



If the Gene Fits: *The trials and tribulations of delivering two different gene therapies during a global pandemic.*

Derval Reidy

Assistant Director of Nursing

Wellcome HRB Clinical Research Facility

Wellcome HRB – Clinical Research Facility at St. James's Hospital



8 Years since our doors opened...

Our Impact

Since opening in May 2013, the CRF has grown from strength to strength supporting a wide variety of clinical trials and studies, more notably the CRF has successfully conducted the first gene therapy clinical trial in haemophilia in Ireland along with a Phase 1 overnight clinical trial in neurology.



Disease Areas

19

St. James's Hospital is Ireland's largest acute academic teaching hospital. We support a wide range of studies in multiple disease areas.



Investigators

105

We collaborate with a wide range of investigators across a variety of disease spectrums.



Regulated Clinical Trials

76

This includes early Phase I /II to Phase III and medical device studies.



Non-Regulated Clinical Studies

137

This includes observational studies and interventional studies.

8 years and counting... CRF and NCC Partnership

- PERSONAL trial
- BAX326 Factor IX CFC
- BH30071 Haven 3
Emicizumab (Hemlibra)
- Irish personalised approach to the treatment of Haemophilia **iPATH**
HIGH PERSONALIZED APPROACH TO THE TREATMENT OF HAEMOPHILIA
- FIX gene therapy (Freeline and UniQure Hope study)
- Spark FVIII gene therapy



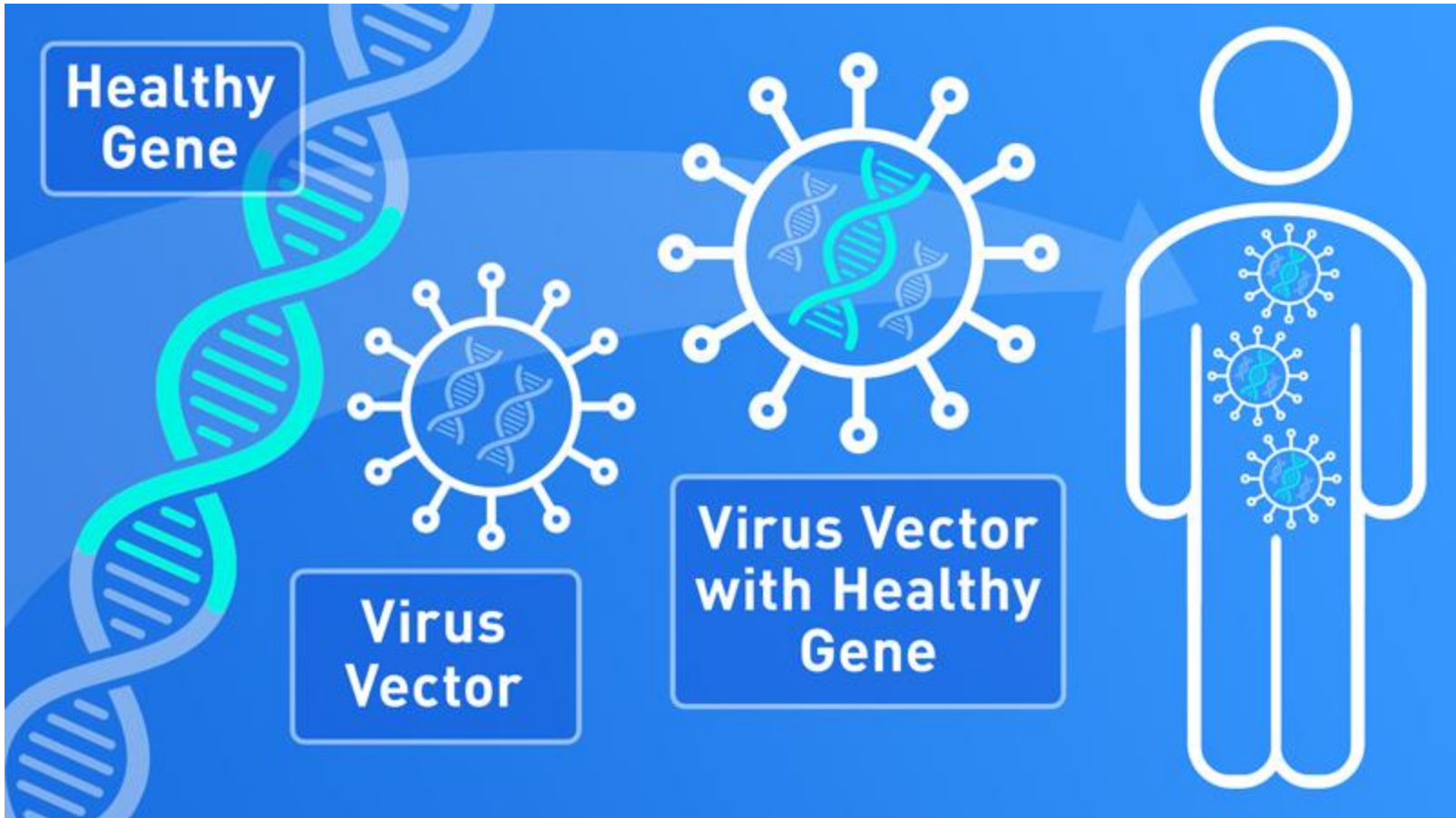
Ireland uniquely placed to participate in Gene therapy trials for Haemophilia

- National Haemophilia service
- Longitudinal data
- EHR (indici) and scanning of home treatment
- Engaged patient community
- Committed MDT
- Changing expectations
- Partnership that can work



The NCC and NCL team!





Clinical Trial

- Phase III, **open label**, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon optimized **human factor IX gene** (AAV5-hFICco-Padua, AMT-061) administered to adult patients with severe or moderately severe hemophilia B
- A total of **56 patients** recruited across North America, EU, UK, Ireland and South Africa
- SJH site target **n=2**

Study visits

LEAD IN PERIOD

- Screening Visit
- 6 month lead in – visits every 2 months

DOSING

- IMP Dosing

INTENSE FOLLOW UP

- Week 1-12 (Every Week)
- Months 4 to 11 (Every Month for 7 months)

LONG TERM FOLLOW UP

- Months 18-60 (Every 6 months)

Working Groups established

- **ATIMP room/Pharmacy**
- **Quality and Regulatory Affairs**
 - Ethics review
 - HPRA submissions
 - EPA submissions
 - Standard Operating Procedures
- **Nursing**
 - Standard Operating Procedures
 - Training
 - Patient Safety
 - Numerous Dry runs

Institutional Readiness



Create an ATIMP room



Sought out other sites



Trip to Southampton to see patient being administered tx



Internal working group established

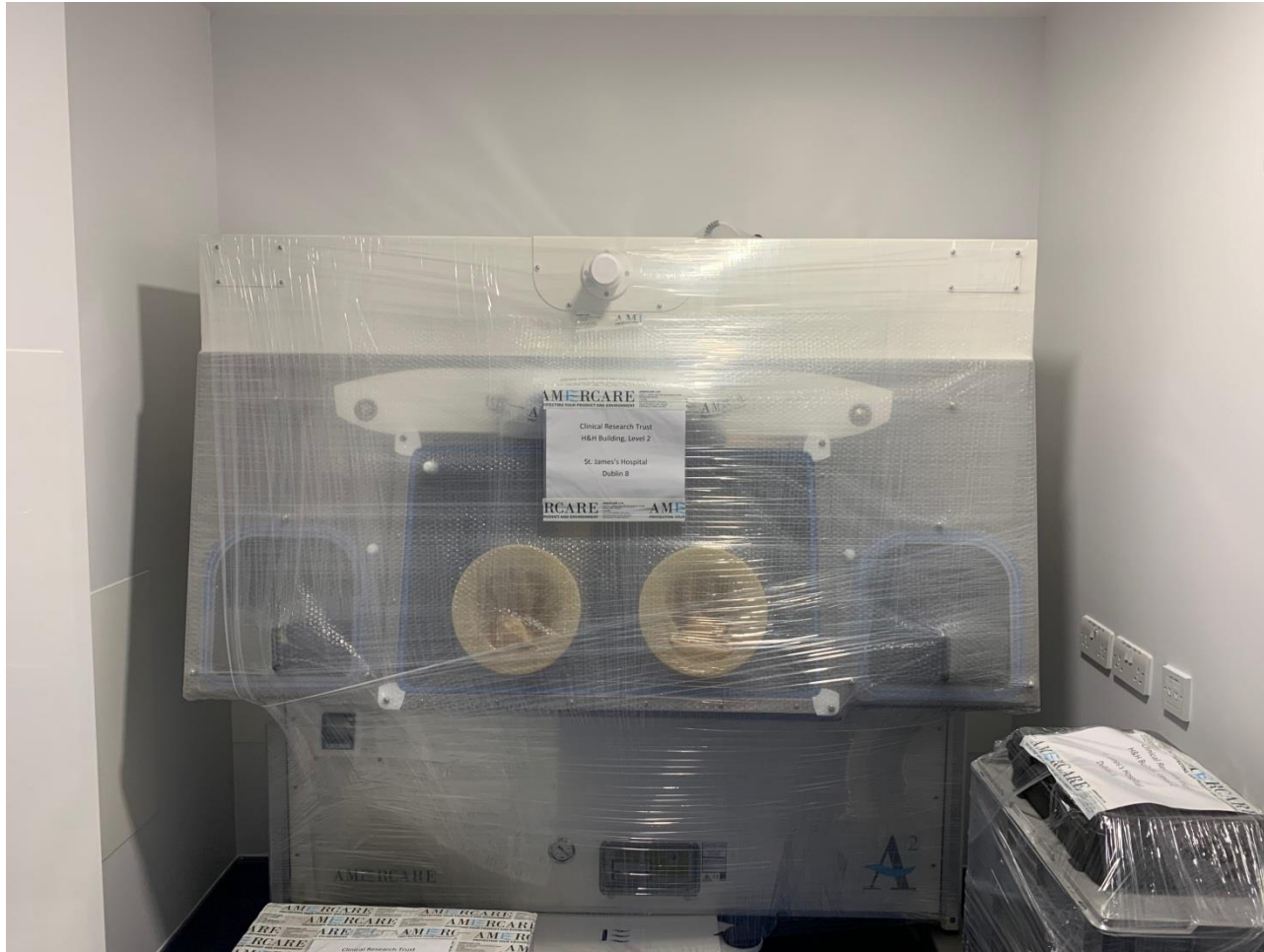


Patient engagement

ATIMP room

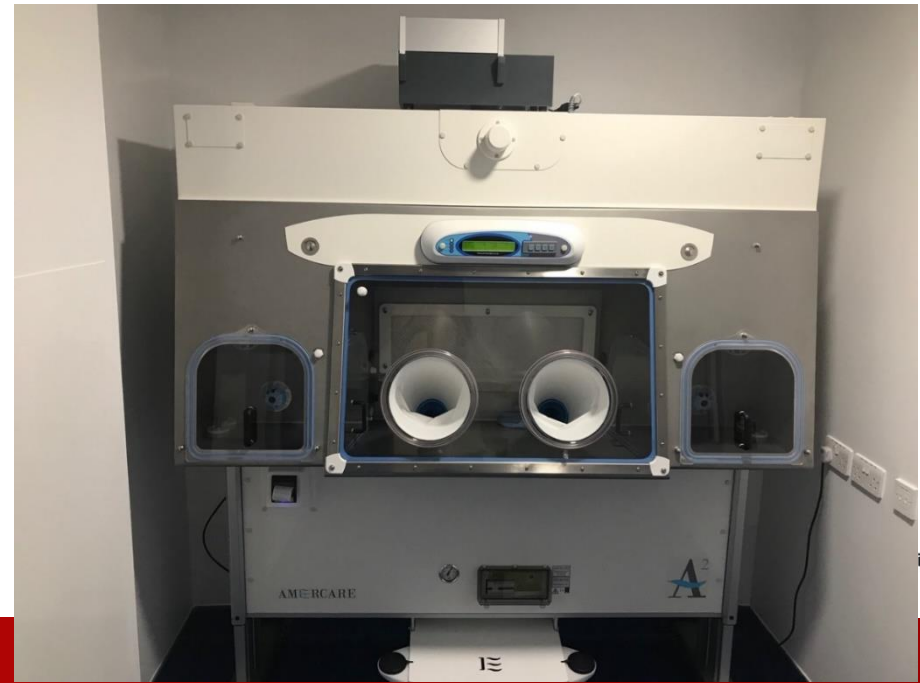
- Advanced Therapeutics Investigational Medicinal Product
- Designated room
- Purpose to protect the user, the environment
- GMO

Isolators Arrived





***Gene Therapy
Room
Grade A Isolator
Grade D Room***

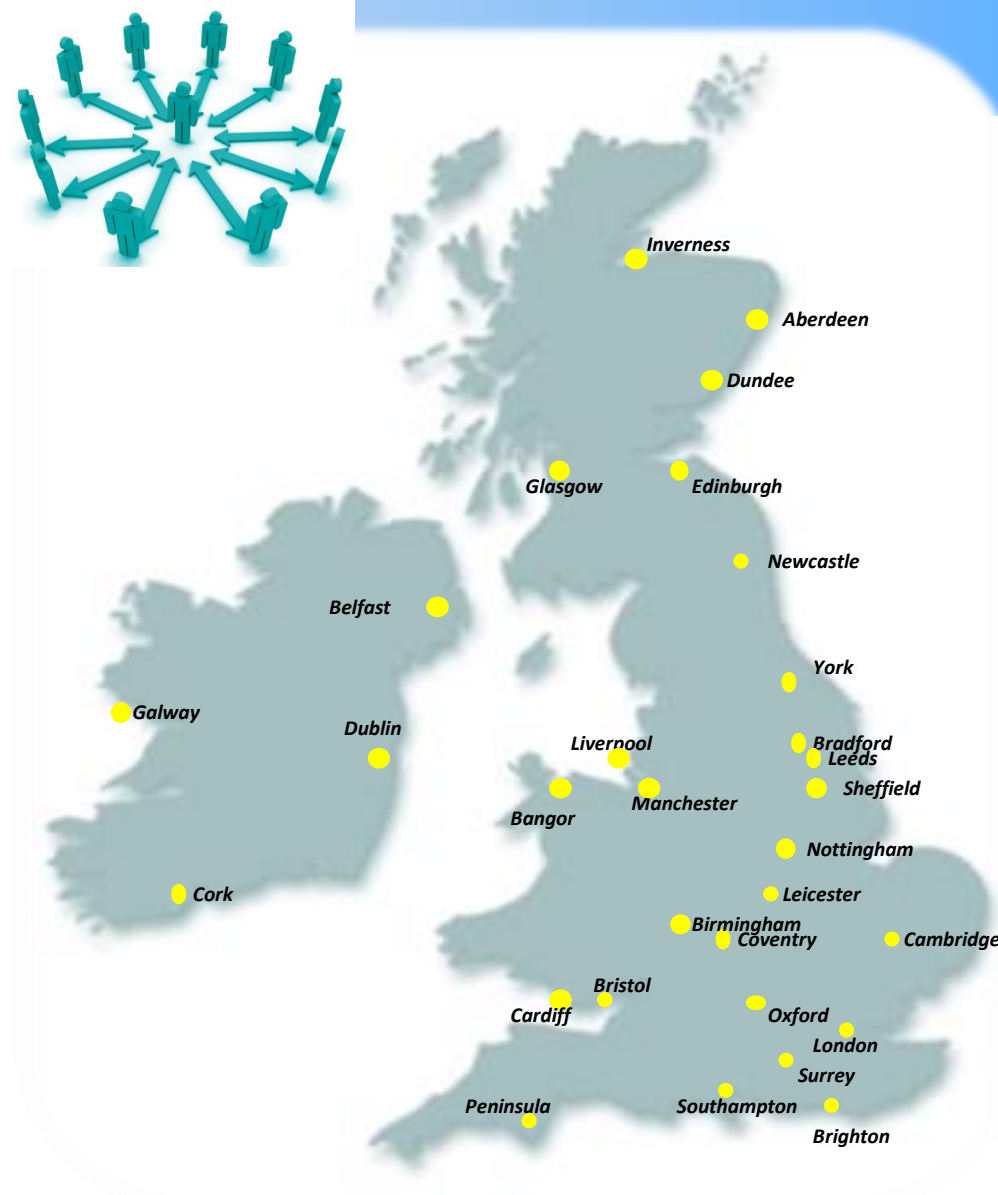


UKCRF NETWORK

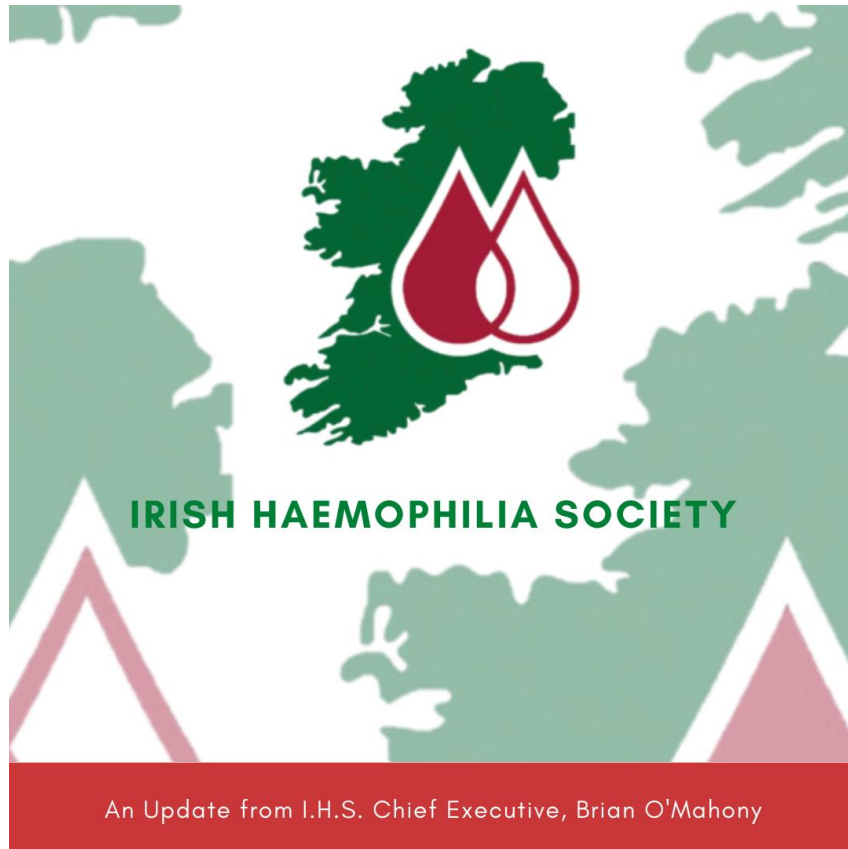
UK Clinical Research Facility Network

Part of UKCRF network

Allowed us to shadow the pharmacy journey and the research nurse journey



Patient Engagement



Haemophilia
Society of Ireland

Discussions on
pipeline of drugs

PPI

Informed Consent

- Experimental drug
- PIL 20 page document
- Early engagement
- Informed consent an iterative process

Regulatory Requirements

- Ethics Approval
- Health Product Regulatory Authority Approval
- **Bio-Safety Committee (TCD)**
- **Environmental Protection Agency**
 - Inspection
 - Recommendations
 - Notice in paper
 - Approval

GMO Considerations

- Requires special licence
- EPA inspection
- Requires special handling
- Chain of custody
- Vector shedding
- Special handling of waste
- Special disposal of waste



Medical Equipment

PPE- Standard Surgical Gown/Plastic Aprons, PrimaSoft Surgical Mask, Disposable Gloves-non Sterile, Disposable Eye Shield



**Standard Surgical Gown
/Plastic Aprons**

Disposable Gloves

PrimaSoft Surgical Mask

Disposable Eye Shield

Study opening

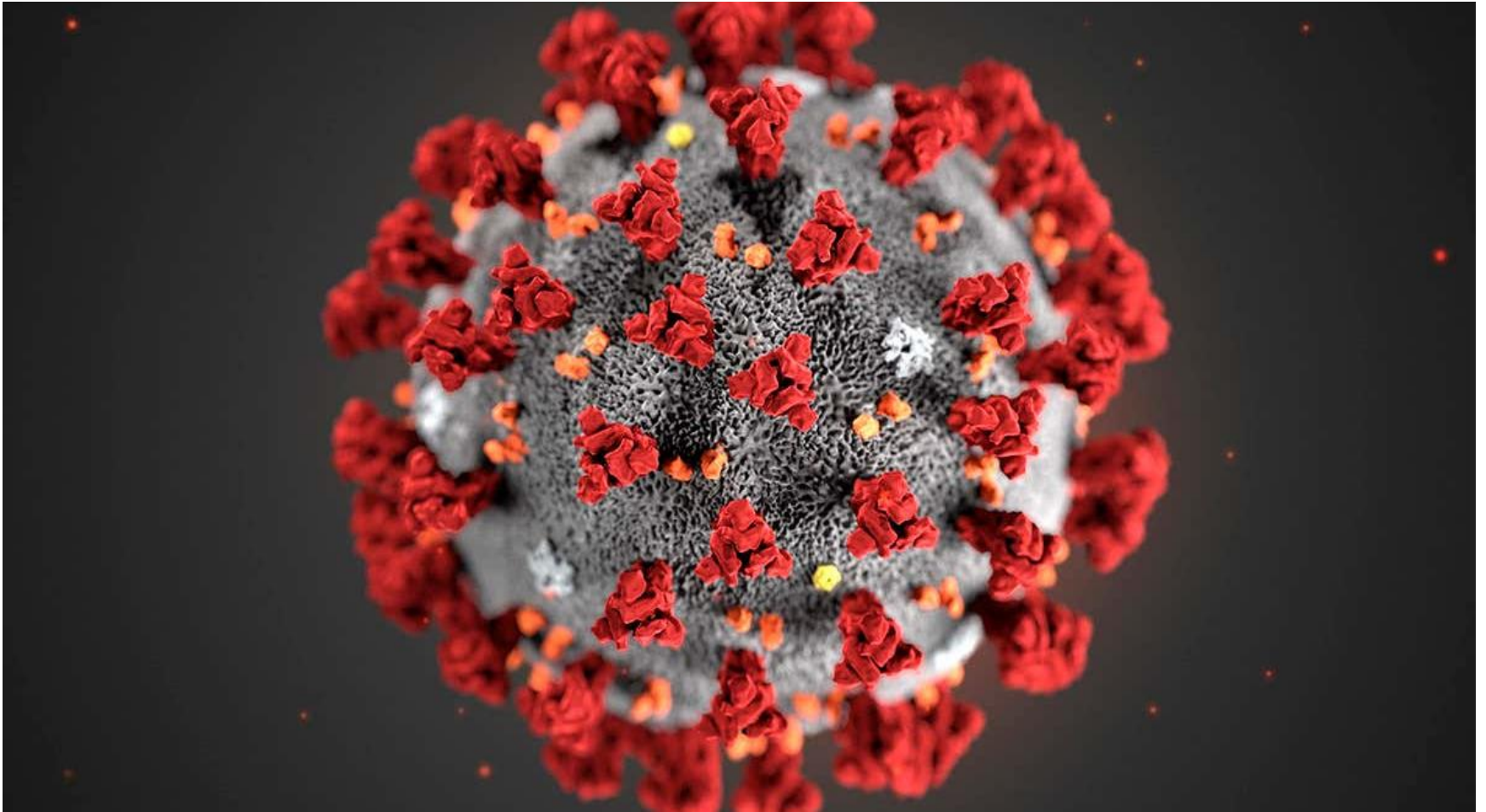
- SIV 26 Mar 2019
- 6 month lead in
- Informed discussion Apr 2019
- FPFV 08 May 2019

IV infusion



- 1 hour treatment
- Remain for safety monitoring 3 hours post
- Additional cannula placed for safety purposes
- GMO product – special considerations

Then Covid happens....



Then Covid happens....

- Protect the Staff
 - Halted investigator led studies into the unit
 - Halted new recruitment into open clinical trials
 - Side entrance
 - Minimize interactions with other staff , canteen etc
- Protect the Patient
 - Advised patient to cocoon
 - Symptom screening in advance of tx

Thinking Fast and quick

- Satellite unit set up in TTMI in nursing school
- Separate entrance
- All clinical trial patients seen here
- Risk assessed
- Informed resus
- Divided the team – covid vs non covid



Outcomes



No missed visits

Able to assess patients
as per protocol

No serious adverse
events

Living with Covid

- Patients are in the Long term follow up of the protocol, so seen 6 monthly
- Patients have been vaccinated
- No Serious adverse events
- Patients have not needed any Factor IX treatment since their dosing 18 months ago

Team work in NCC and CRF



Baby Genes



Baby Genes



Spinal Muscular Atrophy

- Rare disease
- Inherited genetic condition that makes muscles weaker
- Types 1 to 4
- Life expectancy up to 3 years (depending on type)



Current treatment

- Intrathecal injection
- Administered every 3 months
- Cost approx. €50,000 per dosing



Most expensive drug in the world

ZOLGENSMA
(Onasemnogene
abeparvovec)



\$2.1
Million
Per injection

Behind the Scenes

- Approached by the company – agreements in place
- Discussion with CEO's office here
- Discussions with CEO CHI
- EPA licence required
- Discussions with the HPRA
- Clinical governance
- Clinical Indemnity Scheme

MAP

- Managed Access Program
- Not Guaranteed
- Not a clinical trial
- First gene therapy to be administered to a child in Ireland



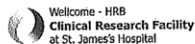
Multidisciplinary Team Approach

- IPATS team identified
- Sealed unit
- CRF Pharmacy
- SJH Pharmacy
- CRF GMO nurse
- Staff training
- SJH security





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Children's Health Ireland at Temple Street

Standard Operating Procedure

Title: Administration of Zolgensma (Onasemnogene abeparvovec)

Page 1 of 7

Document No:
AVXS-SOP-008

Version No:
2

Effective Date:
21 July 2020

Supersedes Version:
1

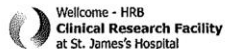
GENE THERAPY ADMISSION

ENTER Date of admission:

- Admission to Temple Street on.....
- On arrival plan to:



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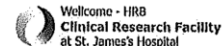
Children's Health Ireland at Temple Street

Aftercare guideline:

Start date: _____ End date: _____



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Children's Health Ireland at Temple Street

Standard Operating Procedure

Title: Management of Spills of Genetically Modified Organism (GMO) (Onasemnogene abeparvovec)

Page 1 of 6

Document No:
AVXS-SOP-006

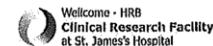
Version No:
1

Effective Date:
6th March 2020

Supersedes Version:
New Document



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Children's Health Ireland at Temple Street

Standard Operating Procedure

Title: Management of Accidental Exposure and Needlestick Injury (Onasemnogene abeparvovec)

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Document No:
AVXS-SOP-007

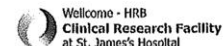
Version No:
1

Effective Date:
6th March 2020

Supersedes Version:
New Document



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Children's Health Ireland at Temple Street

Standard Operating Procedure

Title: Post infusion monitoring of SMA patients who have received Onasemnogene abeparvovec

Page 1 of 6

Document No:
AVXS-SOP-009

Version No:
1

Effective Date:
16th March 20

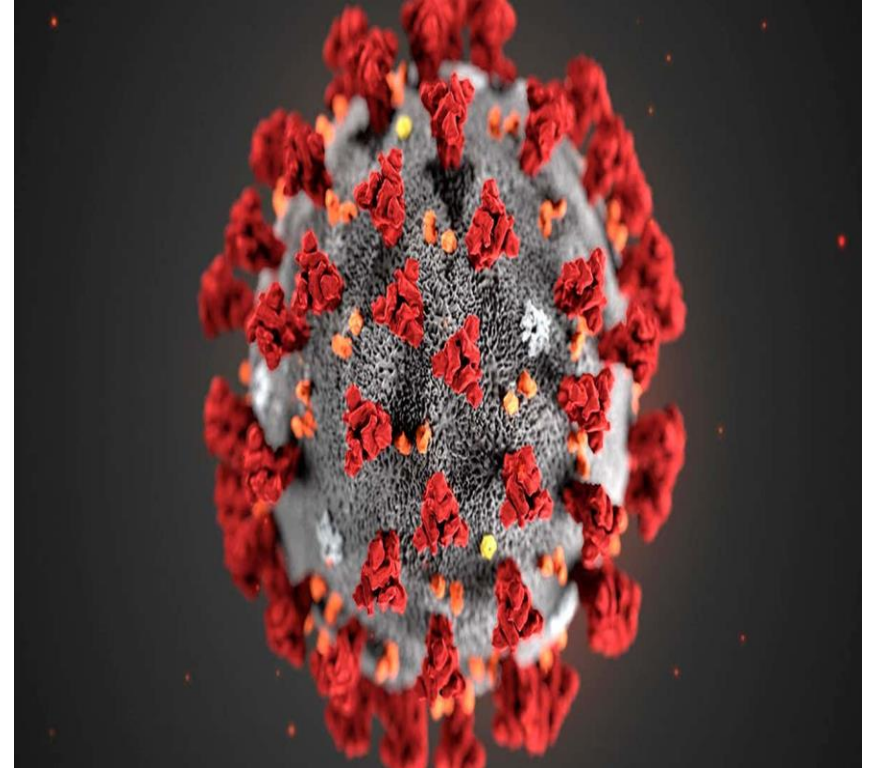
Supersedes Version:
New Document

Prepared by:



The Covid Effect

- Family advised to cocoon
- Dosing date brought forward
- Drug arrived on the last flight out of USA



Patient preparation

- Admitted to CHI day prior to treatment
- 2x iv lines placed
- Prednisolone 1mg/kg po given



Day of treatment

- Transport team (IPATS)
- 0700 Prednisolone 1mg/kg po given
- 0800 Arrives on ward. Receives handover
- 0830-0900 Transfers child to CRF
- 0900-1000 Settle in patient.
- 1000-1030 Drug prep
- 1030-1130 Zolgensma administration iv over 60min
 - Vital sign monitoring (HR, RR, SaO2, Temp, BP)
- 1130-1230 Observe patient x 1 hour
- 1230-1300 Transfer patient back to CHI



Example of a Dosing Crib Sheet

Pre-visit tasks – Friday 13 th March 20		
CRF	Source data file	<ul style="list-style-type: none"> Confirm appointment booked with CRF, Pt and Temple Street Consultant Ensure isolation room is ready Confirm patient medical file available Notify study team of upcoming dosing visit
		Contact SJH Security Team to confirm visit going ahead
Eligibility & Prescription [Sunday 15 th March 20]		
PI	Medical History	<ul style="list-style-type: none"> Bloods to be taken at ward level Bloods to be reviewed by Declan Vital signs to be taken 4-6 hourly Document patients eligibility Insert x2 PIVC patient(*Highlight best cannula. This will be used for dosing)
Morning of Dosing [Monday 16 th March 20]		
PICU Nurse and		<ul style="list-style-type: none"> Ensure IV line patent (ward) Vital signs am (Ward) Reviewed by PI – patient cleared for transfer Medical notes in situ (Mochana) Blood results printed off (Mochana) Consent for drug in medical notes (Mochana)
Patient arrives to CRF [10:00]		
PICU arrival	Whatsapp group set up. Karen to confirm on group once patient has left	

Dates/Times

Who is Responsible?

Assigned Tasks

Ensure Dosing Team knows assigned Tasks on the day

Dose Preparation – Our Approach

- Prepared in our cleanroom dedicated to gene therapies in a Grade A negative pressure pharmacy isolator located adjacent to the CRF gene therapy infusion suite



Infusion was administered using a Syringe Infusion Pump

- Braun Perfusor® space



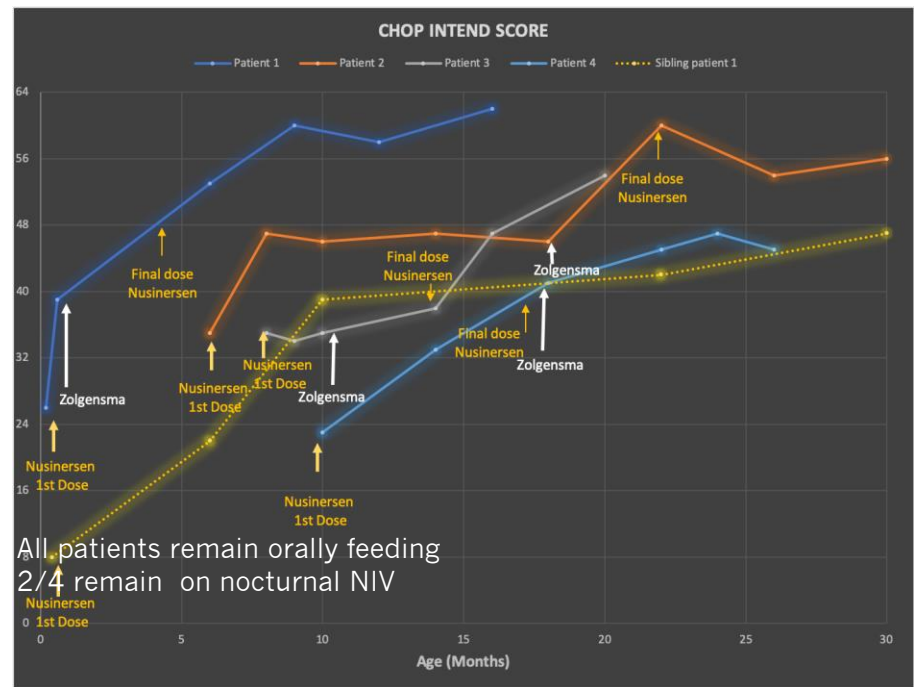
In the isolator, dose drawn into a pump compatible syringe and attached to the infusion line via a three way stopcock. The line and connector were first primed with normal saline



Patient Outcomes

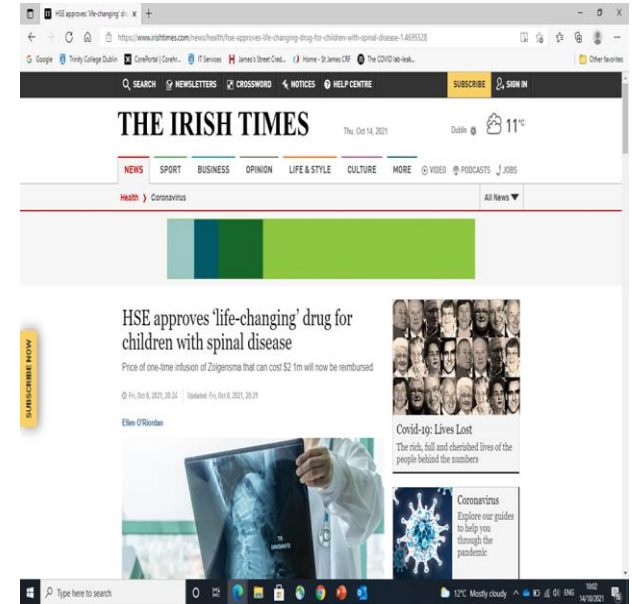
Functional assessments

- CHOP-INTEND
- HINE
- RUML
- Baseline and 4 monthly



Game Changer

- Price agreement has been reached
- BeNeLuxA agreement
- HSE reimbursement



Lessons we learned...

- Anything is possible!!
- Regulatory advice
- Clinical indemnity
- Standard operating procedures
- Handling and disposal of GMO product
- International delivery of GMO
- Training of staff
- Clearly defined roles and responsibilities
- Collaborative work and support of our hospital and colleagues

Acknowledgments

Haemophilia Gene Therapy

- All of the staff of the CRF
- NCC
- Wonderful group of research nurses based in the CRF and NCC
- SJH Pharmacy department
- Director of Nursing
- Momentum Cleaning staff
- TTMI
- Resus

SMA Gene Therapy

- All of the staff of the CRF
- CEOs of both hospitals
- Temple St hospital staff
- IPATS team
- SJH Pharmacy Department
- Director of Nursing
- SJH security
- Momentum cleaning staff

Questions/ Thank You



Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin



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