Overview of AHCDO's Gene therapy roadmap

Huyen Tran

Director Haemophilia treatment Centre

Head, Haemostasis Thrombosis Unit

The Alfred Hospital, Melbourne Australia

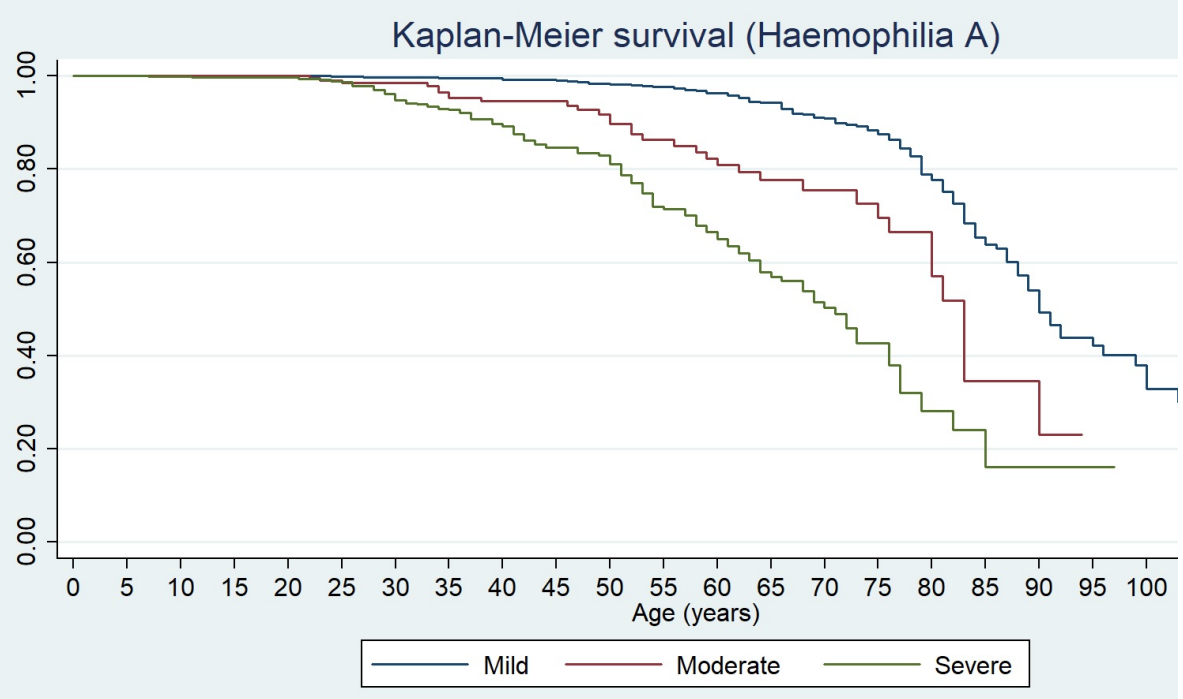
The Australian Centre for Blood Diseases,

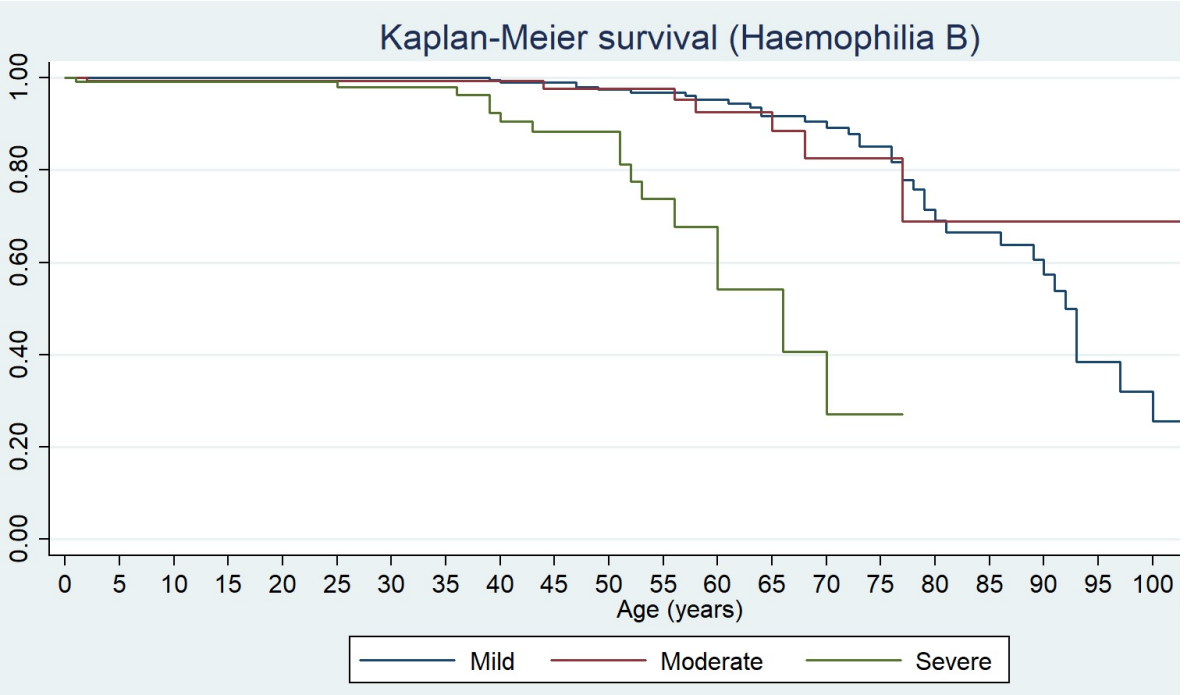
Monash University

Chair, Australian Haemophilia Centre Directors' Organisation

Chair, Clinical Trials group, THANZ

Survival by severity of haemophilia in Australia





Tran et al., ISTH Congress Montreal 2023

Broad medical patient eligibility for AAV-mediated haemophilia therapy

- **Severe haemophilia A (≤1%)**
- **No past history or current inhibitors**
- **No pre-existing immunity against AAV**
- No significant liver disease
- No HIV/ HIV with CD4 count >200 (depends on study)

- **Moderate-severe haemophilia B (≤2%)**
- **No past history or current inhibitors**
- **No immunity against AAV***
- No significant liver disease
- HIV with CD4 count >200 eligible

*not HOPE-B study

Considerations in patient selection

For people living with haemophilia, the choice to undergo gene therapy will be a significant decision. In addition to the eligibility criteria set out by manufacturers and regulators, AHCDO believes there are several factors that should be considered by clinicians when assessing the suitability of gene therapy for patients.

Eligibility criteria

Based on restrictions that have been applied in clinical trials, AHCDO expects that the below eligibility criteria may be applied to gene therapy for haemophilia in Australia:

- Adult male patients with moderate to severe haemophilia.
- No pre-existing immunity to AAV vectors*.
- No active hepatitis.
- No severe liver or lung disease.

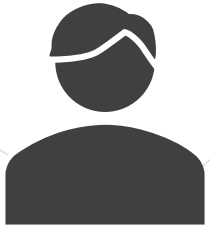
A history of factor inhibitors has been an exclusion criteria in many clinical trials, though AHCDO considers that this may be eased in future.

Additional factors in assessing patient suitability for gene therapy

Identity and mental health
Undergoing gene therapy can have a material impact on a patient's sense of self as a person with haemophilia, as well as their sense of connection to the broader haemophilia community.

Tolerance of uncertainty
Gene therapy requires patients to tolerate uncertainty about how long therapeutic effects will be sustained, given lack of long-term data about durability.

Commitment to follow-up
Gene therapy will require frequent follow-up appointments to monitor outcomes and detect side effects. This commitment is intensive for the first twelve months.



Possible need for steroids
Gene therapy patients may need to undergo steroid treatment in response to adverse events. Steroids can significantly impact mood, appetite, sleep and other functions.

Lifestyle impacts
Gene therapy can require patients to make lifestyle changes, including adherence to contraception for a period of time and abstaining from alcohol to reduce the risk of adverse events to the liver.

Timing of gene therapy
Gene therapy can only be given once at this current time. Patients should consider the best timing based on their circumstances, expected benefits, and possibility of new therapies becoming available.

AHCDO'S POSITION

3.1. All eligible patients who make an informed decision to undergo gene therapy should be able to receive it.

3.2. Treating clinicians must inform patients about the logistical, psychosocial, and lifestyle implications of receiving gene therapy.

3.3. Treating clinicians should work with eligible patients to identify the optimal timing for gene therapy that best suits the patient and their circumstances.

3.4. Gene therapy will not be a treatment option for every patient. Many eligible patients may not be suited for, or willing to undergo, gene therapy. Its use in each patient must be assessed in relation to all available therapies.

*Not AMT-060/061 haemophilia B

Haemophilia gene therapy studies

Clinical trials assessing gene therapy for haemophilia (both A & B) are well progressed. The safety of an in-vivo AAV approach has been demonstrated in several Phase 1 & 2 trials, with Phase 3 trials now underway to assess dosing, durability of gene expression, predictability and the balance of patient risks and benefits.

Table 1. Gene therapies for haemophilia at or approaching Phase 3 clinical trials[1,11,12,13,14,15]

Sponsor	Study	Clinical target	Status
BioMarin Pharmaceuticals	Val-Rox / Roctavian *Valoctocogene roxaparvovec, BMN-270*	Haemophilia A	**Phase 3B:** Phase 3 results from the GENEr8-1 study published in January 2022 demonstrated an 85% reduction in annual bleeding rate in 134 adult men with severe haemophilia A. However, subsequent data has indicated that effectiveness decreases over time. A Marketing Authorisation Application is now under review with the European Medicines Agency (EMA), with a decision expected ~June 2022. A regulatory submission to the US FDA is expected in mid 2022 following completion of a Phase 3B trial (Roctavian + corticosteroids).
UniQure (CSL Behring)	EtranaDez / Etranacogene dezaparvovec *CSL222, AMT-061*	Haemophilia B	**Phase 3:** Phase 3 results from the HOPE-B study published in February 2022 demonstrated a 64% reduction in annual bleeding rate and durable, sustained therapeutic effect after 18 months following a single infusion in 54 patients with severe haemophilia B. Marketing Authorisation Application now under review with the European Medicines Agency, with a decision expected around September 2022.
Roche (via Spark Therapeutics)	SPK-8011	Haemophilia A	**Phase 3:** Phase 1 & 2 results published in July 2021 demonstrated a 91.2% reduction in annual bleeding rate and sustained FVIII expression in 16 of 18 participants at four years follow up. Phase 3 trials are expected to commence once immunogenicity concerns are addressed.
Pfizer (via Spark Therapeutics)	Fidanacogene elaparvovec *SPK-9001*	Haemophilia B	**Phase 3:** Phase 3 trial commenced in July 2018 for 43 adult men with moderately severe to severe haemophilia B.
Pfizer (via Sangamo Therapeutics)	Giroctocogene fitelparvovec *SB-525-1603*	Haemophilia A	**Phase 3:** Phase 1 & 2 trial results from the Alta study published in December 2021 demonstrated sustained bleeding control in the highest dose cohort in patients with moderately severe to severe haemophilia A after two years. Giroctocogene fitelparvovec was well tolerated. Phase 3 trials (AFFINE study) are underway with 60 adult male participants with moderately severe to severe haemophilia A.

Put forward for regulatory assessment in 2022 for launch in Europe, Middle East and USA

FDA NEWS RELEASE

FDA Approves First Gene Therapy to Treat Adults with Hemophilia B

For Immediate Release: November 22, 2022

Today, the U.S. Food and Drug Administration approved Hemgenix (etranacogene dezaparvovec), an adeno-associated virus vector-based gene therapy for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

"Gene therapy for hemophilia has been on the horizon for more than two decades. Despite advancements in the treatment of hemophilia, the prevention and treatment of bleeding episodes can adversely impact individuals' quality of life," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research. "Today's approval provides a new treatment option for patients with Hemophilia B and represents important progress in the development of innovative therapies for those experiencing a high burden of disease associated with this form of hemophilia."

FDA Approves First Gene Therapy to Treat Adults with Hemophilia B | FDA. Accessed 23/11/22

Haemophilia B (2017)

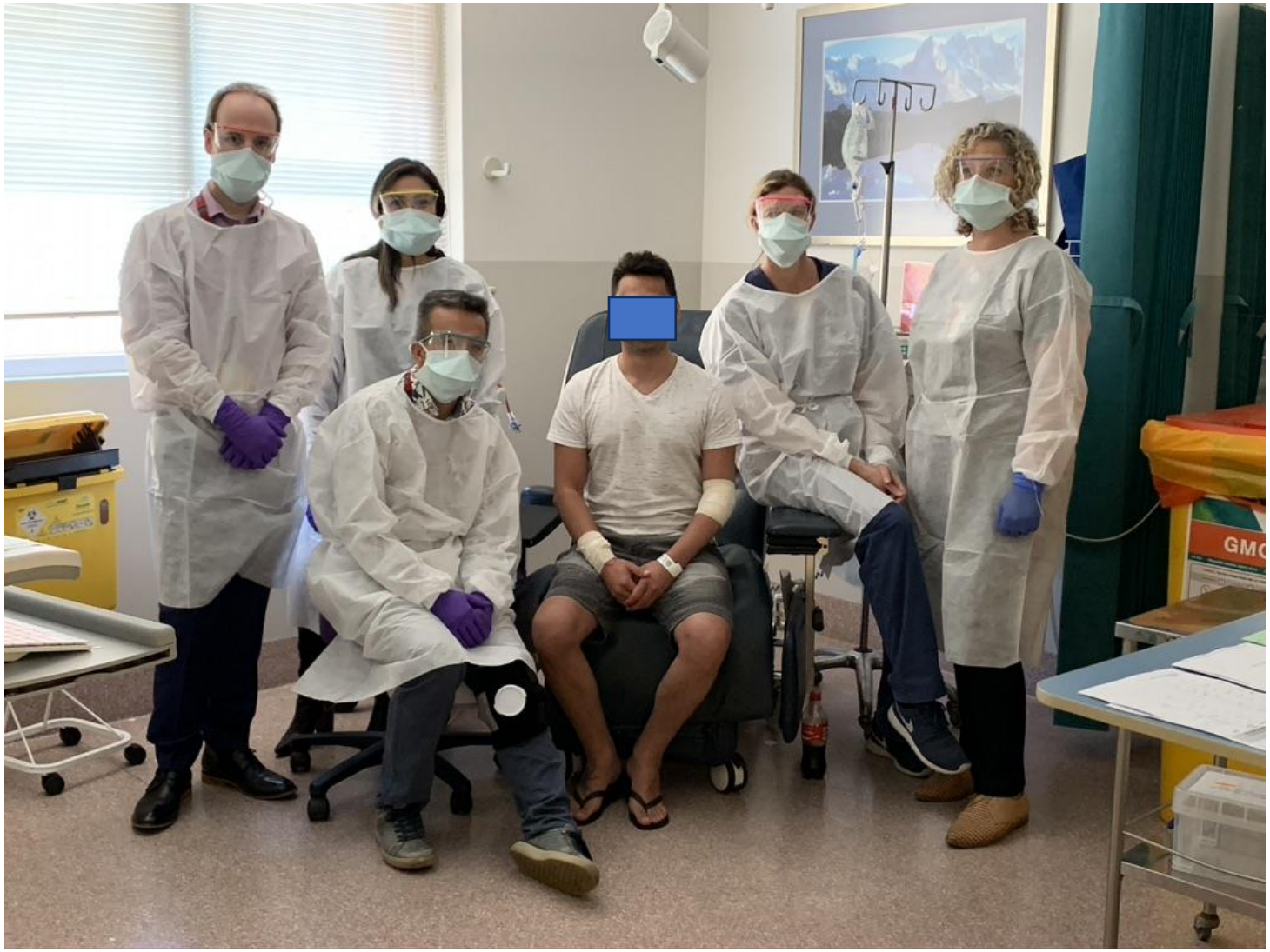
- George et al.,
  - **10 patients**
  - AAV vector containing FIX gene with **Padua mutation**
  - Levels, median **~33%** (some normal)

ML, FIX 81% at 6 years

ABC Dec 7 2017
George NEJM 2017;377(26):2515-27

Haemophilia A AAV-gene therapy Alfred Oct 30 2019

- 35 yo male severe HA
- SHL x3 pw prophylaxis since childhood
- October 2022, FVIII remains 45-55%
- **No bleeds/no factor usage**
- Wants to move O/S for a period of time because GH allows him the opportunity



With patient's permission

Clinical Implementation Plan

A roadmap for the implementation of gene therapy for haemophilia in Australia

November 2022

Australian Haemophilia Centre Directors' Organisation

Acknowledgements

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Executive Summary

Gene therapy is on the horizon as a durable treatment for Haemophilia. On a global scale, the first gene therapy candidates for the treatment of haemophilia have demonstrated good results in clinical trials and are now being assessed by regulatory bodies. AHCDO expects that gene therapy will become available for Australians living with haemophilia within the next five years.

AHCDO will advocate for a nationally consistent, patient-centred and equitable approach to gene therapy. As a novel therapy, there are choices to be made about how gene therapy is made available to patients and how care is delivered. A model that leverages the expertise of our national network of Haemophilia Treatment Centres (HTCs) and national framework of care will support safe and high-quality multidisciplinary team care.

All HTCs* will have a role to play in gene therapy, whether as a 'hub' site (responsible for administering gene therapy) or as a 'spoke' site (supporting patients before and after their gene therapy infusion). The 'hub-and-spoke' model is recommended for the delivery of gene therapy by leading international organisations to support patient access whilst concentrating expertise and resources. Hub and spoke centres must work in partnership so that patients can benefit from continuity of care.

Implementation of gene therapy will be complex and require national cooperation. Gene therapy is highly specialised. There are many important steps in patient care in the lead-up to receiving a gene therapy infusion and in the months or years afterwards as patients are monitored and, if required, treated for side effects. Clear roles and responsibilities, a national model of care and collaborative implementation planning will be important to prevent delays to patient access.

It is time to start preparing. Gene therapy is rapidly evolving, so we should expect that the range of therapies on offer for people with haemophilia will continue to develop. However, there are many complexities and long lead-times involved in introducing a new therapy – particularly for highly complex and specialised products such as gene therapy. AHCDO welcomes the opportunity to engage with governments, clinicians, patients, patient organisations, industry and other stakeholders to ensure that Australians living with haemophilia can access proven and effective treatments in a timely and equitable manner.

*Haemophilia Treatment Centres (HTCs) were established by the Australian Health Ministers' Advisory Council in 1998 to provide **quality care and an equitable distribution of resources** to support patients.

AHCDO's vision: Implementation of gene the

As a novel and specialised treatment, the implementation of gene therapy for haemophilia must prioritise safety and quality. AHCDO proposes a product-agnostic approach that balances the needs, preferences and quality of life of patients with the capability and capacity of Haemophilia Treatment Centres (HTCs) to safely deliver gene therapy as a standard of care treatment, informed by evidence and clinical practice.

AN OPTIMAL SERVICE DELIVERY MODEL…

…IS NATIONALLY CONSISTENT

Referral pathways, patient screening, administration protocols and ongoing monitoring of gene therapy should be nationally consistent, with minimal variability between treatment centres.

…LEVERAGES EXISTING GOVERNANCE

Implementation of gene therapy should make use of the strong national framework between AHCDO, the National Blood Authority (NBA), HTCs, the **Australian Bleeding Disorders Registry** (ABDR) and patient representatives.

…BUILDS ON REAL-WORLD EXPERIENCE

Several treatment centres in Australia have administered gene therapy as part of clinical trials. Future implementation should make use of the expertise and infrastructure at these sites.

…IS ADAPTABLE TO INNOVATIONS IN CARE

Exponential growth in the availability of gene therapies is expected over the next decade. Implementation of gene therapy must be flexible and adaptable to future innovations.

THE IDEAL PATIENT EXPERIENCE INVOLVES…

…EQUITABLE ACCESS

There are no barriers to care for eligible haemophilia patients who wish to receive gene therapy. There must be equity of access to gene therapy, irrespective of where a patient lives.

…PATIENT CHOICE AND EMPOWERMENT

All eligible patients should be given the choice to receive gene therapy and be able to access it in a timely fashion. Patients' needs, preferences, and quality of life are put first.

…TRANSPARENT COMMUNICATION

All patients with haemophilia are informed about gene therapy by their clinicians. The risks, benefits, unknowns, follow-up commitment, and trade-offs are made transparent upfront.

…PSYCHOSOCIAL SUPPORT

The decision to undergo gene therapy is not to be taken lightly. All patients should have access to specialist psychosocial support before, during, and after a gene therapy infusion.

Making gene therapy accessible to patients

The selection of treatment sites is a key consideration for the implementation of gene therapy. AHCDO's position is that an adapted 'hub and spoke' model of service delivery is optimal for Australia to achieve a balance between facilitating patient access and concentrating expertise, resources, and costs.

What could a hub and spoke model look like in Australia?

What is a hub and spoke model?

The 'hub and spoke' model is gathering momentum internationally as an approach for delivering gene therapy.

Under the model, a selection of treatment centres become 'expert hubs' that prescribe and administer gene therapy. Other centres then become 'spokes', responsible for pre- and post-gene therapy care.

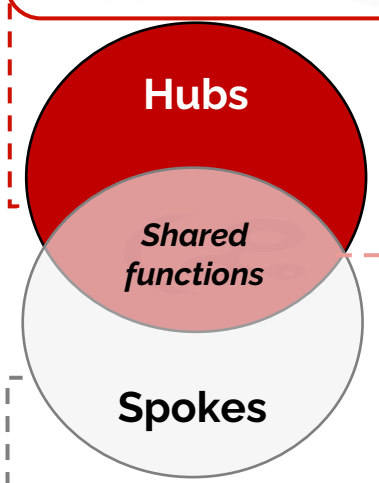
The model relies on hubs and spokes collaborating on treatment decisions and co-managing adverse events to provide safe and high-quality continuity of care to patients.

The hub and spoke model has many benefits including centralising expertise, facilitating consistent care and reducing regulatory and administrative burdens.

Full resourcing of both hubs and spokes to accommodate the introduction of a new therapy will be critical to success.

Hubs would be responsible for…

- Setting national guidance to spoke centres and patients on gene therapy for haemophilia.
- Managing supply of gene therapy including prescribing, ordering, compounding, and disposal.
- All aspects of care associated with administering gene therapy to approved patients.
- Managing immediate post-infusion side effects and co-managing adverse events with spokes.



Shared responsibility would be needed for…

- Making the decision to approve patients for gene therapy.
- Determining post-infusion monitoring and care.
- Managing and reporting adverse events.

Spokes would be responsible for…

- Assessing patients' suitability for gene therapy, including undertaking screening tests.
- Referring eligible patients to a Clinician Advisory Group to be assessed for gene therapy.
- Conducting follow-up appointments and tests with patients after their gene therapy infusion.
- Communication with patients' primary care and allied health physicians as needed.
- Providing or facilitating access to psychosocial support at all stages of gene therapy.

AHCDO'S POSITION

1.1. Gene therapy should be implemented with a 'hub and spoke' model, in line with emerging international best practice.

1.2. All adult Haemophilia Treatment Centres (HTCs) nationally should be designated as hub or spoke sites. Some hub sites will perform the roles of both hub and spoke where they are the primary point of care for haemophilia patients.

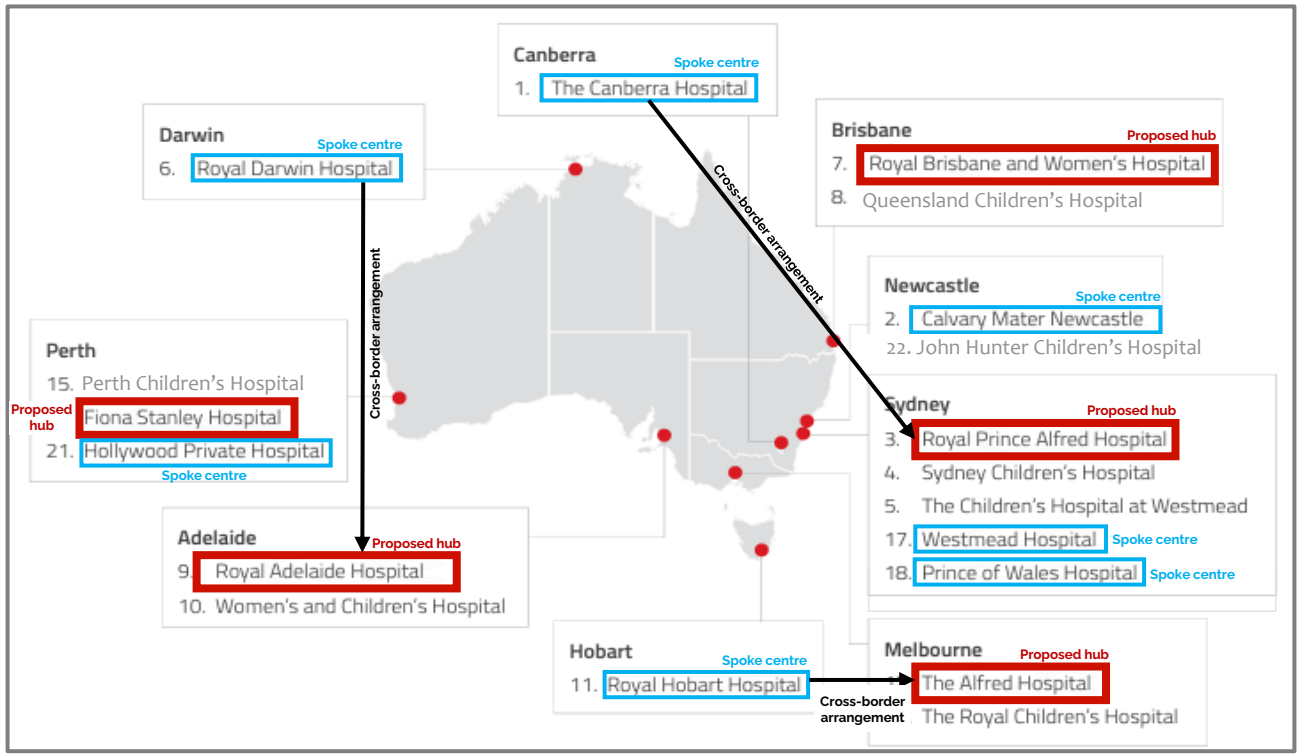
1.3. Hubs should provide national guidance to inform patient selection, monitoring and other elements of care.

1.4. Hub and spoke centres must work in partnership to ensure continuity of care to patients receiving gene therapy.

1.5. Identification of hubs and spokes should focus initially on adult treatment sites, although it is noted that gene therapy could become an option for paediatric patients in the future.

Proposed approach to site selection

AHCDO's assessment of current Haemophilia Treatment Centres (HTCs) as potential gene therapy sites



Commentary: This map shows AHCDO's proposed distribution of hub and spoke centres for gene therapy for haemophilia across Australia. It applies the principle of selecting one expert 'hub' per State/Territory for the treatment of adult patients. Paediatric treatment centres have been excluded from consideration, as much longer lead-times are anticipated for regulatory approval for gene therapy among patients aged younger than 18 years.

AHCDO'S POSITION

2.1. There should be one hub per State/Territory to balance patient access with the high costs of setup and ongoing delivery.

2.2. There must be equitable access for patients from spoke centres to access hubs, including cross-border arrangements.

2.3. The first hub sites should be clinical trial sites that already have the requisite infrastructure and expertise for gene therapy:

- Royal Brisbane & Women's Hospital (QLD)
- Royal Prince Alfred Hospital (NSW)
- The Alfred Hospital (VIC)
- Royal Adelaide Hospital (SA)
- Fiona Stanley Hospital (WA)

2.4. If sufficient funding, resources and expertise can be secured, **all States and Territories should be able to establish one gene therapy hub** in the future.

AHCDO's proposed model of care

In this Clinical Implementation Plan, AHCDO has put forward a proposed model of care that prioritises patient safety, timely access, and feasibility across the existing network of Haemophilia Treatment Centres.

Key steps in the proposed model of care

Stage	Description	Hub activity	Spoke activity	Shared activity
Identification	Identification of haemophilia patients that are eligible to undergo gene therapy. This stage includes patient education and initial discussions about risks, benefits, side effects, and the end-to-end treatment process.		✓	
Screening	Assessment of relevant clinical factors against eligibility criteria to inform the decision to proceed with gene therapy.		✓	
Decision	**Patients provide enhanced consent to undergo gene therapy. Clinician approval to treat with gene therapy is facilitated via a Clinician Advisory Group with hub and spoke representatives.**			✓
Supply	Prescription, ordering, storage, and compounding (if applicable) of gene therapy products.	✓		
Administration	Administration of gene therapy to eligible haemophilia patients as a day procedure (with option of overnight stay if clinically indicated or if travel home exceeds 3 hours), including pre-infusion preparations and post-infusion monitoring.	✓		
Monitoring	Twelve months of testing (initially on a weekly basis) and monitoring for patients who have received gene therapy, with check-ups at regular intervals thereafter. This stage also includes management of adverse events should they occur.		✓	✓ [1]

[1] Routine patient monitoring will be primarily managed by spoke centres. Should any adverse events arise, a shared care approach between the hub and spoke site will be needed.

AHCDO'S POSITION

4.1. The model of care should leverage good practices from clinical trials, making use of existing expertise and resources.

4.2. Hub sites will be responsible for prescribing, ordering, and administering gene therapy.

4.3. Spoke sites will remain the primary point of care for patients with haemophilia. They will oversee pre-care and post-care for gene therapy patients.

4.4. Shared care will be required for the decision to treat with gene therapy and for **managing adverse events** post-infusion.

4.5. Expert hubs and spokes must work in partnership to manage monitoring, follow-up and any adverse events.

4.6. Patient education and psychosocial support must be a core focus – before, during and after gene therapy.

Summary

- AAV-mediated haemophilia gene therapy shows promise in clinical trials (especially haemophilia B)
- **Requires significant preparation, and extended & careful follow up for efficacy & potential adverse effects not expected to be seen in short term trials**
- Implementation should be nationally consistent
  - involve HTC leveraging comprehensive care