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ISCT Committee Paper

An International Society for Cell & Gene Therapy working group short report on the future of expanded access to unapproved cell and gene therapies

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ABSTRACT

Patient interest in non-trial access pathways to investigational cell-and gene-based interventions, such as expanded access in the USA, is increasing, while the regulatory and business environments for non-trial access in the cell and gene therapy field are shifting. Against this background, in 2022 the International Society for Cell & Gene Therapy (ISCT) established a Working Group on Expanded Access to identify practical, ethical, and regulatory issues emerging from the use (and possible misuse) of the expanded access pathway in the cell and gene therapy field. In this Short Report, the Working Group sets the stage for its future activities by analyzing the history of expanded access and identifying three examples of questions that we anticipate arising as uses of expanded access for investigational cell and gene-based interventions increase and evolve.

Introduction

The cell and gene therapy field is at an opportune moment to consider the future of non-trial access to investigational cell-and gene-based interventions. "Non-trial access" refers to the provision of unapproved interventions, when the primary purpose is treating patients rather than studying the safety and effectiveness of such interventions within the context of clinical studies.

In the USA, patients are increasingly interested in obtaining cell- and gene-based interventions through "expanded access." This is the most frequently used US pathway for non-trial access to unapproved products and is available under US Food and Drug Administration (FDA) regulations. The FDA received 417 expanded access requests for biological products in fiscal year 2021, up from 100 requests 10 years before in 2011 [1]. This growing interest in expanded access likely reflects the tremendous hope regarding the potential of cell- and gene-based interventions—hope that has been amplified by several recent FDA approvals for gene therapies—as well as hype about the field that might result in some patients overestimating benefits and underestimating risks associated with use of investigational products. The coronavirus disease (COVID-19) pandemic may also be contributing to awareness of the expanded access pathway. Expanded access served as a mechanism for treating COVID-19 patients with biological products such as convalescent plasma and antibody products (before the FDA issued emergency use authorizations) as well as cell-based interventions [2].

In addition to increased patient interest in non-trial access, the regulatory environment is also evolving. In 2018, the federal Right to Try law created a new pathway in the USA for non-trial access, which does not require the FDA's authorization before a developer may provide an intervention [3,4]. Not many product developers have publicly expressed interest in providing access to investigational products through the "right to try" pathway, but cell and gene therapy developers are among the few that have [5,6]. In the USA,

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individual states have also passed "right to try" laws specifically focused on access to cell- and gene-based interventions. For example, a Texas law passed in 2017 sought to increase access to "investigational stem cell treatments," and in April 2022 Arizona enacted a "Right to Try 2.0" law that aims to increase access to "individualized investigational treatments" such as "individualized gene therapies." More generally, in 2021, the FDA ended its policy of not enforcing pre-market approval requirements for certain regenerative medicine interventions. This latter development might push developers and patients to more frequently explore mechanisms for non-trial access. Beyond patients' hopes that investigational products will help them, the current regulatory interest in finding ways to use reliable real-world evidence may push the FDA and developers to increasingly look to expanded access as one important source of such evidence. The FDA is also exploring the possibility of "intermediate" pathways to market—providing more flexibility than a full biologics license application—for certain cellular interventions [7]. Although there are few publicly available details concerning the shape such intermediate pathways might take, references by FDA officials to such a development point to possible changes in the regulation of at least some cell-based products.

In this shifting regulatory environment, the commercial environment is also in a state of flux. For example, in the USA, as in many other countries, clinics market purported stem cell therapies for a wide range of indications. Some of these businesses use rhetoric of expanded access and "right to try" in their marketing representations [5]. New business models are also emerging, such as contract research organizations promoting themselves as assisting with "right to try" requests or with gathering real-world evidence from expanded access programs as well as entities seeking to monetize procedures offered as part of non-trial access to unapproved interventions, if not the interventions themselves [8].

Against this background, in 2022 the International Society for Cell & Gene Therapy (ISCT) established a working group on expanded access. Comprising members with scientific, regulatory and ethical expertise, the working group aims to identify practical, ethical and regulatory issues emerging from use—and possible abuse—of the expanded access pathway in the cell and gene therapy field. Although questions about how to provide appropriate, limited non-trial access to unapproved interventions while maintaining clinical trials are not unique to the USA, the working group is focusing on expanded access and the US context as a starting point for cell and gene therapy stakeholders to consider these issues. ISCT members have elsewhere explored the related topic of hospital exemptions for advanced therapy medicinal products within the European Union, and the working group plans to monitor international developments related to non-trial access as it proceeds with its work. The working group will examine how to make the most of the opportunities—and minimize the risks—presented by expanded access and will develop resources for cell and gene therapy stakeholders to help ensure that uses of expanded access serve the interests of patients and the cell and gene therapy industry. In this initial short report, the working group sets the stage for its future activities by analyzing the history of expanded access and identifying three examples of questions that we anticipate arising as uses of expanded access for investigational cell- and gene-based interventions increase and evolve.

The Expanded Access Pathway

In the USA, there are two primary pathways within which developers may provide patients with non-trial access to unapproved products: the relatively new "right to try" pathway and the long-standing expanded access pathway. ISCT's working group is, at least initially, focused on the use of expanded access for cell- and gene-based interventions both because it is the more frequently used pathway and because many bioethicists and patient groups generally agree that, compared with the "right to try" pathway, expanded access offers greater protections and benefits for patients without substantially delaying access [9].

Expanded access refers to non-trial access that is provided under section 360bbb of the Federal Food, Drug, and Cosmetic Act and FDA regulations. This section requires that the FDA authorize a developer to distribute its unapproved product for treatment purposes [10]. There are three categories of expanded access depending on the size of the patient population that would gain access: (i) individual patient programs, for one or just a few patients, available in emergency and non-emergency contexts; (ii) intermediate-size programs; and (iii) treatment programs available for large groups of patients. For all three categories, the FDA will authorize product distribution for expanded access when patients have serious or immediately life-threatening conditions, the potential benefit justifies the potential risk and expanded access will not interfere with clinical trials. Certain safeguards must be in place, including that an institutional review board authorize the access (in addition to the FDA's authorization), that patients' informed consent be obtained and that records be kept. There are also additional criteria and safeguards specific to each category of expanded access.

The FDA authorizes the overwhelming majority of the expanded access requests it receives. Most of these requests are for individual patient programs. For example, in fiscal year 2021, the FDA's Center for Biologics Evaluation and Research (CBER) authorized 411 of the 417 requests it received (roughly 99%) [1]. Of those 417 requests, 408 (roughly 98%) were individual patient requests. At ISCT's 2022 annual meeting, the FDA presented numbers regarding products regulated by CBER's Office of Tissues and Advanced Therapies, and consistent with the overall CBER numbers, the FDA authorized 99% of the expanded access requests for Office of Tissues and Advanced Therapies products in 2021. Although concerns about agency delays have been raised at times, the agency conducted a study of expanded access requests submitted to the Center for Drug Evaluation and Research, finding that expanded access decisions are often made in a matter of days—or hours in the case of emergency requests [11].

Additionally, FDA regulations limit what sponsors may charge for an investigational product provided through expanded access [12]. For individual patient programs, sponsors may charge only for the direct costs of providing the drug. Direct costs include costs related to the raw materials used to manufacture the quantity of drug needed for the expanded access program. For intermediate-size patient populations and treatment programs, sponsors may also charge for monitoring and administrative costs associated with running the expanded access program. Although sponsors must submit documentation of their costs to receive FDA authorization to charge for an investigational product, the FDA may face resource and expertise challenges in assessing such documentation. Furthermore, there appears to be little public information about sponsors' justifications for fees charged patients and how the FDA assesses those justifications.

Finally, it is important to note that the FDA has no legal authority to guarantee that any patient receives access to a desired investigational product. FDA authorization of an expanded access program permits a developer to distribute its product for such access, but the FDA cannot compel a developer to provide expanded access generally or specifically to any individual patient. This means that developers are important gatekeepers for determining access, a fact often overlooked in policy discussions that sometimes misleadingly frame the FDA as obstructing access to investigational products.

The Rationale for Expanded Access

Access to unproven products, by definition, is not known to be a benefit for patients, may pose risks of physical and financial harm to patients and can come with opportunity costs if patients and their

loved ones expend considerable effort obtaining access to investigational products that do not improve clinical outcomes. Nonetheless, patients have long been interested in, and the government has long been open to, access to unapproved products provided outside clinical trials. For example, in the 1970s, patients with cancer brought a lawsuit against the FDA seeking access to laetrile—a substance derived from fruit pits and promoted as a cancer treatment notwithstanding the lack of scientific support for that use. The US Supreme Court ultimately rejected the plaintiffs' arguments that FDA approval requirements do not apply to drugs intended for terminal illnesses [13]. However, the FDA was not wholly opposed to non-trial access during this era. From the time the FDA's modern drug approval authority was created in 1962, the agency used various informal processes to allow such access. In the 1970s, the FDA and the US National Institutes of Health established the "Group C" program providing non-trial access to certain patients with cancer. The FDA would subsequently create a similar program for patients with HIV in 1986 [14].

These examples suggest societal recognition that some limited mechanism for access to investigational products other than clinical trials may be necessary to balance patients' interest in accessing such products against the need to develop rigorous information about safety and effectiveness. Expanded access is the mechanism that the FDA developed to provide such access while protecting clinical trials, with the agency first formally establishing non-trial access regulations in 1987 [15].

However, establishing regulations for non-trial access in 1987, perhaps inevitably, did not mark an end to debates about how to appropriately allow for access to investigational products. Patients, patient advocacy organizations and political organizations have continued to push for changes to non-trial access, and the FDA has continued to refine its approach to expanded access. For instance, in the 2000s, the Abigail Alliance, a patient advocacy group, brought a lawsuit against the FDA arguing that patients have a constitutional right to access investigational drugs. Consistent with decisions of the European Court of Human Rights, a US federal appeals court rejected this claim of an access right [16,17]. Following the case, however, the FDA updated its expanded access regulations in 2009 to clarify its policies and address various concerns [18]. Since then, the agency has continued to work to improve expanded access processes and physicians' and patients' experiences with those processes, including by issuing guidance documents to clarify agency positions, minimizing the paperwork necessary for individual patient requests, creating a pilot project known as Project Facilitate to assist health care professionals making expanded access requests for oncology indications and identifying expanded access as a priority in the agency's action plan for neurodegenerative diseases.

In certain instances, expanded access has appeared to be a useful mechanism. Through expanded access, patients have been treated with investigational interventions that were later approved as safe and effective for their condition—under FDA and institutional review board oversight providing various protections—as with the expanded access program for Yescarta (Kite Pharma, Santa Monica, CA, USA) (axicabtagene ciloleucel) that was initiated before approval and the global expanded access program for Gleevec (Novartis, Basel, Switzerland) (imatinib) in which patients experienced similar outcomes as patients in the clinical trials that supported the drug's approval [19,20]. Many larger expanded access programs are started only after clinical trials that generate the safety and effectiveness evidence needed for FDA approval are completed or nearly complete [21]. Expanded access programs have also allowed patients to retain access to approved products when release criteria are not met, as with the expanded access program for Breyanzi (Bristol Myers Squibb, New York City, NY, USA), an approved lisocabtagene maraleucel product [22]. This is similar to how the FDA can use expanded access programs to address traditional drug shortages, including those that result from issues with manufacturing practices. Moreover, some bioethicists have argued that, for gene therapy companies developing interventions for patients with rare diseases, expanded access is not only a worthwhile mechanism but also one that such developers have an ethical obligation to at least carefully consider [23].

Emerging Expanded Access Issues

Although expanded access to investigational cell- and gene-based interventions can be appropriate for patients (and potentially have important benefits for developers), it can also pose difficult regulatory, ethical and practical issues. Indeed, ongoing heated debates about when and under what circumstances patient access to unproven interventions is appropriate underscore how difficult it can be to find the right approach [24]. Here we offer three examples of the kinds of regulatory, ethical and practical issues that, although not necessarily unique to the cell and gene therapy field, are particularly relevant for the field moving forward.

Access versus evidence generation

A fundamental issue in non-trial access to unapproved cell and gene therapy products is the inevitable tension between facilitating early access and supporting ongoing generation of safety and efficacy evidence through clinical trials. This challenge is neither new nor peculiar to the cell and gene therapy field [25]. Although accelerated or conditional approval and non-trial access to unapproved products are quite distinct regulatory pathways, issues that have arisen with the former might inform proper management of the latter. As has been argued before, allowing conditional approval of promising therapeutic modalities, including cell and gene therapies, can divert resources and patients away from more definitive clinical trials, providing patient access to novel products but without clear understanding of the risk–benefit ratio [26]. Furthermore, drugs the FDA has approved via accelerated approval frequently lack evidence of clinical benefit because follow-up confirmatory trials are not conducted or are delayed [27]. Similar issues may arise with non-trial access to novel investigational cell- and gene-based interventions, especially if intermediate-size or large programs are extensively employed before clinical trials are completed. This problem can be particularly salient for rare conditions when patient populations are small, recruiting sufficient numbers of research participants into adequately powered clinical studies is challenging and established evidence-based treatment modalities are unavailable [28]. Non-trial access programs may present similar issues in countries with small populations, where clinical trials even for common conditions may face enrollment challenges if access is widely available outside trials. In such cases, patients' interest in obtaining access to therapeutic use of an investigational product may severely interfere with recruitment for clinical trials.

As the field of regenerative medicine matures and increasing numbers of cell and gene therapy products enter clinical trials, it is critical for the field to grapple with these issues and explore options for balancing patient interest and robust evidence generation [29]. For example, broadening of eligibility criteria for clinical trials, as has been suggested for cancer drug clinical trials [30], can alleviate the need for non-trial access. Although non-trial access is mostly focused on therapeutic use of investigational products, options for collecting reliable real-world data on clinical outcomes, whenever possible, merit consideration. This may require incentives and mechanisms for coordinating efforts of treating physicians, product developers and regulators, including the development of properly managed patient registries, alongside guardrails to ensure such data are used judiciously and their collection and use do not supplant well-designed and carefully conducted clinical trials.

Expanded access as a route to commercialization

Another issue important for the cell and gene therapy field is ensuring that developers can provide appropriate non-trial access to unapproved products without allowing such access to be used as a means for commercialization. As noted earlier, FDA regulations generally allow sponsors to recover only limited costs associated with investigational products provided through expanded access. Nonetheless, for various reasons, providing expanded access might provide commercial opportunities for companies that do not have sufficiently compelling safety and efficacy data to obtain pre-marketing authorization for their investigational products.

Although FDA regulations restrict what may be charged for investigational products, the regulations do not as clearly cover charging practices for medical services that expanded access patients may need. For example, expanded access patients might be charged for nursing care, instrumentation and use of equipment, clinical procedures and pharmacy-related activities. Moreover, although FDA regulations prohibit promoting investigational products as safe and effective [31], there is considerable debate about when the line is crossed from genuine scientific exchange to product promotion [32]. This area of regulatory ambiguity may open the door to public representations about expanded access programs and products that may be challenging for the FDA to take action against but nevertheless seem somewhat promotional.

Thus, there is reason to think that a sponsor could provide access to an investigational product, make representations that play a role in generating substantial demand for access to such a product and then charge sizeable fees that patients may need to pay out of pocket because public and private insurers might not cover care related to unapproved interventions. There have been reports indicating that instances of patients charged such fees when obtaining investigational cell-based products through expanded access might already exist [33,34]. Additionally, it has been reported that at least one publicly traded US company appears to have plans to develop such a commercial model at scale, building a chain of infusion clinics, which it is believed will provide expanded access to investigational cell-based interventions [8]. Parents interested in providing their children with autism spectrum disorder cell-based cord blood products that are not authorized by the FDA for this indication constitute one potential client category for this business [8]. Although there might be circumstances in which using the expanded access pathway in this manner is appropriate, such business models also pose important questions about whether hyperbole, hope, unrealistic expectations and outright desperation could result in patients and their loved ones being exploited by businesses that have not yet engaged in the difficult work of demonstrating that their cell-based interventions are safe and effective for particular indications. The possibility of such a concerning scenario prompts questions about how the cell and gene therapy field can work to prevent such negative outcomes.

Equity in expanded access

A third example of an issue critical for the cell and gene therapy field is how to provide equitable expanded access to investigational products. The US health care system is rife with disparities in both access to and outcomes of care. Access to unproven products, which by definition are not known to benefit patients, through expanded access should not be understood as equivalent to accessing proven therapies. At the same time, increased use of expanded access or other non-trial access pathways may exacerbate existing social and economic disparities or perceptions of such disparities both within the USA and elsewhere. Limited data (from a single company's experience) indicate that non-trial access requests for unapproved products disproportionately originate from patients in high-income countries [35]. It may also be the case that even within a single country, patients (or the parents of patients who are minors) with higher socioeconomic status may be more aware of access options or more likely to request and successfully obtain non-trial access to investigational products, or both [36]. Even with existing FDA limits on charges for investigational products provided through expanded access and even if developers charge only for direct costs (and not for any medical services), patients may incur substantial costs for the intervention itself as well as for travel or extended absences from work [37]. Medical crowdfunding (on sites such as www.gofundme.com and Facebook) has emerged in recent years as a strategy to raise funds both to gain access to investigational products through expanded access and to cover unreimbursed costs associated with accessing these products in clinical trials [33,34,38–42]. However, studies have found that medical crowdfunding campaigns are more likely to be successful when they are led by or conducted on behalf of those who are already well connected, capable of crafting compelling personal narratives and able to generate favorable news media coverage and accompanying public support [43]. As a result, the practice of crowdfunding ultimately does little to address and may actually further exacerbate existing disparities.

In addition to questions about equitable access within expanded access programs, a developer's decision about whether to create an expanded access program at all may involve equity considerations [44]. Because product developers must agree to provide the investigational product, they are key partners in any expanded access request. They must balance multiple considerations when considering an expanded access program, including costs (some of which may not be fully recovered even if the developer elects to charge patients), available supply of the investigational product, manufacturing capacity and whether providing access to investigational products on a non-trial basis will have an adverse effect on clinical trials they are conducting or intend to conduct. They must also weigh the potential positive and negative public relations considerations relevant to their decisions. On the one hand, firms could potentially benefit from real or even perceived benefits of an investigational product. On the other hand, although adverse events in expanded access only very rarely have any regulatory impact [45], companies' public images could also be materially harmed by adverse publicity arising from such harms. Some firms have been the subject of highly visible public campaigns where patients or advocacy groups have pressured them to provide investigational products. All of these considerations may inform a company's judgment about whether an expanded access program, on balance, benefits patients or poses too many risks and could result in delays in product development and possible regulatory approval. Navigating these issues may be particularly challenging for smaller biotechnology firms that may be focused on developing a single novel product as opposed to a larger pharmaceutical firm with a larger product portfolio, greater financial reserves and staffing and public relations officials available to address public campaigns and other advocacy efforts.

Future Work

In certain circumstances, non-trial access to unapproved products has the potential to serve as an appropriate route for seriously and terminally ill patients to obtain investigational cell- and gene-based interventions. Expanded access to investigational products can be particularly important for patients with rare diseases and few opportunities to participate in clinical studies. Our working group hopes to contribute to efforts to ensure that expanded access is available in an equitable manner and in appropriate circumstances. However, we also recognize that, especially amid evolving regulatory and business environments, developments regarding non-trial access to unapproved cell- and gene-based interventions, such as ways that expanded access may be used for commercial activity, deserve careful consideration. Using expanded access in the US context as a starting

point, we plan to work with other participants in the cell and gene therapy space to develop guidelines that embody the values of accessibility and equity while also minimizing the risk of problematic uses of expanded access that undermine clinical research or could lead to the commercialization of unproven interventions and the possible exploitation of patients and their loved ones.

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Declaration of Competing Interest

PJZ has served as a consultant to the US FDA. LI wrote an expert report for a class action lawsuit filed against a business selling unproven "stem cell"-based interventions on a *pro bono* basis. LT, on a *pro bono* basis, wrote an expert report and testified in court for a class action lawsuit filed against a business alleged to have marketed unproven "stem cell"-based interventions. In a separate criminal case, LT served as a compensated expert witness for the US government. BG owns QB Regulatory Consulting, LLC, which provides regulatory and project management support to clinical-stage biotechnology companies. BER owns Roxland Consultants Ltd and The Roxland Law Firm, both of which advise publicly and privately held entities and individuals involved in research and development, cell and gene therapy and clinical research. BER is also a *pro bono* member of the Memorial Sloan Kettering Cancer Center, Weill Cornell and Rockefeller University Tri-Institutional Stem Cell Research Oversight Committee and co-chairs the New York State Bar Association's Committee on Medical Research and Biotechnology *pro bono*.

Author Contributions

Conception and design of the study: All authors. Acquisition of data: All authors. Analysis and interpretation of data: All authors. Drafting or revising the manuscript: PJZ, LI, ADL, and LT each wrote portions of the first draft, and all authors participated in revisions to make intellectual contributions. All authors have approved the final article.

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