Progress in advanced cellular and gene therapies in South Africa and barriers to patient access: A National Consortium paper on behalf of the BloodSA Cell and Gene Therapy working party

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The fields of molecular and cellular medicine have, in recent years, witnessed a great deal of progress globally, particularly in understanding disease pathogenesis and through the development of advanced cellular therapy products and gene therapies. Despite the transformative potential of these new therapies, low- and middle-income countries face significant barriers to their access. Advanced cellular therapy legislation in South Africa (SA) has not kept up with this fast-advancing field, and requires a fast-tracked renewal. Furthermore, the prohibitive cost of commercial therapies, including chimeric antigen receptor (CAR) T-cell products, and the lack of infrastructure, manufacturing and research capacity, must be addressed to make equitable patient access an achievable goal in our setting. To this end, a national cell and gene therapy consortium, comprising clinicians, clinician-scientists, scientists, legal experts, postgraduate students and representatives from industry, the national blood service and the pharmaceutical industry, was initiated. The mandate of this group is to aid the progression of advanced cellular therapies in SA, and the purpose of this article is to outline the progress that has been made. We will highlight the gaps in each core field of practice within this space, and provide a proposal for making these therapies more accessible in SA.

Keywords: advanced cellular therapy products, cellular therapy regulation, gene therapy regulation, equitable access, health equity, cell and gene therapy access, South African health regulation, chimeric antigen receptor (CAR)-T cell therapy, haemophilia gene therapy

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In the past decade, there has been a paradigm shift globally to targeted immunotherapies, specifically an accelerated development of cellular therapy products (CTPs) and gene therapy products (GTPs) (jointly CGTPs).

CTPs encompass regenerative medicine (RM)[1] and adoptive cell therapies (ACT), among others. RM uses adult stem cells to restore or replace damaged tissues.[2] An example of this is haematopoietic stem cell transplantation (HSCT), where haematopoietic stem/progenitor cells replace bone marrow and restore haematopoiesis.[3] In contrast, ACT involves administering immune cells that have been adapted *ex vivo* to target and eliminate disease.[4] These treatments include chimeric antigen receptor T-cell (CAR-T) cell therapy, tumour-infiltrating lymphocyte therapy, engineered T-cell receptor therapy and natural killer (NK) cell therapy.[4] The therapies may either be autologous or allogeneic. Many of these therapies are now approved for clinical use by regulatory authorities (32 gene therapies, 29 RNA therapies and 68 cell therapies),[5] with the anti-CD19 CAR therapies for B-cell malignancies leading the way.

The unmet needs of rare haematological, muscular, metabolic, ophthalmic and neurological diseases are also being addressed through these therapies. Treatments for single gene disorders (e.g. Huntington's chorea) and mono-protein abnormalities (e.g. haemophilia and beta-haemoglobinopathies) have become available, but at high cost. Among these are four adeno-associated

virus (AAV)-mediated gene therapies approved for haemophilia A and B by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[6-9] These one-time therapies administered intravenously deliver a modified, codon optimised transgene (B-domain deleted FVIII or FIX Padua variant) to the liver using a natural or synthetic AAV with liver affinity. Follow-up (≥2 years) has shown that gene therapy is efficacious in bleed prevention.[6-9] While many cell and gene therapies remain in the preclinical space, there is now a consistent pipeline of 30 or more products completing their phase 3 stage of development.[5]

South Africa (SA), with its high disease burden and unparalleled genetic diversity,[10-12] is a vibrant hub of biomedical research. Despite these unique features, the adoption of advanced CTPs involving human cells, tissues and organs has been slow. This is attributed to several factors, including high cost, limited expertise, insufficient infrastructure as well as a legislative environment that fails to accommodate the complexities of recent advances.

This article aims to shed light on the progress made in the field of advanced CTP in SA after an initial plan was outlined.[13] It provides a way forward to address each barrier to making these therapies more equitable and accessible for the SA population. The opinions expressed are those of the National BloodSA Cell and Gene Therapy working party. This working party, comprised of multiple stakeholders from different but complementary sectors within the cell and gene therapy (CGT) space, is mandated to harmonise the strategy for equitable provision of these treatment modalities in SA.

Developing a regulatory framework

The provision of advanced CGTPs can only occur within an appropriate regulatory framework. Regulatory frameworks are jurisdiction-specific, and are underpinned by Acts of Parliament establishing broad regulatory principles and regulations to implement specific sections of the Acts. Acts may also establish regulatory authorities to implement and enforce the Acts and regulations. Non-binding guidelines and standards further support regulatory frameworks.[14]

SA lacks a regulatory framework for advanced CGTPs. However, there are regulatory frameworks for medicines under the Medicines and Related Substances Act 101 of 1965 (MRSA),[15] human biological materials under chapter 8 of the National Health Act 61 of 2003 (NHA)[16] and genetically modified organisms (GMOs) under the Genetically Modified Organisms (GMO) Act 15 of 1997.[17] However, these Acts and their regulatory frameworks have not kept pace with the rapidly evolving field of advanced CTPs, tissue-engineered products and GTPs, leaving regulatory gaps that restrict patient access. Fig. 1 shows the regulatory gaps between these three Acts. For example, it is essential to define the transition from minimally processed blood, cells and tissue used for transfusion or transplantation to blood cells and tissue used as starting materials for manufactured health products.[18] The GMO Act was primarily designed for the agricultural use of GMOs, and does not adequately address the specifics of human GTPs and gene-modified CTPs. The terminology used can also create ambiguity. Finally, although the MRSA was amended in 2015 to establish a regulatory authority for health products, rewriting the Act into a more progressive 'Health Products Act' that fully addresses the SA Health Products Regulatory Authority (SAHPRA)'s mandate is long overdue.

Advanced CTPs such as CAR T-cell products are located at the intersection of these three Acts. They are health products consisting of genetically modified living cells. The current legislation and regulatory frameworks need significant updates to provide a unified framework to bridge the existing gaps. A future regulatory framework should also support research in and development of these products, their clinical application and their commercialisation or non-commercial use.

This can be achieved using a two-phased approach. Firstly, within the existing legislative environment's boundaries and after consultation, it is in the Minister of Health's authority to issue a regulation dealing with a specific subject matter, as *lex specialis*, to address the specific requirements of advanced CTPs. The *lex specialis* principle states that if two laws govern the same factual situation, a law governing a specific subject matter (*lex specialis*) overrides a law governing only general matters (*lex generalis*).

A parallel workstream should address the creation of a carefully considered strategic overview of the existing legislation, and develop an understanding of how the affected areas can be partitioned to make the required overhaul more manageable. This will allow expert groups in different themes to address specific matters in separate highly focused workstreams.

The CGT working party is finalising a white paper that will be presented to SAHPRA and the National Department of Health. The paper provides legislative guidelines for regulating advanced CTPs in SA.

Determining the clinical need

An impediment to understanding the full clinical need for advanced CTPs in SA is the lack of formal registries. This, in addition to substantial economic inequality, scattered geography and a limited number of treatment centres with expertise in specific diseases, makes determining the size of the problem difficult.

BloodSA is a nationally established non-governmental organisation that aims to identify barriers and standardise all matters related to haematological disorders in SA. Through a process of engagement, this consortium has identified several areas in need of expert capacity development. The development of national patient registries for specific disease areas, including plasma cell myeloma, aplastic anaemia, acute leukaemia, haemophilia and inherited coagulopathies, has been identified as a priority. For adult patients in particular, data are required for plasma cell myeloma, as an example, and the need for autologous HSCT, before the need for B-cell maturation antigen (BCMA)-CAR therapy can be understood. Similarly, for paediatrics, the number of affected relapsed/refractory B-acute lymphoblastic leukaemia (B-ALL) patients is required to extrapolate the need for anti-CD19 CAR-T cell therapies. Attempts to overcome these data shortages are being addressed by BloodSA within the multiple myeloma and paediatric HSCT working parties, among others.

Considering that the provision of HSCT in SA is limited, resources must be identified concurrently for the development of training programmes in both HSCT and CGT, and for the establishment of specialised management centres. A budget must be prepared to cover personnel and the therapies themselves that will be administered to patients.

Clinical trials as the first step in patient access

Without an appropriate legislative framework from which to regulate the academic and commercial use of advanced CTPs, the most effective way to provide patient access is through clinical trials. Through the substantial efforts of local clinical haematologists, SA has managed to register two clinical trials, both of which are actively recruiting patients. At Netcare Pretoria East Hospital in Pretoria, Dr Brittain and colleagues made history by infusing the first patient in Africa with a locally manufactured autologous CD-19 CAR T-cell gene therapy product for refractory/relapsed non-Hodgkin's

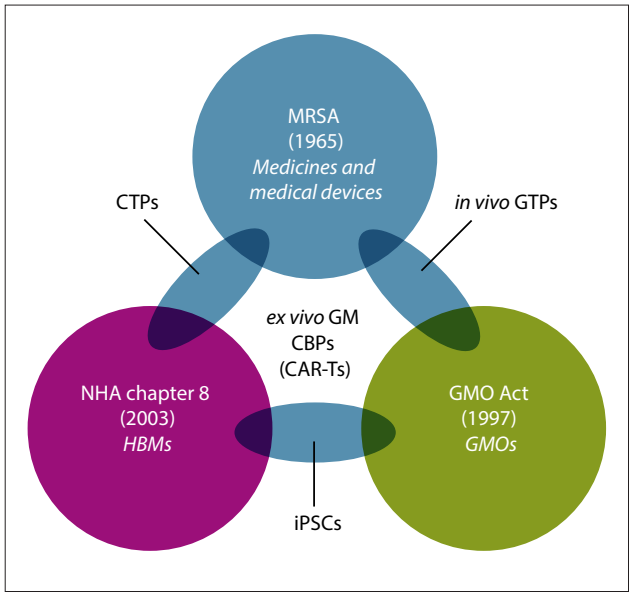

Fig. 1. Gaps in South African legal and regulatory frameworks: the intersection of the Medicines and Related Substances Act 101 of 1965 (MRSA), National Health Act 61 of 2003 (NHA) and Genetically Modified Organisms (GMO) Act 15 of 1997 (GMO Act). No one Act adequately addresses all cell and gene therapy product regulation, with different CTPs and GTPs overlapping with different Acts. (CTPs = cellular therapy products; GTPs = gene therapy products; GM CBP (CAR-T) = genetically modified cell-based products (chimeric antigen receptor T-cells); HBMs = human biological materials; iPSCs = induced pluripotent stem cells.)

lymphoma. This trial is open to both public and private sector patients, driving the 'equitable access' goal of the CGT working party. More recently, at the Wits Donald Gordon Medical Centre in Johannesburg, Drs Thomson, du Toit and team commenced a first-in-human (phase 1) clinical trial infusing patients with allogeneic NK cells engineered to express CARs targeting CD-19 in difficult to treat B-cell malignancies. These 'off-the-shelf' NK-CAR cells are manufactured abroad and imported into SA for the trial.

These two therapies, one autologous and one allogeneic, provide different advantages. With autologous products, genetically modified CTP products can be manufactured locally, and have the potential to allow for the manufacture of CAR-T cells to treat different diseases in the near future. The allogeneic NK product is, however, not HLA-restrictive, and has the potential to treat many more patients as it is readily available and not patient-specific.

Outside of CAR-T cells, SA has made strides in the delivery of GTPs for haemophilia under the leadership of Prof. Johnny Mahlangu at the University of the Witwatersrand, Johannesburg. Through clinical trials, >30 SA patients have received a haemophilia A or B gene therapy product manufactured abroad, with marked improvement in bleed rates, as shown in the 5-year follow-up in the >300 global recipients of this treatment. There are no immediate safety concerns; however, long-term durability and safety remain to be established.

Targeting growth in research capacity

While clinical trials are ongoing with established GTPs and techniques, research is required for capacity-building in scientific skills. The approach to cultivating research capacity should be multifaceted, with focus on key areas such as human capital development,[19] local and international collaboration[20] and ethical considerations.[21]

While established scientific skills may be helpful initially, training students in specific CGT-related techniques should be a core mandate when addressing research and development (R&D) capacity.[13] Given the nature of good laboratory, clinical and manufacturing and distribution practices, the absence of cell therapy-specific Health Professions Council of SA (HPCSA) courses/registrations and the paucity of cell therapy facilities in the country, capacity-building in terms of expertise will likely fall on academic-industry partnerships.[19,20]

Due to the substantial resource requirement to establish such training facilities, creating a centralised training centre through which these techniques are disseminated[22] may be required initially until decentralisation of skills and techniques is possible. Adequate funding from one source is unlikely to be sustainable, necessitating funding streams from both the public and private sectors.[19,23] This would also include partnering with the Global North, which maintains a substantial lead in the field of CGT R&D.[13] International funding sources increasingly encourage collaborative health science research,[20] which should motivate more ambitious grant applications from the SA research community. As capacity improves, and the patient need is better established, SA research institutions would be able to offer a clear CGT track that prepares for an attractive career path.[19]

Advocating for improved CGT training must be met in consultation with SA ethical review boards (ERBs) that have been prepared for CGT. These ERBs must be guided by the local regulatory landscape, and amend ethical guidelines accordingly. Sensitive topics such as benefit sharing[24] and access to locally produced, research-grade cells, biological materials and associated data must be addressed in order for CGT R&D to advance.[22]

Leading the way in research within the CGT working party is the Institute for Cellular and Molecular Medicine at the University of Pretoria, which has a number of postgraduate students working on CGTPs. These students have had training from international collaborators, and discussions with local ERBs regarding CGT research implications have commenced. Several past students are currently employed in the CGT sector in SA.

Building manufacturing capacity

A substantial advance in addressing local manufacturing capacity has been initiating the CAR-T trial at Netcare Pretoria East Hospital. The international partnership between Albert's Cellular Therapy (Pretoria) with Miltenyi Biomedicine (Germany) for this trial (SA National Clinical Trials Register reference DOH-27-042024-8987) plays a key role in the operational strategy when bringing these therapies to the clinic. However, although a ground-breaking endeavour, it is currently insufficient to meet the demand for local manufacturing expertise. The ultimate goal of targeted interventions aimed at building CGT manufacturing capacity in SA should be to introduce sustainable, easily replicable, standardised models that will result in increased efficiency in clinical implementation.[25]

One of the main barriers to implementing more robust local manufacturing capacity is cost,[13,19,20] with two major drivers being (*i*) vector costs, and (*ii*) the expense of shipping good manufacturing practice (GMP)-grade products from centralised manufacturing facilities abroad to SA.[25] To address the matter of the cost of viral vectors, SA may need to leverage existing non-viral CGT methods,[26] which have been shown to be more cost-effective. A country that has managed to decrease costs significantly is India.[27] They advise aligning with non-profit international organisations that aim to bring CGTs to low- and middle-income countries at a significantly lower price.

Secondly, the number of GMP-compliant facilities, crucial for advanced CTP manufacture,[19] must be increased, and outdated

guidelines amended to alleviate the prohibitive costs of establishing these facilities. Funding from government and/or international consortia must be sought, and interventional actions (training, mentoring, teaching and structured lecture series) administered by and to such teams will be key in augmenting CGT manufacturing workflows.[20] Furthermore, the impact of technology and skills transfer activities must be measured by investigating and following up on practical implementation goals and deliverables.[28]

Centralised v. decentralised service

SA will need to decide whether a centralised or decentralised service would facilitate equitable access to CGT for our patients. The CGT model currently most commonly employed includes three arms: (*i*) a clinical haematology unit managing patients; (*ii*) a collection facility performing the apheresis collection of source material; and (*iii*) a processing facility/cellular therapy laboratory that tests, processes, stores and transports the product. In order to determine the best way to approach this in our setting, all three arms should be addressed from the perspectives of access, availability of expertise, financial viability and long-term sustainability.

In SA, <30 clinical haematologists are currently in practice, and serve a population of >60 million inhabitants.[29] This amounts to only 5% of the number of clinical haematologists recommended by the World Health Organization for our patient population.[30] In addition to the dearth of clinical expertise, there are only two Joint Accreditation Committee for ISCT (International Society for Cell and Gene Therapy) (JACIE)-Europe and European Society for Blood and Marrow Transplantation (EBMT)-accredited processing facilities located in Gauteng Province. CTPs must be provided within JACIE or Foundation for the Accreditation of Cellular Therapy (FACT)-accredited units, and it is therefore imperative to prioritise improved quality management systems within existing HSCT units and any other units that may be planned.

The merits of a centralised model include centralisation of patients, resources and expertise, overall systems integration, the minimisation of costly logistics and associated risks, facilitation of consistency in manufacturing, easier quality control and regulatory oversight. However, this requires disaster risk management (e.g. storage redundancy), and referral of all patients to one facility, potentially limiting access. Decentralisation is an option in CGTs that are off-the-shelf, including *in vivo* gene therapy, allogeneic source material and/or point-of-care manufacture. This in theory increases patient access, but practically is limited by cost and availability of resources and expertise.

A hybrid programme, with decentralisation of some services (clinical unit and collection facility) and centralisation of others (testing and processing facility), is likely our best option for the foreseeable future. The SA National Blood Service has a decentralised collection service that includes mobile apheresis collection, and a centralised processing facility, placing it in the advantageous position of being able to advise, and potentially becoming a service provider in this space. With this approach, we can include multiple patients and address both financial viability and scarcity of expertise.

How will we afford it?

CTPs are the most expensive medicinal products registered to date, and even in high-income countries, affordability is a concern. In the USA alone, it is conservatively estimated that an additional USD20.4 billion/annum would need to be allocated over the next 10 years for CGTs.[31]

Healthcare funders are hesitant to approve GTPs. This is due to the lack of long-term efficacy data, the high initial cost compared with the more evenly distributed expenditure on standard-of-care therapies[32] and the lack of engagement between manufacturers, funders and regulatory agencies.[33] Much research has also focused on the cost-effectiveness of these therapies at their current cost. While some have shown it to be cost-effective,[34] others have not.[35,36] One study showed improved survival but lack of cost-effectiveness using the CAR-T product.[35]

Several innovative funding models have been proposed to provide equitable access to CGTs, including funder rebates and staggered payments based on patient outcomes,[32] as well as reinsurance and supplemental risk-pooling strategies.[37]

Consultation between funders (private and public), manufacturers and regulatory agencies will be essential to ensure the successful and equitable establishment of advanced CTP programmes in SA. The starting point will be to do our own robust cost-effectiveness calculations to determine how these products may be funded within our health system.

Discussion

SA has managed to push past the barrier of not being able to make CTPs available to patients, by enrolling the first set of patients in clinical trials. This has required focus and dedication from many stakeholders, all with a vested interest in ensuring that our patients have equal opportunity to those in high-income countries. As a CGT consortium, we are positive, albeit realistically so, that we have the necessary skill set, international networks and a holistic plan in place to work towards the sustainability of these treatments in our country. We remain dedicated to pursuing access driven by diversity, equity and inclusion,[38] which is a challenging endeavour in the most unequal country in the world. We will strive to avoid a disparity in access to clinical trials between low- and high-income households, which has been highlighted by others.[39,40]

The next steps for the CGT working party involve providing guidance on optimal CGT regulation to the necessary parties as a matter of urgency. Local manufacturing capacity is being expanded, as are alternative gene therapy strategies to benefit more patients. Finding ways to bring the existing research to the clinic will be imperative, and skills gaps will be identified and filled. Cost-effective strategies are being explored, and local medical insurers are involved to determine the best strategies to afford these therapies. General matters related to HSCT services and protocols are being prioritised by the BloodSA Paediatric HSCT and aplastic anaemia working parties, which is the first step before patients requiring CTPs can be identified. With focus and clarity regarding the specific challenges to overcome, the collaborative efforts of the working party will capitalise on each other's strengths to achieve our common goals. The next few years will see streamlined efforts to ensure improved patient access and outcomes.

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