Gene therapy task force update

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First gene therapy to treat severe haemophilia A

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News 24/06/2022

EMA has recommended granting a conditional marketing authorisation in the European Union (EU) for Roctavian (valoctocogene roxaparvovec) for the treatment of severe haemophilia A in adults who do not have factor VIII inhibitors (auto-antibodies produced by the immune system which make factor VIII medicines less effective) and no antibodies to adeno-associated virus serotype 5 (AAV5).

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First gene therapy to treat haemophilia B

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News 16/12/2022

EMA has recommended granting a conditional marketing authorisation in the European Union (EU) for Hemgenix (etranacogene dezaparvovec) for the treatment of severe and moderately severe haemophilia adults who do not have factor IX inhibitors (auto-antibodies produced by the immune system which mak factor IX medicines less effective).

Current situation in the UK

Hemgenix under consideration by NICE

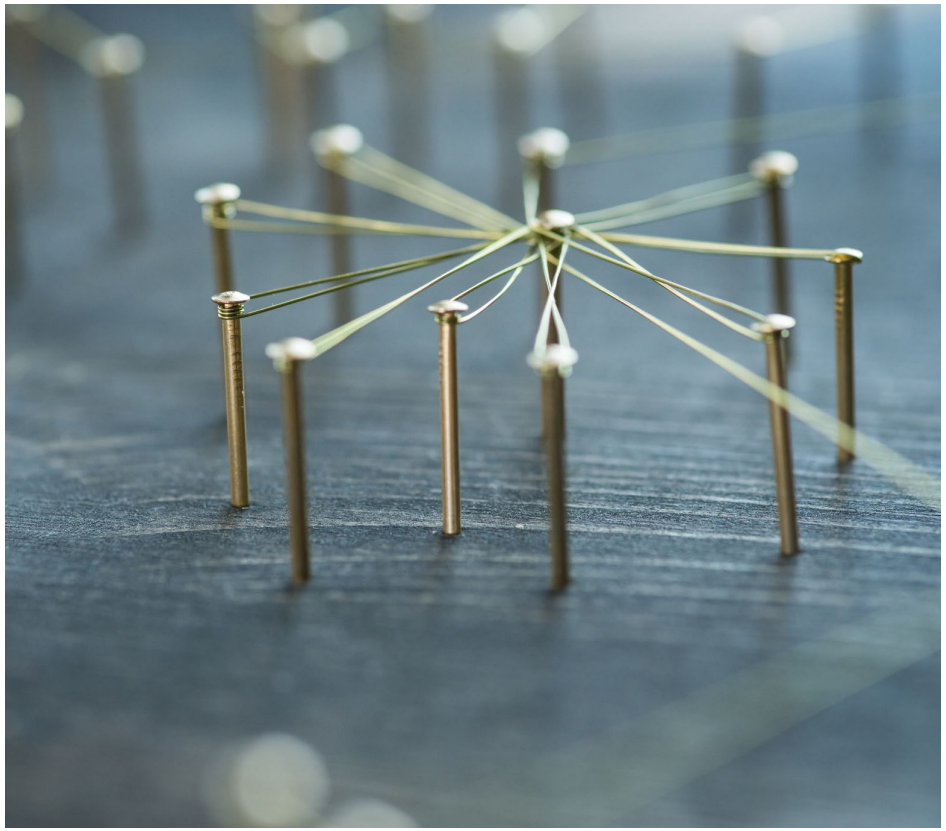
- Outcome pending (delayed compared to estimated time-lines)

NHSE gene therapy dosing centre tender

- In advance of NICE decision but in preparation for potential NICE approval
- Worked with UKHCDO draft guidelines: plan ‘hub’ and ‘spoke’ model of care
- 1 gene therapy dosing centre in each commissioning region, with 2 in London ie 8 total
- Outcome almost completed

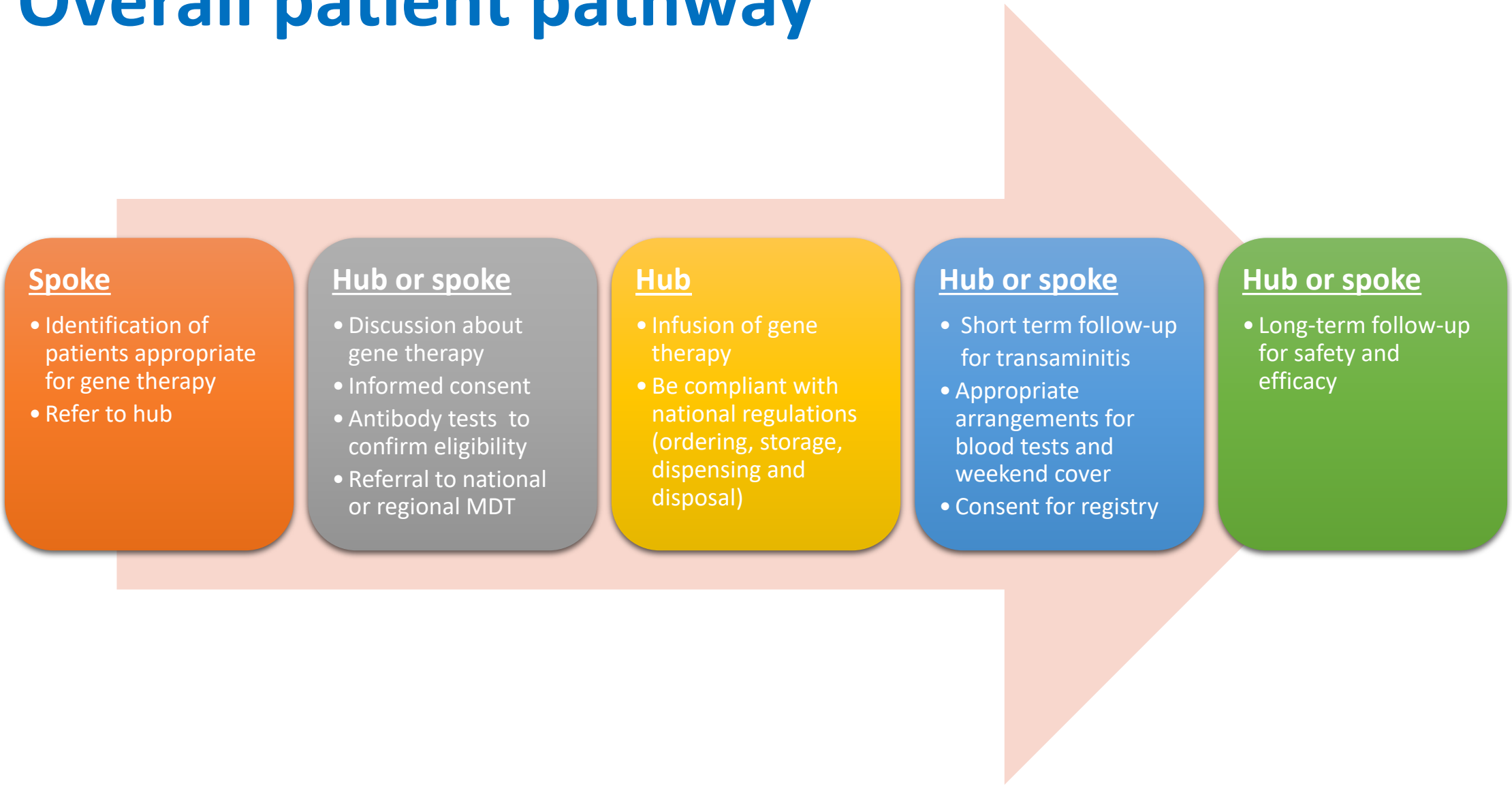
A hub and spoke delivery model may be important for access and safety

- EAHAD and EHC recommend that first-generation therapies should be managed in a hub-and-spoke model
  - Experienced currently restricted to Centres involved in clinical trials (approx. 1/3 in the UK)
  - Number of patients likely to be small
  - Need to build experience/share knowledge/equitable and ease of access
- Expert haemophilia comprehensive care centres act as national hubs, retaining management and prescribing responsibility for ATMP
- All CCCs provide ongoing monitoring, including long-term surveillance in close communication with national hubs
- Ensure
  - Cost-effective
  - Equity of access
  - Right treatment for the right patient
  - Build and share experience nationally



Delivery of AAV-based gene therapy through haemophilia centres-A need for re-evaluation of infrastructure and comprehensive care: A Joint publication of EAHAD and EHC; (Nov 21) EAHAD: European Association for Haemophilia and Allied Disorders; EHC: European Haemophilia Consortium; HTC: Haemophilia treatment centre.

Overall patient pathway



Hub and spoke

Pathway discussions / fluidity

Spoke centres will have varying levels of experience with gene therapy. Exact relationship between the Hub and Spoke may be modified locally based on experience

- Review local arrangements
- Review capacity on both sides
- Agree on a communication plan
- Agree on escalation plan
- Agree on contact details
- Discuss plan for consent
- Organise visits to the infusion centre
- Agree on follow-up arrangements
- Agree on data management and submission

Hub requirements

- Responsible for procurement and administration of ATMP
- Need to comply with pharmaceutical regulations of specific ATMPs
- Staff and facilities for
  - Liaising with hubs and establishing local pathways
  - Supporting individual consent
  - Administration of vector, including monitoring and responding to adverse reaction
  - Longer-term monitoring
  - National reporting of data
  - National MDT
- Experience with clinical trials of gene therapy
- Gene therapy dosing tender only included funding for the ‘day of treatment.’ F/u appointments are planned to be activity based

After consent

Set date for infusion

Hub to order gene therapy product

- NB repeat bloods (LFTs) 2 weeks prior to infusion date

Day of dosing

- Medical team to assess patient, confirm eligibility
- Final consent for gene therapy and gene therapy registry
- Administration requirements, plus monitor for at least 3 hours post-dose
- Before discharge
  - Contact details in case feeling unwell
  - Date for initial f/u bloods
  - Clear plan for prophylaxis (usually until endogenous factors >5%)
  - Prescription for 7 days of steriods

Routine monitoring (Hub/Spoke)

- Months 0-3
  - Weekly FBC, renal, liver, AST, CK, FVIII/FIX (twice a week?)
- Months 4-6
  - Weekly to monthly bloods tests as above
- Months 7-24
  - Quarterly investigations as above
  - Liver USS 12 and 24 months
- Years 2-15
  - 6 monthly investigations and annual liver USS
- Consider impact of inter-lab variability on liver function and factor levels results

Liver transaminases (Hub/Spoke)

- Liver function and immunosuppression
  - Elevation in transaminases should trigger repeat LFTS, AST, CK, LDH
  - Check alcohol, hepatotoxic medications, exercise
  - Strongly consider course of steroids if ALT increases to >2xbaseline or 1.5xULN
  - Consult individual product literature
  - Early discussion at national MDT

Steps to support shared decision making on Gene therapy and optimise safety and outcomes

- Training and education HCP
- Gene therapy discussed with all potentially eligible patients in clinic
- Discussion to cover
  - Benefits of treatment
  - Variability of response (expression levels and clinical impact)
  - Treatment failure
  - Durability of expression
  - Risks/side-effects including initial adverse reaction, immunosuppression
  - Long-term safety
  - Patients expectations and motivations
  - Other therapeutic options

Three step consent process involving Spoke and Hub Step 1 – spoke

- Concept of gene therapy with an AAV vector
  - Preliminary investigations of assessing eligibility
  - Potential benefits and risks, knowns and unknowns
  - Practical aspects of treatment
    - Single day of dosing
    - Intense monitoring especially for the first 6-12 months
    - Immunosuppression
    - Need for long-term f/u

Step continued

- If person (SHA, HB with FIX <3%) interested then SPOKE to
  - Confirm/double check eligibility against absolute exclusion criteria
    - History of FVIII/FIX inhibitor
    - Severe hepatic impairment
    - Active infection
    - Immunosuppression (within last 30 days)
    - Hypersensitivity to product excipients
    - Age <18 years old or women with child bearing potential
    - Significantly limited life expectancy
    - NB HIV not an absolute contraindication but patients need careful counselling as only a limited number of patients with controlled HIV have been included in the trials
  - Send blood for AAV Abs (central lab)

Detailed consent (2) AAV vector Ab negative

- Joint HUB and SPOKE eg Hub to join Spoke clinic virtually
- Cover why gene therapy/ why now/ the safety consideration and explicitly document benefits/risks/potential for failure supported by a consent proforma
- Inclusion of a psychologist is recommended
- Encourage individual to speak with family and friends
- Along with discussions, baseline assessments of musculoskeletal health, quality of life and liver health

Consent proforma

Consent checklist

Potential benefit

- Average response per gene therapy product
- Impact on Haemophilia
- Cessation of regular factor prophylaxis post-gene therapy when endogenous factor levels are around 5% or greater
- On-demand treatment for bleeds and surgery – dictated by factor levels

Outcomes post–gene therapy at six months

- No response or minimal, continue with the current treatment
- Mild response, factor levels > 3 to 5 %, cessation of prophylaxis, and switch to on-demand treatment and monitoring

Potential benefit

- Average re
- Impact on
- Cessation
- On-deman

Outcomes post–ge

- No respon
- Mild respo
  for trauma
- Good resp

Expected response

- Factor leve
- Duration o
- Difference
- Potential f

Immediate side eff

- Allergic rea
- Headache,
- Flu-like illn

Immune response

- Causes of
- Impact of i
- Immunosu
  - P
  - R
  - M
  - D
  - Si
- Review of
- Advice avo
  products and nutritional supplements)

Long term safety

- Baseline screening for liver health
- Unknown risk of liver cancer – theoretical basis and documented cases to date
- Advise for long-term liver monitoring with an annual blood test (AFP) and liver USS.
- Participation in a long-term registry

Vector shedding (Spread of Vector to other body tissues, including semen).

- Male patients should be informed of the need for contraceptive measures for them or their female partners of childbearing potential.
- Patients treated with gene therapy must not donate blood, organs, tissues and cells for transplantation.

Risk of thrombosis if levels in the supraphysiological range

- Patients with severe disease have had reduced mortality from cardiovascular disease and venous thromboembolism compared to the general population. Increasing factor levels is likely to increase the risk and regress to the population mean, particularly in those patients with additional risk factors, e.g. smoking, hypertension, high cholesterol, and diabetes.
- Treatment on an individual basis is based on active ongoing risk assessment

The intensity of the required follow-up

- Frequency of investigations during the first six months, first year and subsequently Weekly investigations for the first 3-6 months.
- Additional visits if concerns about liver function tests.
- Liver monitoring with an additional blood test (AFP) and liver ultrasound scan annually

Psychological aspects

- The rationale for choosing gene therapy and patients' life circumstances, particularly the need for time commitment and regular reviews.
- Immune response to vector and not able to re-treat with the same gene therapy vector
- What success and failure look like

Consent for gene therapy registry

ith the same gene therapy vector

Consent for gene therapy registry

3rd step consent (3) HUB and SPOKE

- Discussion at national /regional MDT to confirm eligibility prior to 3rd step of consent

- Final' discussion 6-8 weeks after the second discussion
  - Confirm the patients understanding and expectations before written consent
  - Mixed F2F and virtual meeting, involving both Hub and Spoke

Additional considerations

- Need to develop standard educational material for patients to avoid bias/ Panglossian thinking by HCP
- Need for lifestyle modifications
- Psychosocial impact of gene therapy with loss of identity and ‘burden of normalcy’
- Educational support development to facilitate learning by PwH to ensure participation in shared decision-making, understand the role as key stakeholders and share in pharmacovigilance responsibilities
- Aggregation of key outcomes to facilitate early AE signal detection

Long-Term Follow Up : WFH Gene Therapy Registry

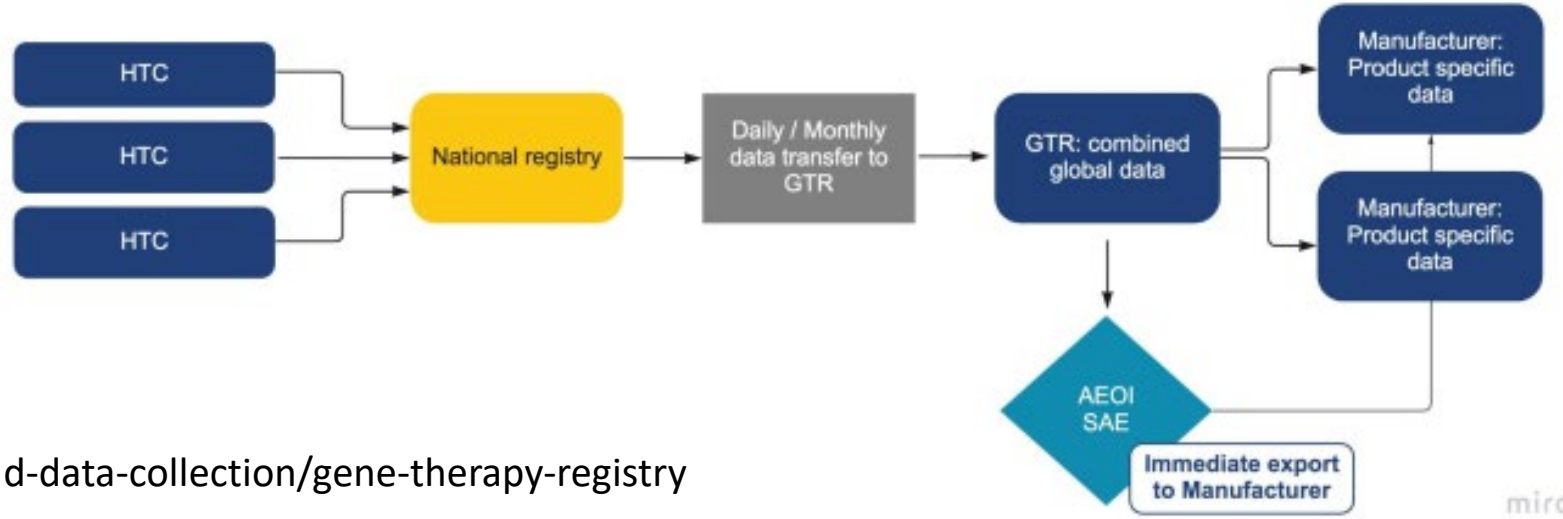
Prospective & Retrospective WFH Registry Objectives

1) Long-Term Safety
2) Long-Term Efficacy & Durability
3) Long Term QoL & Burden of Disease

GTR
WFH GENE THERAPY REGISTRY

Data Sources

- Patient consent
- National registries (e.g., NHD) or Haemophilia Treatment Centres



https://wfh.org/research-and-data-collection/gene-therapy-registry

WFH Gene Therapy Registry

Core Data Set

Demographics

Medical history

Gene Therapy Infusion Details

Safety (AE of interest)
- Inhibitors
- Thrombosis
- Autoimmune disease
- Malignancies
- Liver function
- Death

Efficacy
- Bleeding events
- Factor levels
- Haemostatic treatment usage

Patient Reported Outcomes

Mortality

Collection Timepoints

- Baseline & Vector Infusion
- Follow-up visits

Month 3, 6, 9, 12, 18 & 24

- Annually

Current Unknowns of AAV Gene Therapy in 2023

- **Variability :** What are the causes of inter-individual variability ?
- **Durability :** Why do levels reduce for some products (FVIII) ?
- **Early Safety :** Cause & treatment of transaminitis
- **Long-Term Safety :** Does AAV impact on liver health ?
- **Long Term Safety :** Does AAV integrate after treatment ?
- **Long Term Safety :** Is there a risk of genotoxicity (malignancy) ?

Liver biopsy studies may help to answer these questions

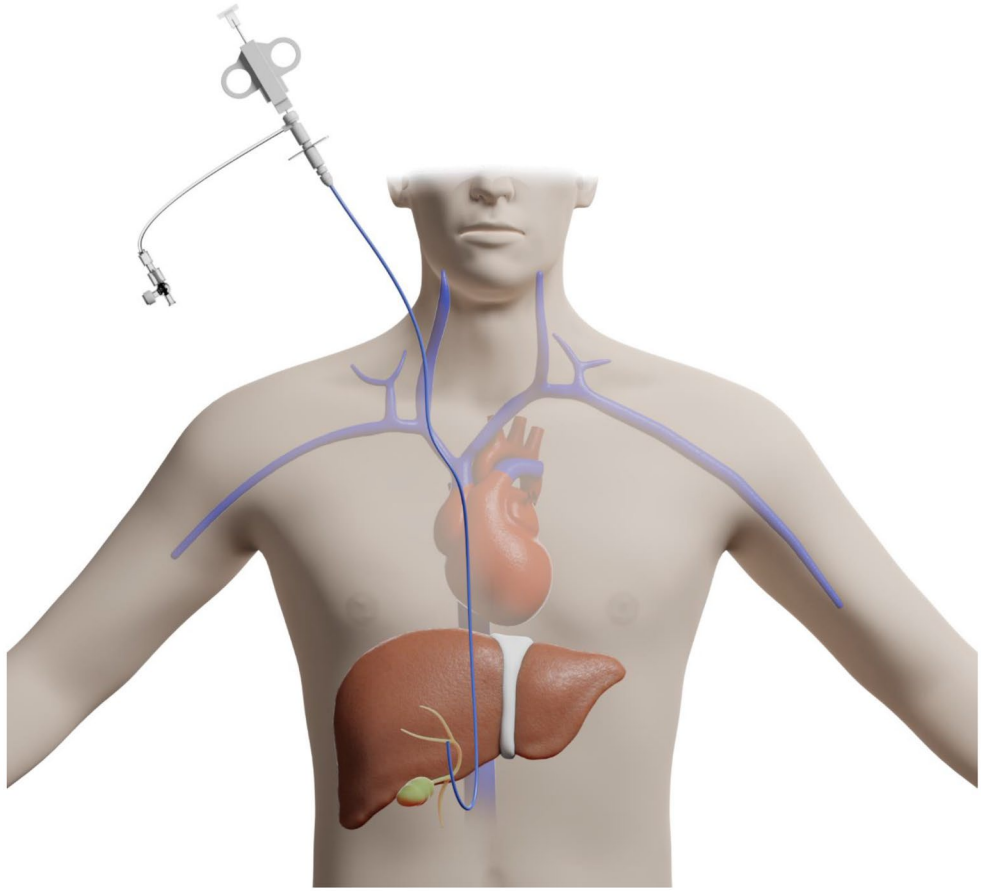
Long-Term Follow Up : Current UK Gene Therapy Research

Liver Biopsy In Haemophilia Gene Therapy (UCL)

- **Haemophilia B :** AGT4HB (EudraCT No 2005-005711-17)
- **Haemophilia A :** GO-8 (EudraCT No 2016-000925-38)
- **Haemophilia B :** FLT180a-01 (EudraCT: 2017-000852-24)

Liver Biopsy In Haemophilia Gene Therapy (UCL)

- Evaluate Implication of Liver Health (Safety)
- Evaluate Mechanism(s) of AAV Persistence
  - Variability & reduction in expression (Efficacy)
  - Episomal v Integrated (Efficacy / Durability)
- Evaluate relevance of vector integration (Safety)



Formal referral to Hub and National MDT

Referral to Hub (ideally before 2nd consent step, and certainly afterwards)

- Patients who meet the eligibility criteria and are keen to proceed
- Referral to be supported by a proforma
  - Haemophilia history incl inhbitors
  - PMH, Medications
  - Height/Weight
  - Baseline investigations incl AAV Ab

Referral to National MDT

- Fully completed proforma including baseline liver US and fibroscan
- Signed copy of written consent

National MDT

- Ensure eligibility
- Check onwards referral to Hub is sensible based on logistics and capacity

National MDT – potential roles and responsibilities

Review the patient's eligibility – final ratification.

Help with capacity – direct patients to the nearest Centre

Develop any relevant SOPs

Standardise pathways, PIS and ICF

Registry – oversight, data collection and provide updates

Help with learning and education

Review outcomes and equity of access

Multiprofessional representation – Hubs, Nurse, Physiotherapist, One spoke, Psychologist, NHD, Pharmacist – ATMP, Hepatologist

Likely to evolve over time

Thank you for your attention