanism of action and/or the biological function to support clinical use;
- insufficient data from *in vitro* assays, animal models and/or clinical studies regarding the safety profile to support the use in patients;
- lack of a standardized approach to confirm product quality and ensure consistency in cell manufacturing based on adherence to mandatory guidelines;
- inadequate information disclosed to patients to enable proper informed consent;
- use within non-standardized or non-validated administration methods;
- uncontrolled experimental procedures in humans;
- supervision, review and approval by competent government organizations is lacking; and
- payment, often of exorbitant fees, for experimental treatments or for participation in so-called clinical studies ("pay-to-participate").

This list of potential "red flags" can be used as practical guidance by patients, families and caregivers trying to assess the legitimacy of offered CGT products.

In the absence of clinical trial data to establish safety and efficacy, unproven CGT-based interventions are often marketed through patient testimonials, celebrity endorsements and other tools of persuasion. Clinic websites may include positive statements purportedly obtained from patients or contain videos featuring patients discussing improvements that they claim resulted from the marketed intervention. While these testimonials often seem compelling, they are, even if believed to be accurate by the patient, problematic for use in medical decision-making. In addition, their veracity is often in question, for a variety of reasons, further limiting their utility. First, it is impossible to know whether the purported benefits, either transient or long-term, result from CGT administration. This includes placebo effects, which may play a role in any given patient's sense of improvement. Second, patients may have been paid or offered discounts on procedures in exchange for providing positive statements. In any case, evidence-based medical treatments cannot rely on anecdotal cases but are developed on the consistency of results following a standardized procedure that has to be authorized, supervised and evaluated by regulatory bodies.

Another common characteristic of unproven CGT-based interventions is the supposed ability of the same treatment approach to help patients with many different and unrelated conditions. Cells, particularly purported "stem cells," are sometimes claimed to have special abilities to seek out and repair damaged tissues in such a manner that the same unproven intervention could potentially help patients with conditions ranging from neurological disorders to male-pattern baldness. These broad claims of efficacy across unrelated conditions do not align with established CGTs nor with those under legitimate clinical investigation and may be a useful indicator of clinics offering interventions not supported by appropriate evidence.

These unproven interventions are often marketed in a manner that appears to suggest they are supported by stronger scientific evidence than exists. These marketing strategies are collectively referred to as "tokens of scientific legitimacy" (Table 1), and they have been discussed in the literature [8–10]. Although each of these might be a characteristic of legitimate clinical research, none on its own provides sufficient evidence to establish a novel therapy as safe and effective. Their widespread use in direct-to-consumer advertising makes it more difficult for patients, families or caregivers considering their treatment options to assess if these interventions are appropriate. As a result, these tokens may mislead some patients into choosing unproven interventions without fully understanding the extent to which they are unproven rather than supported by appropriate scientific evidence.

Patients considering their medical options, as well as clinicians and others involved in the development of CGTs that may be called on to offer advice to patients, should be aware of the various marketing tactics and tokens of legitimacy commonly used by providers of unproven cell and gene therapies.

Approved and Proven CGT Products

How can patients and providers navigate the commercial CGT landscape described in previous sections and be sure that products advertised or otherwise offered to them meet established standards

Table 2
Regulatory agencies and their jurisdictions.

Regulatory agency	Hyperlink
Australia: Therapeutic Goods Administration (TGA)	https://www.tga.gov.au/
Brazil: Agência Nacional de Vigilância Sanitária (Anvisa)	https://www.gov.br/anvisa/pt-br
Canada: Health Canada	https://www.canada.ca/en/health-canada.html
China: National Medical Products Administration (NMPA)	http://english.nmpa.gov.cn/
European Union: European Medicines Agency (EMA)	https://www.ema.europa.eu/en
India: Central Drugs Standard Control Organisation	https://cdsco.gov.in/opencms/opencms/en/Home
Iran: Iran Food & Drug Administration	https://www.fda.gov.ir/en
Japan: Pharmaceuticals and Medical Devices Agency (PMDA)	https://www.pmda.go.jp/english/index.html
New Zealand: Medicines and Medical Devices Safety Authority (MEDSAFE)	https://www.medsafe.govt.nz/
Singapore: Health Sciences Authority (HSA)	https://www.hsa.gov.sg/
South Korea: Ministry of Food and Drug Safety (MFDS)	https://www.mfds.go.kr/eng/index.do
Switzerland: Swissmedic	https://www.swissmedic.ch/swissmedic/en/home.html
USA: Food & Drug Administration (FDA)	https://www.fda.gov/

of safety and effectiveness? CGT products must undergo a rigorous process of quality, safety and efficacy demonstration under the oversight of regulatory agencies authorized by law to evaluate and approve drugs, biologics and medical devices. Such agencies can be either national, as with organizations such as Health Canada and the FDA, or transnational, as in the case of the European Union's (EU's) European Medicines Agency (EMA) (Table 2). National medicine agencies of each EU country are accountable for clinical trials, manufacturing laboratories or "Hospital Exemption" authorizations. In general, a considerable body of preclinical research that establishes biological mechanisms of action and demonstration of safety and potential efficacy in (small and/or large) animal models is required before a new CGT product can be tested in humans [11,12]. The latter process takes place through phased clinical trials and can be accelerated by specific mechanisms, such as the Regenerative Medicine Advanced Therapy designation in the United States [13], the PRIME designation in the EU [14] and the SAKIGAKE designation in Japan [15].

Once a CGT product has been shown to be safe and effective, it can receive marketing authorization by the respective regulatory agency [16]. In some cases, products receive conditional approval for a finite period, and post-market surveillance is required as additional data are collected [17]. After additional data are generated, such conditionally approved products can receive full marketing authorization if safety and efficacy support such a determination, or they can have their conditional approval status withdrawn if post-marketing data prompts concerns about the safety and/or efficacy of such products. Approved and proven CGT products, where benefits are determined to exceed risks, are also usually eligible for reimbursement by health insurance providers (private or public). As already noted, pay-to-participate studies that do not meet these criteria and are not eligible for reimbursement may be signs of concerning/unconventional clinical practice.

There are additional mechanisms that ensure the access of patients with unmet and/or serious medical needs to unapproved products under the supervision of medicines agencies, such as the US FDA "Expanded Access" program and the "Hospital Exemption" program available in some European countries [18,19]. Regulatory flexibility providing access to investigational products is important, as not all individuals who have reasonable grounds for seeking access to investigational products meet clinical trial inclusion criteria. However, regulatory exceptions are sometimes abused and need to be carefully monitored so that they do not become problematic loopholes. Therefore, such mechanisms need to be used judiciously and importantly remain under the oversight of regulatory agencies.

An unfortunate abundance of CGT products that are unproven and unapproved by regulatory agencies is offered worldwide for various conditions and diseases. Many of these products and their administration have been shown to result in adverse physical effects, from blindness to infections or even death, and considerable financial and psychological harm [20]. These adverse outcomes clearly demonstrate the need for conducting appropriate clinical trials, ensuring through early safety testing that products with high-risk profiles do not enter the marketplace.

In contrast, approved and proven CGT products are marketed after their quality, safety and effectiveness have been demonstrated through carefully conducted and monitored clinical testing under oversight of regulatory agencies. Although approved CGTs are not totally free of risk, they must have a favorable benefit-to-risk ratio before they are approved. Furthermore, regulatory oversight makes possible their withdrawal from the marketplace should the additional data obtained post-marketing demonstrate that benefits of use do not outweigh risks.

Levels of Evidence Required for Widespread Approval

Since current levels of scientific evidence do not justify or do not yet justify the commercial or clinical use of many CGT interventions, it is reasonable to ask what criteria should be applied before a product might be considered "proven" and sufficiently evidence-based for inclusion in current standard of medical care. The gold standard for any medicinal product to be considered "proven" is well-designed and sufficiently powered, strictly supervised, regulated, peer-reviewed, published clinical research studies. Preferably these studies are randomized in a double-blind fashion with a control arm using a placebo, sham surgical intervention or current standard of care. However, there are sometimes factors that prevent the attainment of gold standard randomized trials, such as in ultra-rare diseases that limit accrual of sufficient numbers of research participants and preclude randomization.

There are considerable risks involved if proper evidence of clinical benefit and safety are not proven by a structured and phased approach to clinical trial progression. If a medical product receives accelerated approval without evidence of effectiveness, then the likelihood of ever generating scientific evidence is greatly reduced. Sponsors and product developers would not be motivated to demonstrate effectiveness because they are already in the market and often have no direct competition. Patients and their family members do not wish to miss any chance that a therapy might offer a benefit, especially if the risks or harm are perceived as low. Subsequent efforts to conduct randomized controlled trials are therefore likely to experience significant difficulties recruiting study participants. Social media and internet-based communications often exacerbate the ambiguity perceived between "proven" and "unproven" therapies in patient communities. Regulators may be unable to challenge political lobbying, advocacy and market forces.

It should also be recognized that economic interests and nationalism may spur regional variances in regulatory standards [21]. These national differences in standards and oversight structures can lead to regulatory arbitrage, in which parties attempting to distribute and sell unproven CGT products cluster in jurisdictions with lax regulatory standards or ineffective law enforcement mechanisms. If the metaphorical horse has bolted from the barn and approval is granted before at least one pivotal trial is completed, then possibly effective medicinal products may languish in a perpetual state of uncertainty.

Reporting Mechanisms in the United States and Worldwide

Multiple factors drive practitioners to create businesses that offer medical services (which can be lucrative) using biological materials that have not been adequately tested for safety and/or efficacy. Once treated, patients who experience negative consequences, such as side effects, infections or other harms, risk having little recourse against such clinicians [22–24]. Complications may also not be recognized by the patients as resulting from the treatment received. Litigation can be costly, and protracted, with no assurance of a favorable outcome for plaintiffs. Patients who believe they have been harmed as a result of being administered such products can encounter difficulties finding legal representation if settlements of any kind are likely to be modest due to caps on medical malpractice verdicts or other constraints. Furthermore, some businesses and clinicians are inadequately insured, and there is little prospect of plaintiffs recovering their funds. Furthermore, patients with serious health problems often are in a poor position to participate in what can be years of costly, stressful and demanding litigation, all of which can unfold while patients suffer and their health declines [25]. Patients may self-censor reporting adverse events or lack of response from an intervention that they have paid for out-of-pocket. Where can a patient go when they believe they have been harmed by an unproven CGT product, suffered financial losses with no clinical benefits or otherwise conclude they suffered harm of some kind [26]?

Unproven CGT products as well as various autologous tissues and other products, such as primary human cells and exosomes, that are not manufactured for use in humans are reasonably easy to access. For a practitioner who sells unlicensed and unproven cell-based interventions, obtaining such products is a straightforward process. For example, many products can be purchased online, from both reputable and suspect sources, marked up in price, and then sold to patients at a considerable profit. Similarly, medical devices may be repurposed for non-authorized CGT-related uses through relatively minor changes in the operating procedures. From there, and using local personnel, the practitioner can manufacture unlicensed and unproven CGT products on the premises. These products and devices as well as other scientific and medical equipment can be used to suggest the legitimacy of the practitioner's office. It is also not uncommon for a clinic or business to have had inspection of the devices by a regulatory agency and use this to further legitimize use of the devices in unproven CGT offerings. For example, having a centrifuge inspected and validated for operation does not confer or imply approval for use in unproven or unauthorized CGTs. In parallel with suggestion of "legitimacy" of the physical space in the clinic, patients/consumers may further be attracted to displays and videos of patient testimonials [27–29]. Although some states in the United States and regions of the EU may have requirements that businesses post displays stating that the procedures being provided are not approved by regulatory agencies, the majority of the world has no such requirements.

One mechanism that would seem to alleviate ambiguity in the use of unproven CGTs would be obtaining consent from patients before treatment. In a research setting, such consent includes a discussion of the procedures, the risks, the benefits, the alternatives and the costs of the intervention. The content of informed consent documents is codified in numerous regulations worldwide, notably the International Conference on Harmonization Good Clinical Practice Guideline [30]. Review of the product-specific or research procedure-specific details as described in the informed consent form is conducted by an ethics committee or institutional review board. Unfortunately, informed consent is not always obtained for unproven CGTs and, when it is, review by an ethics committee or institutional review board is not always guaranteed. Written consent documents may not be provided to the recipients of unproven CGTs and, as noted, the use of misrepresentations is rampant in unproven CGTs.

The sheer volume of direct-to-consumer businesses offering unproven CGTs and the exploitation of regulatory ambiguity and/or loopholes have resulted in a global marketplace with widespread patient exploitation. Further reasons exacerbating this problem are the inability of understaffed regulatory agencies to perform rigorous and extensive inspections of such businesses and take enforcement actions, the absence of global regulatory convergence and transnational travel (also known as medical tourism) of patients seeking unproven CGTs.

Recourse/reporting of unproven CGTs and questionable practitioners

Countries with developed regulatory frameworks for approving CGTs often have product safety reporting systems that consumers, patients and clinicians can use. These systems often reside within the product approval framework under country-specific drug approval agencies. Such systems are intended to capture adverse safety events that appear to result from the use of a therapeutic product intended to confer medical benefit to the recipient. These reporting systems can also be used to report unintended events observed with unproven CGT products.

Examples of such reporting pathways include the following:

a) The US FDA has a program called MedWatch that captures and analyzes potential adverse events and product complaints [31]. For serious adverse events occurring while a product is being studied under an Investigational New Drug Application, reporting to the FDA is mandatory. Reporting serious adverse events to the FDA outside of an Investigational New Drug Application is voluntary. Such voluntary reporting can be done by the patient or a health care professional. In plain language, the FDA encourages anyone who has been "hurt or had a bad side effect following treatment with anything that was supposed to be a regenerative medicine product, including, for example stem cell products and exosome products" to report such events to them. The form used for reporting serious adverse events, also referred to as FDA form 3500, is online and includes clear guidance regarding how it should be completed. The voluntary reporting form provides room for the patient or their health care provider to describe the event and the outcome of the event, the suspected product, health information about the patient and contact information for the individual reporting the event (although the reporting individual can ask for such information to not be shared with the manufacturer). The FDA uses these reports for safety surveillance. Patients, consumers and health care providers can stay informed of ongoing MedWatch activities by subscribing to one or more electronic distribution tools. The US Federal Trade Commission (FTC) works with FDA as needed to bring legal proceedings against providers who engage in deceptive advertising. The FTC files a complaint when it has "reason to believe" that the law has been or is being violated and it appears to the Commission that a proceeding is in the public interest. Stipulated final injunctions/orders have the force of law when approved and signed by the District Court judge. The FTC has been particularly active during the pandemic, focusing on businesses selling unproven and unlicensed stem cell products and other interventions as purported treatments, "immune boosters," or preventive measures for coronavirus disease 2019 [32]. Consumer complaints can be filed online.

   American Medical Association members are bound by a code of medical ethics to act professionally [33,34], but the American Medical Association does not have the legal authority or possess the proper resources to investigate individual cases and complaints. Therefore, practitioners are principally subject to oversight at the level of their state medical licensing boards.

b) The EMA has issued public warnings about using unproven cell therapies that may be unsafe or ineffective [27]. Physicians,

institutions, companies or individuals who have questions about the regulatory status and/or proven safety and efficacy characteristics of a product are encouraged to contact the EMA or their National Competent Authority. EMA-reported Safety Adverse Event information is disclosed through language/country-specific databases. The centralized European database, EudraVigilance, is obligatory for marketing authorization holders and sponsors of clinical trials and since June 2022 it is mandatory to report side effects.

c) Health Canada has issued public notice of the risks associated with using unproven CGTs [35]. A position paper by Health Canada [36] on autologous cell therapy products notes the legal distinctions between the Canadian regulatory framework and the EMA regulatory framework. However, on a practical level, there is shared emphasis in warning against the risks posed by unproven CGT use. Health Canada provides a consumer reporting portal for reporting product complaints, as well as the ability to specifically report Adverse Events by a variety of means. In addition, consumer complaints can be filed to Canada's Competition Bureau.

d) Australia's Therapeutic Goods Administration uses reporting portals for practitioners and patients similar to those previously described. In particular, the Agency clearly encourages consumers to report advertising that may be false, misleading or deceptive. New Zealand's Commerce Commission allows for registering complaints regarding false and misleading behavior, of which offering unlawful therapies or making unfounded marketing claims for unproven CGTs would be representative examples.

e) Asia has regulatory agencies of multiple jurisdictions actively engaging with the regenerative medicine industry. Japan's Pharmaceuticals and Medical Devices Agency is responsible for pharmacovigilance activities including both pre-marketing safety reporting as well as post-market vigilance. Japan has a separate consumer protection government organization that spans all consumer impact areas. Likewise, Korea has a system called KAERS (Korea Adverse Event Reporting System) that facilitates reporting and management of adverse event reports.

f) In South and Central America, there are also examples of systems developed to capture reports of adverse events in patients, inclusive of licensed and unlicensed products. In Brazil, such data can be reported in a system known as VigiMed. Argentina has an online form that also allows for reporting of such events.

See Table 3 for more information and the related web links on reporting pathways.

Overall, some countries have well-defined, accessible and easy-to-use mechanisms for patients/consumers to file complaints and adverse events. However, not all jurisdictions provide such reporting mechanisms. Even within countries that have developed regulatory frameworks, reporting may be limited to health care professionals and industry (and enforcement is not guaranteed to follow reported complaints). Even more concerning, many low- and middle-income countries have minimal or no regulations regarding medicinal products. When considering unproven CGT products, these gaps become even more concerning. Many regions would benefit from better-defined and more effective reporting mechanisms inclusive of patient-reported adverse events. This reporting would facilitate collection of data on adverse effects resulting from administration of unproven and unlicensed CGTs and may also increase the likelihood of more effective regulatory responses to agents and facilities selling and administering such products. In parallel, a push toward global, coordinated efforts to curb the growth of the direct-to-consumer industry offering unproven CGTs is gaining traction. The World Health Organization has already issued a white paper proposing a global risk-based system for evaluation of CGT products and regulatory convergence that includes increasing collaboration between regulatory agencies from high income and low- and middle-income countries [37]. In this context, the proposal for a World Health Organization Expert Advisory Committee on Regenerative Medicine [38] is timely and puts emphasis on existing international health policy bodies to effect change and provide guidance.

Clinical research and development are a continuum. Complex biological products are created first from an idea or hypothesis based on understood biological mechanisms of action. The research that follows bears out the hypothesis or fails to support it and/or branches off into related treatment areas. This is a costly, often non-linear and time-consuming process of incremental investigations before treating any patient. The return on investment or approved, commercially available treatment timelines are typically many years. By contrast,

Table 3
Adverse event reporting mechanisms and databases worldwide.

Country or jurisdiction	Regulatory or professional body	Hyperlink
Argentina	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT)	https://www.argentina.gob.ar/sites/default/files/farmacovigilancia-ficha-eventos-adversos-pacientes.pdf
Australia	Therapeutic Goods Administration (TGA)	https://www.tga.gov.au/safety-information https://www.tga.gov.au/news/news/stem-cell-treatments-and-regulation-quick-guide-consumers https://www.tga.gov.au/complying-advertising-requirements https://www.tga.gov.au/advertising-enforcement-and-outcomes
Belgium	Federal Agency for Medicines and Health Products (FAMHP)	https://www.famhp.be/en
Brazil	Agência Nacional de Vigilância Sanitária (Anvisa)	https://primaryreporting.who-umc.org/BR
Canada	Health Canada	https://healthycanadians.gc.ca/apps/radar/MD-IM-0005.08.html https://www.competitionbureau.gc.ca/eic/site/cb-bc.nsf/frm-eng/GH%c3%89T-7TDNA5 https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html
EU	European Medicines Agency	https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/access-eudravigilance-data https://www.adrreports.eu/
France	Agence nationale de sécurité du médicament et des produits de santé (ANSM)	https://ansm.sante.fr/documents/reference/declarer-un-effet-indesirable
Japan	Consumer Affairs Agency	https://www.caa.go.jp/en/law/
New Zealand	Commerce Commission	https://comcom.govt.nz/make-a-complaint
South Korea	Korea Institute of Drug Safety & Risk Management (KIDS)	https://www.drugsafe.or.kr/iwt/ds/en/report/WhatIsKAERS.do
USA	Federal Trade Commission	https://reportfraud.ftc.gov/#/
USA	Food and Drug Administration (MedWatch Program)	https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program
USA	Federation of State Medical Boards (FSMB)	https://www.fsmb.org/contact-a-state-medical-board

Box 1
Regardless of outcome, patients, family members and physicians who believe they have experienced or witnessed deceptive, unethical practices, been mistreated or, sadly, suffered negative consequences from treatment should:
- inform their state/local jurisdictional physician licensing agency;
- inform their state/local jurisdictional Department of Health and Consumer Affairs; and
- inform their National Competent Authority or Authorities and National Consumer Protections Bureau(s).

unproven CGT providers, aided by low-cost barriers to entry, prey on patients who believe they have exhausted all credible options. Although costs for unproven cell and gene interventions can vary widely, patients frequently endure considerable financial strain, as witnessed by the increase in crowdfunding campaigns for such interventions and patient reports of substantial financial losses without evident improvement in their condition [26,39]. Patient options for redress are limited to what they can economically afford and have the knowledge, persistence and time to pursue. The financial burden can be particularly onerous for the most vulnerable patients, such as low-income individuals or individuals with limited access to vetted medical information and health care. Deployment of savvy marketing techniques by direct-to-consumer businesses affect disproportionally such individuals and may lead to a downward spiral of accumulating financial debt and physical and psychological harms [40,41]. Importantly, many patients, families, and caregivers are unaware of the reporting mechanisms described previously and in Table 3. Patients (and patient families) therefore need assurance before committing that any treatment being considered as well as relevant alternatives have been thoroughly reviewed by legally recognized regulatory authorities. As shown in Box 1, there are steps that patients and caregivers can take if they believe one has been harmed by administration of unproven cell- or gene-based interventions.

Local and national agencies in many countries are acting to warn, investigate and take action against businesses selling unproven CGTs [42]. However, often they are resource-constrained and only able to effectively respond when they have broad knowledge and insight. Patients can assist such bodies in launching investigations by filing detailed reports when there is reason to believe they have been harmed as a result of receiving an unproven CGT ([22,25] and Table 3).

Actions ISCT Members Can Take to Address Direct-to-Consumer Marketing of Unproven CGTs

Government agencies such as the US FDA, the EMA and their regional equivalents across the globe are ultimately responsible for determining when a CGT is considered “proven” to be safe and effective or where the potential benefits outweigh the risks. However, we can all play a role in reinforcing the need for rigorous evaluation and helping consumers avoid harm [34], from products that have entered the marketplace without being subjected to such careful and independent assessment. Physicians can be particularly effective in addressing the direct-to-consumer marketing of unproven CGT products as they discuss treatment options with their patients. Oftentimes physicians are unprepared to address patient questions related to CGTs due to a lack of education regarding novel cell-based treatments and their experimental status. Regrettably, clinical practitioners can themselves became purveyors of unproven CGTs, frequently outside their scope of training [43] and sometimes with dire consequences, as research in Canada [44], the United States [45] and Australia [23] has shown.

Here are some simple ways ISCT members can make a difference whether they are researchers, CGT developers in industry, clinical practitioners or quality professionals:

- Take care when you communicate your science: Ensure that you do not add to community misunderstanding about the availability of CGTs. When discussing your work -or advances in the field- with journalists, the public or in social media, stick to claims that are evidence-based and avoid engaging in hyperbole [46]. Carefully review any announcements prepared and promoted by your institution, university or company to ensure that the communication strikes the right balance between sharing your enthusiasm for your work and outlining the steps that will be required before the intervention may be available to patients. Where you are involved in conducting clinical research, be prepared to publish and discuss the outcomes, and their implications, no matter whether the findings are encouraging, discouraging or ambiguous [47].
- Correct misrepresentations about CGTs in the media: Where you see your work or that of colleagues misrepresented, make efforts to correct the reporting. Journalists are as interested in getting the story right as you are, so get in touch. In the unlikely event that they fail to respond, contact professional bodies that oversee journalism and report your concerns.
- Report concerning practices: Take a stance if you come across clinics or companies making therapeutic claims that cannot be scientifically substantiated. Report your concerns about coverage online, in mainstream or social media or through other forms of advertising to the relevant regulatory body. This includes those charged with oversight of manufacturing and provision of therapeutic products as well as agencies who oversee standards in health care or the practice of medicine, such as US state medical boards and Canada’s provincial Colleges of Physicians and Surgeons. There is usually a simple online form on which you can report questionable practices, such as the provision of unapproved therapeutic products. (See also “Reporting mechanisms in the US and worldwide” in Table 3 of this guide.)
- Contact the ISCT Committee on the Ethics of Cell and Gene Therapy and/or relevant professional society or association in your region and alert them to what you have seen. They may know of research groups or agencies who monitor the advertising and provision of unproven therapies in your jurisdiction and your report will provide valuable insight into contemporary practices.

  This advice is not just relevant to those involved in laboratory and clinical research but also to manufacturers and suppliers who may be alerted to irregular practices through product, equipment and reagent requests coming from clinics and health care providers involved in the sale and administration of unproven CGTs.
- Partner with patient advocacy groups and support services: Reach out to groups in your community that share an interest in a particular condition or application. Offer to speak or write about your work. This can be a meaningful way to enhance community understanding about current research and clinical applications in CGTs and to warn about practices that may be bypassing clinical evaluation and regulatory approval. It is also an effective way to meet people in your community and learn more about the condition in which you are interested -particularly for graduate researchers and students.
- Respond to those asking for help: You have probably already been asked by a stranger or maybe even a relative or a friend for advice about whether CGTs or regenerative medicine could help them or their loved one. Carefully listen to their inquiry and then provide them with links to reputable sources of online information, such as the ISCT, the International Society for Stem Cell Research and

Table 4
Resources related to proven and unproven CGTs.

Source of information	Resource name and hyperlink	Notes
International Society for Cell & Gene Therapy (ISCT)	ISCT Committee on the Ethics of Cell and Gene Therapy	Includes the ISCT Reference Guide on Unproven Cell-Based Interventions, the ISCT Guide of Cell/Gene Products with Marketing Authorization and a COVID-19 Research Spotlight
International Society for Stem Cell Research (ISSCR)	Closer Look at Stem Cells	Includes the "Patient Handbook on Stem Cell Therapies" and disease-specific Fact Sheets
Stem Cells Australia	Stem Cells Australia	Includes Q&A on stem cell treatments and information on the status of cell-based treatments for a wide variety of diseases/conditions
EuroStemCell (a European network of scientists and academics)	EuroStemCell	Includes information on various stem cell types, diseases/conditions, and educational videos
German Stem Cell Network	Unproven Stem Cell Therapies	
CIRM (California Stem Cell Agency)	CIRM Patient Resources	Includes information on CIRM-funded clinical trials, disease research programs, and patient stories
Stem Cell Network (Canada)	Stem Cells	Includes educational videos and profiles of stem cell researchers
American Society of Gene+Cell Therapy (ASGCT)	Gene & Cell Therapy Education	
European Society of Gene & Cell Therapy	Gene & cell therapy 101	
Children's Medical Research Institute-Australia	What is Gene Therapy?	
US Food & Drug Administration (FDA)	CBER Untitled Letters	
	What Is Gene Therapy?	
	Approved Cellular and Gene Therapy Products	
	Resources Related to Regenerative Medicine Therapies	
Consumer Reports	The Trouble With Stem Cell Therapy	
ProPublica	The Birth-Tissue Profiteers	
Paul Knoepfler's lab	Stem Cell Outreach Program for Education	

CGT, cell-based, cell-derived and gene-based therapies/interventions; COVID-19, coronavirus disease 2019.

regional initiatives such as CIRM, EuroStemCell and Stem Cells Australia (Table 4). You could also encourage the person making the enquiry to contact an appropriate patient foundation or advocacy or support group. Finally, and importantly, encourage them to talk to their medical specialist or family physician, rather than the doctor or clinic trying to sell them a simple solution, about their health care options.

Conclusions

Businesses selling unlicensed and unproven stem cell interventions and related "regenerative medicine" products have now operated in the global marketplace for approximately two decades. ISCT has played an important role in drawing attention to problematic commercial and clinical activities that put patients at risk and expose them to unnecessary and foreseeable risks. ISCT has also been an engaged participant in broader public conversations about the importance of ensuring that safety and efficacy of CGTs are evaluated in well-designed and carefully conducted clinical trials that comply with all applicable ethical, legal, scientific, and clinical standards. This document reflects ISCT's commitment to promoting patient safety and public understanding by helping ISCT members, patients and other parties identify "red flags" associated with concerning practices and also understand the importance of conducting robust pre-clinical and clinical research to determine whether CGTs are backed by substantial safety and efficacy data and can justifiably be marketed for particular indications.

Author Contributions

Conception and design of the study: BLL, LI. Acquisition of data: LI, NC, MF, BJG, ADL, MM, JEJR, LT, HRB, RC, FG, AS, DJW, PZ, BLL. Analysis and interpretation of data: LI, NC, MF, BJG, ADL, MM, JEJR, LT, HRB, RC, FG, AS, DJW, PZ, BLL. Drafting or revising the manuscript: LI, NC, MF, BJG, ADL, MM, JEJR, LT, HRB, RC, FG, AS, DJW, PZ, BLL. All authors have approved the final article.

Declaration of Competing Interest

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compensation and equity from Capstan Therapeutics as a co-founder and member of the Scientific Advisory Board. As co-founder of Tmunity Therapeutics, he received equity. Conflict of interest is managed in accordance with University of Pennsylvania policy and oversight. Megan Munsie is a member of the International Society for Stem Cell Research and its Ethics Committee and Public Policy Committee. She is also the President of the Australasian Society for Stem Cell Research. Munsie's research program is supported by the Novo Nordisk Foundation Center for Stem Cell Medicine (NNF21CC0073729). John E. J. Rasko: employment: Royal Prince Alfred Hospital; consultancy and honoraria: Rarecyte, Gilead, Roche, Novartis, Bluebird Bio, Spark therapeutics, Cynata, Pfizer; equity: Genea; shareholder: Rarecyte, Woke; DSMB: Diamond Fanconi anemia trial; research funding: National Health and Medical Research Council (NHMRC), New South Wales Cancer Council, Cancer Institute NSW (CINSW), Therapeutic Innovation Australia, Philanthropic foundations; Chair, Gene Technology Technical Advisory Committee, Office of The Gene Technology Regulator, Australian Government. Leigh Turner served as a compensated expert witness for the US government in a criminal case and as a pro bono expert witness in a class action lawsuit. He is a member of ISCT and its ECGT committee. He is also a member of the International Society for Stem Cell Research and its Ethics Committee and Membership Committee. Turner's research program is supported by the Pew Charitable Trusts. Daniel J. Weiss served as a compensated expert witness for the US government in a criminal case and as a pro bono expert witness in a class action lawsuit. He is a member of ISCT and its ECGT committee and is former Chief Scientific Officer of the ISCT. He is not paid for his roles in the ISCT. Dr. Weiss has received compensation for consulting with Mesoblast Inc., NextCell Inc., United Therapeutics. Inc. and Vertex Inc. Conflict of interest is managed in accordance with University of Vermont policy and oversight. Patricia J. Zettler reports serving as a consultant to the US Food & Drug Administration. All the other authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

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