ISSUES IN MEDICINE

Ethical considerations in the application of cell and gene therapies in children

M S Pepper,[1] MB ChB, PhD, MD; **A Pope**,[2] BA LLB, PG Dip Int Research Ethics; **S Kling**,[3] FC Paed (SA), MMed (Paed), MPhil (Applied Ethics); **M Alessandrini**,[4] PhD; **W van Staden**,[5] MB ChB, MMed (Psych), MD, FC Psych (SA); **R J Green**,[6] PhD, DSc

[1] *South African Medical Research Council Extramural Unit for Stem Cell Research and Therapy, Institute for Cellular and Molecular Medicine, Department of Immunology, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa*
[2] *Emeritus Associate Professor, Department of Private Law, Faculty of Law, University of Cape Town, South Africa*
[3] *Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa*
[4] *Department of Pathology and Immunology, Faculty of Medicine, University of Geneva, Switzerland*
[5] *Centre for Ethics and Philosophy of Health Sciences, Faculty of Health Sciences, University of Pretoria, South Africa*
[6] *Department of Paediatrics and Child Health, School of Medicine, Faculty of Health Sciences, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa*

Corresponding author: *M S Pepper (michael.pepper@up.ac.za)*

Rapidly evolving fields such as cell and gene therapies that involve state-of-the-art technology hold out possibilities that may be ahead of what ethics, guidelines and the law have considered. This results in a regulatory lag. Furthermore, ethical and legal considerations are often debated in real time as issues pertaining to these technologies that were previously not considered begin to come to the fore. Finding the appropriate balance between facilitating potential therapeutic gains and ensuring the safety interests of recipients of the new treatments requires close attention, especially for minors. This vulnerable population frequently has off-label treatment prescribed on the basis of extrapolation of clinical trial data derived from adults, which is ethically and scientifically questionable. In this article we discuss how best to maintain ethical integrity while introducing innovative cell and gene therapies to minors. We advocate that clinical trials of promising innovative therapies should be designed so that testing in adults is followed as soon as possible by testing in minors, given the impressive gains that have recently been reported.

S Afr Med J 2018;108(12):1027-1029. DOI:10.7196/SAMJ.2018.v108i12.13585

High-throughput, high-quality genome sequencing is becoming increasingly accessible as a result of advances in sequencing technology and analytical capacity, and reduced cost. Coupled with rapid advances in genome engineering, this increased accessibility is driving the creation of novel and highly efficacious medicines that are changing the way in which we practise. The recent introduction of chimeric antigen receptor T (CAR T)-cells for certain leukaemias and lymphomas is a case in point.[1] One of the two products currently available was tested in a clinical trial that involved minors;[2] nevertheless, many ethical and legal issues pertaining to this patient group remain unresolved. Many medicines are used off label for children, especially older drugs and antibiotics, on the basis of extrapolation of clinical trial data from adults to children. However, this practice is ethically and scientifically questionable, especially for very young children, because children are physiologically different from adults and safety profiles of medicines may be different too. Consequently, it is important that as the number of clinical trials in the cell and gene therapy field increases, minors are included to ensure that they too benefit from these therapies.

The regulatory landscape

Minors are protected by the law from their limited life experience and their own emotional, cognitive and physical immaturity. Section 71 of the National Health Act No. 61 of 2003 (NHA)[3] stipulates specific requirements for their participation in research. These are described in the National Department of Health's *Ethics in Health Research Guidelines* (DoH 2015),[4] in which minors are considered a vulnerable population for which various regulatory requirements and considerations pertain so as to ensure appropriate protection from risk of harm. This means *inter alia* that the safety profile of new medicines should at least be known to a reasonable extent before clinical trials are conducted to test new therapies with minors. Further, the ethical approach is to adopt a phased introduction of new medicines. This serves to mitigate the probability and magnitude of risk of harm to younger minors. Before children below puberty are included in clinical trials, cell and gene therapies should have been tested with adults and then with older minors (adolescents) so that knowledge of the safety profile in humans at various stages of development increases incrementally. The principles of cell therapy in children v. adults have not been established clearly. For example, their effects on growth and development are unknown. Adopting the developmentally phased approach that tests adults and then older minors before younger minors is likely to assist in clarifying these principles.

The South African (SA) regulatory framework requires that all research (including new cell and gene therapies) in minors (persons aged <18 years) only be conducted with the consent of the parent or guardian of the minor, and if the minor is capable of understanding, with the consent of the minor. Voluntariness of the choice to participate in research on malignancies in minors may cause a sense of desperation, especially for the parents. Such emotions may increase vulnerability and may therefore affect the informed consent process.

For example, a feeling of desperation may change a 'small' chance of benefit into a 'reasonable' chance.

The DoH 2015[4] guidelines explain the informed consent requirements for minors (section 3.2.2) as well as how to manage innovative therapies or experiments (section 3.5.1). The overarching principle is that involving minors in research to test the use of an innovative cell or gene therapy should not be against the best interests of that minor (section 3.2.2). This is especially significant when adult data are used to inform research designs for trials with minors.

Research v. innovative therapies

An important distinction is drawn in the DoH 2015[4] guidelines between research and innovative treatment. The possibility of using cell or gene therapy may be presented in either form. The primary distinction lies in the purpose of each. Research pursues generalisable knowledge for the benefit of future patients where the therapeutic best interests of a particular individual is not the main aim of the study. On the other hand, innovative treatment, while using the same product, is focused on the single recipient and all actions should therefore be carried out in the best interests of the particular minor.

This distinction has bearing on the minimum age that is legally required for giving informed consent. A minor is defined as anyone below the age of 18 years. For research, in principle, all minors must be assisted with informed consent. For treatment, on the other hand, the Children's Act No. 38 of 2005[5] creates exceptions to the general rule that minors may not make significant decisions without the assistance of a parent or guardian. Among others, it provides that a minor older than 12 years may consent to medical treatment if sufficiently mature and appropriately informed. However, great caution should be exercised regarding innovative treatment to prevent undue influence on a young sick person. Considering the gravity of the decision, we contend that for minors older than 12 years of age the ethical stance should be, even if not (yet) strictly required by law, that parents, guardians or caregivers must be involved in the discussions and decision-making. Minors younger than 12 years must also be included in discussions and decisions about their health in so far as their capacity allows (see section 129 of the Children's Act[5]). The decision to proceed must be based on a reasonable chance that the intervention may work in the minor, in light of the adult and/or adolescent data available (see DoH 2015[4] Appendix 3, 'Novel, innovative or unproven treatment').

Individual-specific factors are fundamental when cell or gene therapies are being considered in the context of a clinical trial or an innovative therapy. The clinical status of the participants, the effects of prior and concurrent treatments, cell collection risks, and variability in cellular starting material and the manufacturing process are therefore all significant. Also important are ethical considerations related to process failures in the production of a complete therapeutic dose of, for example, gene-modified T-cells. Failure could be due to inadequate T-cell harvests, poor gene modification rates or poor CAR T-cell expansion. The information provided in the informed consent documentation must include these possible outcomes, as they are directly relevant when making a decision about whether to participate.

Conducting a clinical trial using cell and gene therapy therefore requires consideration of numerous product-related factors that will influence patient and trial outcomes, and cell preparations should meet strict criteria at each step. In the case of gene-engineered T-cell therapies, such as CAR T-cells, these factors include apheresis collection of T-cells, where adequate cell numbers need to be harvested; gene transfer/engineering rates, which tend to vary between patients; and T-cell expansion, which also varies from sample to sample. Specific issues that must be considered for children include the onerous nature of cell harvesting – apheresis is an invasive and time-consuming procedure. Additionally, the labour-intensive manufacturing processes, as well as an increased likelihood of obtaining suboptimal yields relative to those obtained in the adult population, need to be considered.

If the yield of the therapeutic product post manufacturing is suboptimal but all other quality control standards are met, two options may be envisaged: the samples are excluded and the treatment is abandoned, or patients are still treated but stratified into a separate analysis group. Weighing up the levels of risk of harm against the likelihood of benefit is very important in determining what may be in the best interests of the individual minor. Given the onerous nature of cell harvesting in children, the labour-intensive nature of manufacturing and the expectations created in the patient and her/his family, the latter, i.e. stratification into a separate analysis group, might be more appropriate.

The NHA[3] provides for innovative or experimental treatment (section 11) and requires that, prior to treatment, the patient must be informed of the experimental or innovative status of the intended treatment (see also DoH 2015,[4] section 3.5.1 and Appendix 3). However, this decision involving the minor with the parents or guardian should be made with the involvement of several clinicians rather than a single clinician, considering the many implications and the gravity of the decision. Also, a properly described risk-benefit decisional analysis schema should be used. Once clinically warranted to offer the innovative treatment to the minor patient, the informed consent process is subject to the general requirements of informed consent as applicable to other interventions regarding, for example, provision of sufficient and adequate information as well as time in which to deliberate and choose.

The distinction between research and innovative treatment should also be applied in the case of individual use of cell and gene therapies. If the purpose is research, a research ethics committee registered with the National Health Research Ethics Council must review and decide whether to approve it. If it is experimental treatment for a specific patient rather than research, it is ethically appropriate for a clinical ethics committee (CEC) to review the available data including the potential risk of harm and the likelihood of benefit, even though this is not currently a legal requirement (see DoH 2015,[4] Appendix 3). In SA, few standing CECs exist and their requirements are not regulated at this time. A significant consideration is that no insurance cover for treatment of bodily injury suffered by the patient would be available for experimental treatment as it would be for a research participant. The potential use of CAR T-cell therapies with minors underscores the desirability of establishing CECs, which should have an oversight role in all matters pertaining to the innovative or experimental treatment, including the informed consent documentation. The nature of a desirable structure for CECs should be discussed, e.g. whether there should be institutional CECs or regional CECs. These may help to establish a database for reporting on experimental treatment, by which to inform future use and trials.

Regulatory frameworks in other jurisdictions

The development of cell and gene therapies for child populations in Europe is subject to provisions of the European Medicine Agency, which 'has a number of important tasks and responsibilities relating to the development of paediatric medicines. These responsibilities, granted through the European Union (EU) Paediatric Regulation,

enable the Agency to stimulate research into the uses of medicines in children and to lead to their authorisation in all age groups.'[6] An important part of this process involves the development of a Paediatric Investigation Plan which is aimed at 'ensuring that the necessary data are obtained through studies in children, to support the authorisation of a medicine for children.'[7]

In the USA, the Food and Drug Administration (FDA) regulates the use of medicines in children through the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA).[8] 'The Pediatric Research Equity Act originally was passed in 2003. PREA requires pharmaceutical companies to assess the safety and effectiveness of new drug and biologic products in pediatric patients. BPCA was passed in 2002. BPCA provides a financial incentive to pharmaceutical companies to test drugs with remaining patent life in pediatric patients. In addition, this Act creates a process by which FDA and the National Institutes of Health (NIH) can partner to obtain studies of off-patent drugs in pediatric patients. A key difference between the laws is that PREA is a mandatory law and BPCA is voluntary.'[9]

Benefits v. risks

Finally, after more than two decades, gene therapy is proving to be beneficial for a number of disorders. This includes primary immunodeficiency, sickle cell disease, haemophilia, haematological malignancies, retinal disorders and dermatological disorders such as epidermolysis bullosa.[10,11] However, as is the case with most pharmaceuticals, benefits need to be weighed against risks for cell and gene therapies, which fall under the ambit of biological medicines in SA.[12] The case of Jesse Gelsinger, who was 18 when he died as a result of his immune system's reaction to the viral vector used to introduce a functional copy of an enzyme his body lacked, is a sober reminder of the factors that need to be considered.[13] Likewise, a recent publication[14] has reported a greater number of off-target effects of the CRISPR-Cas9 gene editing technique than had previously been identified. However, given the potential benefits to be derived from these innovative therapies and the rigour to which their application and manufacture are being subjected, it is likely that the potential drawbacks mentioned (and others) will be able to be managed to minimise risk to the patients concerned.

Conclusions

New cell and gene therapies, including novel cancer therapies such as CAR T-cells, raise the question of how best to introduce these innovations to assist child patients. We suggest that clinical trials of promising innovative therapies should be conducted as per the responsible testing described above. The clinical trials in minors should be conducted as soon as possible, averting the need for, and risks of, experimental therapeutic use of cell and gene therapies on an individual basis. If these trials suggest that the therapies are efficacious and safe, they can be approved for use.

Declaration. None.

Acknowledgements. None.

Author contributions. MSP: initial manuscript conception, initial drafting and subsequent editing; AP: conceptual refinement and manuscript editing; SK: conceptual refinement and manuscript editing; MA: conceptual refinement and manuscript editing; WvS: conceptual refinement and manuscript editing; RJG: conceptual refinement and manuscript editing.

Funding. Work in MSP's group is funded by the South African Medical Research Council (University Flagship and Extramural Unit awards).

Conflicts of interest. None.

1. Pepper MS, Alessandrini M, Pope A, et al. Cell and gene therapies at the forefront of innovative medical care: Implications for South Africa. S Afr Med J 2019 (in press).
2. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378(5):439-448. https://doi.org/10.1056/NEJMoa1709866
3. South Africa. National Health Act No. 61 of 2003. https://www.gov.za/documents/national-health-act (accessed 1 November 2018).
4. National Department of Health, South Africa. Ethics in Health Research Guidelines: Principles, Processes and Structures. 2015. www.nhrec.org.za (accessed 5 November 2018).
5. South Africa. Children's Act No. 38 of 2005. http://www.justice.gov.za/legislation/acts/2005-038%20childrensact.pdf (accessed 1 November 2018).
6. European Medicines Agency. Paediatric Medicines: Overview. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&mid=WC0b01ac0580b18c75 (accessed 1 November 2018).
7. European Medicines Agency. Paediatric Investigation Plans. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000608.jsp&mid=WC0b01ac0580925b1b (accessed 1 November 2018).
8. US Food and Drug Administration. Best Pharmaceuticals for Children Act and Pediatric Research Equity Act. https://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm509707.htm (accessed 1 November 2018).
9. US Food and Drug Administration. Office of New Drugs module of the Center for Drug Evaluation and Research (CDER) World Training. https://www.accessdata.fda.gov/scripts/cderworld/index.cfm?action=newdrugs:main&unit=4&lesson=1&topic=5&page=4 (accessed 1 November 2018).
10. Everything you need to know about gene therapy's most promising year. MIT Technology Review, 30 December 2016. https://www.technologyreview.com/s/603206/everything-you-need-to-know-about-gene-therapys-most-promising-year/ (accessed 1 November 2018).
11. 2017 was the year of gene therapy breakthroughs. MIT Technology Review, 3 January 2018. https://www.technologyreview.com/s/609643/2017-was-the-year-of-gene-therapy-breakthroughs/ (accessed 1 November 2018).
12. Medicines Control Council Guidelines for the Registration of Medicines: General information. 2012. https://www.sahpra.org.za/documents/1d9c57df2.01_General_information_Jul12_v8_showing_changes.pdf (accessed 1 November 2018).
13. Gene-therapy trials must proceed with caution. Nature 2016;534(7609):590. https://doi.org/10.1038/534590a
14. Kosicki M, Tomberg K, Bradley A. Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. Nat Biotechnol 2018;36:765-771. https://doi.org/10.1038/nbt.4192

Accepted 27 August 2018.