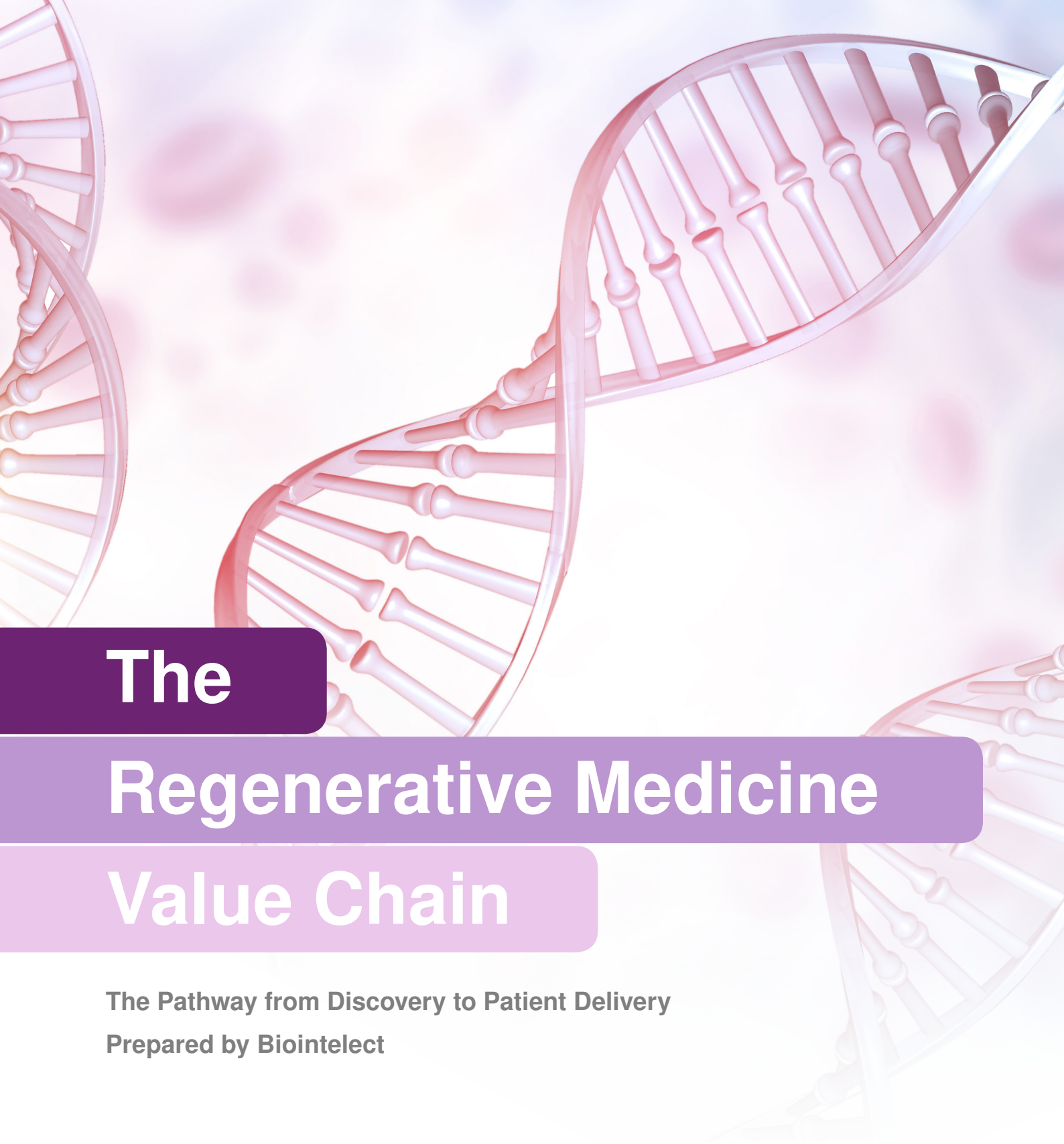

# The Regenerative Medicine Value Chain

The Pathway from Discovery to Patient Delivery

Prepared by Biointelect

AusBiotech

Biointelect

cell therapies

Medicines Australia

Supported by MTPConnect MedTech and Pharma Growth Centre

NOVARTIS

RESEARCH STRATEGIES AUSTRALIA

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# Foreword

The Regenerative Medicine Catalyst Project has brought together seven partners in a consortium to build the foundations for a national regenerative medicines (RM) sector 'catalyst' collaboration body. The Regenerative Medicine Catalyst Project will address priority action areas including: workforce capabilities, collaboration, funding, regulation and policy infrastructure, and Australian manufacturing capability. The Catalyst Consortium and the subsequent Catalyst Body aim to support the Australian RM industry to see it thrive and drive benefits to the health of its people and Australia's economy. This *Regenerative Medicine Value Chain Report* forms a key part of the Regenerative Medicine Catalyst Project.

The significance and need for the Regenerative Medicine Catalyst Project were highlighted in a national, sector-wide report that assessed the current state of the Australian RM sector and made recommendations on the priorities and goals, see *Regenerative medicine: Opportunities for Australia* (MTPConnect, LEK, 2018).

Major outcomes of the project include other reports and data that each add further to the body of evidence and understanding of the sector. The reports include:

- A researched, strategic roadmap for the RM sector's development in Australia, including sub-reports on skills and talent specific to the sector, determining a plan to attract patient venture capital investment and the role of Australian biotech companies partnering with global companies, and case studies;
- Determining a sustainable funding and model structure for an RM sector 'catalyst' collaboration body;
- A regulatory white paper;
- Establishing annual data points and information resources to: map/benchmark GMP manufacturing capability and capacity, establish a model for an annual clinical trial database; and capture investments in Australian RM;
- Mapping the pathway for a typical product from early research to market, and patients receiving a therapy; and
- Mapping the global pipeline of gene and cell therapy products on the horizon.

# Context

Australia has an opportunity to harness and leverage a growing and active global regenerative medicine RM industry. If we get this right, success could be worth at least $6 billion (B) in annual revenue, 6,000 new jobs for Australia by 2035 and earlier access to ground-breaking therapies for Australian patients[1].

RM is a multidisciplinary field that seeks to develop the science and tools that can help repair, augment, replace, or regenerate damaged or diseased human cells, tissues, genes, organs, or metabolic processes, to restore normal function. It may involve the transplantation of stem cells, progenitor cells, or tissue, stimulation of the body's own repair mechanisms, or the use of cells as delivery vehicles for therapeutic agents such as genes and cytokines.

RM includes gene therapies, cell therapies, and tissue-engineered products intended to regenerate or replace injured, diseased, or defective cells, tissues, or organs to restore or establish function and structure.

Globally, the growing sector has more than 1,200 clinical trials in progress, and is attracting about AU$26.3B (or US$19.9B) in financing per year[2]. With 97 ongoing RM Phase 3 clinical trials or products awaiting regulatory decisions in the coming months, therapeutics companies are turning their attention to the RM sector[3]. There are also increasing numbers of gene and cell therapies being developed and brought to Australia for patient access.

Australia has a strong and active RM industry eco-system with basic and translational research capabilities, a clinical trials framework and clinical centres that are all internationally recognised. More than 40 companies in Australia are developing RM products and more than 65 clinical trials in progress[4].

[1] MTPConnect, LEK Consulting. (2018). Regenerative Medicine - Opportunities for Australia

[2] 2020: Growth & Resilience in Regenerative Medicine, Annual Report Cell & Gene State of the Industry Briefing, Alliance for Regenerative Medicine, 2021

[3] 2020: Growth & Resilience in Regenerative Medicine, Annual Report Cell & Gene State of the Industry Briefing, Alliance for Regenerative Medicine, 2021

[4] Regenerative Medicine Catalyst Project. (2021). Australia's Regenerative Medicine Clinical Trials Database.

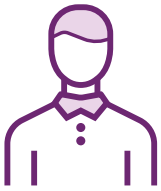
# Abbreviations and icons

## ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AAV | Adeno-associated virus |
| ANZCTR | Australian New Zealand Clinical Trials Registry |
| ARDAT | Accelerating Research & Development for Advanced Therapies |
| ARC | Australian Research Council |
| ATMP | Advanced therapy medicinal product |
| CAR | Chimeric antigen receptor |
| Cas9 | CRISPR-associated protein 9 |
| CDMO | Contract development and manufacturing organisation |
| CMRI | Children's Medical Research Institute |
| CRISPR | Clustered regularly interspaced short palindromic repeats |
| CRO | Contract research organisation |
| CTA | Clinical trial assessment |
| CTN | Clinical trial notification |
| CTP | Cell therapy product |
| FDA | Food and Drug Administration |
| EMA | European Medicines Agency |
| GMO | Genetically modified organism |
| GMP | Good manufacturing practice |
| GTMP | Gene therapy medicinal product |
| hESC | Human embryonic stem cell |
| HREA | Human research ethics application |
| HREC | Human research ethics council |
| HTA | Health technology assessment |
| IMI | Innovative Medicines Initiative |
| IP | Intellectual property |
| iPSC | Induced pluripotent stem cell |
| IPRP | International Pharmaceutical Regulators Program |
| MRFF | Medical Research Future Fund |
| MSC | Mesenchymal stem cell |
| NIH | National Institutes of Health |
| NHMRC | National Health and Medical Research Council |
| NHRA | National Health Reform Agreement |
| NMA | National Mutual Agreement |
| NGO | Non-governmental organisation |
| NSW | New South Wales |
| OGTR | Office of the Gene Technology Regulator |
| PSC | Pluripotent stem cell |
| QA | Quality Assurance |
| R&D | Research and development |
| RM | Regenerative medicine |
| RMT | Regenerative medicine therapeutic |
| RNA | Ribonucleic acid |
| RPA | Royal Prince Alfred Hospital |
| SCA | Stem Cells Australia |
| SME | Small and medium-sized enterprises |
| TGA | Therapeutic Goods Administration |
| TALEN | Transcription activator-like effector nucleases |
| TEP | Tissue engineering product |
| UK | United Kingdom |
| US | United States |
| ZFN | Zinc finger nuclease |

## ICON LEGEND

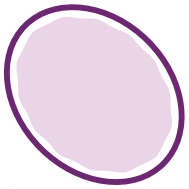

Patient


Healthy donor


Manufacturing Facilities

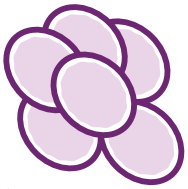

Clinical Setting


Therapeutic delivery


Somatic Cell

Progenitor cell


Stem cell


Expanded cells (cell culture)

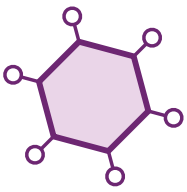

Stem cell cultures

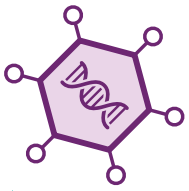

Somatic Cell derived from stem cell culture


No genomic integration

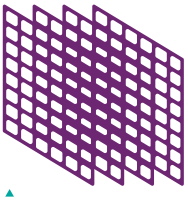

Genomic integration

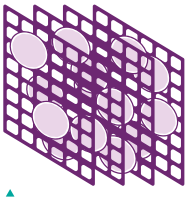

Gene of interest


Viral vector (Empty)


Viral vector (Engineered)

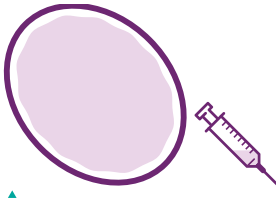

Genetically-modified cells

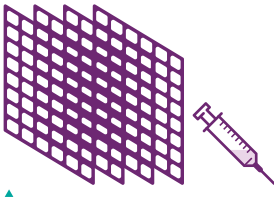

Biomaterial scaffold (acellular)


Biomaterial scaffold (seeded with somatic cells)


Biomaterial scaffold (seeded with somatic cells derived from stem cell culture)


Gene Therapy


Cell Therapy


Tissue engineered product

# Executive Summary

Regenerative medicine (RM) promises to deliver ground-breaking therapies to Australian patients, with innovative approaches targeting a wide range of conditions including rare genetic diseases, cancers, chronic diseases, and organ damage. The global pipeline of clinical trials and investment in RM is booming, with 1,220 ongoing trials and US$19.9B raised in 2020, more than any previous year.(1)

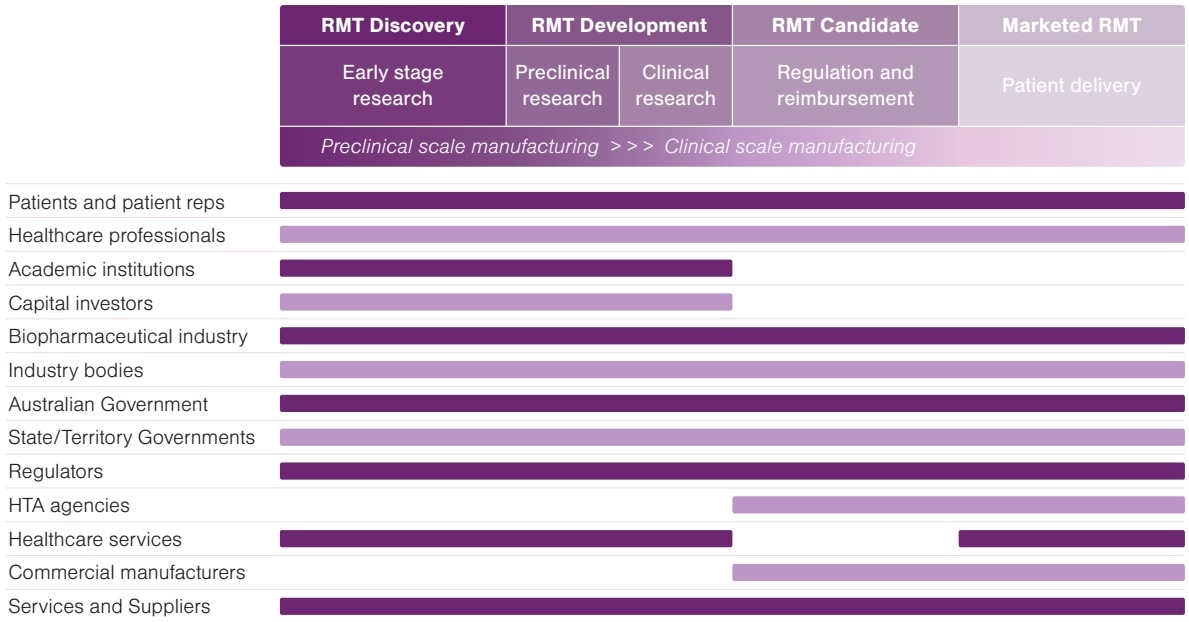
RM therapies (RMT) are transformative and disruptive technologies that require new thinking and approaches across the value chain of research, development, regulation, reimbursement and patient delivery. These ground-breaking therapies will also require unprecedented advanced manufacturing capabilities. The main goals for advancing RM in Australia are to give patients timely access to cutting-edge and potentially life-saving RMTs by promoting a thriving domestic RM sector and ensuring that Australia remains a priority market for global developers. To achieve these goals, the enablers and barriers in the Australian value chain must be identified and respectively supported and overcome.

This report maps the value chain for RM in Australia, from bench to bedside (Figure 1 and in more detail in Figure 2). The development pathway is not linear, but iterative, combining approaches from the biomedical sciences and bioengineering. Many stakeholders are involved across the value chain, although their specific roles change at different phases. The cross-nature of these roles suggests clear opportunities for and benefits from collaboration.

In describing the value chain, it is necessary to generalise across RMTs. Clearly, however, there are variations between gene and cell therapies and tissue engineered products (TEP). Even within these broad categories, all RMTs have unique characteristics, development pathways and implementation requirements.

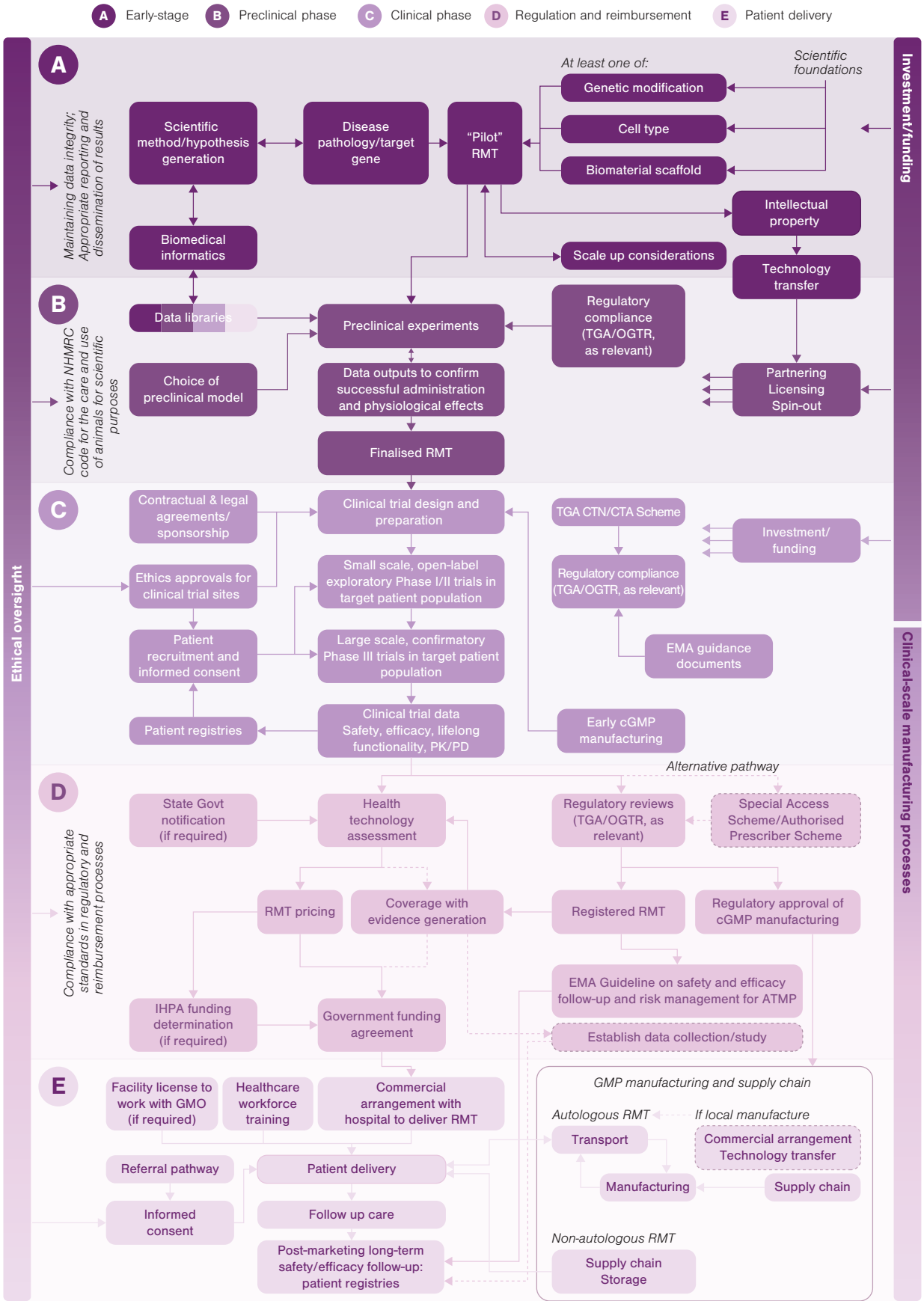
Fostering a globally competitive and patient-centric Australian RM sector requires a critical mass across the entire value chain and stakeholder ecosystem. This includes effective research translation, which is contingent on agile regulatory and reimbursement approaches and forward-thinking implementation strategies that can adapt to an emerging field. In describing the RM value chain, this report aims to highlight the enablers, barriers, and key opportunities within the Australian sector to inform priority areas for action in the roadmap outlined by the Catalyst Consortium.

***Figure 1: Value chain for RM and stakeholder overview***




Note: A more detailed map of the value chain is provided on the next page.

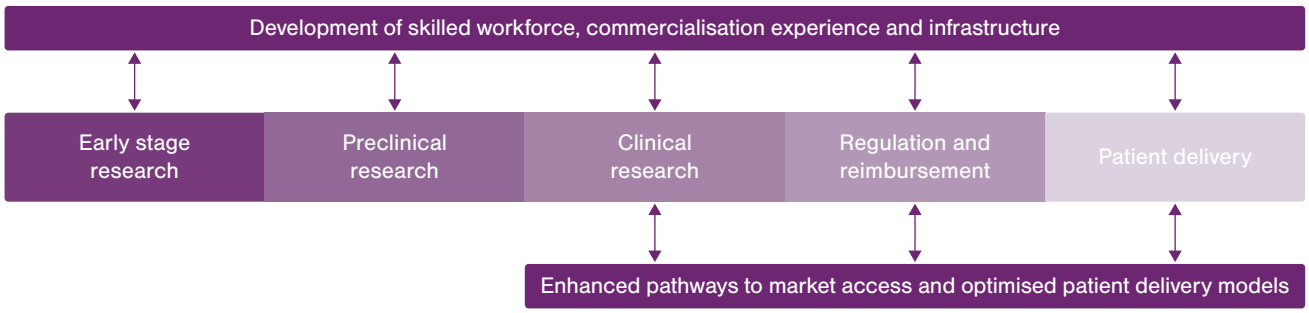
***Figure 2: More detailed RM value chain***



## ENABLERS AND BARRIERS IN THE AUSTRALIAN RM VALUE CHAIN

Priority areas of the Australian RM value chain are described below. Addressing each of these areas will build strength across the value chain, which is greater than the sum of its parts (as illustrated in Figure 3). For example, building research capability attracts investment in clinical trials, which in turn facilitates pathways to market access and implementation of RMTs in the Australian healthcare system. Clinical trials offer opportunities for Australian patients to access cutting-edge RMTs prior to their commercial launch, and investments in healthcare system capability and skilled workforce enhance the attractiveness of Australia as a destination for RM clinical trials. While pathways have been forged across the Australian value chain, further advances are required to support Australia's position in this rapidly growing sector.

***Figure 3: Combined effects of strength across the value chain***




### Research capabilities: workforce and infrastructure

Australia has a strong academic workforce and research output in RM. Recent and ongoing efforts aim to capitalise on this strength: building and supporting a workforce with skills in intellectual property (IP), research translation, and commercialisation.

These strengths are impeded, however, by a lack of infrastructure that is GMP-compliant and staff trained in these processes. GMP manufacturing facilities and materials (critically, viral vectors and pluripotent stem cell lines) are required to conduct early stage and preclinical research that can be readily translated to clinical trials, and ultimately into RMTs to treat patients. These limitations also represent opportunities to invest in advanced manufacturing in Australia.

### Supporting Australian research and small and medium-sized enterprises (SMEs): funding, investment and partnerships

Government, academic institutions, and philanthropic sources fund the majority of early-stage and preclinical RM research programs in Australia and (unlike in the US and EU) there are few venture capital investors and research partnerships between industry and academia. Grants tend to reward the generation of publications, rather than the development of IP or return on investment from commercialising RMTs. This lack of focus on commercialisation of biomedical research in Australia is not unique to RM, but it impedes our ability to take advantage of the record levels of investment seen in RM globally in recent years.

### Attracting investment in clinical trials: streamlined approvals and incentives

Remaining globally competitive is key to maintaining Australia's position as a destination for clinical trials. Our reputation for conducting high quality trials, coupled with the R&D Tax Incentive, helped to attract AU$1.4B(3) in investment in Australia in 2019. Regulatory processes to register trials via the CTN/CTA scheme are streamlined with international agencies; however, lack of harmonisation across ethical review and governance processes between states and territories remains a challenge. Costs and delays to trial start-up impact on Australia's international competitiveness.

## Clear pathways to patient delivery: healthcare system preparedness

The first CAR-T and gene therapies have successfully gone through both regulatory and reimbursement approvals, enabling local treatment of Australian patients through the emergence of Centres of Excellence. But some issues remain to be solved, with hospitals and health services still facing challenges in accessing the required infrastructure and in building and training a workforce skilled in the delivery of RM. Coordination of patient prioritisation committees are also key to ensure consistent and equitable access to high-cost reimbursed cell and gene therapies. Meanwhile, negotiations regarding federal and state government funding contributions towards RMTs remain complex. Each RMT will have unique requirements and characteristics, and since complexity is expected to increase as technology advances, the healthcare system will need to be able to adapt to this complexity.

## Data-driven approaches across the value chain

Data from patient registries, health information systems, biobanks, and other global research sources have the potential to shape activities across the RM value chain. This data can contribute to assessing disease burden and the need for research in a particular condition or patient group, designing RMTs and trials, and informing regulatory and reimbursement decisions. Post-marketing, RMTs typically require patient registries to monitor long-term real-world safety and efficacy as part of TGA-mandated Risk Management Plans and commonwealth funding risk-sharing arrangements. The lack of a coordinated, standardised, and long-term approach to collecting and reporting patient outcomes via linked datasets in Australia limits the utility of existing sources.

**This report provides an overview of the RM value chain in Australia, highlighting enablers and barriers to inform the Catalyst Strategic Roadmap. Further work is required to prioritise and explore options to build upon the enablers and address the barriers identified in the Australian RM value chain.**

**Access to innovative RMTs offers enormous potential to save lives and enhance quality of life for Australians. RMTs are complex and face additional challenges in advancing along the development pathway to patient care, compared with conventional therapeutics. While the global RM sector remains nascent, the pace of innovation and investment is accelerating rapidly. A coordinated, national approach that includes engaging with regional and international collaborators will support Australia's position in the global sector.**

# Introduction

## REGENERATIVE MEDICINE (RM) IN AUSTRALIA

RM promises to deliver ground-breaking therapies to Australian patients, with innovative approaches targeting a wide range of conditions including rare genetic diseases, cancers, chronic diseases, muscle loss and organ damage. 2020 marked the delivery of the first CAR-T therapy to patients and regulatory approvals of the first in vivo gene therapies in Australia. A booming global pipeline of clinical trials and investment in RM indicates a wave of new therapies on the horizon.(1)

To help Australia capitalise on this wave, desktop research into the RM value chain was conducted by Biointelect and validated by interviews with key opinion leaders from across academia and industry. The final report was then reviewed both internally at Biointelect and externally by consortium members. This report provides an overview of RM therapy types and then describes each stage of the Australian value chain, highlighting key barriers and enablers along the way.

Australian researchers and biotech companies make an important contribution to RMT discovery and development, with innovations in gene therapy, cell therapy and tissue engineering. Government and non-government organisations play substantial roles in supporting RM through funding for research, training initiatives, and facilitating collaboration – particularly for early-stage and preclinical research.(2) Enhancing translation of research into therapies that will enter the market and ultimately benefit patients is a particular focus for many stakeholders in the Australian life sciences sector.

Clinical trials are an important contributor to the Australian economy, injecting AU$1.4B in direct expenditure (including AU$1.1B from commercial entities) and directly employing more than 8,000 highly skilled staff in 2019. While RM trials represent a small proportion of this investment currently, Australia is well-positioned to contribute to RM in our region and internationally with high quality infrastructure, a skilled workforce, robust regulatory frameworks and R&D tax incentives. Global competition is fierce, however, and sponsors are attracted to countries where trials may be initiated and conducted efficiently.(3)

CAR-T and gene therapies have progressed through regulatory and reimbursement pathways in Australia. Centre of Excellence models have begun to develop in the healthcare system around areas of clinical expertise and investments in the infrastructure required to deliver RMTs. A manufacturing facility operated by Cell Therapies Pty Ltd at the Peter MacCallum Cancer Centre was able to be approved by the TGA as a manufacturing site for a commercial sponsor of reimbursed CAR-T products. These activities provide further stimulus to the local RM sector.

## THE RM VALUE CHAIN

The RM value chain (see The Regenerative Medicine Value Chain: A Guided Tour, below) consists of the set of activities performed to make an RMT available to the patients that will benefit from it(4), from discovery through to patient delivery. Each activity in the chain contributes to the end goal, and efficient and streamlined activities across the chain will optimise the value that is ultimately delivered to patients.

RM challenges traditional biopharmaceutical value chains and business models due to complex development approaches, limited access to raw materials and personalised therapeutic approaches that are difficult to scale.

## OPPORTUNITIES FOR REGIONAL AND INTERNATIONAL COLLABORATION

Regional and international integration is essential to advancing the Australian RM sector. International markets present the greatest opportunities for innovations developed in Australia. Similarly, RMTs developed overseas offer great hope for Australian patients, who already benefit from RMT clinical trials conducted in Australia and the first launches of CAR-T and gene therapies. Finally, the international pool of capital and highly skilled talent has vast potential to catalyse activities across the RM value chain in Australia.

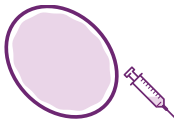
Globally, the field of RM is rapidly growing and evolving. Global RM financing has increased from US$7.5B in 2017 to US$19.9B in 2020, and 1,220 clinical trials are ongoing in the RM sector.(1) This rapid growth presents both opportunities and challenges. Steps taken by the Australian RM sector to integrate and build networks within our region and internationally will be critical to securing our position as a leading destination for research and development, clinical trials, treatment availability, and delivery of cutting-edge therapies for the benefit of all Australians. These steps could include participating in international programs that drive clinical programs and the development of regulatory standards, including Horizon 2020 IMI (Innovative Medicines Initiative) and ARDAT (Accelerating R&D for Advanced Therapies) working groups, in addition to the ongoing International Pharmaceutical Regulators Program (IPRP) cell and gene therapy working groups.

## KEY DEFINITIONS

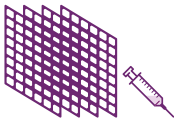
*"RM is the branch of medicine that develops methods to regrow, repair or replace damaged or diseased cells, organs or tissues. RM includes the generation and use of therapeutic stem cells, tissue engineering and the production of artificial organs."* - Nature(5)[5]

The following definitions are used in this report:


**Gene therapy** is the introduction, removal or change in the content of a patient's genetic code, with the goal of treating or curing a disease. "Gene therapy" as used in this report is delivered in vivo (where the genetic modification occurs inside the patient, Figure 4, right panel). Gene therapies are delivered to specific cells of interest and include gene transfer (also known as gene replacement) and genome editing.



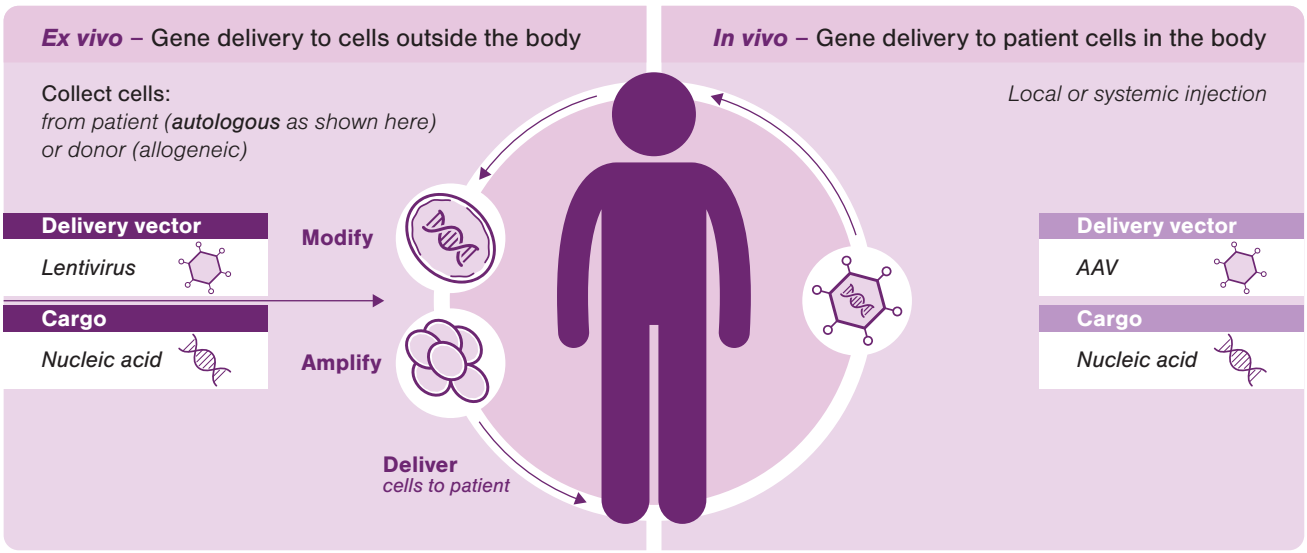
**Cell therapy** is the transfer of intact, live cells into a patient. It may be used to replace cells that are missing or non-functional, or to provide cells that have improved functionality. Cell therapies may include cells that originate from the patient themselves (autologous), or from a human (allogeneic) or animal (xenogeneic) donor. This can include genetically modified cell therapies, which can also accurately be referred to as "ex vivo gene therapies"



**Tissue engineering** combines biomaterial scaffolds with cells and/or biologically active molecules. Scaffolds are supporting materials that may be populated or "seeded" with cells before they are implanted, or may be implanted without cells (acellular) and interact with cells in vivo.

[5] Only somatic gene therapies are discussed in this report. Genetic modification of "germline" cells that would contribute to the next generation (i.e. sperm and eggs) is currently illegal in Australia and is not discussed here.

***Figure 4: Ex vivo (on left) and in vivo (on right) genetic modifications***




Source: (6).

Note: Lentivirus and AAV are currently the dominant delivery vectors used for ex vivo and in vivo genetic modifications, respectively.

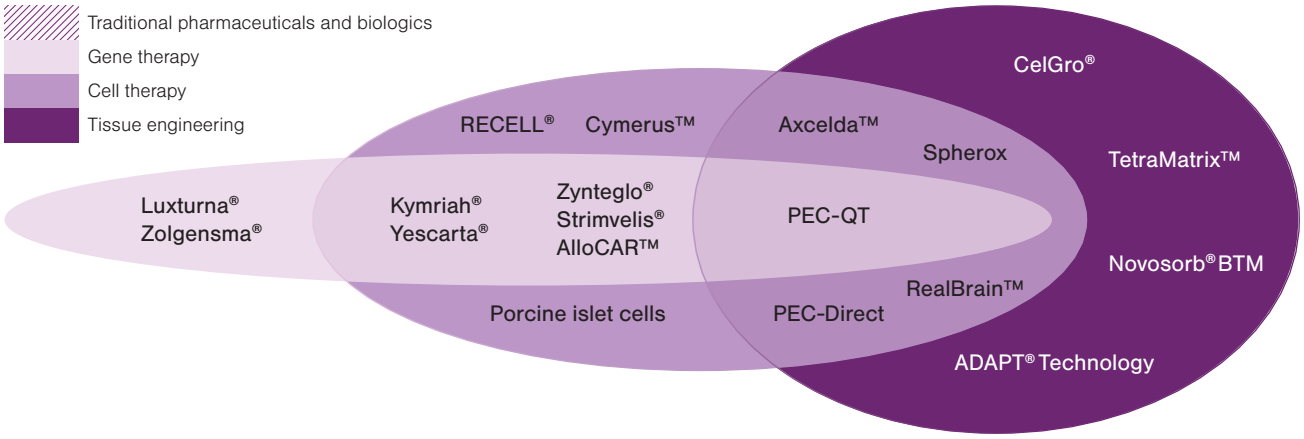
## STATEMENT ON DEFINITIONS USED IN THIS REPORT

RM therapeutic approaches are complex and may include concepts that fit under two or even all three of the definitions in this section. The groupings and definitions used here have been pragmatically chosen based on the similarities and differences in the value chains of various therapeutic approaches[6]. Future innovations are likely to introduce further complexity.

Figure 5 provides an overview of the RMT therapeutic groupings and examples of where available and prospective therapies fit. When reading this report, it is worth considering the degree of integration across these fields, as advances in one area may offer opportunities for advancement in another. Similarly, challenges may compound when dealing with technically complex therapeutic approaches that span multiple fields.

[6] RNA blocking technologies (small interfering RNA and antisense oligonucleotides [siRNAs and ASOs]) have been omitted. Although they fit definitions of gene therapies, their value chains (from reimbursement, to manufacturing, to patient delivery) are relatively comparable to traditional pharmaceutical value chains.

***Figure 5: Overlapping therapeutic groupings of RMTs (non-exhaustive, for illustrative purposes)***




**Cells**

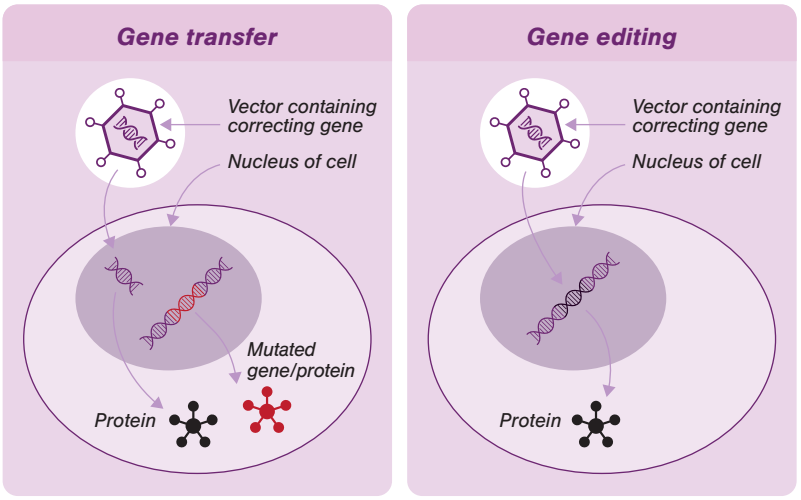
| Biomaterial scaffolds | No cells (in vivo) | Autologous | Allogeneic | Xenogenic | Genetic modifications |
|---|---|---|---|---|---|
| No scaffold | | RECELL®, Bone marrow transplant | Cymerus™, mesenchymal stem cells | Porcine islet cells | No GM |
| | | Kymriah®, Yescarta®, Zynteglo®, Strimvelis® | AlloCAR T™ | | Integrative |
| | Luxturna®, Zolgensma® | | | | Non-integrative |
| Autologous | | Spherox, 3C Patch® | | | No GM |
| | | | | | Integrative |
| | | | | | Non-integrative |
| Allogeneic | | Axcelda™, Cultured epithelial autografts | RealBrain™ | | No GM |
| | | | | | Integrative |
| | | | | | Non-integrative |
| Xenogenic | CelGro® ADAPT® Technology | | | | No GM |
| | | | | | Integrative |
| | | | | | Non-integrative |
| Synthetic | NovoSorb® BTM, TetraMatrix™ | | PEC-Direct | | No GM |
| | | | PEC-QT | | Integrative |
| | | | | | Non-integrative |

## GENE THERAPIES

Gene therapies are in development for recessive gene disorders (e.g. cystic fibrosis, haemophilia, muscular dystrophy, and sickle cell anaemia), acquired genetic diseases including cancer, and certain viral infections such as AIDS. The initial focus has been largely on rare diseases caused by mutations to single genes and diagnosed using genetic sequencing. These conditions are often characterised by high levels of unmet need. Gene therapies are also being investigated for more common conditions, including wet age-related macular degeneration (AMD) and Parkinson's disease.

Gene therapies aim to reduce levels of a disease-causing protein, increase production of disease-fighting proteins, or produce new, or modified, proteins.(7) There are two main approaches to gene therapies: gene transfer; and genome editing.

***Figure 6: Overview of genetic modification***




Source: Adapted from (8).

Note: Non-integrative gene transfer is depicted on the left, and genetic insertion is depicted on the right.

**Gene transfer** uses a vector to carry genetic material into a cell, placing a new, working gene inside. Depending on the type of vector used, the transferred genetic material may then either alter the patient's genome (integrative) or reside in the nucleus but remain separate from the genome (non-integrative).

Viral vectors are most-commonly based on retroviruses (which include lentiviruses and are integrative), adenoviruses, and adeno-associated viruses (AAVs, which are non-integrative). AAVs are currently the most-commonly used vectors for gene therapies, as they have established safety profiles and because of the utility of having different AAV sub-types that target different tissues. Other viral and non-viral vectors are being developed to improve targeting of certain cell types, to improve the transfer and activity of genetic material, and to minimise interactions with the immune system.(9)

**Genome editing** is an integrative therapy, which involves making small changes (insertion, deletion, modification, or replacement) at very specific parts of the patient's genome. Compared to lentiviral integration, which occurs unpredictably at a range of sites, genome editing technologies (like CRIPSR Cas-9, zinc finger nucleases [ZFN], and transcription activator-like effector nuclease [TALEN]) are more targeted and can be used to edit very specific mutations.(10) Genome editing technologies need to be delivered into the target cells in order to function. In clinical applications, this delivery can be performed using viral vectors, exosomes, electroporation, or other strategies.

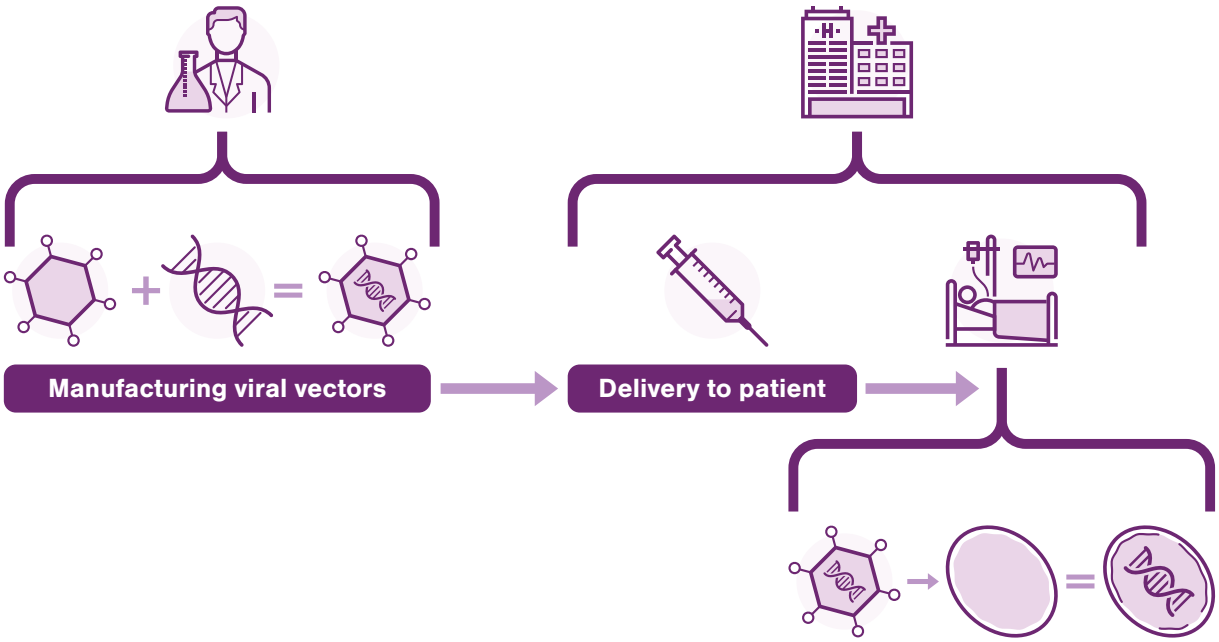
Integrative gene therapies come with a risk of "off-target effects", where the genetic material is inserted in one or more undesirable locations. This could disrupt important genes that may be related to the development of cancer.

***Box 1: Gene therapy example – gene transfer: Luxturna® (voretigene neparvovec)***

**Luxturna®** (Novartis/Spark Therapeutics, Switzerland/USA) is a non-integrative gene transfer therapy (AAV-delivery) for the treatment of patients with inherited retinal dystrophy caused by pathological biallelic RPE65 mutations and who have sufficient viable retinal cells. RPE65 is one of more than 260 genes that may be responsible for an inherited retinal disease, and confirmation of the specific mutation with a genetic test is required.(11)

Marketing authorisation for Luxturna® was approved for use by the TGA (and for reimbursement by MSAC) in 2020. It is delivered to patients admitted to an accredited treatment centre in an inpatient setting, using a surgical procedure (intra-ocular injection). Manufacturing occurs at a centralised location and distribution in Australia is via a global supply chain.

***Figure 7: Delivery of gene therapy***



## CELL THERAPIES

Cell therapies aim to introduce healthy cells to the body, to replace diseased or missing ones. Therapeutic cells may be selected, enriched, genetically modified, and/or expanded prior to implantation. The types of cells administered, and the processes involved in creating the cell product depend on the availability of therapeutic cells, the nature of the disease, and the needs of the patient. Diseases currently targeted by stem cell therapies include diabetes, cutaneous wounds, autoimmune and liver diseases, as well as diseases that affect the cardiovascular, neurologic, and pulmonary systems.(12)

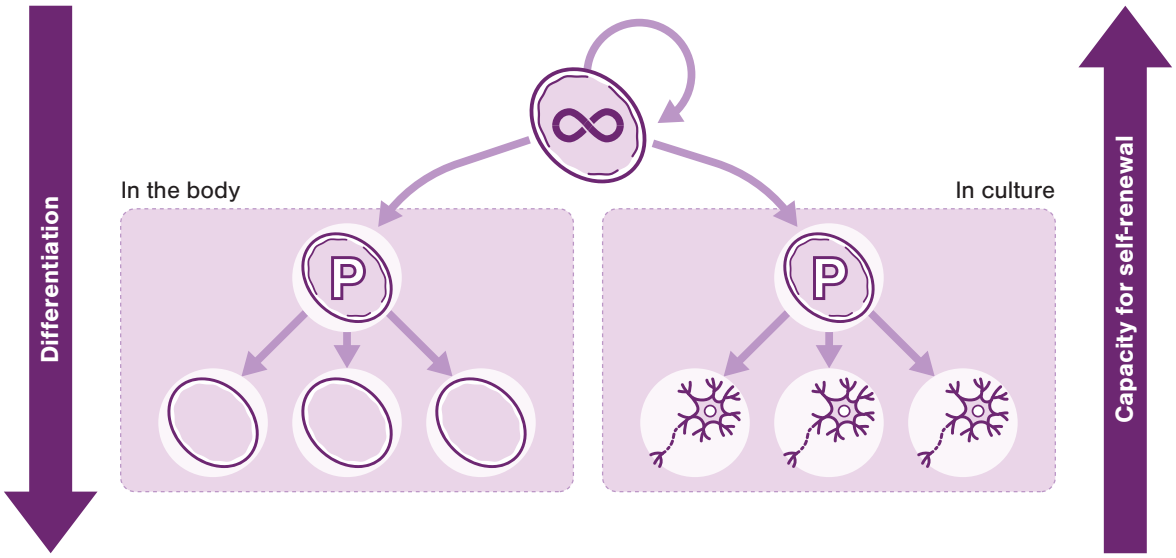
***Box 2: Overview of stem cells and somatic cells***

**Stem cells** are defined by their ability to:

- Expand and be maintained (self-renew) indefinitely; or
- Turn into other types of cells (differentiate).
- Stem cells are then grouped by their source and their potential to differentiate into certain cell types.

Human pluripotent stem cells (hPSCs) can differentiate into any cell in the adult body, while multipotent cells (e.g. haematopoietic cells, HSCs, in bone marrow) can only differentiate into a smaller set of cell types. Most of the cells of the body are “somatic sells”, including skin, muscle and fat cells and nerves. Differentiation from stem cells to somatic cells, or between types of stem cells may involve intermediate cell types known as progenitor cells (Figure 8).
While hPSCs were initially derived from early-stage human embryos (embryonic stem cells, ESCs), they can now also be created from differentiated cells (induced pluripotent stem cells, iPSCs) in a process called cellular reprograming. Somatic cells may also be converted directly into other types of somatic cells in a process called transdifferentiation.(13, 14)

***Figure 8: Stem cells self-renewing and differentiating, via progenitor cells, to somatic cells***

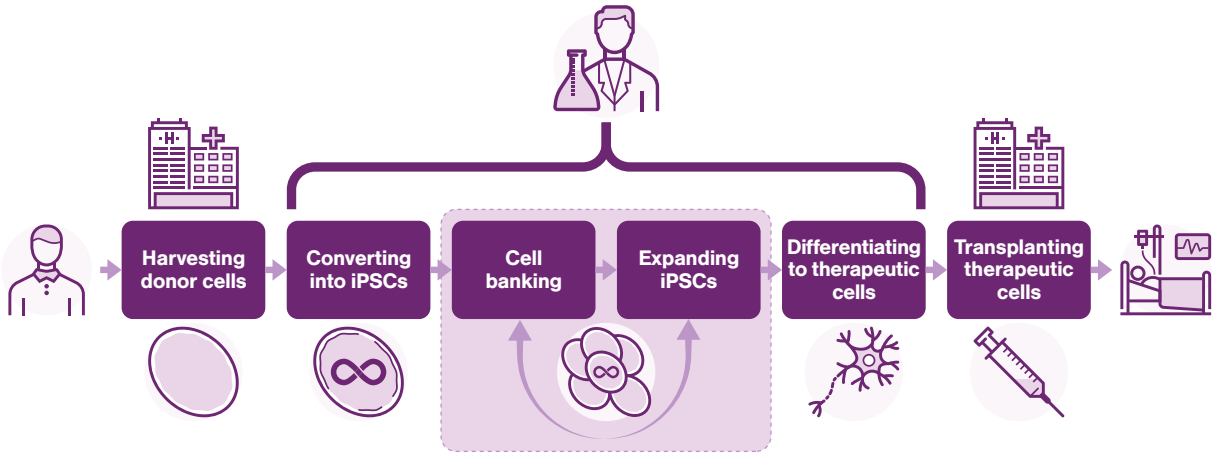


***Box 3: Allogeneic cell therapy example – iPSC-derived cells: Cymerus™ Platform***

**The Cymerus™ Platform** (Cynata Therapeutics, Victoria) is an allogeneic iPSC-based method that can produce therapeutic cells including mesenchymal stem cells (MSCs), with the potential to treat a range of diseases.

Starting cellular material was donated by a single healthy individual and converted into iPSCs in a laboratory-based process. The iPSCs were banked and expanded, creating an effectively unlimited source of cells. In a multi-step process, the iPSCs are then turned into therapeutic MSCs, which undergo strict quality control testing before they will be transported to the hospital and transplanted into the patient(15). MSCs are thought to have a therapeutic effect by migrating to the site of damage, and treat joint degeneration, reconstruct bones and cartilage, or repair the damage of musculoskeletal tissues.

***Figure 9: Delivery of iPSC-derived cells***




Source: (16).

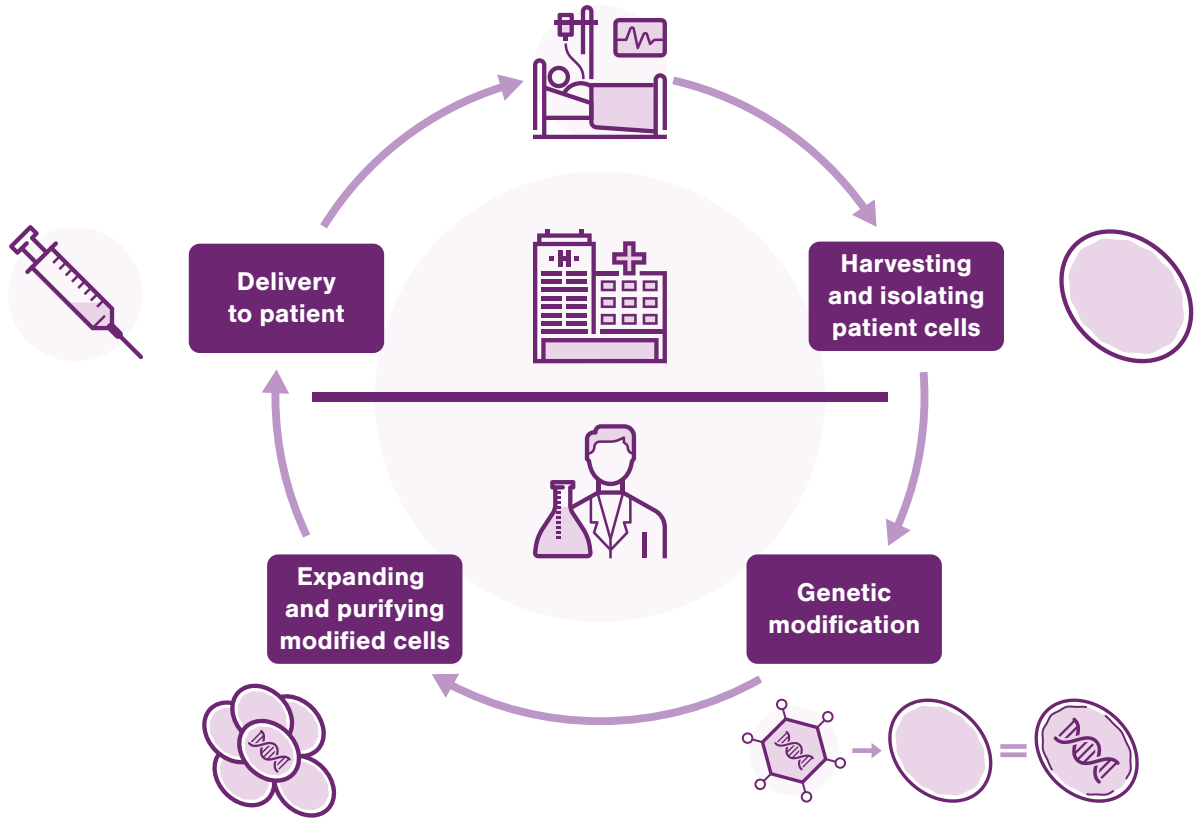
Note: An additional culture and banking step is not shown in the figure. The process after "converting into iPSCs" is equivalent to therapies that involve cells derived from human embryonic stem cells.

***Box 4: Autologous gene-modified cell therapy example – CAR-T cells: Kymriah® (tisagenlecleucel)***

**Kymriah®** (Novartis, Switzerland) is an autologous CAR-T therapy that has been approved by the TGA and is publicly-funded in Australia for the treatment of eligible patients with specific types of blood cancer[7].

To receive treatment with Kymriah®, patients are admitted as inpatients to an approved treatment centre, where the T cells of their immune system are collected (in a process known as leukapheresis). While the patient remains hospitalised, their cells are sent to a manufacturing facility to be genetically modified (using viral vectors), so that the cells are better able to recognise and attack cancerous cells. The modified cells are then expanded and transported back to the treatment site for injection into the patient (Figure 10)(17). Approval has recently been granted for Kymriah® to be manufactured by Cell Therapies Pty Ltd in Melbourne, marking Australia's first on-shore commercial production of CAR-T therapy.(18)

***Figure 10: Delivery of autologous gene-modified cell therapy***




Source: (18)

[7] Kymriah® is approved in Australia for the treatment of eligible adult patients with relapsed or refractory DLBCL (diffuse large B cell lymphoma), and eligible paediatric and young adult patients up to 25 years of age with relapsed or refractory ALL (acute lymphoblastic leukaemia). Source: Kymriah® approved product information: https://www.novartis.com.au/products/healthcare-professionals

## TISSUE ENGINEERING

Tissue engineering seeks to restore, maintain, improve, or replace damaged tissues and organs through treatment with biomaterial scaffolds (see Box 5) that can be delivered alone (Box 6) or when seeded with cells (Box 7), and/or biologically active molecules. Tissue engineered products (TEP) have a wide range of applications, including orthopaedics, musculoskeletal, cardiovascular, neurological, dental, skin/wound healing, gastrointestinal, gynaecology, urology, and cancer.(19)

***Box 6: Tissue engineering example – acellular scaffold: CelGro™***

Biomaterials include any substance engineered to interact with a patient's living biological system for a medical purpose. Biomaterial scaffolds can coat 2D surfaces, or form a range of 3D shapes and sizes. Cells may interact with the outside of the scaffold and/or move within the scaffold. The scaffold's structural and mechanical characteristics are driven by the needs of the patient and the needs of the relevant cell types.

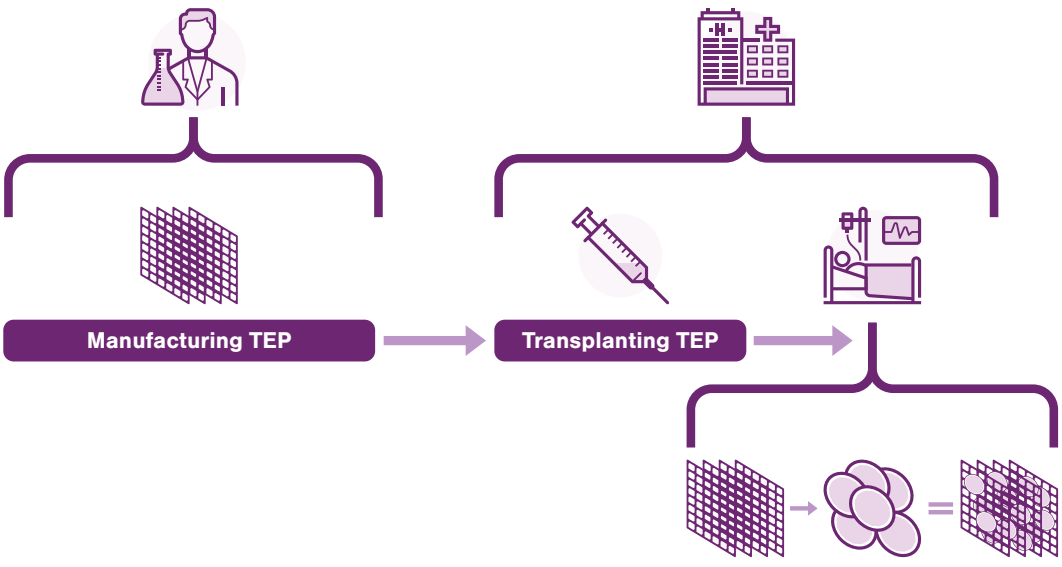
Scaffolds are typically porous, permeable, and/or composed of fibrous (long and thin) molecules that may be structural (providing a physical structure to support cells) and/or functional (chemically interacting with cells in the body to change their behaviour). They can also be composed of combinations of multiple materials from different sources. Scaffold biomaterials may come from autologous, allogeneic, xenogeneic or synthetic sources and can be produced by:

- Extraction from existing tissues (decellularized scaffolds) – a biopsy is taken from either a patient, a healthy volunteer, or an animal then the cells are removed, and the molecularly complex material that remains contributes to a scaffold.
- Isolation from cell cultures – in a similar way to biologic medications, the materials are extracted from cultures of specific productive cell-types. This can result in purified versions of a specific type of molecule, or complex mixtures of many different molecules types.
- Synthesis from inorganic chemicals – techniques including polymer chemistry and electrospinning form long chains (polymers) that mimic the natural environment of the cells. These polymers may be modified with small molecules or coated with other biomaterials to produce the final scaffold.

***Box 5: Overview of tissue engineering***

**CelGro™** (Orthocell, Western Australia) is a collagen-based scaffold. CelGro™ has been approved by the TGA for dental guided bone and soft tissue regeneration applications, and is being developed for applications in nerve and tendon repair. The components of the scaffold are extracted from porcine (pig) material. The acellular scaffold is then implanted, where the patient's cells interact with and grow into the scaffold, forming the regenerated tissue.(20)

***Figure 11: Delivery of an acellular scaffold***

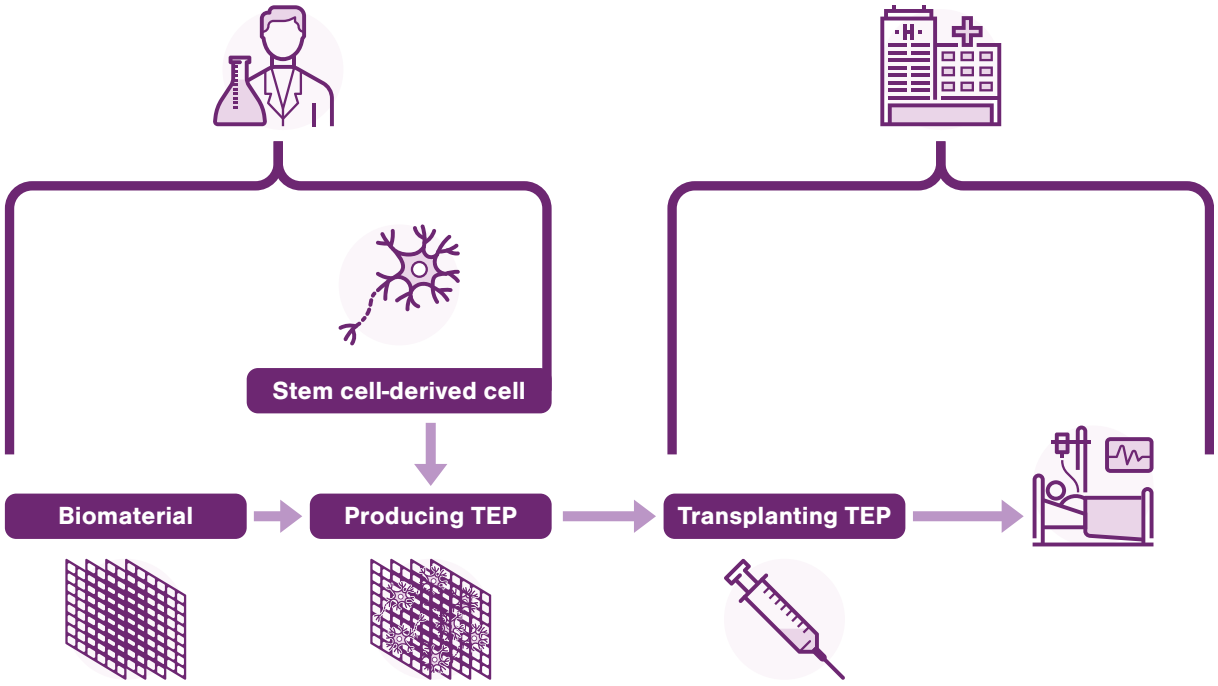


***Box 7: Tissue engineering example – stem cell-derived cells in a synthetic matrix: RealBrain®***

**RealBrain®** (Tessara Therapeutics, Victoria) is a TEP that models brain tissue and has potential in drug screening and treatment of neurological diseases including Alzheimer's disease, neonatal stroke and traumatic brain injury.

RealBrain® engineered neural tissue is composed of proprietary biomolecules in the form of a gel (RealBrain® hydrogel) that is manufactured in a laboratory and seeded with hPSC-derived neural stem or precursor cells. After seeding, the cells differentiate and form neural networks, resulting in a product that resembles human cortical brain tissue. For clinical use, these tissues would be transported to the hospital where it would be implanted into the brain of a patient.

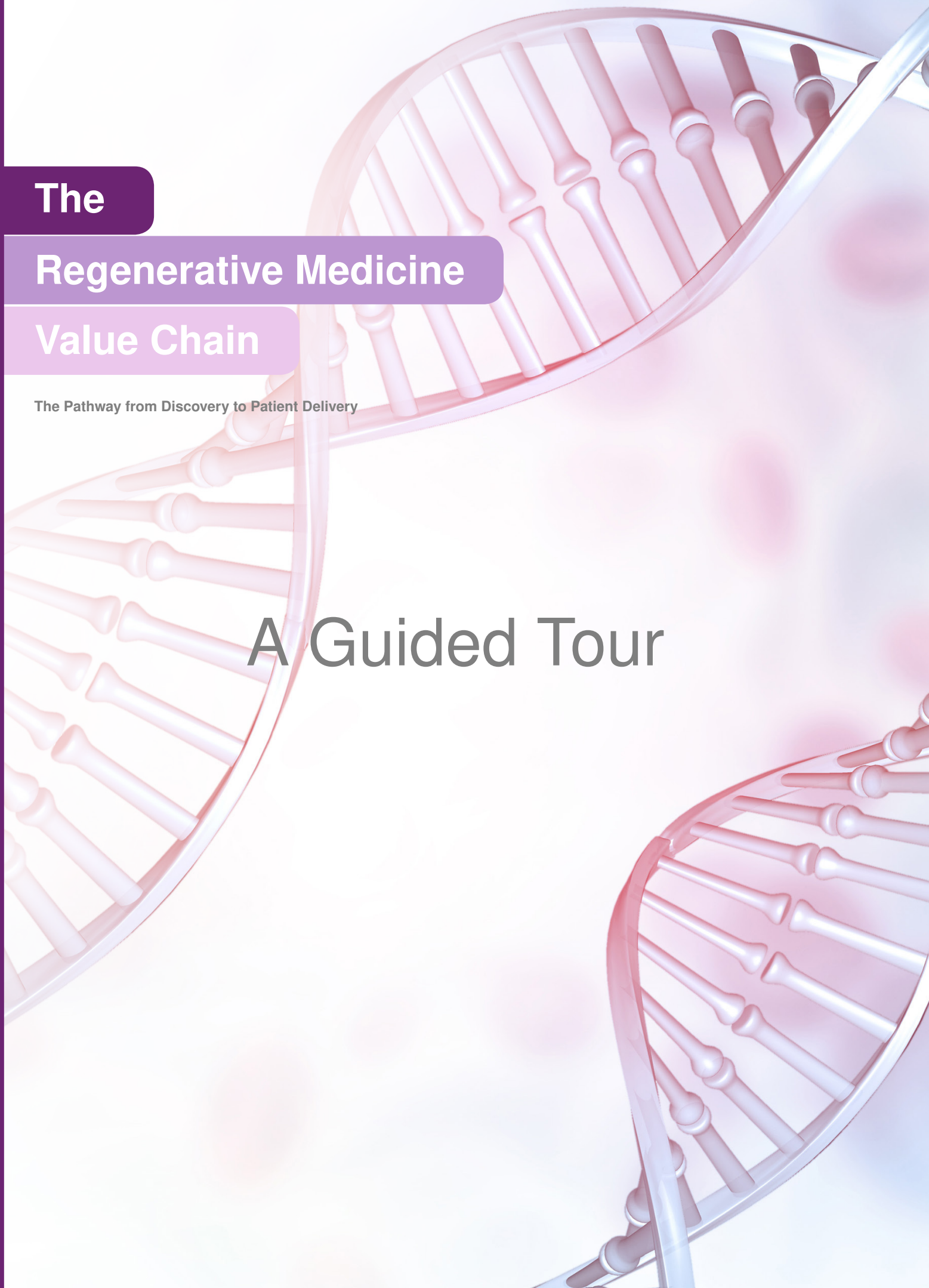
***Figure 12: Delivery of stem-cell derived cells in a synthetic matrix***




Source: (21)

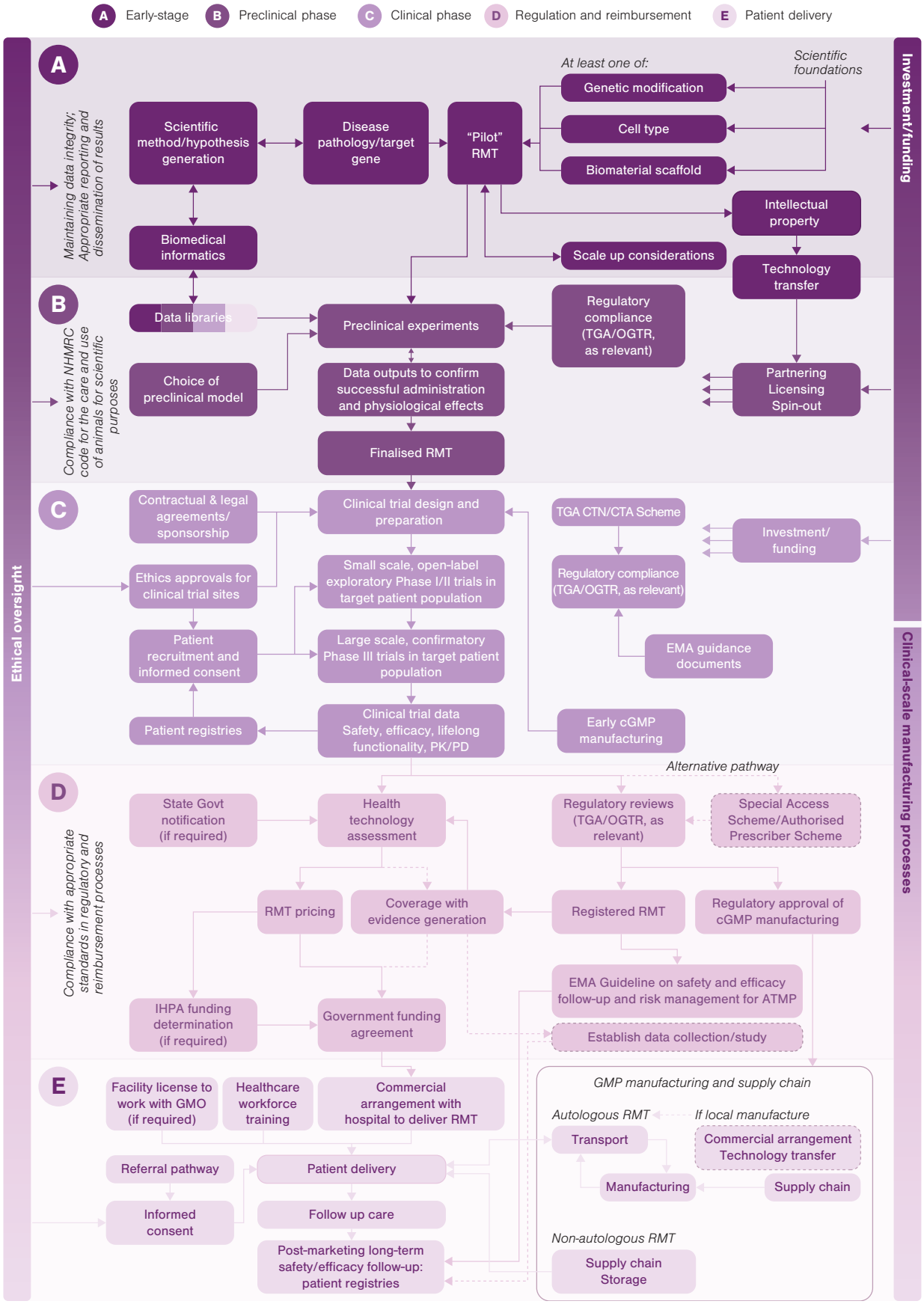
# The Regenerative Medicine Value Chain

The Pathway from Discovery to Patient Delivery



## A Guided Tour

*Figure 2: More detailed RM value chain*



# Early-stage Research

*Early-stage RM research is exploratory, often multidisciplinary, mainly undertaken by research groups in academic institutions, and funded through government initiatives. It builds upon existing scientific foundations to identify and address areas of unmet need through innovative therapeutic approaches.*

*The aim of this research is to develop clearly defined "pilot" products that can enter preclinical testing.(22, 23) It is important to consider regulatory and manufacturing requirements even from early-stage research. Processes that begin optimisation during early-stage research are essential to later product development. Particularly for cell therapies and tissue engineering: "the process is the product".*

***Figure 13: Value chain: early-stage RM research***

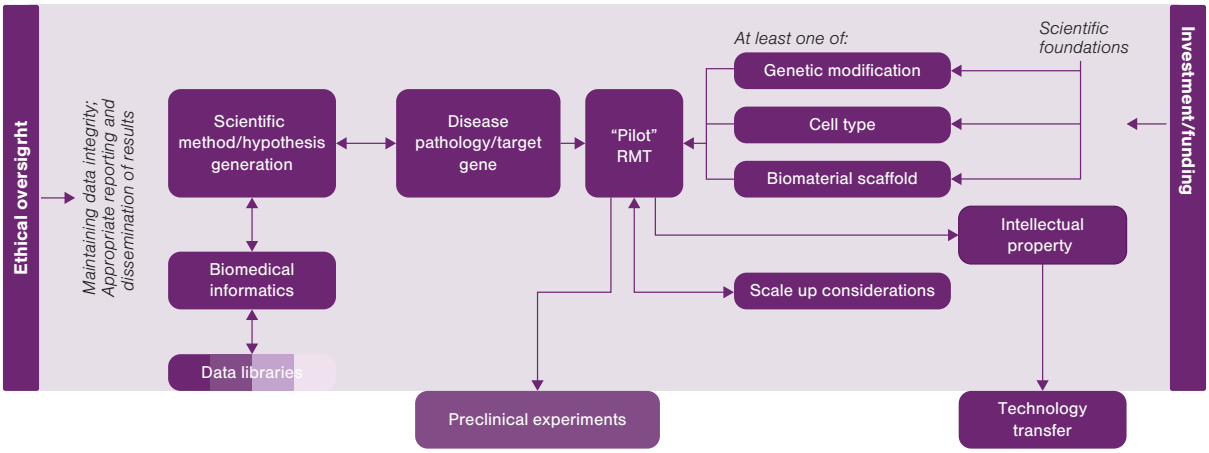


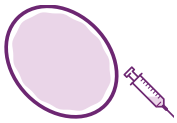
***Table 1: Stakeholders: early-stage RM research***

| Stakeholder group | Roles |
|---|---|
| Patients and patient representatives | • Raise disease awareness and funds for early-stage research<br>• Define and provide understanding of unmet need |
| Academic institutions | • Drive the majority of early-stage RM research in Australia<br>• Contain technology transfer offices, which oversee identification, protection and management of the IP created by academics<br>• Ethics Committees facilitate and manage research in accordance with the requirements of the National Health & Medical Research Council (NHMRC) |
| Healthcare professionals | • May be principal investigators or research collaborators<br>• Help understanding of unmet clinical need and clinical viability of RMTs |
| Healthcare services | • Collect, label and store patient specimens for early-stage research<br>• Provide facilities (e.g. labs) and equipment for conduct of early-stage research |
| Biopharmaceutical industry | • May offer guidance regarding future requirements for commercialisation<br>• SME biotech companies conduct early-stage RM research in Australia<br>• Multinational biopharmaceutical companies conduct early-stage RM research in Australia |
| Industry bodies | • Support researchers at the preclinical stage and foster collaboration between researchers and other stakeholders<br>• Provide funding opportunities |
| Commercial manufacturers | • May offer guidance regarding future scale-up and/or use of clinical-grade processing equipment and materials |
| Australian Government | • Provide funding for early-stage RM research<br>• Provide ethical guidelines via the NHMRC |
| State & Territory Governments | • Provide funding for early-stage RM research |
| Other agencies | • NHMRC – government agency which:<br>  • Manages grant schemes for funding of early-stage research<br>  • Advises the Australian Government<br>• Maintains and promotes ethical and responsible conduct of early-stage research |
| Capital investors | • Provide funding (philanthropic groups in particular invest in early-stage research) |
| Services and Suppliers | • Consultancies advise research groups and SMEs on product development and assist with project and grant management<br>• Cell and tissue banks provide access to validate cell lines and tissues and associated quality control services<br>• Contract development and manufacturing organisations (CDMOs) supply researchers with technology platforms, tools and equipment supporting early-stage research |

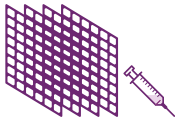
## DEVELOPMENT APPROACH

RM development builds upon scientific foundations for gene therapies, cell therapies and TEPs:


**Gene therapies** are developed from understanding the basics of disease, signalling pathways, and genetic and molecular control of human cell development and differentiation. Gene therapy builds upon the foundations of molecular genetics, microbiology, endonucleases and genome repair mechanisms. It also draws on innovative therapeutic approaches from vectorology and gene editing technologies, such as CRISPR-Cas9, TALEN and ZFN.



**Cell therapies** are developed out of the study of cellular and molecular biology, cell culture and characterisation (including phenotypic and functional analysis).



**TEPs** introduce complex and multidisciplinary approaches that integrate principles of life sciences (cell biology, chemistry, molecular biology) with materials science, bioengineering, computer modelling and nanotechnology.

Access to cell lines is essential to early-stage development. While research-grade cell lines are readily available in many institutes, access to lines that would be suitable for later stage clinical trials and clinical practice is very limited. Successful translation of hPSC therapies will require particularly careful consideration of manufacturing and regulatory processes, even at the early stage. Box 8 explores this issue and the ongoing investments into infrastructure and elsewhere that are required to address this barrier.

***Box 8: Manufacturing and regulatory considerations for hPSC-derived therapies***

hPSCs include embryonic stem cells and induced pluripotent stem cells (iPSCs, see Box 2). hPSCs are very sensitive to the conditions in which they are cultured, and each hPSC line has a unique growth rate and differentiation bias (tendency to turn into certain types of cells). Manufacturing processes must therefore be adapted to suit each cell line. Regulators will ultimately require data to be collected from the series of preclinical and clinical experiments that were performed using the cell line that will reach the clinic.

Therapies based on hPSCs (and other cell therapies) used in later stage clinical trials and in clinical practice are required to comply with Good Manufacturing Practice (GMP) guidelines, under the *Australian Code of Good Manufacturing Practice for Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products.* Working with GMP-grade materials as early as possible will therefore minimise the need to repeat experiments.

The establishment or licencing of GMP-grade lines has been estimated to cost over AU$1 M, 40-80 times the cost of establishing research (non-GMP) grade lines.(24) Without meeting GMP requirements, research-grade hPSC lines may be obtained from cell and tissue banks, and can be cultured and stored indefinitely (as new frozen stocks can be made from each thawed culture).

While it is more expensive and difficult to access GMP-grade than research-grade hPSC lines in early-stage research, early access to GMP-grade hPSC lines may reduce development costs in the long run and enhance return on investment. Taking these future manufacturing and regulatory processes into account, even at the early stage, is part of the commercialisation mindset that is key to successfully translating research into products that may be used by patients.

The Stem Cell Therapies Mission aims include support for research into the production of clinically-relevant hiPSC lines that would be available to industry members within Australia.(25) This may assist in addressing this barrier, provided GMP-compatible research grade media and equipment is available to maintain and propagate the cell line.

## ETHICAL OVERSIGHT OF EARLY-STAGE RM RESEARCH

Ethical oversight of early-stage RM research falls into the category of human research. This research is overseen by the Human Research Ethics Committees (HRECs) associated with major sites where research is conducted. Standards are set out in the N*ational Statement on Ethical Conduct in Human Research* issued by the NHMRC. Research that involves the use of genetically modified organisms (GMOs) is also monitored by the OGTR, under the *Gene Technology Act 2000*. Ethical issues associated with the provenance of hPSCs are outlined in Box 9.

***Box 9: Provenance of hPSC-derived therapies in early-stage research***

The provenance of research-grade hPSC lines can become complex. As the lines are maintained, shared between laboratories, genetically modified to improve their utility, and shared again, the records tracking the nature and history of the cells can become unclear. Different research groups may even refer to the same cell line by different names.

Unlike the US and the UK, Australia lacks a bank where hPSC lines are stored, or even a database containing cell line information. These systems contribute to integrating clinical and regulatory aspects into early-stage design, ensuring that the regulatory processes are fit for purpose, easing the path to international quality control assays, and improving collaboration between industry and academia, and between the regulatory bodies.(24, 26)

The lack of any such system in Australia complicates the reportability and reproducibility of research and is a barrier moving forwards, both for the progress of research in general and in the regulatory approval of hPSC-based RMTs. As one researcher put it, “It’s quite striking that Australia has nothing at all in this space.”

## SCIENTIFIC METHOD AND HYPOTHESIS GENERATION

Broadly speaking, the scientific method involves the review and consolidation of available evidence to produce ideas (hypotheses) that may then be tested by experimentation. The repeated production and testing of hypotheses underlies the creation of scientific knowledge.

Early-stage RM research involves studying the natural history of target diseases, and the development of therapeutic approaches that may include genetic modifications, cells, and biomaterial scaffolds. Hypotheses are developed from evidence gathered from academic journals, conference presentations, and clinical and experimental data stored in various databases (including registries and libraries).

## PROCESS TO IDENTIFY A PILOT RMT

The development of a pilot RMT to the point that it can enter preclinical testing is the key output of early-stage RM research. Research translation and commercialisation in RM requires consideration of a range of factors across the value chain, including manufacturing and regulatory concerns.

Although Australia’s skilled academic workforce is a key enabler, the challenges associated with commercialisation of research from academic programs are well documented (Box 10). Stakeholders highlighted the value of initiatives to support industry mentoring and partnership that are available in the RM sector. Some examples are described in Box 11 and Box 12.

## GENERATION OF INTELLECTUAL PROPERTY AND TECHNOLOGY TRANSFER

The rights to IP will be sought by researchers and is generally owned and managed by the academic institutions where research is conducted. Academic institutions are committed to the identification, protection, management and commercialisation of IP created by their academics (as outlined in the National Principles of Intellectual Property Management of Publicly Funded Research)(27). Involvement, consultation, and remuneration of the inventors (primary researchers) varies between institutions.

Securing patents allows researchers to protect their IP, and may provide an advantage over competitors. It also contributes to packaging the outcomes of early-stage research to enable technology transfer and future partnering/licencing/spinout arrangements. Technology transfer offices at academic institutions facilitate this process.

IP generation alone, however, does not guarantee successful translation of research. Although patent applications arising from stem cell research in Australia have had a high success rate (96% awarded), very few have developed into products entering clinical trials(28).

***Box 10: Academic workforce***

Academic research groups have developed vast skills and knowledge in the development of novel RM products. These groups commonly serve a range of clinical programs (across a range of organs/systems/diseases) and are closely linked to the academic researchers/investigators. The staff within these laboratories have developed a valuable breadth of knowledge, techniques and skills in developing new viral vectors, and in processing and characterising cells, organoids, and/or biomaterials.

Many stakeholders commented that commercialisation expertise and knowhow is lacking in the academic sector. This is evident where, for example, academics are not trained to work under GMP. More generally, successful research translation is affected by the incentive structure faced in academia, which emphasises “publish or perish” over activities that would support commercialisation.

Australia attracts global expertise to join research teams and to the leadership of key research institutes. Skilled migration continues to be an important consideration for building the RM workforce.

The Researcher Exchange and Development within Industry (REDI) initiative aims to build Australia’s medical technology, biotechnology and pharmaceutical workforce, address skills gaps and enhance the entrepreneurial ecosystem. Industry surveys have identified key gaps to be addressed across the value chain. These include product development and commercialisation knowhow, as well as specialist and technical skills in genomics. The work program includes training, mentoring and industry placements to address these gaps.(29)

***Box 11: Collaborations in early-stage and preclinical RM research***

Research translation and commercialisation of RMTs is perhaps best learned through experience. Stakeholders involved in early-stage and preclinical research suggested that greater access to mentorship from individuals with real-world experience in taking products through to clinical research and entering the market would be beneficial, and more needs to be done in this space.

- Innovation Connections is an Australian Government program that offers access to facilitation services and financial support (grants)
- BioCurate collaborates with Monash University, the University of Melbourne and their affiliated medical research institutes to identify, develop and commercialise research by creating therapeutic products that are financially viable with the potential to generate real patient impact.
- Therapeutic Innovation Australia (TIA) invests in translational research infrastructure to enable access for SMEs and researchers to specialised RM capabilities and provides translational support services, with involvement in key RM programs at Westmead and Royal Prince Alfred Hospitals (NSW), Peter MacCallum Cancer Centre (Victoria), QIMR Berghofer (Queensland), and Royal Perth Hospital (Western Australia)(30)
- The Translational Research Initiative for Cell Engineering and Printing (TRICEP) was established at the University of Wollongong and is supported by the ARC Centre of Excellence of Electromaterials Science (ACES) and the Australian National Fabrication Facility (ANFF) Materials Node. TRICEP works closely with research institutions and industry to develop innovative technologies using 3D bioprinting. Access to TRICEP's state-of-the-art research facilities (e.g. printer manufacturing, biomaterials, bioinks), assists companies to expedite development of novel technologies from concept stage to market.
- Cell Therapies is an Australian-based contract development and manufacturing company specialising in regenerative medicine that works with academic researchers and biotech companies moving into early-stage trials to provide assistance with manufacturing, technology transfer and process development. This fosters longer term relationships that may then progress to collaboration in conducting clinical trials, and ultimately clinical use.(31)

***Box 12: International public-private partnerships in early-stage and preclinical RM research***

Collaborative efforts in early-stage and preclinical research, such as industry-funded research institutes and public-private partnerships are prevalent internationally:

- The Innovative Medicines Initiative (IMI) is a partnership between the EU and the European Federation of Pharmaceutical Industries and Associations with a total budget of €3.3B over 2014-2024 to support the development of therapeutics and vaccines. Specific objectives include increasing the success rate of clinical trials, speeding up the earlier stages of drug development, and developing new biological markers to diagnose diseases and assess treatments. IMI supports collaborative research projects bringing together universities, industries, SMEs, patient organisations, and regulators.(32)
- ARDAT is a consortium of 34 international partners from academia, industry, and SMEs across ten countries. ARDAT is developing tools to accelerate the development of new treatments for rare diseases using viral gene and cell therapy. Five initial work packages focus on immunology and metabolism of viral gene and cell therapies and engagement with regulators.(33)

There may be opportunities in Australia to explore these initiatives to build up the RM sector.

# Preclinical Research Phase

*Preclinical studies are performed on the pilot RMT (developed in early-stage research) in model systems. The aims of preclinical studies are to enable optimisation of the RMT and to confirm that the mechanism is safe, can be effectively delivered, and achieves the desired physiological effects. At the completion of successful preclinical testing, a finalised RMT is ready for clinical trials.(34-36)*

*Preclinical testing of RMTs is generally undertaken by academic research groups, although limited venture-funded preclinical research is also conducted in Australia by SME biotechnology companies, with or without the assistance of Contract Research Organisations (CROs).*

***Figure 14: Value chain: Preclinical testing in RM***

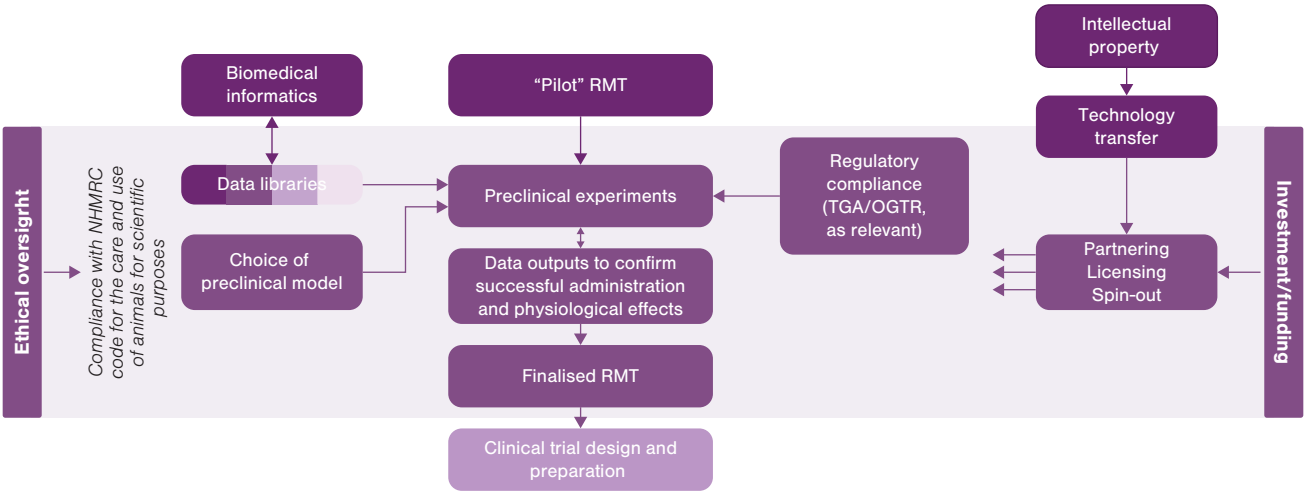


***Table 2: Stakeholders: Preclinical testing in RM***

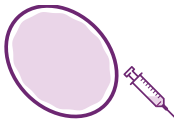
| Stakeholder group | Roles |
|---|---|
| Patients and patient representatives | • Raise disease awareness<br>• Provide funding for preclinical research |
| Healthcare professionals | • Some conduct preclinical research |
| Academic institutions | • Undertake preclinical testing of RMTs<br>• Ethics Committees facilitate and manage preclinical research in accordance with the requirements of the NHMRC<br>• Contain technology transfer offices, which oversee identification, protection and management of the IP created by academics and also assist translation of research into platform, products or services for further clinical development (through establishment of start-ups, spinouts, licencing) |
| Healthcare services | • Collect, label and store patient specimens for preclinical research<br>• Provide facilities (e.g. labs) and equipment for conduct of preclinical research |
| Biopharmaceutical industry | • SMEs undertake preclinical testing of RMTs<br>• Multinationals might collaborate with research institutes and SMEs in preclinical research |
| Industry bodies | • Support researchers at the preclinical stage and foster collaboration between researchers and other stakeholders<br>• Provide funding opportunities |
| Commercial manufacturers | • Provide research facilities and guidance |
| Australian Government | • Provide funding for preclinical research<br>• Provide ethical guidelines via the NHMRC |
| State & Territory Governments | • Provide funding for preclinical research |
| Capital investors | • Provide funding for preclinical research |
| Services and Suppliers | • Consultancies advise research groups and SMEs on product development and assist with project and grant management; Regulatory consultants may also provide guidance on regulatory aspects of preclinical research<br>• Cell and tissue banks provide access to validate cell lines and tissues and associated quality control services<br>• Suppliers of laboratory animals provide preclinical research models<br>• CDMOs supply researchers with technology platforms, tools and equipment supporting preclinical RMT testing<br>• Contract Research Organisations (CROs) assist preclinical research with animal models, histology services and specialty platforms and consulting services |
| Regulators | • Can provide early advice on preclinical RMT testing |
| Other agencies | • NHMRC:<br>  • Provides grants to fund preclinical research<br>  • Advises the Australian Government and facilitate networking in the research community<br>  • Maintains and promotes ethical and responsible conduct of preclinical research e.g. provision of guidance in the Australian code for the care and use of animals for scientific purposes |

## DEVELOPMENT APPROACH

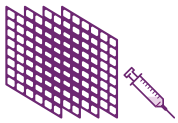
Preclinical studies are conducted to establish proof-of-concept, feasibility and rationale for clinical use of the pilot RMT.(37) The most important aspect of this is characterising the safety profile. Studies should aim to determine the feasibility of the administration route, and a safe and biologically effective dose to be used in clinical trials, providing sufficient information for a proper risk-benefit assessment of the use of the product in humans.(35)

Preclinical studies involving:


**Gene therapies** must define how effectively the vector is delivered to specific tissues and cells, how effectively those cells are transformed, how strongly the gene is expressed, how long gene expression lasts, and how the body will respond to the changes in gene expression, as well as risks of immune responses, off-target effects (in which either the wrong genes or the wrong cells are modified, or both), and germline transmission (where the modification can be passed onto future children).



**Cell therapies** must define a consistent and robust process for the derivation of the cell product, how consistent and homogenous the therapeutic cell populations need to be to be therapeutically effective, where the cells move within the body, how long they survive, and how functional they will be, along with risks around whether an appropriate/acceptable amount of growth will occur, how likely tumours are to form, how much genetically-modified cells (if relevant) might shed virus, how the immune system responds over the short- and long-term, and the potential for toxicity.(36, 37)

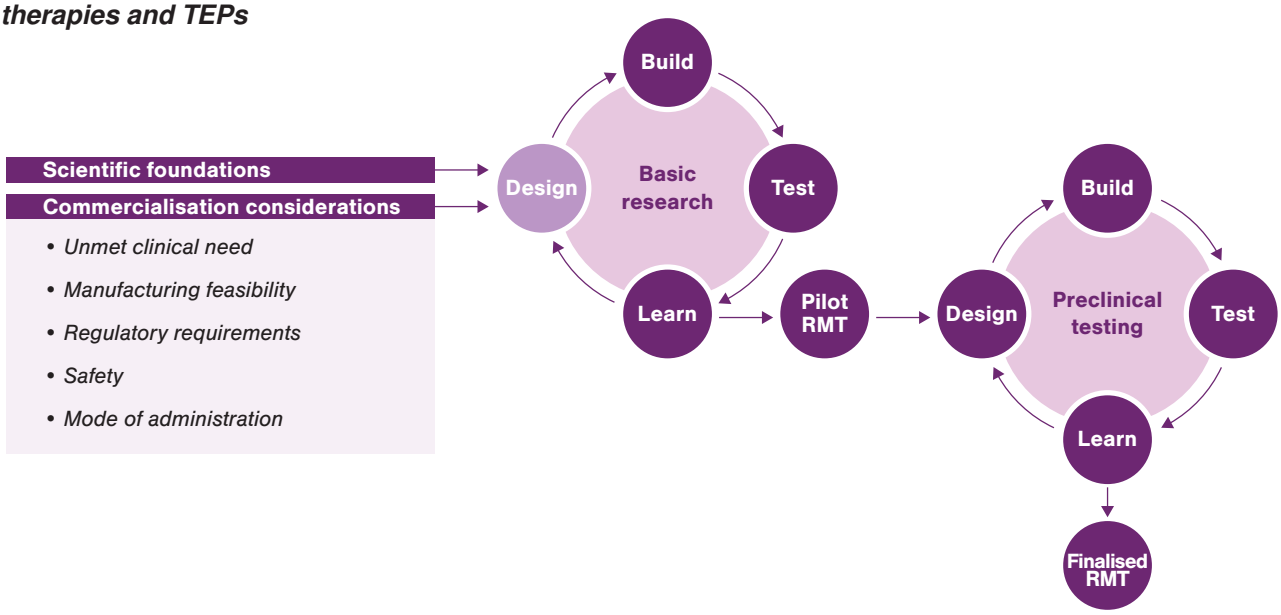


**TEPs** must define how the materials change inside the body (including their physical and chemical properties, and how stable and functional they remain), as well as how the materials will interact with the recipient's body, including toxicity, the infiltration of recipient cells, blood vessels, nerves, and interactions with the immune system such as immune rejection.(38)

The items listed above are general considerations for preclinical studies involving RMTs, although each pilot RMT will have unique characteristics. The complexity of RMTs (including the use of living cells) has prevented the development of standard data requirements for preclinical testing, which results in some ambiguity for developers and regulators.(37)

Research in cell therapy and tissue engineering utilises the design-build-test-learn iterative process common to bioengineering (Figure 15). This should consider not only safety and efficacy, but also key aspects related to commercialisation of the RMT, including confirmation of patient need, delivery system, manufacturing requirements, and regulatory compliance. Identification of a well-defined target pilot therapy at an early stage is essential to prevent endless optimisation, although the process is frequently iterative up until the completion of the preclinical phase.(23) consideration of manufacturing and regulatory processes, even at the early stage. Box 8 explores this issue and the ongoing investments into infrastructure and elsewhere that are required to address this barrier.

***Figure 15: Idealised design-build-test-learn through preclinical and clinical development of cell therapies and TEPs***




Source: Adapted from (23)

Global shortages of viral vectors for the development of gene therapies are a barrier to conducting early stage and preclinical research in Australia. Box 13 explores this, and the investments required to address this barrier.

***Box 13: Availability of GMP-compatible viral vectors***

Custom-made viral vectors are essential to the development of many RMTs. Intensifying global research activity in cell and gene therapies coupled with limited manufacturing facilities has resulted in limited global supplies of lentiviral and AAV vectors. This is a major barrier to translational research. Stakeholders indicated that it may take up to two years and consume over a third of a biotech company's R&D budget to obtain vectors from overseas manufacturers to support clinical trials and commercial supply.

To address this barrier, in late 2019, the NSW Government announced an investment of AU$25M in a viral vector manufacturing facility based at the Westmead Health Precinct. This facility will produce AAV and lentiviral vectors, with the potential to serve local and international gene therapy markets for the translation of research to the clinic, specifically for pilot first-in-human clinical trials. Groups at Westmead Health Precinct are also focusing on the development of new viral vectors. Nationally, there still exists a gap in the large-scale GMP manufacture of AAV for late-stage clinical trials and commercial supply, and for lentivirus manufacture for both clinical trial and commercial scale virus.

Manufacturing of viral vectors is in many ways comparable to that of biologicals, like monoclonal antibodies and other recombinant proteins (e.g. insulin). Cultured cells are genetically modified (using circles of DNA called "plasmids") to act as factories and synthesise the biological product, which is then purified. However, viral vectors involve more complex manufacturing processes than biological drugs, and next generation vectors will introduce additional complexity.(39)

Existing viral vectors are suboptimal in terms of production titre, carrying capacity, and their ability to home to target cells. Improving these qualities would reduce the amount of vector required for each dose or experiment.

On the supply side, viral vector manufacturing processes that may require optimisation include:

- Components (raw materials [i.e. plasmids] are neither easily available or affordable)
- Cell lines (to improve cell growth, viral yield)
- Equipment (to enable scale-up or scale-out)
- Manufacturing processes (i.e. automation or optimisation of methodologies).

Despite the scale of the ongoing investment and the associated increasing expertise, limitations in supply of viral vectors is expected to remain an ongoing barrier to the development of RMTs in Australia, with the supply of plasmids remaining an underlying issue.

## PARTNERING, LICENSING AND SPIN-OUT

Partnering, licencing and spin-out are options for seeking support in the form of finances (see Box 14) and/or capabilities to contribute to the further development of an RMT:

- Partnering involves joining with local or international companies that can contribute to one or more aspects of product development. For example, early-stage RM companies may wish to partner with an experienced CRO to outsource some preclinical experiments or regulatory processes. They may also partner with a multinational biopharmaceutical company, to gain from their experience in commercialisation.

- Licencing out an RMT allows the permitted party (the licensee) to produce the RMT owned by the licensor in a limited capacity. In RM, the licensor may be able to produce, develop, and sell the RMT in certain jurisdictions.

- Spin-out involves the formation of a new independent corporation from either an academic group or a division from an existing company. This allows each group to commit to focusing on their own priorities.

There are various risks and rewards with each of these types of agreement, which must be considered carefully for each case.

***Box 14: Funding and investment for RM R&D in Australia***

Funding for biomedical R&D can come from a variety of sources, including public, private and non-governmental organisations. Early-stage R&D programs are generally funded through various public and philanthropic sources, while private investment generally occurs later, when the technology is more mature. Private investment in the RM sector in Australia has been fairly limited so far.

Public funding sources include grants provided via the NHMRC, the Medical Research Future Fund (MRFF), and the Australian Research Council (ARC), as well as a range of state and territory programs that support medical research. Specific grants for research targeted at the RM sector in recent years include:

- MRFF Stem Cell Therapies Mission - AU$150M over nine years(40)
- ARC Special Research Initiative in Stem Cell Science provided AU$24M over eight years to Stem Cells Australia(41)
- NSW Government Gene & Cell Therapy PhD Program(42) and Early-Mid Career Fellowships (43)
- Victorian Government support for the Australian Regenerative Medicine Institute at Monash University(44)
- Despite the impressive clinical outcomes produced by gene therapies and gene-modified cell therapies to date, Australia lacks a dedicated scheme for gene therapy funding. These investments are important to stimulate the local research sector, but more is required to support research translation and commercialisation.

RM is a capital-intensive area that, although still emerging, achieved record global investment of almost US$20B in 2020 – US$5.6B of which was from venture capital and almost US$10B from initial public offerings and secondary stock offerings.(1) SMEs typically have access to a smaller pool of available funds in Australia than in other regions.

## MODEL SYSTEMS FOR PRECLINICAL TESTING OF RMTS

Preclinical testing of RMTs is conducted using model systems, which may be in vivo (animal models) or in vitro (in a laboratory, without animals). The selection of a model system is a major consideration in preclinical testing of RMTs. The choice of model generally depends on the disease of interest and the testing methods available.(38)

Model systems ideally reflect human physiology as closely as possible. Testing the RMTs within preclinical models provides insights into their effectiveness and safety (including toxicity) without risking the safety of human participants.

While recent progress in the use of in vitro models is promising, the TGA still usually requires data from experiments on at least two animal models (including at least one large animal) to allow progression to clinical studies. However, testing human cells in a non-human animal model also brings challenges.(36, 37)

***Figure 16: Overview of in vitro and in vivo models for preclinical testing***

| | |
|---|---|
|  In vitro model (e.g. organoid systems, TEPs, organ-on-a-chip) | • Avoids the use of animals<br>• Potentially lower cost<br>• Reliable, efficient and can produce robust results, but lack the inherent variability of a physiological system that animal models offer |
|  In vivo model (large animal)<br>  In vivo model (small animal) | • Key considerations include the comparability of the animal model to the patients of interest in terms of genetics, pathology and physiology, as well as the age of the animal and, in the case of transplants, anatomic site, size of the defect/lesion and the scale-up of a 3D therapeutic structure required for treating humans<br>• Large animal models (e.g. sheep or cattle) may be considered superior to smaller models (e.g. rats or mice) for preclinical studies to determine stability over a longer time period |

## ETHICAL CONSIDERATIONS FOR PRECLINICAL TESTING

In Australia, State and Territory governments are responsible for animal welfare, including their use for scientific purposes. The states follow the Australian code for the care and use of animals for scientific purposes, released by the NHMRC. This code is upheld by animal ethics committees that are located at major research institutes.

## REGULATORY COMPLIANCE FOR PRECLINICAL TESTING

Progression of a pilot RMT from the preclinical to clinical research phase in Australia requires TGA review of early-stage and preclinical data. This data is typically assessed under the Clinical Trial Approval (CTA) scheme (see Clinical Research Phase). Global standards for preclinical data are set by the International Committee of Harmonisation (ICH).(45)

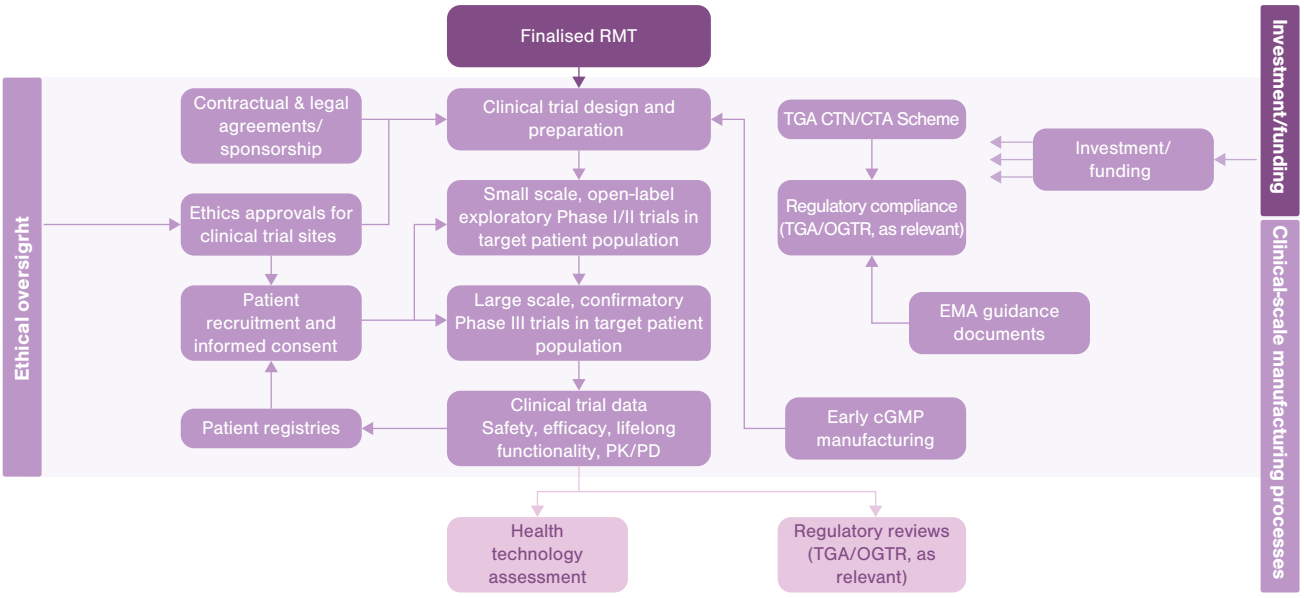
A license from the OGTR may also be required where GMOs are used in preclinical and clinical testing (see Regulation and Reimbursement for further details).(46)

# Clinical Research Phase

*Australia has an active clinical trial sector in RM and attracts studies from both Australian and international sponsors, driven by a well-developed healthcare system, high quality infrastructure, a skilled workforce, robust regulatory frameworks and the R&D Tax Incentive. Global competition is fierce, however, and trial sponsors are attracted to markets with efficient start-up times and favourable market access environments.*

*Prior to broader distribution, RMTs ("investigational products") must progress through Phase I/II and Phase III trials, meeting safety and efficacy endpoints. Trial design for RMTs typically deviates from the conventional three-phase approach and may be single-arm, accommodating lower patient numbers and excluding healthy control groups.*

***Figure 17: Value chain: Clinical research phase***




Note: PK/PD=pharmacokinetics and pharmacodynamics

***Table 3: Stakeholders: Clinical research in RM***

| Stakeholder group | Roles |
|---|---|
| Academic institutions | • Provide clinical and scientific expertise for design and conduct of trials<br>• Research groups or individual researchers can sponsor smaller scale trials |
| Biopharmaceutical industry | • Large pharmaceutical companies act as sponsor for most clinical trials<br>• SMEs sponsor smaller scale clinical trials |
| Industry bodies | • Can help accelerate clinical trials by providing expertise, education and funding opportunities<br>• Foster collaboration between stakeholders across the RMT lifecycle |
| Healthcare services | • Provide the sites for the bulk of clinical trials and all that that entails<br>• Sponsor investigator-initiated clinical trials |
| Healthcare professionals | • Conduct the trials, deliver therapeutics and monitor patients<br>• Can also sponsor smaller scale trials (particularly for TEPs) |
| Commercial manufacturers | • Provide GMP-compliant manufacturing capacity, facilitate scale-up/scale-out process development including quality assurance and quality control to produce robust RMT product that meets regulatory standards |
| Australian Government | • Offers R&D Tax Incentive<br>• Provides other non-dilutive funding for conduct of clinical trials |
| State & Territory Governments | • Provide funding for conduct of clinical trials<br>• Enhance recruitment and awareness of clinical trials<br>• In charge of ethical review through ethics committees [for selected states via the National Mutual Acceptance (NMA) scheme] |
| Capital investors | • Capital investors provide funding of clinical trials (particularly Phase 1 and 2 trials)<br>• Philanthropic investors and NGO can also provide funding for small scale trials |
| Services and Suppliers | • Consultancies assist with clinical trial feasibility assessment and project management, provide regulatory advice and support engagement with Key Opinion Leaders (KOLs) and regulators/payers<br>• CROs support design and conduct of clinical trials with patient recruitment and site selection, clinical operations and project management, data management, and clinical and regulatory consulting<br>• Cell and Tissue banks and CDMOs can assist in scale-up/out process development of GMP-compliant RMTs for small and large-scale clinical trials |
| Patients and patient representatives | • Participate in and can contribute to design and conduct of clinical trials<br>• Raise awareness of clinical trials within the community |
| Regulators | • TGA approves and regulates the use of RMTs in trials under the *Therapeutic Goods Act, Regulations and Orders*, ensuring safety is monitored<br>• TGA provides guidelines on technical requirements for clinical trials for RMTs<br>• The Office of Gene Technology Regulator (OGTR) gives licences for the use of therapies involving genetic modification in clinical trials |

## CLINICAL TRIAL DESIGN AND PREPARATION

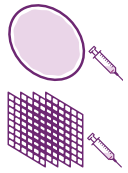
Before a clinical trial can commence, the sponsor must design the study, obtain funding, and achieve ethics and governance approvals as well as regulatory compliance. Feasibility assessment should be conducted prior to commencing the trial, considering these factors as well as potential logistical and manufacturing considerations, which are particular to RMTs.

Clinical trial design for RMTs differs from small-molecule therapeutics (Figure 18). Studies are typically conducted as two main phases (Phase I/II), followed by a confirmatory Phase 3 study. The first two phases are truncated, as it is typically not feasible to conduct trials with healthy participants, due to the heightened risk associated with some RMTs.

Single arm trials may be justified for RMTs where it is not feasible or ethical to include a comparator group that is randomised to receive a placebo. This is more common in oncology, where patients may have limited life expectancy, and CAR-T therapy trials have been conducted as single arm.(47) Evidence from single arm trials is subject to greater uncertainty than for randomised controlled trials. Nevertheless, recent approvals including CAR-T therapies indicate that such evidence may be accepted by local and international regulators. Strong knowledge of the natural history of the condition (what is likely to happen to patients left untreated) is important to understanding the clinical benefit of the RMT.(48,49)

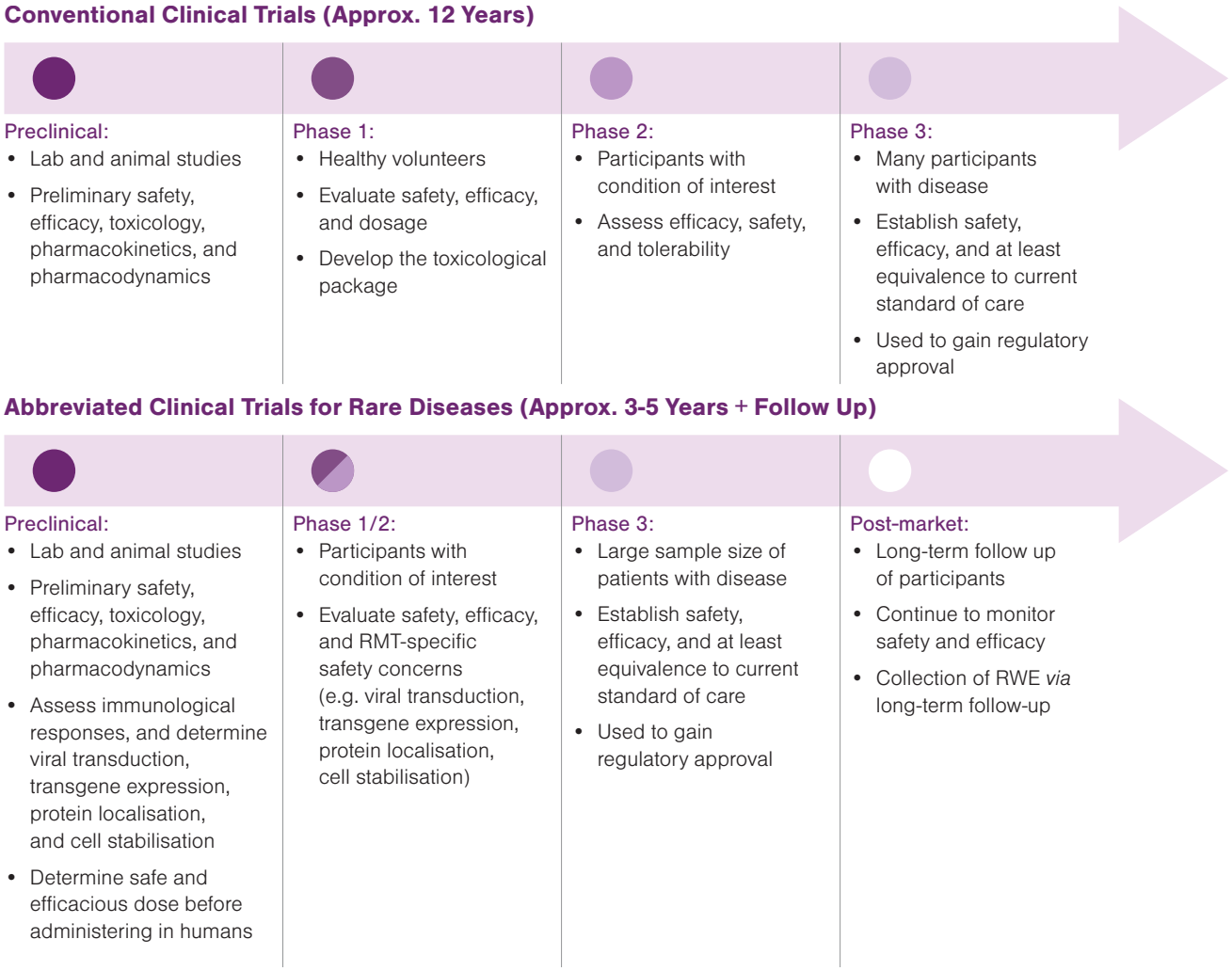
Specific benefit-risk considerations must be taken into account in the design of clinical trials for RMTs:


**Gene therapies** may result in uncontrolled expression of a delivered gene, interfering with normal function. Integrative gene therapies (which enable long-term expression of the integrated genes) could lead to tumour formation via activation or inactivation of neighbouring genes. Viral particles may also be shed and transmitted to others in the short term.



**Cell therapies and TEPs** carrying living cells are dynamic in nature. Once introduced to the patient, cells may differentiate into undesired cell types, or develop undesired autonomous functions. Cells may also be distributed outside of the desired location and to a variety of tissues in the body, with unintended effects.(37)

***Figure 18: Comparison of trials for conventional small molecule and gene therapy for rare disease***




## *Investment and funding*

Encouraging investment in the Australian clinical trials sector is a key objective for government policy. The R&D Tax Incentive promotes the conduct of trials in Australia. Coupled with initiatives such as a streamlined regulatory environment (see Regulatory Compliance, below) this contributed to generating AU$1.4B in international investment in clinical trials in Australia in 2019.

The cost of developing and manufacturing RMTs leads to high upfront sponsor costs, especially when conducting large-scale clinical trials. Limited access to private financing in Australia is a challenge for local companies looking to establish clinical trials. This is further described in Preclinical Research Phase (Box 14). Collaborations with treatment centres provide opportunities for access to funding, infrastructure and workforce to support Australian clinical trials (Box 15).

***Box 15: Collaborations to support clinical trials***

Prescient Therapeutics Ltd and Peter MacCallum Cancer Centre signed an agreement in 2021 to advance a new research CAR-T program, utilising the OmniCAR platform. OmniCAR is a platform that may be deployed across other developers of CAR-T and oncology therapies. It aims to give clinicians greater control and flexibility, leading to better patient safety and efficacy, improving the performance of CAR-T against acute myeloid leukaemia, HER2-positive solid tumours and glioblastoma multiforme.

The agreement gives Prescient access to the expertise and facilities at the Peter MacCallum Cancer Centre, as well as two dedicated post-doctoral research scientists and two research assistants. Prescient will own any IP generated through the program. This builds upon an existing partnership between the two parties, focusing on the Cell Therapy Enhancement program, which seeks to improve current generation CAR-T approaches.

This example highlights the ongoing benefits to Australian research and development gained through investments in infrastructure and workforce across the value chain. Centres of Excellence such as the Peter MacCallum Cancer Centre benefit not only the patients who are treated there, but also the sector as a whole and potential future patients through the improvement of RM technologies.(50)

### *Participant selection*

Participants are typically selected for Phase I/II trials based on a wide range of inclusion and exclusion criteria. Beyond diagnosis with the target disease, considerations include age, sex, other diseases the patient may have, and other treatments they may be receiving. The patient's suitability as a donor must be also considered for autologous RMTs.

The risk-benefit ratio of participant selection in RMT trials can be complex and must be considered on a case-by-case basis. Inclusion of participants with severe disease may lead to uncertainty in the data generated in the trial, as a result of complex or variable underlying symptoms. On the other hand, due to the mechanism of action of some RMTs, some trials will be restricted to participants in the early stages of their disease. Participant selection is particularly important, given that early phase clinical studies are not typically conducted on healthy individuals.(37)

### *Site selection*

In RM (more than with conventional therapeutic approaches) site selection for clinical trials has important implications – including considerations for dealing with GMOs, related to the OGTR and clinical Institutional Biosafety Committees (IBCs). Each RMT has specific requirements related to manufacturing, logistics, staff training requirements and route of administration. Some RMTs involve an invasive procedure and extended inpatient stay, and there may be safety considerations that require access to on-site intensive care facilities to manage potential adverse events. The sponsors will do a capability assessment of each site accounting for specific key infrastructure.

Sites that are initially equipped by sponsors to conduct trials will have access to the required facilities, and develop knowhow in the complex delivery of the RMT, making them likely candidates for future therapeutic delivery. Despite this advantage, it is important to note the additional considerations and challenges associated with transition to clinical practice (see Patient Delivery).

### *Regulatory compliance*

Compliance with regulatory requirements for market authorisation (see Regulation and Reimbursement) is essential during the design and conduct of clinical trials. The following interactions are required with regulators at the clinical trial phase:

- Notification of a clinical trial involving an unapproved therapeutic good to the TGA, via the clinical trial notification/assessment (CTN/CTA) scheme (see Box 16).
- Approval from the OGTR to conduct trials involving the introduction of a genetically modified organism (GMO) to a human (under the Gene Technology Regulations 2001), where relevant to gene therapies

***Box 16: TGA Clinical Trials Notification (CTN) and Approval (CTA) schemes***

Prior to ethical approval by a HREC, the TGA monitors proposed clinical trials in Australia through the CTN /CTA schemes. The choice of which scheme to follow lies firstly with the sponsor, but can be determined by the HREC if necessary.

The CTN scheme is rapid and aims to reduce the burden on the sponsor and the TGA. It simply involves notifying the TGA of the intention to start a trial before the standard HREC review. The CTN does not involve any additional regulatory review and can take as little as one month However, many RMT studies may not qualify for a CTN, such as "first in man" trials and trials including new technology, new material, or a new treatment concept – this includes studies of unapproved Class 4 Biologicals, such as genetically-modified cell therapies.

Studies that do not qualify for a CTN must follow the more rigorous CTA scheme (formerly known as CTX). In the CTA pathway, the sponsor must provide the TGA with a detailed dossier of summary information about the product, which may include chemistry and manufacturing data along with preclinical and early clinical data. The HREC is still responsible for assessing the scientific and ethical issues of the proposed clinical trial following CTA review.

A key benefit of the CTA/CTN system is that trials already established in comparable jurisdictions (e.g. the US or Europe) can be rapidly extended to Australia through the CTN scheme. This can greatly accelerate the local commencement of RM trials.

***Figure 19: Comparison of CTN and CTA schemes***

| | Clinical Trial Notification (CTN) | Clinical Trial Approval (CTA) |
|---|---|---|
| Process | No TGA review of data | TGA review of relevant scientific data |
| Applicable to | Majority of trials except for high-risk therapies | High-risk, novel treatments, and all Class 4 Biologicals (except those that have previous clinical evidence, or that have approval for a clinical trial from another international regulatory body with comparable requirements) |
| Opportunities | Fast route to clinic | Involves GMP certification of manufacturing, which is often required in Asian jurisdictions |

Source: (46).

Note: CTA requirements are still under review.

## *Ethics and governance*

Ethics and governance approvals of all proposed clinical trials are required prior to commencement. Recent efforts have been made towards national harmonisation of ethics and governance requirements for multisite clinical trials, although challenges remain (see Box 17).

- HRECs act according to the National Statement on Ethical Conduct in Human Research. HREC applications require a range of documentation, including the Human Research Ethics Application (HREA) form, completed CTN/CTA, Patient Information and Consent Form(s)[9], any patient-facing documentation (e.g. diaries for data collection or advertisements for recruitment), investigator's brochure(s)[10] and proof of insurance.
- Governance approvals are required at each site and are coordinated between the sponsor of the trial and the site. Governance documents describe how the trial is conducted at each site and which resources will be required. This includes compliance with legislation, legal matters, financial management, policies and procedures for responsible research conduct, and reporting requirements. (51)

Trials must also be registered on clinicaltrials.gov or with ANZCTR prior to the registration of the first patient.

***Box 17: Harmonisation of clinical trial ethics and governance***

Coordination of the HREA process by the National Mutual Acceptance (NMA) agreement allows trials conducted at up to ten sites around Australia to be approved by any single ethics committee. RM clinical research in Australia would benefit from further harmonisation of clinical trial ethics and governance processes:

- Some state-specific requirements remain in excess of the NMA, for example first-in-human studies involving a site in NSW can only be approved by a limited selection of HRECs
- Lack of a National Clinical Trials Governance Framework means that governance processes (including budgets) must be negotiated with individual sites
- Ethics and governance processes are all conducted on online platforms, which differ by state and can be complex to navigate.

This lack of harmonisation adds to administrative burden and can delay the timing of study start-up, which is crucial for maintaining Australia's competitiveness as a destination for clinical trials.

Source: (52, 53)

[9] These must be written at the reading level of a 12-year-old and describe the background of the trial, what is involved in participating, the risks of participating, the way the trial data is handled, the right of refusal and the ability to withdraw at any time.

[10] These contain all preclinical, manufacturing, and clinical information about the "investigational product(s)".

Conducting an RMT clinical trial involves unique features related to recruitment and consent of participants, administration and dosage of the investigational therapy, and participant follow-up.

### *Participant recruitment*

Recruitment of participants into clinical trials involving RMTs can be challenging due to restrictions on selection, which further limit patient numbers already restricted by disease rarity. Identification and recruitment can be facilitated by properly designed and executed patient registries (see Box 26, Patient Delivery), active patient support groups, and active referral pathways from clinics that identify patients for trial sites. Patients with genetic diseases can be identified early through large scale screening of newborn babies for genetic conditions (see Box 18), like the screening program for Spinal Muscle Atrophy that is ongoing in NSW and the ACT.(54)

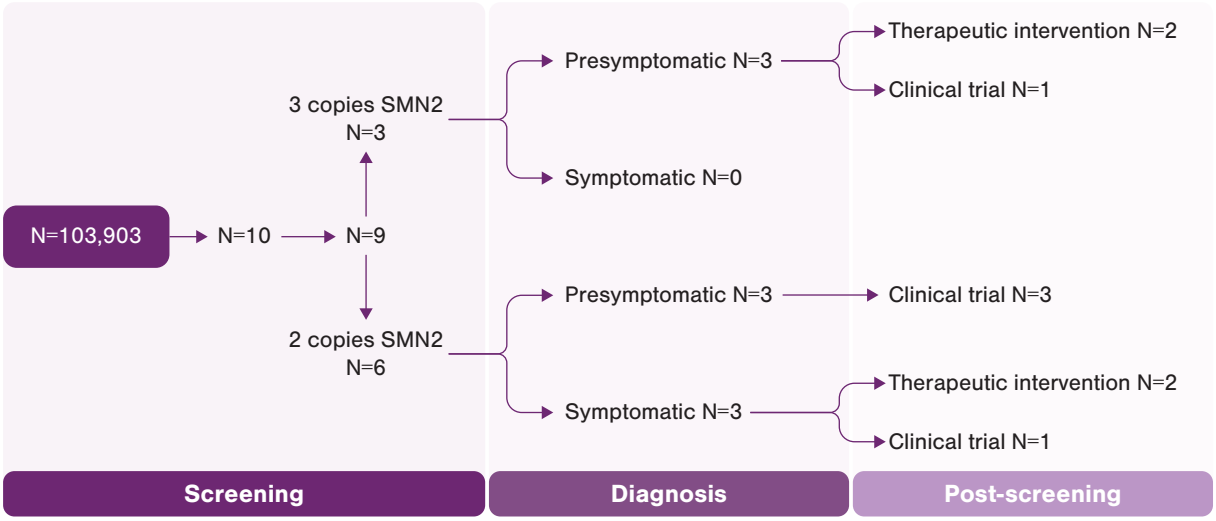
It should be acknowledged at this point that for-profit RMT clinics providing inadequately tested therapies in Australia and overseas have been found using self-described "educational seminars" and other approaches to recruit patients into their clinics. Policy engagement and public education is key to prevent this unethical practice and Stem Cells Australia, and particularly Prof Megan Munsie has been proponents of greater regulatory oversight in this space.

***Box 18: Newborn screening for spinal muscular atrophy in NSW***

Newborn screening for genetic conditions can enable early treatment intervention and assist in recruiting participants to gene therapy clinical trials. The Australian Government's Newborn Bloodspot Screening Program tests for around 25 genetic conditions, including phenylketonuria, hypothyroidism, cystic fibrosis and galactosaemia.(55) A pilot program to expand testing to include spinal muscular atrophy (SMA) in NSW and the ACT began in 2018, in response to the availability of new therapies and a gene therapy trial.

Over the first year of the program, 103,903 newborns were screened, with nine receiving a confirmed diagnosis of SMA (Figure 20). Care plans were implemented within 37 days from birth, enabling potentially life-saving interventions to be given as early as possible.(56)

***Figure 20: Screening, diagnosis and treatment pathways for newborns screening positive for SMA***




Source: (56).

Note: Number of functional copies of the SMN2 gene is associated with severity of muscle weakness in individuals with spinal muscular atrophy.

### *Informed consent to participate in RM clinical trials*

All participants of clinical trials in Australia must give their informed consent, using the Patient Information and Consent Forms provided as part of the HREA. Obtaining informed consent for RMT clinical trials includes unique challenges that are not well understood among the general population.

Key considerations include difficulty in explaining the complex (and potentially permanent) nature of the therapeutic approach and the associated risks and benefits of participating in the trial. Early-stage trials, where technologies have limited experience, may pose additional risks.(57)

These challenges are amplified in trials of paediatric patients, who may have reduced capacity to understand what the research entails, may be more vulnerable to coercion, and may have conflicting values and interests with their parents who provide consent for their participation.(57)

### *Dosage and administration*

Establishing appropriate dosage and administration are challenges for early clinical phase studies of RMTs[11]. Dose exploration and identification of a maximum tolerated dose is typically a consideration of Phase I and II studies. For some RMT trials, dose exploration is limited due to concerns over potential toxicity or because there are practical limits on the amount of RMT that can be produced or administered. Where this is the case, trials may focus on feasible (rather than maximum) tolerated doses.(37)

Failure to define optimal dosage may result in inconsistent findings between doses and clinical benefit across preclinical and clinical studies of RMTs. Other reasons for inconsistent results may include variation in dose concentration and route of administration. Repeated studies may be required to establish consistent results in early phase clinical studies, before moving on to pivotal (later stage) trials. (58)

### *Follow up*

Long-term follow up and collection of real-world evidence from clinical trial participants is particularly important for RMTs to establish safety and efficacy. RMTs are typically given as a single dose and may aim to demonstrate long-term (even curative) clinical effects. Long-term follow up is required for these claims to be verified.

Potential risks related to the manufacturing, handling, administration, and clinical follow-up associated with RMTs include:

- Disease transmission
- Tumour formation (due to off-target or unintended on-target mutations)
- Persistent infection with viral vectors
- Graft vs. host disease when donor cells are implanted in a patient
- Immunogenicity reactions (provoking an immune response to the RMT)
- Environmental risks (to clinicians or family members) due to viral shedding.(59)

The TGA has adopted the EMA guidance for follow up of patients treated with RMTs. Both the EMA (60, 61) and FDA (59) have issued specific guidance documents for the follow up of trials of gene therapies and genetically-modified cell therapies that take these concerns into account.

[11] Dosing is less relevant for some TEPs, especially if their primary function is mechanical. In many cases the size of the TEP is determined by the size of the area requiring treatment.

# Regulation and Reimbursement

*Australian regulatory and reimbursement agencies play key roles in ensuring the safety of therapeutic goods marketed in Australia and the sustainability of healthcare budgets. The rate of advance of RM requires agile approaches from regulators, health technology assessment (HTA) agencies and governments. Similar challenges are faced globally and international collaboration between regulatory agencies has been instrumental in RMT approvals in Australia to date.*

*The structure of Australia's healthcare system presents additional hurdles to reimbursement, with new pathways to consider joint funding from the Australian and State/Territory Governments.*

*A fit-for-purpose regulatory and reimbursement environment for RMTs will help to ensure that Australia remains a priority launch country for international companies sponsoring RMTs. This, in turn, will support the development of infrastructure and workforce expertise in RMT implementation and delivery, with flow-on benefits to RM research and development.*

***Figure 21: Value chain: Regulation and reimbursement***

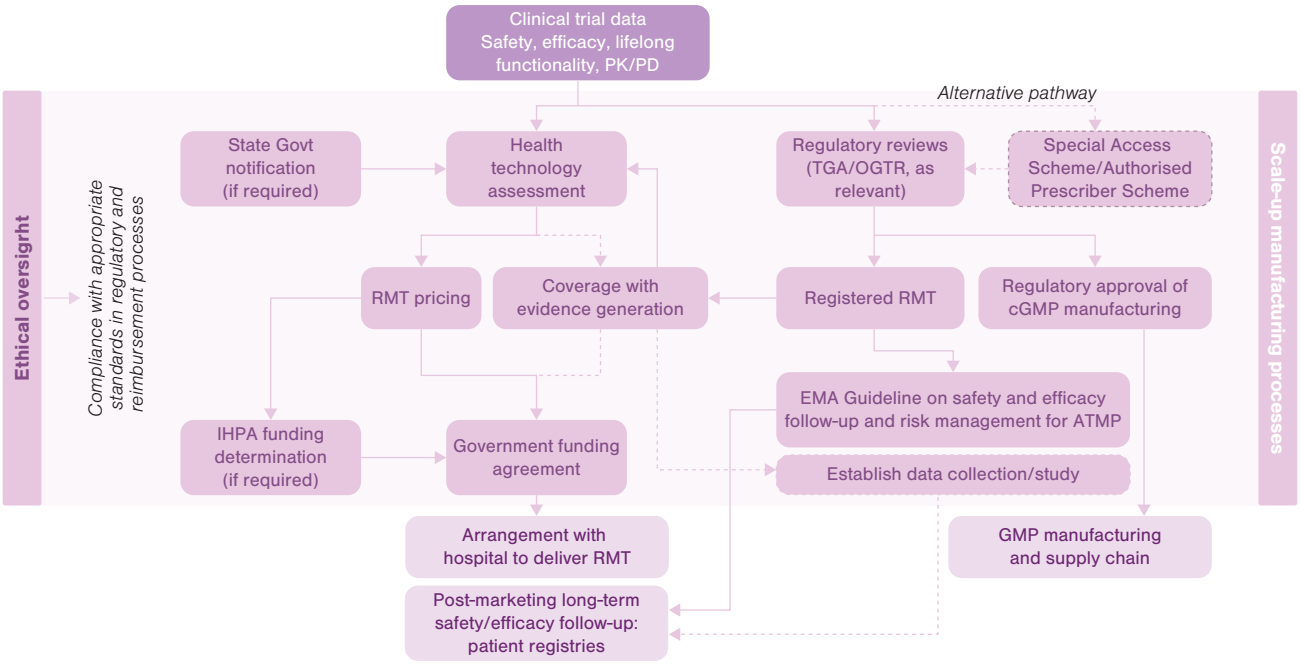


*Table 4: Stakeholders: Regulation and reimbursement*

| Stakeholder group | Roles |
|---|---|
| Patients and patient representatives | • Provide a voice for the patient experience in consideration of the reimbursement for RMTs |
| Healthcare professionals and peak bodies | • Provide clinical expertise to regulatory and reimbursement decision makers on the place of RMTs in therapy and potential patient benefits |
| Biopharmaceutical industry | • Sponsor regulatory and reimbursement submissions for RMTs |
| Industry bodies | • Advocate on behalf of industry for efficient and effective regulatory and reimbursement processes |
| Australian Government | • Endorse guidelines for regulatory and reimbursement processes<br>• Negotiate funding agreements with sponsors to supply RMTs in Australia |
| State/Territory Governments | • Fund RMTs via NHRA arrangements, service planning and healthcare system preparedness for implementation of RMTs |
| Regulators | • TGA issues regulatory guidance and approves marketing authorisation of RMTs (may grant exceptional approvals under the Special Access Scheme)<br>• OGTR oversees the accreditation of organisations to work with GMOs and issues licenses for GMOs |
| HTA agencies | • PBAC and MSAC conduct HTA reviews for RMTs |
| Healthcare services | • Advise regulatory and reimbursement processes on RMT implementation |
| Commercial manufacturers | • Ensure that ISO TGA-GMP certification requirements and other relevant standards are met<br>• May provide advice to regulatory and reimbursement processes for RMTs related to implementation |
| Services and suppliers | • CROs and consultants support submissions to regulators and HTA agencies |

To gain marketing authorisation in Australia, all RMTs must be approved from the TGA and be listed on the Australian Register of Therapeutic Goods (ARTG). RMTs involving GMOs[12] may also require an approval or license from the OGTR. Table 5 provides an overview of regulatory pathways for RMTs and is followed by some examples to illustrate the TGA classifications for Biologicals (Figure 22). Boxes 19 and 20 respectively outline regulatory challenges faced by RMTs, and moves towards global harmonisation of regulatory approaches.

***Table 5: Regulatory Pathways for RMTs in Australia***

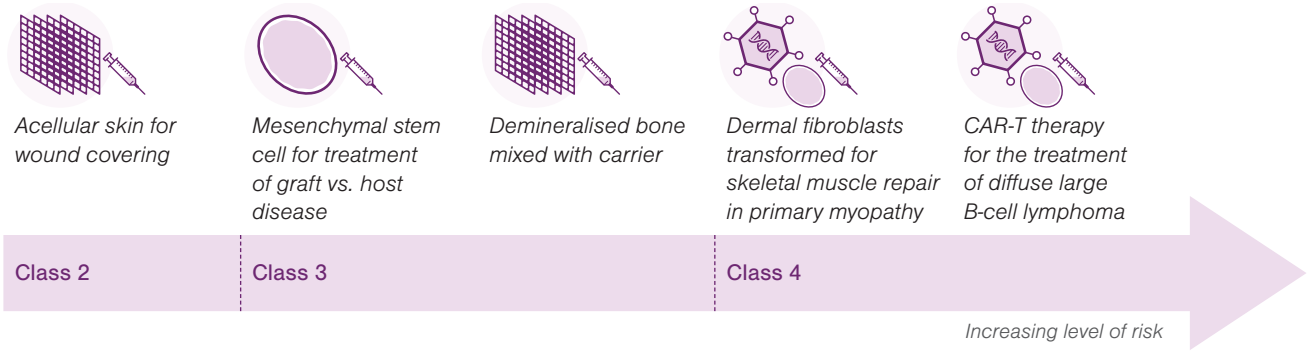
| Type of therapy | OGTR approval[1] | TGA classification[3] |
|---|---|---|
| Gene therapy | NLRD/DNIR/DIR[2] | Prescription medicine |
| Cell therapy and TEP: cells/tissues with substantial manipulation altering immunological, physiological and biochemical properties (e.g. iPSC, CAR-T) | NLRD/DNIR/DIR/ Exempt[2] | Class 4 Biological |
| Cell therapy and TEP: cells/tissues with substantial processing, affecting structure but not intrinsic activity of cellular component | Exempt | Class 3 Biological |
| Cell therapy and TEP: cells/tissues with minimal processing (no change in structure or intrinsic activity of cellular component) | Exempt | Class 2 Biological |

Source: (62, 63).

Notes:
[1] TGA requires approval from the OGTR for medicines that: contain or consist of GMOs; or are manufactured in Australia and subject to regulation by the OGTR.
[2] OGTR licences for gene therapies are issued as, in increasing levels of assessed risk: Notifiable Low Risk Dealings (NLRD), which must be assessed by an Institutional Biosafety Committee (IBC); Dealings Not Involving an Intentional Release (DNIR), where the viral vector is contained within the human host without shedding; or Dealings Involving an Intentional Release (DIR), which take place outside of containment facilities. DNIR and DIR required licenses. Approvals and licences granted by the OGTR are publicly disclosed via the OGTR GMO Record.
[3] Prescription Medicines are regulated under the Australian Regulatory Guidelines for Prescription Medicines, and Biologicals are regulated under the Australian Regulatory Guidelines for Biologicals.

[12] GMOs are defined in the Gene Technology Act 2000 as: (i) an organism that has been modified by gene technology; or (ii) an organism that has inherited traits from an organism, where the traits occurred in the initial organism because of gene technology. GMOs may be exempt from OGTR review if there is no intentional release to the environment.

***Figure 22: Classification of RMTs that are regulated as Biologicals by the TGA***



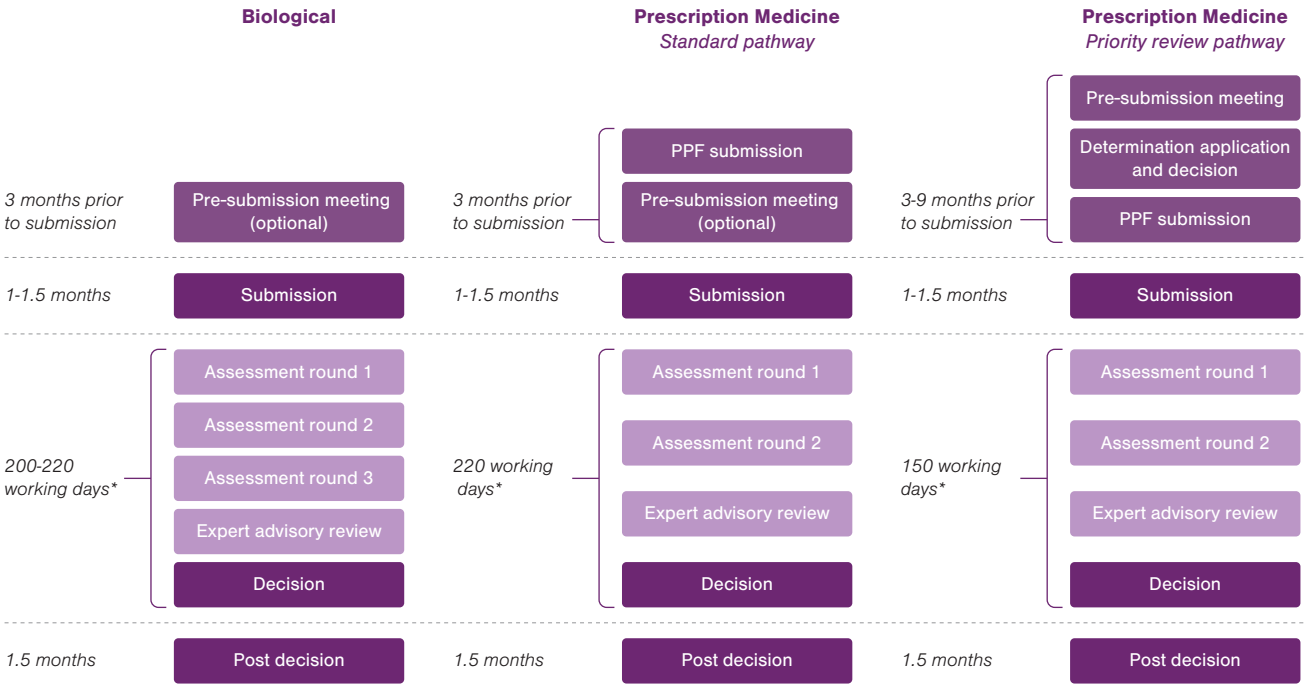

Source: (64)

Gene therapies may be eligible for fast track TGA processes and fee waivers, which are available to Prescription Medicines, but not to Biologicals (including cell therapies and TEPs):

- Priority Review, which shortens review time by approximately 70 working days (see Figure 23)
- Provisional approval, which makes the medicine available while the sponsor completes clinical trials (bringing forward marketing by around two years)
- Orphan designation, which allows some regulatory and reimbursement application fees to be waived, including for the first application to the PBAC.

Applications for provisional approval and orphan designation must be made and accepted prior to submission of the pre-submission planning form. Regulatory approaches to gene editing around outlined in Box 21.

***Figure 23: Comparison of TGA pathways for Biologicals and Prescription Medicines***




**These represent target timeframes. There are also legislated timeframes, which are 255 days for all pathways. PPF=pre-submission planning form.*

***Box 19: Regulatory challenges for RMTs***

There are several key features of developing and manufacturing RMTs, which propose new and unique regulatory challenges in ensuring safety and efficacy for these products in comparison to traditional therapeutics:

- Manufacturing uses living cells and tissues as the base products. This poses challenges as cells are inherently variable, their manufacturing processes are complex, and products require extensive quality assurance and quality control testing to ensure clinical consistency.
- Personalised therapies, which may not require scale-up of manufacturing, or where automation and large-scale manufacturing is challenging.
- Reliance of many products on cell metabolic function, which may be sensitive and vary from 'normal' after being given to the patient, and affect the outcome of treatment.
- Lack of product quality assurance and quality control standards, such as cell viability, cell function, and cell characterisation, which may be used as indicators for regulatory bodies to assess to ensure product efficacy.
- Potential for communicable disease transmission through allogeneic cell use, or if cells are stored and/or processed in a facility that handles cells from multiple donors.
- Products are unable to be sterilised due to the live cell and tissue components, which creates potential safety concerns in using these products.(65)

Due to these regulatory challenges, additional Good Manufacturing Practices have been put in place to ensure a high level of quality when manufacturing RMTs for commercial use. In 2013, the TGA introduced the Australian Code of Good Manufacturing Practice for human blood and blood components, human tissues and human cellular products. These guidelines detail principles specific to RMTs around collection and processing, and quality control, aiming to address some of the challenges associated with these products.

***Box 20: Harmonisation of regulatory requirements with international regulators***

Alignment between the TGA and international regulators on basic regulatory guidelines, terminologies, and frameworks for RMTs aims to reduce duplication of effort and shorten timelines to market authorisation. Initiatives to share best practices and support harmonisation that the TGA is currently engaged with include:

- Gene Therapy Working Group and Cell Therapy Working Group, established via the International Pharmaceutical Regulators Programme (IPRP) – participating agencies include the FDA, EMA, Health Canada, MLWH/PDMA (Japan) and HSA (Singapore)(66)
- Access Consortium – with Health Canada, HSA (Singapore), Swissmedic and MHRA (UK)(67)
- Project Orbis, focused on oncology, with the FDA, Health Canada, EMA, PDMA (Japan) and Swissmedic.(68)
- The Pharmaceutical Inspection Co-operation Scheme (PIC/S), which aims at harmonising inspection procedures worldwide in the field of GMP.(69)

TGA guidelines for RMTs are closely aligned to EMA guidelines. This enables, for example, more efficient post-marketing surveillance, as EU risk management plans (RMP) that are under consideration by the EMA, or a global RMP aligned to the EU RMP are accepted by the TGA.(70) A number of specific EU guidelines relating to RMTs have been adopted by the TGA:

- Guideline on potency testing of cell-based immunotherapy medicinal products for the treatment of cancer (EMA/CHMP/BWP/27145/2006)
- Reflection paper on clinical aspects related to tissue engineered products (EMA/CAT/573420/2009)
- Guideline on Human Cell-Based Medicinal Products (EMEA/CHMP/410869/2006
- Guideline on the Non-Clinical Studies required before First Clinical Use of Gene Therapy Medicinal Products (EMEA/CHMP/GTWP/125459/2006)
- Guideline on Non-Clinical Testing for Inadvertent Germline Transmission of Gene Transfer Vectors (EMEA/273974/2005)
- Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99)

Harmonisation of approaches may make achieving marketing authorisation in Australia streamlined with other major global markets, in addition to managing the burden of undertaking regulatory reviews for the TGA.

***Box 21: Regulatory approaches to genome editing***

A number of regulatory bodies have release guidelines covering some aspects of genome editing, and clinical trials for genome-edited products are underway in Australia. Despite this, the TGA guidance in relation to genome editing, (which refers to the EU guidance) is currently less complete than for other types of gene therapies. The EMA has approved a number of products that alter genetic material within the human body as Gene Therapy Medicinal Products (GTMP); however, some products may not fall within this definition.

A GTMP is defined as containing, or consisting of, 'recombinant nucleic acid'. Nucleic acids within CRISPR and other similar genome editing methods may not always be produced by recombination, and protein-based molecules such as ZFNs or TALENs could be out of scope altogether if they do not include any nucleic acid.

If genome editing therapies fall outside the definition of a GTMP, they would be reviewed outside of the specialised scrutiny of the EMA's Advanced Therapeutic Medicinal Products (ATMP) regulation that covers cell and gene therapies. The US National Academy of Sciences has recommended the use of existing gene therapy review mechanisms for somatic gene editing; however, it is not clear whether the EMA and TGA will adopt this approach.(71)

### *Special Access Scheme*

The TGA Special Access Scheme permits the importation or supply of an unapproved product for a single medical procedure or for personal importation.(72) Access to RMTs through the Special Access Scheme is limited by the need to manage complex supply chains and logistics.

Arrangements may also need to be in place to cover the hospital or healthcare service costs incurred to deliver a therapy. These factors require special consideration in the establishment of Special Access Schemes for RMTs.

## REIMBURSEMENT OF RMTS

Reimbursement pathways have been applied to RMTs in Australia to date, although only a handful have been approved. With a strong pipeline and many more RMTs on the horizon, questions and uncertainties remain in relation to reimbursement.

There are two main health technology assessment (HTA) pathways in Australia:

- Pharmaceutical Benefit Advisory Committee (PBAC), which reviews products for listing on the Pharmaceutical Benefits Scheme (PBS) [13]
- Medical Services Advisory Committee (MSAC), which reviews products for a range of alternative public funding programs and initiatives.

The HTA and funding pathway for RMTs classified as Highly Specialised Therapies (HST; notably, with average annual treatment cost per patient above AU$200,000[14]) is set out in the NHRA (Box 22). The majority of gene and genetically-modified cell therapies (such as CAR-T therapies) would be defined as HSTs, which may also include other cell therapies and TEPs, although none have been reviewed under these arrangements to date.

While the NHRA has formalised this process, there are only a few precedents to date and there remains some ambiguity among stakeholders regarding which pathway will be selected for RMTs on the horizon. This is likely to increase as new and more complex RMTs are launched in Australia.

[13] The PBS is an Australian Government program.

[14] The NHRA Addendum 2020-25 defines HSTs as "TGA approved medicines and biologicals delivered in public hospitals where the therapy and its conditions of use are recommended by MSAC or PBAC; and the average annual treatment cost at the commencement of funding exceeds $200,000 per patient (including ancillary services) as determined by the MSAC or PBAC with input from the IHPA; and where the therapy is not otherwise funded through a Commonwealth program or the costs of the therapy would be appropriately funded through a component of an existing pricing classification."

***Table 6: Reimbursement pathways for RMTs that have been reviewed in Australia***

| Type of therapy | Reviewed products | HTA pathway | Treatment setting | Funding pathway |
|---|---|---|---|---|
| Gene therapies | Zolgensma®<br><br>Luxturna® | PBAC<br><br>MSAC | Public hospital outpatient<br>Public hospital inpatient | Australian Government<br><br>Australian and State/ Territory Governments |
| Cell therapies (HST)[1] | Kymriah®<br><br>Yescarta® | MSAC<br><br>MSAC | Public hospital inpatient<br>Public hospital in/ outpatient | Australian and State/ Territory Governments<br>Australian and State/ Territory Governments |

Source: PBAC and MSAC Public Summary Documents. HST=Highly Specialised Technology

Note: [1] Cell therapies and TEPs classified as HSTs under the NHRA would follow the MSAC pathway.

***Box 22: National Health Reform Agreement (NHRA) arrangements for funding HSTs***

The NHRA is an agreement between the Australian, State and Territory Governments that sets out principles and funding responsibilities for healthcare services. The HTA pathway for RMTs classified as Highly Specialised Therapies[15] is determined by a joint decision between the Chairs of the PBAC and MSAC and a Health Council (Australian, State and Territory Health Ministers) representative.(73)

Legislation (National Health Act 1953) defines 'drugs and medicinal preparations' eligible for PBS funding and that may be assessed by the PBAC; other RMTs will be assessed by the MSAC. RMTs that are assessed by the MSAC and delivered in a public hospital are funded 50:50 by the Australian and relevant State/Territory Government. Funding contributions from the Australian Government are determined by the Independent Hospital Pricing Authority (IHPA).

While the NHRA provides greater clarity over HTA pathways and the roles of the Australian and State/Territory Governments in funding RMTs, many stakeholders expressed ongoing uncertainty about the MSAC pathway, which represents a departure from the standard PBAC assessment and Australian Government funding of innovative biopharmaceuticals. Further evolution of processes and funding arrangements may be expected over time.

[15] TGA approved medicines and biologicals delivered in public hospitals where the therapy and its conditions of use are recommended by MSAC or PBAC; and the average annual treatment cost at the commencement of funding exceeds $200,000 per patient (including ancillary services).

***Box 23: The value of RMTs and challenges for HTA***

RMTs already in clinical practice and undergoing trials offer hope to save lives and provide the first treatments (potentially even cures) for rare and devastating genetic conditions that have previously been considered untreatable, such as muscular dystrophy. Nevertheless, capturing this value to patients and society within standard HTA methodologies remain challenging.

HTA conducted by PBAC and MSAC relies heavily on assessments of clinical effectiveness, safety and cost effectiveness (value for money), compared with other treatments. Put simply, cost effectiveness is assessed using a metric of cost per patient outcome ($/quality adjusted life year, QALY). Other factors include budget impact, stakeholder views, implementation considerations and equity among all Australians.(74)

Three key considerations arise in applying standard HTA methodologies to RMTs:

- Health outcomes and value – the value of a potentially curative treatment, with lifelong benefits to patients, may be considered differently to treatments with smaller incremental benefits across larger populations
- Uncertainty – RMT clinical trial design (see Clinical Research Phase) and the limited availability of follow-up data when applying for initial reimbursement introduce uncertainty around expected patient outcomes to treatment, including which patients will respond and whether treatment will be truly curative
- Discounting – Costs are more heavily weighted in the cost-effectiveness assessment for RMTs compared with other therapies, as HTA methodologies discount patient benefits (e.g. extended lifespan) in future years, while the costs of RMTs are incurred upfront.(75)

Innovative funding and risk sharing models go some way to addressing these concerns within current PBAC and MSAC processes (Box 24); however, stakeholders considered that these and other methodological issues may create challenges for the introduction of RMTs in Australia. In England, the need for new approaches to HTA for RMTs is a factor driving the 2021 review of National Institute for Health and Care Excellence (NICE) Methods of HTA. Although there are currently no plans in Australia to review HTA guidelines for RMTs, review of the National Medicines Policy document is being considered.(76)

***Box 24: Innovative funding and risk sharing models for RMTs***

Single-dose RMTs represent a new paradigm for clinical treatment and funding models. Costs are incurred upfront when the RMT is delivered to the patient, unlike for other therapies where costs would be split over the course of treatment.(77) This creates a financing challenge which, coupled with long-term clinical uncertainties (see Clinical Research Phase), has led to the generation of innovative funding and risk-sharing models.

Below are two basic models that have been proposed to fund RMTs:

- One-year, milestone-based contract (Figure 24), where the payment is made upfront and the outcome (patient response to therapy) is assessed after one year. If there is no response, the manufacturer pays back a rebate.
- Multi-year performance-based annuity (Figure 25), where there is an upfront payment, and then instalment payments on an annual basis for patients that respond (and continue to respond) to treatment. This may be combined with a rebate for patients with no response after one year, and the number of annual payments may be tailored to the specific RMT and the attitudes and risk preferences of the parties entering into the contract.

***Figure 24: One year, milestone-based contract***

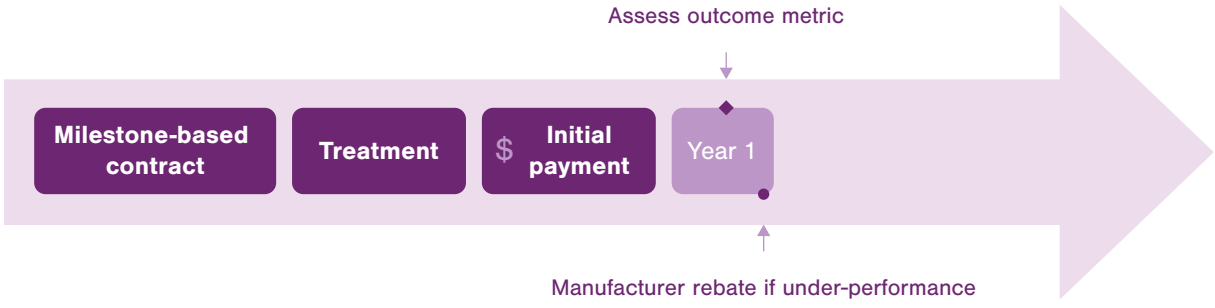
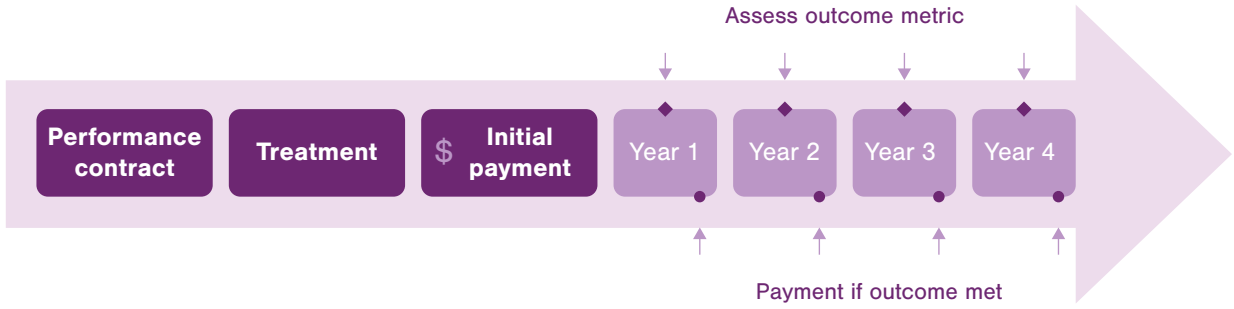


***Figure 25: Multi-year performance-based annuity***




Source: (78)

Administrative burden to manage contracts and the costs and burden on the healthcare system of data collection are important considerations for both parties to the agreement. Early CAR-T therapy approvals in Australia limit annuity payments to one year and require sponsors to fund a post-marketing registry study to report patient outcomes. Approvals are conditional and subject to full review after two years in the market.

Innovative funding models and risk sharing agreements have facilitated the market entry of RMTs in Australia. Approaches to date have been somewhat limited in scope, however, and there may be opportunities for further innovation, provided that government and sponsors can agree on terms.

***Box 25: Co-dependent technologies***

The personalised nature of RMTs will require a combination of diagnostic testing and therapeutics to determine the most appropriate treatment. In the case of a gene therapy, for example, testing for a specific genetic mutation will be required, as will a test for antibodies that may impact on the effectiveness of the viral vector to deliver the therapy. Near-future innovations may also include the use of digital tools (apps) to manage patient follow-up care. Australian HTA processes define these complementary technologies as co-dependent, and consider their combined value.

There are established processes to conduct coordinated reviews for co-dependent technologies that span both the PBAC and MSAC (which assesses diagnostic tests). Stakeholders, however, indicated that the need to follow separate processes is cumbersome and inefficient and limits scope for future innovation.(79)

While co-dependent technologies are not unique to RM, they will be relevant for many RMTs, and will increase in complexity as the RM field advances. Agile approaches from HTA agencies are required to ensure that assessments remain rigorous, but that innovation is not stifled.

# Patient Delivery

*Delivery of RMTs to Australian patients is the central goal of the RM value chain. It is complex and multidisciplinary, and requires the introduction of new referral pathways, models of care, education programs for healthcare professionals and quality management processes.*

*Centres of excellence have already begun to arise to support clinical trials and delivery of RMTs in Australia. The benefits of this centralised expertise and infrastructure must be balanced against equity considerations for patients living outside of major centres and the need to provide support for travel to ensure that all Australians may benefit from the introduction of RM.*

*Investments in skilled workforce and infrastructure to deliver RMTs generate flow-on benefits across the RM value chain in Australia, providing opportunities to mentor early-stage and preclinical researchers and building the expertise of clinical researchers.*

***Figure 26: Value chain: Patient delivery***

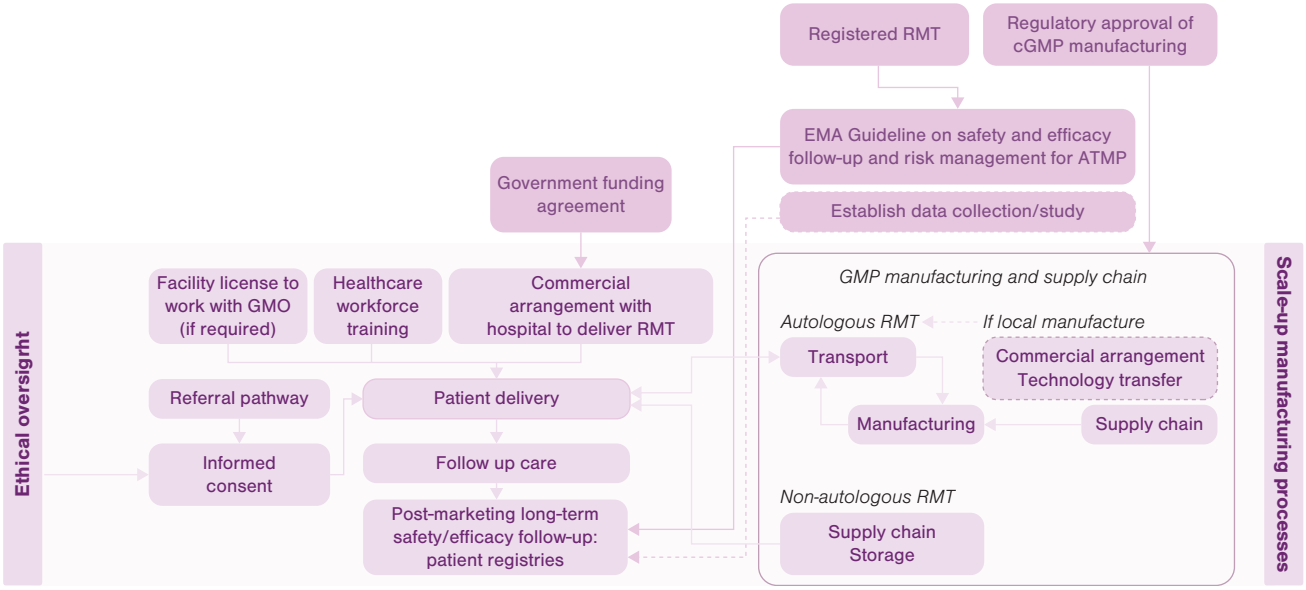


***Table 7: Stakeholders: Patient delivery***

| Stakeholder group | Roles |
|---|---|
| Patients and patient representatives | • End user of RMTs<br>• Advocate for unmet need in disease diagnosis and management and timely access to novel therapies |
| Healthcare professionals | • Handling and administering RMTs, clinical care of patients including diagnosis, referral, treatment, and follow-up |
| Healthcare services | • Service provision to deliver RMTs, including quality management |
| Sponsor | • Undertakes post-marketing surveillance and pharmacovigilance and reports regularly to TGA<br>• Shares responsibility with manufacturers to ensure sufficient supplies of RM products; logistics with shipping/transport and appropriate implementation of systems for continuous long-term follow up in practice<br>• Ensures all healthcare professionals handling and/or administering RM products (e.g. surgeons, nurses, specialists), receive appropriate training regarding their correct use, storage and long-term follow |
| Industry bodies | • Provide appropriate training courses for healthcare professionals<br>• Involved with advocacy and policy work related to RMTs |
| Australian Government | • Provides funding and manages agreement with sponsor |
| State & Territory Governments | • Provide funding for delivery of RMTs<br>• Plan and coordinate service delivery |
| Regulators | • Continuous post-marketing surveillance to assess long-term efficacy and safety of RM products |
| Commercial manufacturers | • Share responsibility with sponsors in delivering RMTs as well as in long-term follow up<br>• Inform the TGA on changes in manufacturing processes |

## *Commercial arrangements*

The involvement of multiple parties in the funding and delivery of RMTs leads to complex contracting arrangements. These parties include the Australian Government, State and Territory Governments (where RMTs are joint-funded), hospital networks and the sponsor. A commercial manufacturer (other than the sponsor) may also be contracted to support manufacture and delivery of autologous RMTs. Variation between states and territories regarding the legal status of hospital networks (Local Health Districts, Hospital and Health Services, etc) adds to the complexity of multi-jurisdictional RMT implementation.

The risk sharing arrangements that are typically introduced for RMTs require active contract management and monitoring. Information must be shared between healthcare service providers, patient registries, the sponsor and government funders. These arrangements are agreed between the parties and create an administrative burden.

## *Healthcare system preparedness*

Efficient implementation of RMTs requires the establishment of new services and processes, which must be coordinated with existing services and the broader healthcare system.(80) Service planning in Australian public hospital networks is conducted by State and Territory Departments of Health, in collaboration with the hospitals and services where RMTs will be delivered.

Site selection draws on existing networks of expertise and infrastructure capabilities, which may have been established through clinical trials and/or prior experience in delivery of RMTs. Implementation requirements are considered in decisions regarding regulatory and reimbursement approvals, and treatment centres must meet requirements set out in the Risk Management Plan, which may include OGTR licencing requirements, and/or accreditation requirements for reimbursement.(81)

Key considerations include:

- *Hospital infrastructure requirements*, potentially leveraging RMT clinical trial sites. Requirements relate to the treatment setting (mode of administration and need for intensive care facilities to manage potential adverse events) and access to facilities to manufacture autologous cell therapies (see Manufacturing and Supply Chain).
- *Cold chain distribution and storage at treatment centres* as appropriate to the RMT. For example, some cell therapies require storage in liquid nitrogen or dry ice, and once they have been thawed their shelf lives can be measured in hours, even under ideal conditions. Dry ice and liquid nitrogen may also be required to support delivery.
- *Existing therapeutic area specialist networks*, which support clinical expertise to manage patient care and established referral pathways for patient access.
- *Building and training a skilled workforce* in RMT delivery. Multidisciplinary staff across the hospital will be required to undergo education and training to support delivery and patient follow-up. Education in RM will be broadly required and will include physicians, nurses, hospital pharmacy and administrative staff. While general training in RM could come from universities and TAFEs, product-specific training programs may need to be provided by the sponsor. Growing experience in the hospital workforce may be expected to reduce training requirements over time, although each new RMT will have unique characteristics.
- *Design and implementation of quality management systems and protocols* within treatment centres. Standards do not exist for many RMTs and must be established in each treatment centre, leaving potential for variation.(82) RM protocols are complex and composed of smaller protocols (for example, a broader delivery protocol may consist of protocols for cell harvesting and cell freezing). Protocols may be required for inpatient, outpatient, and follow up care (as appropriate to the RMT). Substantial time and resources may be required.
- *Treatment centre accreditation,* in line with the requirements of the Risk Management Plan and funding agreement.
- *Facility license to work with GMO*, if the OGTR determines that a license is required for the therapy (see Regulation and Reimbursement).

### *Manufacturing and supply chain*

Supply chains and logistics requirements are particular to the RMT and typically rely on global manufacturing and distribution arrangements. Manufacturing at scale, where feasible, is typically conducted in one or two global facilities. Since RMTs may be highly temperature sensitive, logistical networks are required for tracking and temperature control through customs and quarantine systems. This is particularly challenging in such a large and remote country as Australia. Considering the amount of time required to travel to Australia, additional time spent in customs and quarantine can push the limits of temperature control systems.

Figure 27 illustrates two models of RMT supply chain, hub-and-spoke (centralised) or point-to-point (decentralised). In a centralised model, a manufacturing hub is linked to a group of clinical sites. A decentralised model places manufacturing at multiple sites closer to the site of patient care. Choice of model will be particular to the RMT, considering where patients are located, the potential for scaled manufacturing, and capacity for efficient transport under the required conditions.(83)

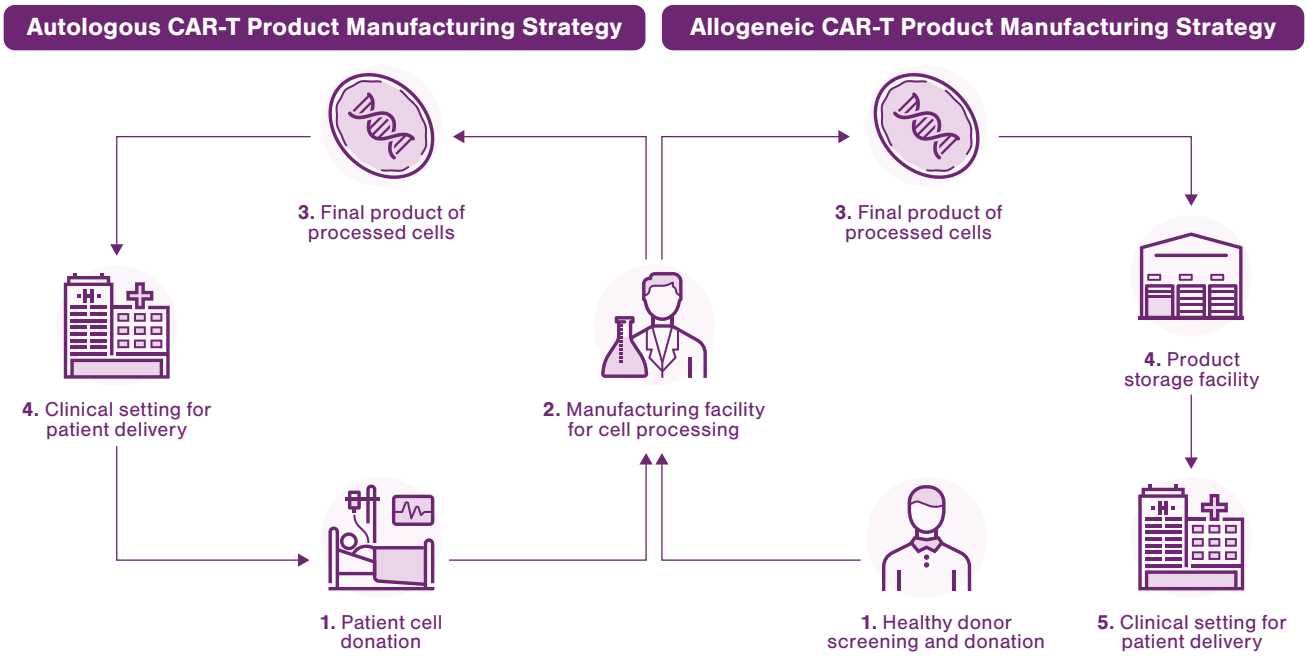
The personalised nature of autologous RMTs (such as autologous CAR-T therapies) is more suited to a decentralised model, as harvested cells must be transported to a GMP facility and modified while the patient is admitted to inpatient care (Figure 28). The proximity of such a facility to the patient may allow faster turnaround times and reduce the costs and risks associated with transportation, but on-site manufacturing is not strictly required.(84)

Australia's GMP-licensed facilities for manufacturing of cell-based products include the Cell Therapies Pty Ltd facility at the Peter MacCallum Cancer Centre in Melbourne, the Cell & Tissue Therapies Western Australia (CTTWA) in Perth, and QIMR Berghofer in Brisbane. Interstate and international transport of cells under appropriate conditions (under a hub-and-spoke model) is also used to support the delivery of autologous RMTs. Hub-and-spoke models offer perhaps the greatest opportunities for investments in advanced manufacturing in Australia.

*Figure 27: Hub-and-spoke vs. point-to-point manufacturing of RMTs*


Source: (83)

*Figure 28: Overview of autologous and allogeneic CAR-T manufacturing*




## *Referral pathways and informed consent*

RM is still an emerging field in Australia. As new therapies are introduced, appropriate patient pathways must be established to facilitate the referral of patients for potential treatment with RMTs, and on to treatment centres. This requires that treating physicians and other healthcare professionals are aware of RMTs as treatment options and to discuss the potential benefits and risks with patients. Patient groups may also provide advice and support to patients on potential treatment options and RMTs on the horizon.

Patients and physicians treating conditions associated with the first waves of RMTs, which focus on rare single-genetic cause conditions and haematological cancers, may have heighted awareness of horizon therapies. As RMTs are introduced for indications across broader and more heterogeneous patient groups, more targeted education may be required.

For the same reasons that clinical trial outcomes are subject to uncertainty (see Clinical Research Phase), there will be challenges identifying the patients that will benefit from treatment with a particular RMT when it is first introduced to clinical practice. The benefits and risks must be clearly explained to and understood by patients in order to provide informed consent to be treated. The complex and permanent nature of changes introduced by some RMTs create particular challenges in obtaining meaningful informed consent.(86, 87)

## *Patient delivery and follow up*

Patient delivery is particular to the RMT and may range from invasive (e.g. surgery or leukapheresis, provided in inpatient setting) to less invasive (e.g. an injection given in outpatient setting). Even within the broad approaches of gene therapies, cell therapies, TEPs and combined RMTs, patient delivery varies substantially and will evolve as the technology advances.

Patient follow-up is required for compliance with regulatory Risk Management Plans and, frequently, to report to receive reimbursement under risk sharing agreements. This is critical to monitor the long-term effects of RMTs and to expand the evidence base that informs clinical practice.

Effective data collection in patient follow-up adds to understanding of the characteristics of patients who respond well to particular RMTs. This may include, for example, monitoring patient response and longer-term outcomes against genomic profile, treatment settings, dosages and combinations of therapies. Patient registries and other data collections are critical to gathering this evidence (Box 26), which may then be utilised to generate hypotheses for the next wave of early-stage RM research.

***Figure 28: Overview of autologous and allogeneic CAR-T manufacturing***

Patient registries have a variety of uses across the RM value chain, including monitoring clinical practice and providing post-marketing data to clinicians, the TGA, Department of Health and sponsors. Risk Management Plans and risk sharing agreements for RMTs typically require sponsors to collect data to monitor safety and efficacy of the RMT in clinical practice, drawing on data registries.

Australia does not have a coordinated approach to collecting and reporting data. Patient registries are tied to a specific therapeutic area and purpose, often collecting different information. Information systems across state and territory public healthcare services and private healthcare providers are not linked to each other or to patient registries. This limits the utility of these data sources.

The National Strategic Action Plan for Rare Diseases highlights this as a particular issue for rare diseases, where there is limited access to information to support clinical decision making. A national, coordinated approach to data collection and monitoring would enable better understanding of the clinical features of rare diseases and, potentially, enhance treatment, research and service planning.(88)

# Concluding remarks

Access to innovative RMTs offers enormous potential to save lives and enhance quality of life for Australians and provide economic returns for Australia. RMTs are complex and face additional challenges in advancing along the development pathway to patient care, compared with small molecule and other biological therapeutics. Development of RMTs varies in important ways from these “conventional therapeutics”, as it incorporates processes from bioengineering, genetics, cell culture, and biomaterials. These processes will evolve as technology advances, existing therapeutic approaches are refined and new approaches emerge.

Australia’s skilled academic workforce has generated a substantial research output and IP, contributing to the global knowledge base underlying the development of RMTs. Recent and ongoing investments in RM workforce and infrastructure programs will stimulate activity across early-stage research, preclinical testing and clinical trials and patient delivery. Greater clarity in regulatory and reimbursement processes and increasing clinical capabilities and experience in delivery of RMTs will contribute to positioning Australia at the forefront of delivering innovative RMTs.

There is still substantial ambiguity and uncertainty across the value chain. Few RMTs have successfully completed clinical trials to enable market entry, and investment and business models are yet to be validated. High ethical and regulatory standards are key to ensuring patient safety and public confidence in RM. This must be balanced against the need to adopt streamlined and agile approaches, to reward and encourage innovation.

While the global RM sector remains nascent, the pace of innovation and investment is accelerating rapidly. Progress is being made with collaborative research programs to guide clinical development of RMTs through international initiatives such as the IMI and ARDAT, and to develop international standards for the regulation of RMTs through the IPRP working groups on cell and gene therapies. A coordinated, national approach that includes engaging with regional and international collaborators will support Australia’s position in the global sector.

This report describes the RM value chain in Australia, highlighting enablers and barriers, with the aim of informing the Catalyst Strategic Roadmap. This exploration of the pathway of ‘typical’ RM products through the value chain provides an overview of the functioning of the Australian RM sector and its stakeholders (while acknowledging that the real-world is significantly more complex), involves a broad set of stakeholders, and will continue to evolve. Further work is required to prioritise and explore options to build upon the enablers and address the barriers that this report has identified in the Australian RM value chain.

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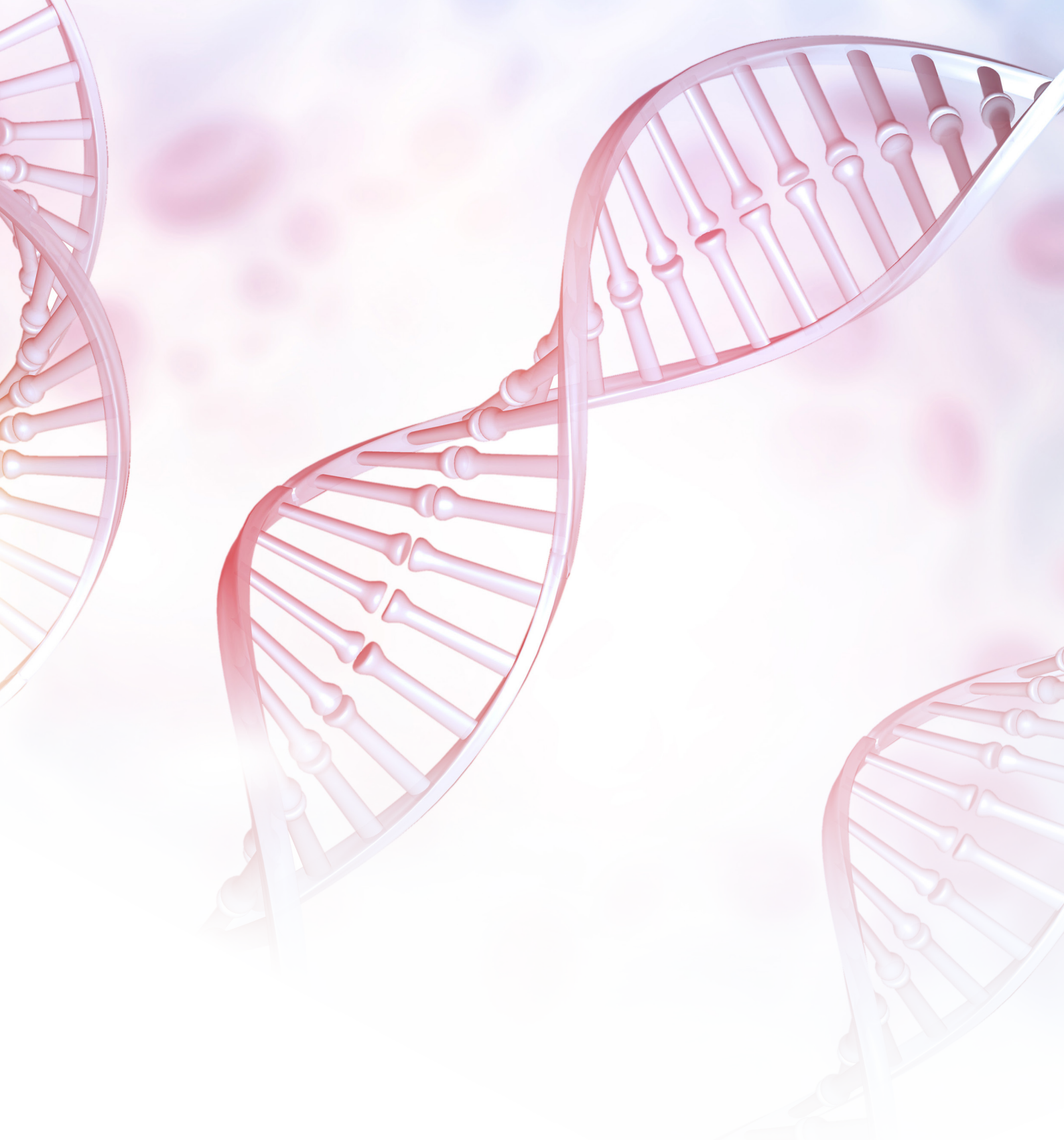

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