



ISCT Committee Statements

International Society for Cell & Gene Therapy Expanded Access Working Group position paper: key considerations to support equitable and ethical expanded access to investigational cell- and gene-based interventions

Elena Maryamchik^{1,*}, Laertis Ikononou², Beth E. Roxland³, Felix Grignon⁴, Bruce L. Levine⁵, Bambi J. Grilley^{6,7}, for the ISCT Committee on the Ethics of Cell and Gene Therapy Expanded Access Working Group

¹ Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA

² Department of Oral Biology, School of Dental Medicine, University at Buffalo, Buffalo, New York, USA

³ Roxland Consultants Ltd, New York, New York, USA

⁴ International Society for Cell & Gene Therapy, Vancouver, Canada

⁵ Department of Pathology and Laboratory Medicine, Center for Cellular Immunotherapies, University of Pennsylvania, Philadelphia, Pennsylvania USA

⁶ Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children's Hospital, Houston Methodist Hospital, Houston, Texas, USA

⁷ Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA

*Correspondence: Elena Maryamchik, MD, MBA, 327 East 64th Street, Room 523, New York, NY 10065 USA. E-mail address: maryame@mskcc.org (E. Maryamchik).

A B S T R A C T

This position paper reviews the Expanded Access pathway for cell and gene therapies, examining its critical role at the nexus of patient need, regulatory frameworks, and scientific advancement. Spearheaded by the International Society for Cell & Gene Therapy's Expanded Access Working Group, it explores how investigational therapies are accessed outside of clinical trials for patients with serious or life-threatening conditions when no approved alternatives exist. Access to cell and gene therapy products are of specific interest to patients because many times the products are bespoke, being used to treat serious and/or incurable conditions, and are potentially curative. As the field of cell and gene therapy rapidly progresses, healthcare professionals face mounting challenges in navigating the balance between access and oversight. Key considerations include transparent communication with patients, robust data reporting, and a discussion of cost recovery models and their implications for long-term commercialization strategies. Equity and inclusivity are central themes, highlighting the need to design pathways that are accessible to diverse patient populations while upholding high scientific and ethical standards. This position paper is presented as a resource for clinicians, researchers, and policymakers navigating the evolving landscape of investigational cell and gene therapies. It emphasizes the importance of ethical frameworks and equitable practices in delivering transformative treatments to patients in need.

Key Words: compassionate use, cell therapy, expanded access, gene therapy, nontrial access, regenerative medicine.

Introduction

In 2022, the International Society for Cell & Gene Therapy (ISCT) launched the Expanded Access Working Group to identify practical, ethical, and regulatory issues emerging from use and possible abuse of nontrial access for cell and gene-based interventions. In its 2023 publication [1], the group analyzed the current landscape of cell and

gene therapy regarding unproven products that implicitly or explicitly make claims of effectiveness without scientific evidence or regulatory oversight. In this publication, the Expanded Access pathway, the primary mechanism through which developers distribute investigational products outside clinical trials in the United States, is reviewed. A key audience targeted here are the physicians and other health care professionals on the frontline of clinical care who may be

<https://doi.org/10.1016/j.jcyt.2025.01.016>

1465-3249/© 2025 International Society for Cell & Gene Therapy. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

new to cell and gene therapy and face a double challenge of finding the best therapeutic option for their patients, while navigating the logistical, ethical and regulatory complexities of nontrial access. Considering the significant advances in the field reflected by several recent high-profile FDA approvals [2,3], the resultant rapid changes in the regulatory and business environments [3–5], and the growing public interest in nontrial access to investigational cell and gene interventions [3,6], it is increasingly important for patients, physicians, and other professionals entering the cell therapy domain to orient in this changing landscape.

The standard way developers evaluate new potential therapeutic interventions or medicines is through clinical trials. However, in limited circumstances, regulators have permitted developers to provide patient access to the investigational products outside of clinical trials for compelling and urgent use in patients with serious or life-threatening conditions rather than to formally study the safety and effectiveness of the product in those particular patients. It is critical to emphasize that the expanded access pathway is not meant to be an alternate pathway to commercialize or market a product. It is intended to allow, in limited circumstances, access to unproven investigational products to patients without other options. It must do so while protecting patient safety and the integrity of research and development programs needed to understand a product's safety and effectiveness (<https://www.federalregister.gov/documents/2009/08/13/E9-19005/expanded-access-to-investigational-drugs-for-treatment-use>) [3].

FDA has been facilitating judicious patient access to investigational therapies since the 1970s. The policy addressing nontrial access was first drafted in 1979, and, after several iterations, finalized into a federal regulation in 1987 (<https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/new-drug-antibiotic-and-biologic-drug-product-regulations>). The access to investigational products outside of clinical trials occurs by a well-defined mechanism and is a subject to FDA approval. The process has been streamlined over the years, and today 99% of requests made by the treating physician on a patient's behalf receive approval, the majority with a turnaround time of only a few days [7]. It is important to note a distinction between the Expanded Access pathway and the Right to Try pathway. The latter is not regulated by the FDA; the patient's physician can submit a request directly to the manufacturer, and is not required to receive an IRB approval [7]. Right to Try's lack of FDA or institutional IRB oversight is concerning, as it foregoes an important safety checkpoint while opening the patient to unproven interventions.

Evaluating the Expanded Access Policy

The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, requires that companies manufacturing or distributing investigational products make their expanded access policies publicly available (<https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act>). These policies must specify, at a minimum, if a company provides expanded access, the procedure for submitting requests, patient eligibility criteria, anticipated response time, and references to relevant clinical trials (<https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf>). Concerningly, compliance with the Cures Act has been wanting. A recent analysis of 423 biopharmaceutical companies manufacturing oncology-related drug (not limited to cell and gene therapies) showed that only about a third of them (32%) implemented the Cures Act requirement to have a public expanded access policy, and just under a third of those (31%) provided all described information [8].

Although regulatory guidelines allow companies to have a single expanded access policy for all of their products, single policies may not be sufficient to provide adequate guidance, especially for companies with pipelines spanning different products for different

indications at various stages of development. A lack of specific guidance can increase the likelihood that requests for expanded access will be denied and divert patient's time and energy from exploring other options.

Another important feature of a well-written expanded access policy is transparency about what a company considers to be a fair and just allocation of resources for a given treatment. The most ethical approach would be to anonymize potential patients to preclude selection based on income, nationality, sex, race, or other sociodemographic factors. A model for such equitable allocation may be developed by the manufacturing company itself, or be delegated to an independent third party to objectively advise on evaluating expanded access use requests [9]. However, a truly nonbiased distribution of access may be difficult to achieve. Certain investigational products are only available in select large academic centers and pose geographical, financial and logistical challenges to many patients. In such cases, patient suitability would be based not only on their medical condition but also on the feasibility of traveling to a collection center or complying with the follow-up schedule. It would be unethical to mislead patients by not clearly delineating such requirements in the policy.

Even when a company's policy is not to provide expanded access, reasoning behind such a policy could help promote public understanding. For example, for small companies, manufacturing capabilities in the early phases of clinical trials may be limited. As a result, re-allocating some of the resources to provide expanded access programs could jeopardize the ongoing clinical trials and ultimately delay or prevent market approval that would bring their product to a larger number of patients [10,11]. This is especially relevant for cell and gene therapies where the cost of manufacturing products is significant. In a situation where patient-specific products are being made and the relative cost of treating even one additional patient (in relation to the available resources) is orders of magnitude greater than the relative cost of treating each patient with a small drug molecule the company may determine that there are inadequate resources for a robust expanded access program. Explaining the rationale behind the inability to provide expanded access (both as a general policy and in individual cases of request denials) could communicate the company's thoughtful approach to the decision, convey respect for patients requesting expanded access and set realistic expectations.

In our social media era, patients and their families rely on online sources and patient advocacy campaigns. Such campaigns, while generally well-intended, often lack reliable information and may inadvertently misrepresent a treatment's actual benefits while vilifying the company withholding expanded access [12]. Informative and well-crafted expanded access policies can improve patient education and facilitate more efficient exploration of available treatment options.

Finally, because an expanded access program should end once the product receives market authorization, a comprehensive expanded access policy should clearly delineate the plan for transitioning the patients to commercial product after product approval.

Informed Consent and Communication About Expanded Access

FDA regulations require documentation of the patient's informed consent for the use of any investigational product (<https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-I/section-312.305>). Such consent must include the discussion of the risks and uncertainties associated with the product [13], particularly the fact that the investigational product has not been approved for the treatment of a patient's condition and that its safety and effectiveness has not been established. It is especially important for cell and gene therapy products with new indications, particularly those that target rare diseases. Given that the vast majority of investigational therapies

entering clinical trials do not receive FDA approval [14], all parties should refrain from claims that could be interpreted as attestation of therapy effectiveness or safety.

In cases when an investigational therapy is already approved for a different indication, or when there exists a growing body of published data from ongoing clinical trials (for example, CD19 CAR-T used either as an approved product or off-label in late-stage clinical trials), a clinician with subject matter expertise may advance an educated guess about the effect of the proposed treatment for the patient seeking expanded access. However, estimating safety or effectiveness would be unethical for rare indications, such as single gene diseases, since there are few patients around the world and very little combined up-to-date experience and expertise.

The issue is compounded in pediatric patients. Not only are these patients unable to make their own decision about using an unproven investigational therapy outside of a clinical trial, but their age also introduces additional complexities into this decision-making process. For example, for certain rare devastating single-gene diseases, the intervention must happen very early in life to minimize the effect of the disease. However, this should be balanced against the possibility of an adverse outcome or the risk that an intervention may disqualify a patient from a future, more effective intervention (for instance, a gene therapy to correct a certain type of muscular dystrophy delivered by an adenoviral vector would disqualify the patient from future clinical trials using the same vector). The risk of receiving an unproven therapy has to be weighed against the risk of forgoing or delaying the treatment, and the parents or caregivers often face an excruciatingly difficult decision.

The terms used to describe the expanded access pathway should be differentiated from the language used for other forms of nontrial access. In vernacular speech, “compassionate use,” “right to try,” “special access program,” “early access to medicines scheme,” and “temporary authorization for use” are often used interchangeably. However, these names can mean different things in different territories [15] and have different connotations in relation to patient access, regulatory oversight, and patient safety. Such distinction is especially important in jurisdictions where both the “expanded access” and “right to try” pathways are available [16,17] and where using incorrect terms can be misleading and generate confusion among patients, clinicians, and other parties [15,18]. It is also important to avoid describing investigational products as “therapy,” “treatment” or “medicine,” as these words may imply greater certainty about a product’s benefits than is evidentiary. Although “preapproval access” is sometimes used to describe a multitude of pathways that lead to the use of investigational products [15], caution is warranted with terms that imply future market authorization. We believe that the term “nontrial access” is a better choice to describe such pathways.

It is worth noting that although the purpose of expanded access is to provide access to the investigational product rather than to generate clinical data as in the conduct of a clinical trial, the creation and approval of an expanded access protocol resembles the processes for a clinical trial (for example, both have defined inclusion and exclusion criteria, require IRB and FDA approval, and permit cost recovery), and this similarity may give the patient a false sense of security in the expected outcome. A physician counseling the patient should take special care to explain the distinction.

Expanded access programs have far fewer reporting requirements than clinical trials, therefore the information available to patients or their physicians may be insufficient for a patient to make a truly informed decision. It is particularly relevant for gene therapy products used for rare disease indications, where the number of patients treated can be as low as one, and therefore the evidence based on prior use is scant or nonexistent. It takes concerted effort from the patient, their treating physician, the institutional review board (IRB), the company manufacturing the product, and FDA (or equivalent regulatory bodies outside of the US) to gather and correlate the available data to determine whether the benefits from receiving the

investigational product through expanded access will outweigh the patient’s risks. Individuals involved in communication about expanded access must have deep understanding of the science behind the investigational product, the current stage of clinical development, and the potential risks and uncertainties associated with its use [19]. The company making the investigational product is expected to have a clinical expert knowledgeable about both the product and alternative treatment options who can, based on the specific patient information, guide the patient and their physician through available clinical options, including but not limited to the company’s expanded access program. The FDA may possess unpublished data and use such information to make recommendations for individual patients. For example, while FDA approved over 99% of expanded access requests between 2005 and 2014, in 11% of cases it made valuable recommendations about dosing, safety monitoring, or informed consent [20].

When obtaining consent from a patient for expanded access, the physician should address not only the medical aspects of the investigational product, but also a range of potential nonmedical consequences, such as time commitment, loss of earning capacity for patients and/or their caregivers during treatment and recovery, and the need to travel to/stay in a location where the investigational product is offered. The importance of these issues is increased in patients with limited incomes, those living distant from the treatment location and those with young children, inclusive of parents of pediatric patients who have other children in the household. The cost of nonmedical supportive services, such as home help while the patient is incapacitated, childcare, or transportation to follow up appointments need to be considered. [21,22]. For example, a common requirement for CAR-T therapy is for a patient and their caregiver to remain within 30 minutes of the treatment center for several weeks after receiving the infusion. There are a limited number of facilities with the capacity to offer CAR-T therapies, and for the many patients who live far away from these centers, this common requirement may not be surmountable, even if the patient qualifies for expanded access from a medical perspective.

Another potential consequence of receiving an unapproved cell or gene therapy product via expanded access is that it could disqualify the patient from future clinical trials or preclude them from receiving an alternative treatment should one become available. [10] For example, receiving a prior gene editing treatment may be an exclusion criterion for a future gene editing therapy. This is particularly important in the context of genetic conditions that may (at least currently) only have one chance at correction via gene editing, and this matter is further complicated for pediatric patients, who cannot themselves make this decision which will have profound effects on their future life trajectory.

Special attention should be given to the manner of communication [23,24]. According to recent research, the risk perception of critically ill patients may be altered, making them more prone to misunderstanding of the investigational nature of the product and the degree of uncertainty about its benefits and risks [25]. Given the hyperbole and misrepresentations often surrounding cell and gene therapies, patients may have hopes and expectations beyond what is warranted for the relevant intervention [1,26–28]. Didactic communication, which assumes people process information rationally, may not be effective for many patients considering or offered expanded access. The physician should be familiar with other evidence-based, engaged styles of communication that might better promote patient understanding and autonomy [19,27,29]. Moreover, even medical and scientific professionals may not be immune to the effects of widespread exaggerated promotional claims. Therefore, care should be taken when communicating with expert audiences [30–32].

Data Reporting in Expanded Access

The regulations for expanded access programs are similar to those for clinical trials. Of note, most expanded access protocols do not

include efficacy outcomes and thus the data reporting is primarily limited to the reporting of adverse events. 21 CFR 312.32 requires reporting of serious and unexpected adverse reactions, such as death, life-threatening adverse events, inpatient hospitalizations or prolongation of the existing hospital stay, as well as congenital anomaly/birth defects, within 7 or 15 days of discovery, depending on severity of the event (<https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-B/section-312.32>). However, the reporting of events not falling into these categories does not have to be immediate and can be included in the IND annual report (if the protocol continues for over a year) or in the final report (if the protocol is closed prior to one year).

Many companies are reluctant to offer expanded access due to the reporting requirement. Patients receiving treatment through expanded access may be at increased risk for adverse events because of their comorbidities or advanced disease. Companies fear that reporting serious adverse events occurring in this patient population might jeopardize their entire drug development program. Such concerns are largely unfounded. A review of Center of Drug Evaluation and Research (CDER) data on expanded access requests versus consequent drug approvals over a 10-year period from 2005 to 2014 identified just two trials (0.2% of total) that were placed on temporary hold due to findings from their expanded access programs. One short-term hold was removed after submission of additional safety data, and one partial hold limiting accrual of a potentially vulnerable population was also eventually removed [33]. Compared to the overall incidence of clinical holds for all commercial investigational drugs of 7.9%, the risk of receiving a clinical hold due to reporting data from expanded access is therefore minimal. FDA specifically states that in reviewing the safety data from expanded access protocols, it considers the context and recognizes that the treatment could have occurred outside a controlled setting, possibly in conjunction with other therapies, or that the patient may have been at a more advanced stage of disease or suffer comorbidities that would put them at higher risk of adverse events (<https://www.fda.gov/media/85675/download>). The intent is to increase the reporting of data gathered through expanded access programs, remove the punitive potential, and promote transparency.

Evidence Generation and Expanded Access

There is an inherent tension between generating the evidence of safety and efficacy of the investigational products through well-designed clinical trials and the nontrial access to these products where the primary intent is therapeutic and evidence generation is secondary or is not considered at all [3]. Some requests for expanded access might come from patients who are eligible for clinical trials but do not want to take the risk of being randomized to a study arm in which the investigational product is not provided. While the desire to access a particular investigational product makes sense on an individual patient level, allowing expanded access in such cases could significantly impact trial accrual (especially for rare diseases) and delay marketing authorization even for products that ultimately demonstrate convincing evidence of safety and effectiveness. Therefore, FDA explicitly prohibits patients who can qualify for clinical trials from entering directly into an expanded access pathway.

Acceptable cases can also contribute to the strain between access and evidence if the focus on data generation is insufficient. Even though the main focus of expanded access is on individual patients rather than long-term societal benefits, careful collection and curation of research data may still be possible. In 2023, FDA issued a guidance on the use of real-world data/evidence to support regulatory decision making for drugs and biological products, in which it acknowledges that the data obtained outside of clinical trials

(including from expanded access protocols) may have a role in regulatory decision-making pertaining to investigational therapies, and outlines the guidelines on collecting, reporting and accessing those data [34].

However, data collection in the context of an expanded access protocol should not impose undue burden on severely ill patients and their physicians [35]. Informed consent forms for expanded access to investigational products should include carefully crafted provisions for clinical data collection or gathering patient-reported outcomes. Such data could be included in patient registries maintained by consortia that include academic centers, patient advocacy organizations, and cell and gene therapy developers. Physicians treating patients under expanded access are in a unique position to collect clinical data and publish case reports that can enhance understanding of the investigational product. However, the limited nature of the data should be acknowledged to avoid generalized therapeutic claims.

Indeed, when data from clinical trials are scarce, such as may be the case with rare diseases with high unmet medical need, FDA and other regulatory agencies, such as EMA, increasingly weigh the data derived from expanded access [35]. Most of the time, such data is used as supportive evidence to supplement clinical trial results or to authorize additional indications of already approved therapies. However, in at least a few instances, regulatory approval was granted based mostly (or in cases where randomization would be unethical—solely) on expanded access data [36]. Of note, almost all these approvals were granted orphan designation. Given the significant role that gene therapies play in addressing rare diseases, establishing a framework to generate evidence and best practices is critical to ensure the expanded access pathway promotes, rather than impedes, patient access.

In summary, evidence generation in the context of administration of investigational, unapproved products through expanded access is possible and may even facilitate product development. Data gathering and use should be done with caution and in accordance with the following three considerations. First, such data are auxiliary and cannot replace data from randomized, well-designed clinical trials. Second, expanded access data should not be used as an advertising tool that commercializes unapproved products. Third, data collection should be performed transparently without violating patient autonomy and privacy.

Cost Recovery

For individuals receiving a clinical trial investigational product, Medicare and certain insurance companies have determined that routine clinical participation expenses associated with clinical trials can be covered (<https://www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies/Downloads/finalnationalcoverage.pdf>). The costs of the investigational product are specifically excluded from such coverage. Investigational agents are often provided to recipients free of charge, though FDA has made certain allowances where sponsors can charge patients for the investigational agent (<https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-A/section-312.8>).

In the expanded access setting, FDA states that sponsors may recover direct costs related to making the investigational agent. Direct costs include raw materials, labor and nonreusable supplies, and shipping and storage of the product. Indirect costs cannot be recovered, with the exception of intermediate sized expanded access protocols, in which a sponsor may recover the costs of monitoring the expanded access protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access IND.

For example, in order to manufacture point-of-care cell therapy products under an expanded access protocol, an academic institution

can hope to recover the cost of supplies, reagents and technician time required for the manufacturing of the actual patient product, but not the cost of product development, validation runs, or administrative services associated with the administration of the product in expanded access.

To obtain an approval for cost recovery, sponsors must submit documentation supporting the determined cost, (such as invoices and related calculations) to the FDA as a part of their IND. The submission must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculations. In addition, the sponsor must demonstrate that charging for the product will not interfere with the development of the product for marketing approval.

Cost recovery approval may be used to justify payment by a third-party payor. However, since FDA authority does not include reimbursement policy, cost recovery approval by the FDA does not guarantee third party payment for either the investigational product or any other related expenses. That leaves treatment recipients open to a risk of a significant financial burden (though in reality most sponsors/manufacturers do not charge patients directly for the product provided through expanded access). Nevertheless, cost recovery can be a useful tool for small developers who may have limited resources, since direct cost reimbursement for product manufacturing may allow those developers to provide products through expanded access.

Benefits and Risks of Cost Recovery in a Pathway to Commercialization

An area of concern is opaque relationships between clinicians and companies with which they may have licensed intellectual property or a financial stake. While the intent of expanded access regulations may be to prevent profiteering, loopholes could allow companies to pursue commercialization of therapies included in expanded access programs (<https://www.fda.gov/media/176308/download>). For example, while the FDA permits charging for administrative fees in intermediate-sized expanded access protocols, there is no mechanism to cap these fees, allowing for potential inflation. Sponsors can recover costs paid to third parties, including profits embedded in those fees, enabling clinical facilities to profit from associated services, such as nursing, equipment, and facility use. If the drug manufacturer is not the IND sponsor but sells the product to the sponsor, the manufacturer can charge any amount. The sponsor can then recover these costs via the FDA cost recovery program, potentially facilitating profit-making via a pass-through model between two business entities. The clarity of intent and the transparency in the informed consent process is therefore crucial to protecting patients' rights.

Considering the Equity and Inclusivity of Expanded Access

The issue of equity is not directly addressed in the guidelines for expanded access in the United States. Given persistent inequities in access to and outcomes from care across the US healthcare system, we argue that equity is an important ethical consideration that should not be overlooked in the development and implementation of expanded access programs worldwide. In particular, insufficient attention to issues of equity by physicians and other clinical staff as well as companies asked to provide cell- and gene-based interventions on an expanded access basis risks exacerbating existing inequities in healthcare systems.

Physicians play a central role in the expanded access system, overseeing the patient's treatment, working with industry to procure investigational products, and working with both the FDA and institutional review boards. In addition, in some cases, physicians directly suggest the possibility of using the expanded access pathway to their

patients. In these roles, physicians should take care to offer information about expanded access or take on the additional burden of managing a patient's care under expanded access based on their understanding of the patient's medical condition, treatment options, and preferences and not on socioeconomic or other demographic factors. While comparisons of patients who are offered and pursue expanded access to investigational products with those who are not offered or do not pursue such medical interventions are limited, evidence from one company's experience indicates that nontrial access requests for unapproved products disproportionately originate from patients in high-income countries [37]. Other, more anecdotal reports, suggest that wealthier, more educated, better-connected patients (or their families) may be disproportionately likely to pursue expanded access or gain access to unapproved products through expanded access.

Contributing to the inequity is the disparity in the familiarity of physicians and other healthcare providers with the expanded access pathway. There is a difference in the awareness, understanding, and comfort level in treating or referring patients for cell and gene therapies among physicians practicing in large academic institutions versus smaller community-based centers, or remote rural practices, and this disparity is even more pronounced in knowledge pertaining to expanded access. As cell and gene therapies are becoming an expanding part of available treatment options, we encourage all physicians to actively seek education in cell and gene therapy advances, stay up to date with both approved treatments and current clinical trials, and develop a good understanding of the expanded access pathway, so they can confidently counsel patients for whom these options could be beneficial. Some useful resources in leading such discussions are summarized in Table 1.

Another ethical question is whether a physician has a moral obligation to proactively discuss expanded access pathway with all their patients or limit such discussions to patients who already seek expanded access, and those who, in physicians' opinions, would most benefit from, qualify for, and comply with its requirements. In a recent article addressing this issue, promoting equality among patients was advanced as a possible reason to support an affirmative duty to proactively discuss expanded access to investigational products as an option for patients to consider [38]. In all such discussions, information provided should be accurate, appropriate for the patient's medical condition, and presented in a manner that supports, to the extent possible, the patient's autonomy to make an informed decision about their medical care. As part of this obligation to disclose, any potential conflicts of interest on the part of the physician should be disclosed to patients. Offers to assume the additional bureaucratic workload associated with expanded access should be made equitably and without regard to patients' ability to pay.

While the question of whether any given CGT developer should provide nontrial access to a specific investigational intervention is beyond the scope of the manuscript, these decisions should be made with equity considerations in mind. Although academic and industry CGT developers may, in accordance with regulatory guidelines, charge for appropriate cost recovery when providing nontrial access to investigational products, it would be highly unethical to grant or deny access based on the patient's ability to pay. While we acknowledge that the feasibility of such practices may vary among different players in the CGT industry (e.g., academic medical centers, small biotechnology companies, large pharmaceutical firms, etc.), we encourage the development of expanded access policies that are blind to the ability of a patient's ability to pay and allocate internal resources to cover relevant costs for expanded access requests that meet relevant inclusion criteria but for which a patient's ability to pay appropriate cost recovery charges would be problematic.

Table 1
 Resources for clinicians navigating expanded access pathway.

Action	Resources
Before considering EAP, explore the available clinical trial options Become familiar with the EAP	ClinicalTrials.gov - Reagan-Udall Foundation (https://reaganudall.org/) - ClinicalTrials.gov (search Expanded Access) - National Organization for Rare Disorders (NORD, https://rarediseases.org/) - Compendia (https://www.nccn.org/compendia-templates/compendia/drugs-and-biologics-compendia) - Peer-reviewed publications - ClinicalTrials.gov (search Expanded Access) - Reagan-Udall Foundation's Company Directory of EAPs at https://navigator.reaganudall.org/company-directory
Explore existing Large or Intermediate Patient Group EAPs Patient must meet specific eligibility criteria for multipatient EAP	https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/expanded-access-experimental-biologics Emergency Requests Contact Information: During normal business hours (8 am–4:30 pm EST weekdays): - For investigational biological products regulated by CBER call 240-402-8020 or 800-835-4709; or e-mail: industry.biologics@fda.hhs.gov. - For all other investigational drugs, call 301-796-3400 or 855-543-3784
If existing multipatient EAPs are not available, consider a Single-Patient EAP - May be emergency or nonemergency Emergent request: - Reserved only for situations where the patient's condition requires treatment before a written submission can be obtained. - FDA may allow the treatment use to proceed without a written submission, provided the applicable criteria are met. - In an emergency situation, the request to use the drug may be made via telephone, fax, or other means of electronic communication, and authorization to ship and use the drug may be given by the FDA official over the telephone.	After hours (after 4:30 pm EST weekdays and all day on weekends): Direct all questions about and requests for expanded access for emergency use for drugs, biologics and medical devices should to the FDA Emergency Call Center at 866-300-4374 or 301-796-8240
Discuss potential EAP with your patient/family, including: - Risk - Safety - Lack of proven efficacy - Logistics - The possibility of not being able to receive another treatment, including standard-of-care, or participate in the trials that may become available later	
Reflect the above points in the informed consent document and submit for IRB approval. Consent must: - Maximally address the risks and uncertainties of using investigational medical products - Be free of unproven claims and allegations	
Request Expanded Access from drug manufacturing company If approved, the company will issue a Letter of Authorization (LOA)	
With LOA in hand, submit an Investigational New Drug (IND) application to FDA FDA will issue an IND application number	- Use FDA Form 3926 (Individual Patient Expanded Access Investigational New Drug Application, available online at Expanded Access eRequest) - For information and help with applying for EAP visit Project Facilitate https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate
Submit the application packet for Institutional Review Board (IRB) approval, including: - FDA forms - LOA - Informed consent document - Treatment protocol	
Report back to FDA, IRB, and manufacturer: - Any adverse events - Annually - At completion of the study	- Use Form FDA 3500A for reporting of adverse events to FDA - For information about FDA reporting requirements, contact FDA's Division of Drug Information at 855-543-3784 or druginfo@fda.hhs.gov

Author Contributions

EM, LI, BER, FG, BLL, and BJG contributed to the conception, design and writing of this paper.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: L.I. has written an expert report in a class action lawsuit filed against a business selling unproven "stem cell" based interventions, and wrote the report on pro bono basis. B.L.L. reports personal fees from Avestas, Cellula Therapeutics, Immusoft, In8bio, Immuneel, Kite Pharma, Ori Biotech, Oxford Biomedica, ThermoFisher Pharma Services, UTC Therapeutics. B.L.L. also holds equity in Tmunity Therapeutics (acquired by Kite Pharma) and Capstan Therapeutics. B.J.G. reports having had agreements with Tessa Therapeutics, AlloVir, Marker Therapeutics and LoKon Pharma AB through QB Regulatory, LLC. All of those agreements have ended. Also through QB Regulatory,

LLC, B.J.G. has equity with AlloVir, as well as agreements with March Biosciences and Emory University.

Acknowledgements

We thank all members of the ISCT Committee on the Ethics of Cell and Gene Therapy Expanded Access Working Group, as well as members of the Committee as a whole. We especially thank Felix Grignon and Fajar Dumadi of the ISCT Head Office.

Funding

No funding was received.

References

- [1] Ikonomou L, Cuende N, Forte M, Grilley BJ, Levine AD, Munsie M, et al. International society for cell & gene therapy position paper: key considerations to support evidence-based cell and gene therapies and oppose marketing of unproven products. *Cytotherapy* 2023;25:920–9.

- [2] Braendstrup P, Levine BL, Ruella M. The long road to the first FDA-approved gene therapy: chimeric antigen receptor T cells targeting CD19. *Cytotherapy* 2020;22:57–69.
- [3] Zettler PJ, Ikonomou L, Levine AD, Turner L, Grilley B, Roxland BE. An International Society for Cell & Gene Therapy working group short report on the future of expanded access to unapproved cell and gene therapies. *Cytotherapy* 2023;25:712–7.
- [4] Bateman-House A, Kearns L. Individualized therapeutics development for rare diseases: the current ethical landscape and policy responses. *Nucl Acid Ther* 2022;32:111–7.
- [5] Sceputa B, Chan M, Kim T, Boehmer J, Goldberg KB, Pazdur R. Oncology expanded access and FDA's project Facilitate. *Oncologist* 2021;26:E1880–2.
- [6] Knoepfler PS. From bench to FDA to bedside: US regulatory trends for new stem cell therapies. *Adv Drug Deliv Rev* 2015;82–83:192–6.
- [7] Walker S. Expanded access versus right-to-try. *Hosp Pharm* 2020;55:79–81.
- [8] Kang S, Chang S, Ross JS, Miller JE. Implementation of 21st century Cures Act expanded access policies requirements. *Clin Pharmacol Ther* 2021;110:1579–84.
- [9] Caplan AL, Ray A. The ethical challenges of compassionate use. *JAMA-J Am Med Assoc* 2016;315:979–80.
- [10] Chapman CR, Moch KI, McFadyen A, Kearns L, Watson T, Furlong P, et al. What compassionate use means for gene therapies. *Nat Biotechnol* 2019;37:352–5.
- [11] Webb J, Shah LD, Bateman-House A. Siblings and discordant eligibility for gene therapy research: considering parental requests for non-trial "compassionate use. *Clin Ethics* 2021;16:359–63.
- [12] Mackey TK, Schoenfeld VJ. Going "social" to access experimental and potentially life-saving treatment: an assessment of the policy and online patient advocacy environment for expanded access. *Bmc Medicine* 2016;14:10.
- [13] Hordijk M, Vermeulen SF, Bunnik EM. The 'false hope' argument in discussions on expanded access to investigational drugs: a critical assessment. *Med Health Care Philos* 2022;25:693–701.
- [14] Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. *Nat Biotechnol* 2014;32:40–51.
- [15] Kimberly LL, Beuttler MM, Shen M, Caplan AL, Bateman-House A. Pre-approval access terminology: A cause for confusion and a danger to patients. *Ther Innov Regul Sci* 2017;51:494–500.
- [16] Lynch HF, Zettler PJ, Sarpatwari A. Promoting patient interests in implementing the Federal Right to try Act. *JAMA-J Am Med Assoc* 2018;320:869–70.
- [17] Spector-Bagdady K, Weatherwax KJ, Gravelin M, Shuman AG. The critical role of medical institutions in expanding access to investigational interventions. *Hastings Cent Rep* 2019;49:36–9.
- [18] Zettler ME, Jeune-Smith Y, Feinberg BA, Phillips EG, Gajra A. Expanded access and right to try requests: the community oncologist's experience. *JCO Oncol Pract* 2021;17:682.
- [19] Turner L, Munsie M, Levine AD, Ikonomou L. Ethical issues and public communication in the development of cell-based treatments for COVID-19: lessons from the pandemic. *Stem Cell Rep* 2021;16:2567–76.
- [20] Jarow JP, Lemery S, Bugin K, Lowy N. Ten-year experience for the Center for Drug Evaluation and Research, part 2: FDA's role in ensuring patient safety. *Ther Innov Regul Sci* 2017;51:246–9.
- [21] Bateman-House A, Shah LD, Escandon R, McFadyen A, Hunt C. Somatic gene therapy research in pediatric populations: ethical issues and guidance for operationalizing early phase trials. *Pharm Med* 2023;37:17–24.
- [22] Woollard L, Gorman R, Rosenfelt DJ. Improving patient informed consent for haemophilia gene therapy: the case for change. *Ther Adv Rare Dis* 2021;2:26330040211047244.
- [23] Darrow JJ, Sarpatwari A, Avorn J, Kesselheim AS. Practical, legal, and ethical issues in expanded access to investigational drugs. *N Engl J Med* 2015;372:279–86.
- [24] Fountzilas E, Said R, Tsimberidou AM. Expanded access to investigational drugs: balancing patient safety with potential therapeutic benefits. *Expert Opin Investig Drugs* 2018;27:155–62.
- [25] Folkers KM, Bateman-House A. Improving expanded access in the United States: the role of the Institutional Review Board. *Ther. Innov Regul Sci* 2018;52:285–93.
- [26] Caulfield T, Sipp D, Murry CE, Daley GQ, Kimmelman J. Confronting stem cell hype. *Science* 2016;352:776–7.
- [27] Kawam O, Zhu X, Eton DT, Martin-Lillie C, Rutten LJF, Shapiro S, et al. Designing persuasive health education for patients seeking unproven stem cell interventions. *Stem Cell Rep* 2023;18:1549–54.
- [28] Zarzeczny A, Atkins H, Illes J, Kimmelman J, Master Z, Robillard JM, et al. The stem cell market and policy options: a call for clarity. *J Law Biosci* 2018;5:743–58.
- [29] Simis MJ, Madden H, Cacciatore MA, Yeo SK. The lure of rationality: why does the deficit model persist in science communication? *Public Underst Sci* 2016;25:400–14.
- [30] Avorn J. Academic detailing "marketing" the best evidence to clinicians. *JAMA-J Am Med Assoc* 2017;317:361–2.
- [31] Gould P, Salam T, Kimberly L, Bateman-House A, Lynch HF. Perspectives of academic oncologists about offering expanded access to investigational drugs. *JAMA Netw Open* 2022;5:13.
- [32] Schwartz LM, Woloshin S. Medical Marketing in the United States, 1997–2016. *JAMA-J Am Med Assoc* 2019;321:80–96.
- [33] Jarow JP, Lemery S, Bugin K, Khozin S, Moscicki R. Expanded access of investigational drugs: the experience of the center of drug evaluation and research over a 10-year period. *Ther Innov Regul Sci* 2016;50:705–9.
- [34] FDA. Considerations for the use of real-world data and real-world evidence to support regulatory decision-making for drug and biological products guidance for industry, 2023. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug>. Accessed: January 28, 2025.
- [35] Kearns L, Chapman CR, Moch KI, Caplan AL, Watson T, McFadyen A, et al. Gene therapy companies have an ethical obligation to develop expanded access policies. *Mol Ther* 2021;29:1367–9.
- [36] Polak TB, van Rosmalen J, Uyl-de Groot CA. Expanded Access as a source of real-world data: an overview of FDA and EMA approvals. *Br J Clin Pharmacol* 2020;86:1819–26.
- [37] Aliu P, Sarp S, Reichenbach R, Behr S, Fitzsimmons P, Shamlajee M, et al. International country-level trends, factors, and disparities in compassionate use access to unlicensed products for patients with serious medical conditions. *JAMA Health Forum* 2022;3:11.
- [38] Vermeulen SF, Hordijk M, Visser RJ, Bunnik EM. Do physicians have a duty to discuss expanded access to investigational drugs with their patients? A normative analysis. *J Law Med Ethics* 2023;51:172–80.