Advanced Therapy Treatment Centres

Northern Alliance Advanced Therapies Treatment Centre

Toolbox

Advanced Therapy Clinical Trials

Funded by

UK Research and Innovation

www.theattcnetwork.co.uk/centres/northern-alliance

nuth.NAATTC@nhs.net @naattc

Coordinated by

CATAPULT Cell and Gene Therapy

Foreword

The Northern Alliance Advanced Therapy Treatment Centre (NA-ATTC) was established in March 2018 and is one of three Advanced Therapy Treatment Centres (the others being iMATCH and the Midland and Wales ATTC) which together form a network across the UK, funded by Innovate UK and coordinated by the Cell and Gene Therapy Catapult. NA-ATTC is a consortium of 20 industry, NHS and academic organisations and is led by The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) and the Scottish National Blood Transfusion Service (SNBTS).

The purpose of NA-ATTC is to develop the systems and infrastructure to support the delivery of cell and gene therapies, with an aim of increasing patient access to Advanced Therapy Medicinal Products (ATMPs) at a regional and national level. Through clearly defined Work Packages (WPs) covering the whole ATMP delivery pathway from drug development and manufacture through to treatment of patients in our healthcare system, our work will accelerate the adoption pathway for these exciting and innovative class of medicines. Work Package 3 (WP3) focuses on Patient-Centred Advanced Therapy Delivery.

Prof. Marc Turner and Prof. Neil Watson, co-Directors of NA-ATTC
(SNBTS) (NuTH)

Preface

The aim of WP3 is to foster best practice in Advanced Therapy clinical trial design and implementation within the NHS ensuring a patient-centred approach to promote accessible, safe and effective trial delivery. Two groups have been established to facilitate this, the NA-ATTC Clinical Advisory Group and the Trial Coordination Unit:

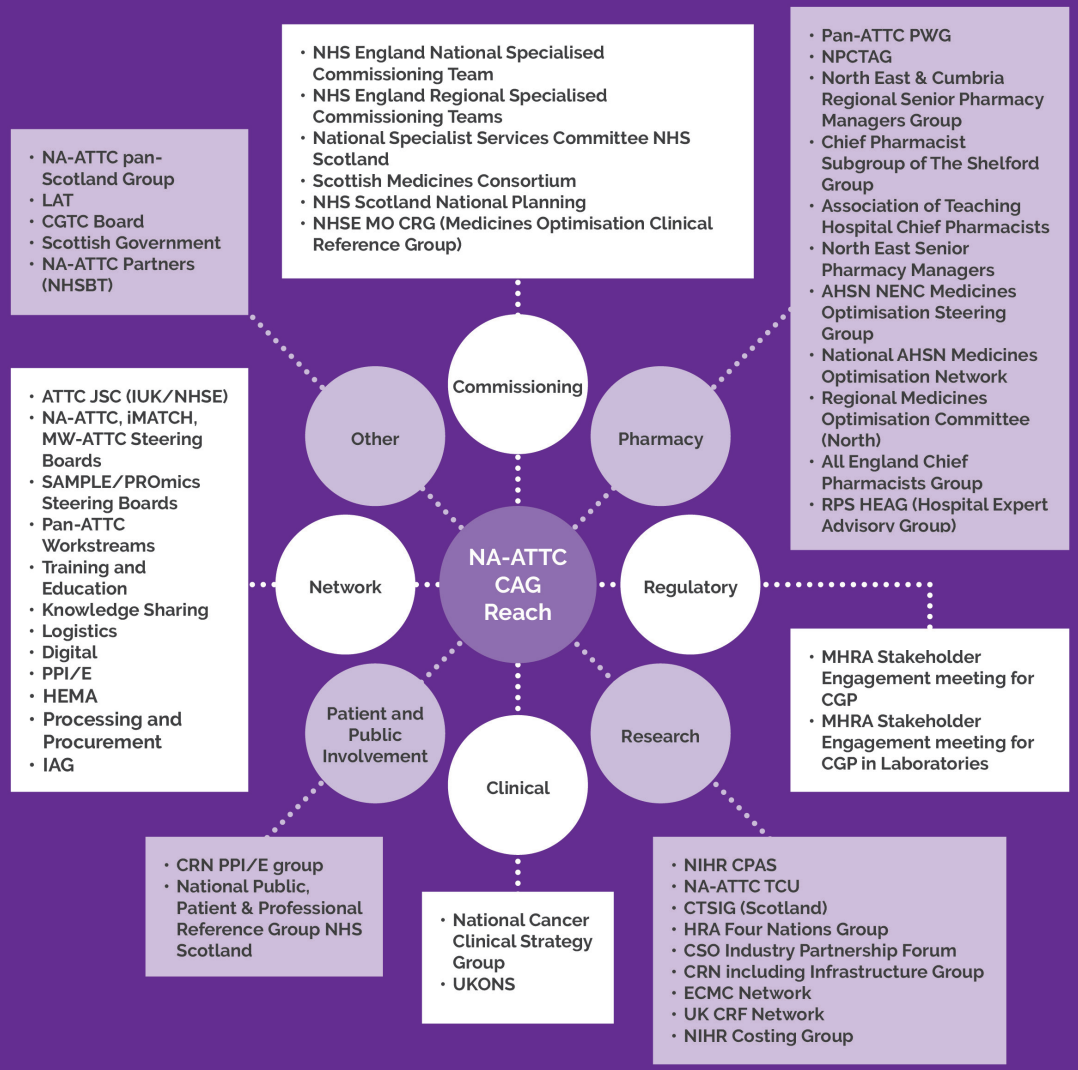
The Clinical Advisory Group (CAG) provides a forum including wide stakeholder representation to foster patient-centred AT development and provision in the UK. The group interacts with the Industry Advisory Group (IAG) to understand barriers to patient-centred AT adoption from an industry perspective; and provides feedback to the Executive Team on overall Northern Alliance progress and direction towards sustainable and equitable AT provision nationally.

The CAG and its members interact with a number of individuals and groups across a broad range of specialist services including Pharmacy, NHS Commissioning, Patient and Public Involvement, Regulatory Affairs, Research and Clinical Care, as well as the broader ATTC network across the UK (illustrated opposite). This ensures that all CAG activities are informed by, and in turn inform, best practice and innovative thinking nationally.

The CAG oversees the remit and activities of the Trial Coordination Unit (TCU).

The TCU, Chaired by Debbie Beirne (NIHR Leeds CRF Manager, Leeds Teaching Hospitals NHS Trust) has been established to facilitate and streamline trial delivery, identify best practice and pathways for sustainable wider adoption and long term patient follow up. The TCU has an open and flexible membership across NA-ATTC partner organisations in order to benefit from regional expertise and promote true collaboration across the Centre's geography. It is through the work of the TCU that this toolkit has been developed, to promote transparency and best practice in the set up and delivery of Advanced Therapy trials.

Prof. James Shaw, WP3 lead; Chair, NA-ATTC CAG



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Title	Type of Document	Author	Audience
Toolbox Introduction	Introduction	Gina Rutherford, NA-ATTC Project Manager, The Newcastle upon Tyne Hospitals NHS Foundation Trust; Prof James Shaw, Newcastle University and NA-ATTC Work Package 3 co-Lead; Debbie Beirne, Leeds Teaching Hospitals NHS Trust and NA-ATTC TCU Chair	Multidisciplinary clinical trial delivery staff including clinical and academic PIs. Commercial sponsors and industry clinical research / trial teams.
Organograms	Guide	Gina Rutherford, NA-ATTC Project Manager, The Newcastle upon Tyne Hospitals NHS Foundation Trust, with input from Leeds Teaching Hospitals NHS Trust, NHS Lothian and NHS Greater Glasgow and Clyde	Multidisciplinary clinical trial delivery staff including clinical and academic PIs. Commercial sponsors and industry clinical research / trial teams.
Costing Guideline for Advanced Therapy Clinical Trials	Guideline	Gina Rutherford, NA-ATTC Project Manager, Maria Allen and Daniel Baston, The Newcastle upon Tyne Hospitals NHS Foundation Trust, with input from Leeds Teaching Hospitals NHS Trust, NHS Lothian and NHS Greater Glasgow and Clyde. Additional input from the John Walton Muscular Dystrophy Research Team, Newcastle University	Multidisciplinary clinical trial delivery staff including clinical and academic PIs. Commercial sponsors and industry clinical research / trial teams. NHS R+D / R+I managers.
Collation of details of creation of guidelines for all regulatory approval documentation across the NA-ATTC region for Advanced Therapy Clinical Trials	Guideline	Information provided by The Newcastle upon Tyne Hospitals NHS Foundation Trust, Leeds Teaching Hospitals NHS Trust, NHS Lothian and NHS Greater Glasgow and Clyde and collated by Gina Rutherford, NA-ATTC Project Manager, The Newcastle upon Tyne Hospitals NHS Foundation Trust	Multidisciplinary clinical trial delivery staff including clinical and academic PIs. Commercial sponsors and industry clinical research / trial teams.

Introduction

The vision of The Northern Alliance Advanced Therapy Treatment Centre (NA-ATTC) is to increase patient access to Advanced Therapy Medicinal Products (ATMPs) regionally and nationally by growing a cost effective clinical delivery pathway which meets the needs of the providers of Advanced Therapy products. The centre has a patient reach of circa 15 million spanning the North of England and Scotland and is working across the two healthcare systems to achieve its key objectives. These objectives have been adopted in recognition of the fact that NHS institutions need to be able to adapt their skills, processes and practices in order to deliver these novel therapies effectively to patients.

Activities required to achieve NA-ATTC's wide-ranging remit have been broken down into a series of work packages (WPs), each with its own emphasis within an overall integrated project structure and led by experts in their respective field. The WPs utilise four exemplar Advanced Therapy products to develop and test systems and infra-structure.

These are:

- **An autologous CAR T therapy**
- **Monocyte derived macrophages**
- **Limbal stem cell products**
- **Gene Therapy products**

The Trial Coordination Unit (TCU) was created to satisfy some of the key objectives within WP3. This work package aims to provide a patient-centred approach to Advanced Therapy delivery and functions to foster best practice in clinical trial design and implementation within the NHS, promoting accessible, safe and effective clinical trial delivery.

The core TCU membership comprises representatives from four NHS sites including The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH), Leeds Teaching Hospitals NHS Trust (LTHT), NHS Lothian and NHS Greater Glasgow and Clyde (GGC), in addition to associated academic institutions Newcastle University and The University of Edinburgh. TCU members include Senior Research Nurses in adult and paediatric care, Senior Clinical Trial Pharmacists, a Clinical Research Facility Deputy Director, R&D/R&I Managers, a Clinical Trials Doctor, Consultant Haematologists, Project Managers and Clinical Trial Coordinators. Together the TCU members have worked to create an Advanced Therapies Clinical Trial Toolbox.

The Advanced Therapies Clinical Trial Toolbox encompasses information and guidelines to assist NHS Trusts, clinical leads, industry and academic partners to better understand the diverse and specialised processes involved in the set-up and operational delivery of Advanced Therapy trials and to streamline trial set-up across each NA-ATTC centre.

To promote verification and agreement, the documents included in this Toolbox have been reviewed by R&D/R&I managers at each NHS organisation. To ensure the Toolbox is up to date and accurate, each document will be reviewed and amended accordingly on an annual basis.

Overview of Toolbox contents

Organograms

Organograms have been created to enable easy identification of key contacts within each NA-ATTC clinical centre. They have been designed to include key points of contact for research in each NHS organisation and are intended to promote transparency, better support industry partners seeking to set-up a clinical trial at NA-ATTC centres and support a collaborative and integrated approach to clinical trial delivery across our NHS organisations.

Costing Guideline for Advanced Therapy Clinical Trials

The costing guideline was developed to support NHS sites to accurately cost Advanced Therapy clinical trials (clinical trials of Advanced Therapy Investigational Medicinal Products - ATIMPs) using the National Institute of Health Research (NIHR) costing template for secondary care. The NIHR template provides a framework to enable transparency and consistency of costs and to support NHS sites in budget negotiations with commercial sponsors. In October 2018, the use of the template was mandated within the NHS. ATIMPs are novel complex medicines and require a large number of distinct departments within the hospital site to work together to deliver the trial safely, efficiently and effectively.

The NA-ATTC Costing Guideline includes key stakeholder activity costs which should be considered for inclusion in the budget to ensure truly meaningful assessment of costs for effective trial implementation and delivery. The guideline has been reviewed by the NIHR costing group and has received the necessary verification and agreement for its use within NA-ATTC NHS sites.

Local Regulatory Approval Documentation

A guideline was created to aid understanding of, and collate the internal approvals required, for Advanced Therapy trials across each of the NA-ATTC NHS sites beyond confirmation of capacity and capability, including additional Genetic Modification / safety review requirements.

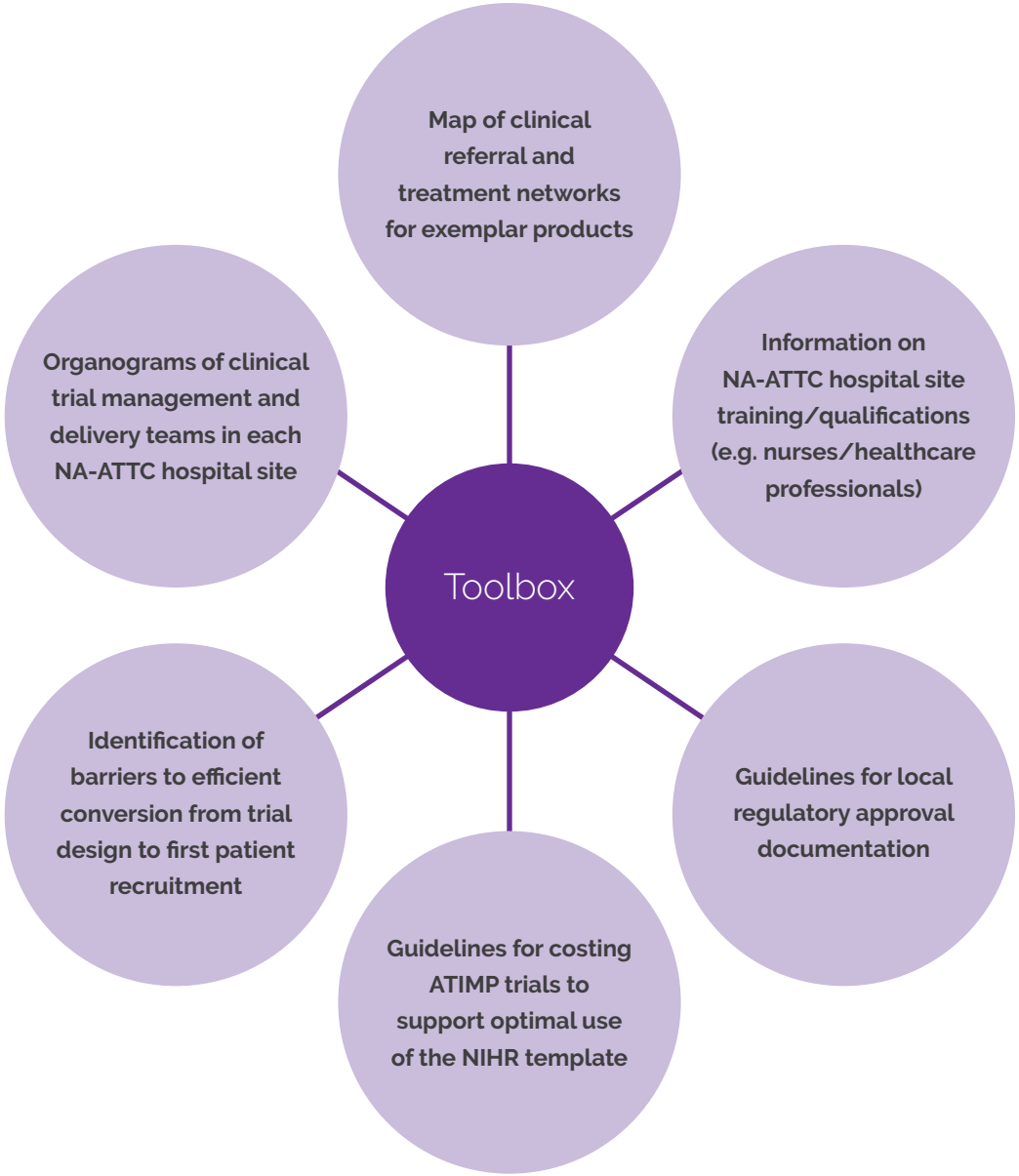
Map of Clinical Referral and Treatment Networks for Exemplar Products

These have been collated for internal use within the NA-ATTC to optimise trial participant identification / recruitment / retention.

Information on NA-ATTC hospital site training / qualifications has been collated.

Identification of remaining barriers to efficient conversion from trial design to first patient recruitment continues.

Toolbox


Map of clinical referral and treatment networks for exemplar products
Information on NA-ATTC hospital site training/qualifications (e.g. nurses/healthcare professionals)
Guidelines for local regulatory approval documentation
Guidelines for costing ATIMP trials to support optimal use of the NIHR template
Identification of barriers to efficient conversion from trial design to first patient recruitment
Organograms of clinical trial management and delivery teams in each NA-ATTC hospital site
Toolbox

Organograms

Organograms

Team	Sub teams	Contact
The Newcastle upon Tyne Hospitals NHS Foundation Trust	Commercial Research	**nuth.trustindustry@nhs.net**
	Non-commercial Research	**nuth.genericqueries@nhs.net**
	Pharmacy	**nuth.pharmacyRandD@nhs.net**
	Newcastle Joint Research Office	**https://newcastlejro.com**
Leeds Teaching Hospitals NHS Trust	Oncology Research Team	leedsth-tr.oncologytrials@nhs.net
	R&I Department	leedsth-tr.lthtresearch@nhs.net
	Children's Research Team	paedonc.research@nhs.net
	Research and Innovation	**https://www.leedsth.nhs.uk/research/**
NHS Lothian and University of Edinburgh	Academic and Clinical Central Officer for Research and Development (ACCORD) - sponsor	Enquiries@accord.scot **https://www.accord.scot/**
NHS Greater Glasgow and Clyde	Research & Development	Melissa.Robert@ggc.scot.nhs.uk
	Commercial– Portfolio 1	Julie.Lang@ggc.nhs.uk
	Commercial– Portfolio 2	Ross.Nicol@ggc.scot.nhs.uk
	Commercial– Portfolio 3	Vacancy
	Non-Commercial - Portfolio 1	George.Bakirtzis@ggc.scot.nhs.uk
	Non-Commercial - Portfolio 2	Graeme.Piper@ggc.scot.nhs.uk
	Non-Commercial - Portfolio 3	Mary.McAuley2@ggc.scot.nhs.uk
	R&D Pharmacy Facilitator	Angela.Carruth@ggc.scot.nhs.uk
	R&D Management Office	**https://www.nhsggc.org.uk/about-us/professional-support-sites/research-development/rd-management-office/**

The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH)

The Newcastle upon Tyne Hospitals
NHS Foundation Trust

As a world class provider of healthcare, and one of the largest NHS organisations in the UK, the Newcastle upon Tyne Hospitals NHS Foundation Trust has a wealth of experience and a successful track record in delivering commercial and non-commercial research.

As a tertiary centre in a wide range of therapy areas, the Trust has in excess of 1.7m patient contacts per annum. NuTH has more nationally accredited specialist services than any other group of hospitals in the UK and works closely with partner organisations including its main partner organisation - Newcastle University. NuTH plays an active role in the local National Institute of Health Research (NIHR), Clinical Research Network (North East and North Cumbria), and is a member of the Shelford Group, the Academic Health Science Network for the North East and North Cumbria (AHSN) and the Northern Health Science Alliance (NHSA). NuTH's breadth of expertise, combined with its unique organisation systems, places it in an optimal position to offer a seam-less service for delivering clinical research.

NuTH has active research teams in most therapy areas, with around 350 designated research staff and a directorate specifically for Research and Development. Clinical research at Newcastle Hospitals is based over three main sites which have Clinical Research Facilities supporting Phase 1, 2 and 3 studies. These facilities are underpinned by NIHR resource and the recently opened, dedicated Phase 3 unit is seen as an exemplar by NIHR. Newcastle has one of eighteen Experimental Cancer Medicine Centres in the UK specialising in early phase (1-2) Oncology studies. Newcastle Hospitals is consistently in the top ranks of the NIHR national league tables for numbers of recruiting studies, number of open commercial portfolio studies and percentage of commercial studies recruiting patients to time and target. For more information visit: **https://newcastlejro.com/**

NuTH ATIMP capabilities:

- **In collaboration with Newcastle University, NuTH offers Advanced Therapies GMP development and manufacturing services in specialist MHRA-licensed facilities**
- **Experience in delivering both cell and gene therapy clinical trials**
- **Ability to carry out class 1a & 2 gene therapy studies**
- **JACIE accreditation**
- **2 Apheresis units (one for adults and one for children)**
- **NHSE approved centre for provision of licensed CAR T products**

NuTH ATIMP specific additional approval committees:

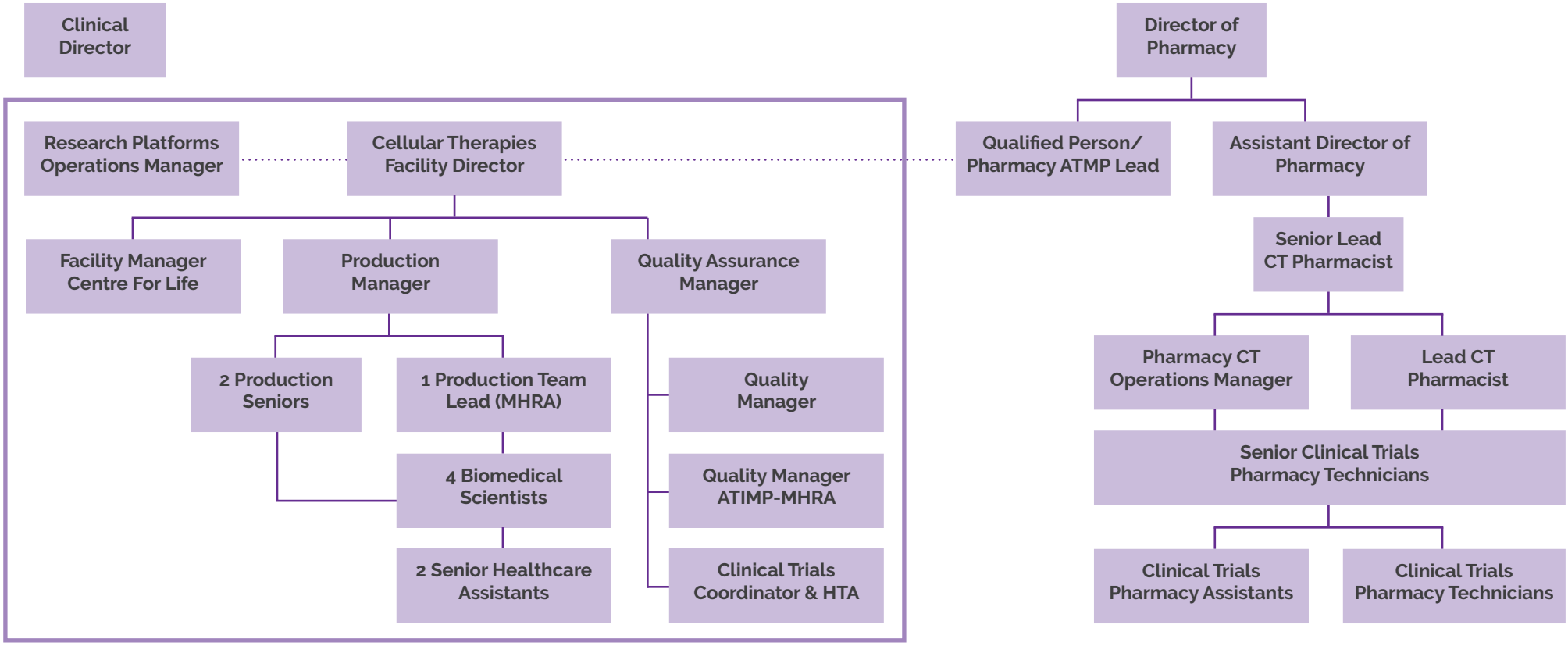
- **Somatic cell therapy and tissue engineered products (New Intervention Procedures Committee)**
- **Gene therapy products (Genetically Modified Safety Committee)**
- **Combination products (both committees)**

NuTH ATIMP portfolio:

- **Delivering both cell and gene therapy clinical trials**
- **Experience of delivering studies in a variety of disease areas including Cancer (Haematology and Solid Tumours), Spinal Muscular Atrophy, Diabetes, Limbal Stem Cell, Cardiology/Vascular, Haematology (non-malignant)**

Newcastle Cellular Therapies Facility and NuTH Pharmacy

The Newcastle upon Tyne Hospitals
NHS Foundation Trust



Leeds Teaching Hospitals NHS Trust (LTHT)

The Leeds Teaching Hospitals NHS Trust

The Leeds Teaching Hospitals NHS Trust is one of the largest and busiest acute hospital trusts in the UK and one of the largest teaching hospitals in Europe.

Leeds is a regional and national centre for specialist treatment, a world renowned biomedical research facility, a leading clinical trials research unit and also the local hospital for the Leeds community. LTHT contributes to life in the Leeds region, not only by being one of the largest employers with almost 18,000 staff, but by supporting the health and well-being of the community and playing a leading role in research, education and innovation. Leeds has access to some of the country's leading clinical expertise and the most advanced medical technology in the world with a £1 billion budget to provide local and specialist services for the immediate population of 770,000 and regional specialist care for up to 5.4 million. The Organisational values … "The Leeds Way" outlines LTHT's approach to providing healthcare and define how staff work together to deliver the best possible care and outcomes for the patients. One of LTHT's strategic goals is to be the best specialist provider and centre of excellence for Research, Education and Innovation. The Trust has a thriving research and innovation culture and firmly believes that being involved in cutting-edge research helps provide better care to patients. LTHT have an integrated Research and Innovation (R&I) team and a new state of the art Clinical Research Facility (CRF) gives industry and academic partners a unique opportunity to work directly with internationally leading senior NHS clinicians and dedicated highly skilled research delivery staff, in the heart of a modern NHS estate with all emergency facilities on site and access to 24/7 senior medical input. With regard to advanced therapy (ATIMP) capacity and capability the CRF provides a focus for the development and coordination of ATIMP delivery, institutional readiness and through R&I appropriate governance and regulatory compliance. (For more information visit **https://www.leedsth.nhs.uk/research/** and **http://leedscrf.nihr.ac.uk/).**

LTHT ATIMP capabilities:

- **Experience in viral therapies in conjunction with the University of Leeds (HSV in neuro-oncology, intrahepatic Vaccinia (VACV))**
- **Emerging expertise in solid tumour NAR T therapies and CAR T expertise in haematological cancers**
- **JACIE accreditation**
- **Biotherapy aseptic suite on campus**
- **ATIMP Community of Practice available for knowledge and expertise purposes, learning and teaching resource and networking, including relationships with NHSBT**

LTHT ATIMP specific additional approval committees:

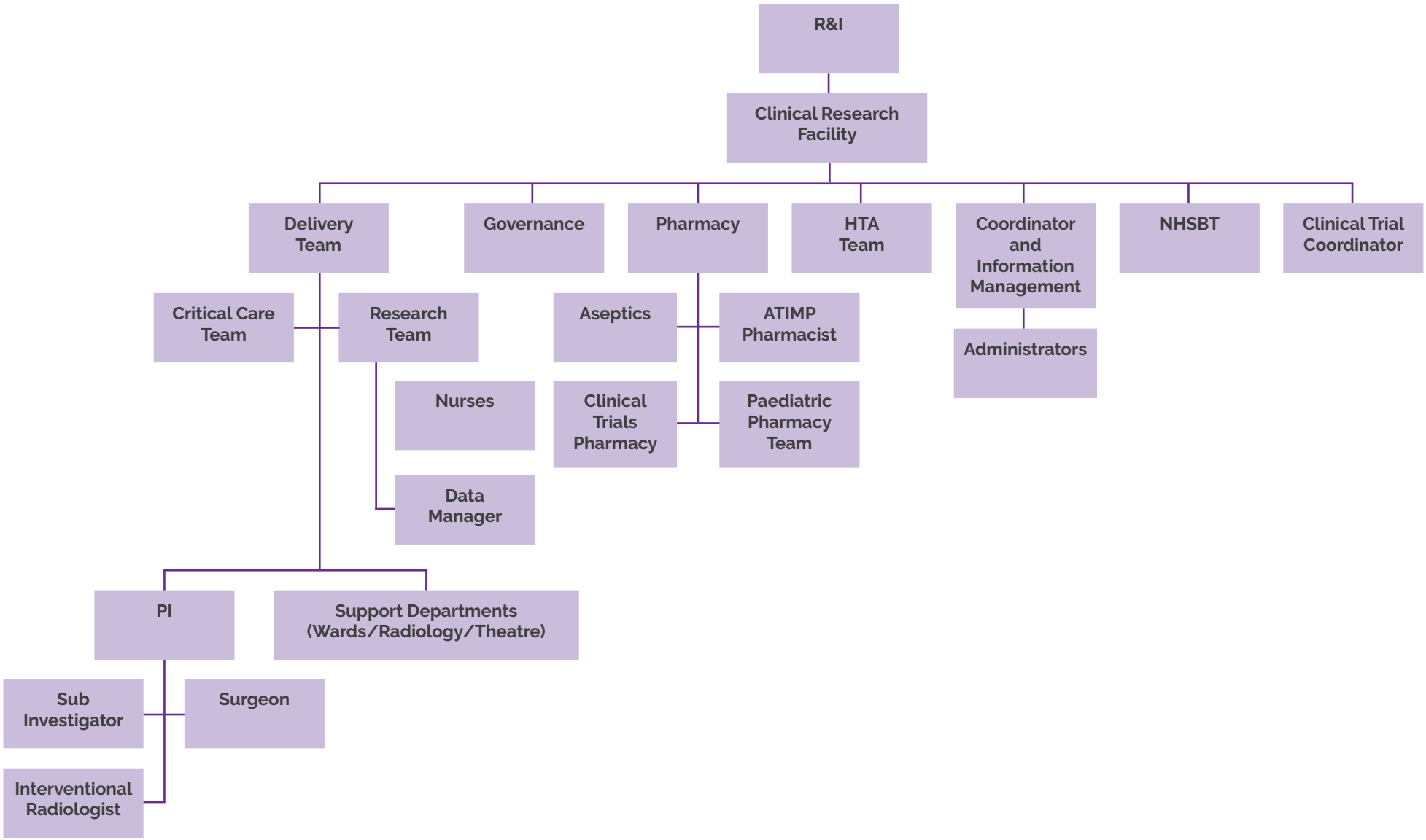
- **Biological Safety Committee**

LTHT ATIMP portfolio:

- **Oncolytic viral therapies**
- **Gene therapies in Oncology - solid tumour and haematology and emerging expertise in children's services**
- **Cellular therapies for Cardiovascular**

LTHT Research and Innovation Structure

The Leeds Teaching Hospitals NHS Trust



NHS Lothian / University of Edinburgh

NHS Lothian provides a comprehensive range of primary, community-based and acute hospital services for the second largest residential population in Scotland - circa 800,000 people.

(https://www.nhslothian.scot.nhs.uk/Pages/default.aspx)

The NHS Lothian and NHS Borders are managed from the ACCORD office in NHS Lothian, which is a partnership between the University of Edinburgh, Scotland's premier research university and one of the top five in Europe for Biomedical Sciences, and NHS Lothian Health Board, with a strong international reputation for its clinical research activities. This partnership is underpinned by the first joint Research Framework Agreement in Scotland. The ACCORD mission is "To promote clinical research excellence for the health and wealth of Lothian and Scotland."
In order to promote the health, economic and academic benefits of clinical research, ACCORD plays a leading role in the support and delivery of academic and commercial clinical research by streamlining clinical research governance systems and facilitating clinical trial start-up. Providing a one-stop support resource for researchers from the inception of their clinical research study to close down, with the aim of ensuring all research governance and regulatory requirements are met and all legal, ethical and scientific obligations are fulfilled, whilst also nurturing and attracting world-class research. **(http://www.nhsresearchscotland.org.uk/research-in-scotland/nodes/south).**

NHS Lothian and the University of Edinburgh work closely with the Scottish National Blood Transfusion Service (SNBTS), and encompass a Clinical Research Facility (Phase 1 accredited) at Royal Infirmary of Edinburgh (RIE), Western General and Sick Kids Hospital, an Edinburgh Clinical Trials Unit, a Clinical Imaging Facility within Queen's Medical Research Institute.

NHS Lothian ATIMP capabilities:

- **GMP MHRA licenced Cellular Therapy Manufacturing Facility (Operated jointly by Roslin CT and SNBTS)**
- **JACIE accreditation**
- **Clinical Apheresis Unit**
- **Ability to carry out Class 1 and 2 gene therapy studies**
- **Capability to handle CAR T products**
- **Stem Cell Lab**
- **Close working relationship with SNBTS to deliver ATMP products**

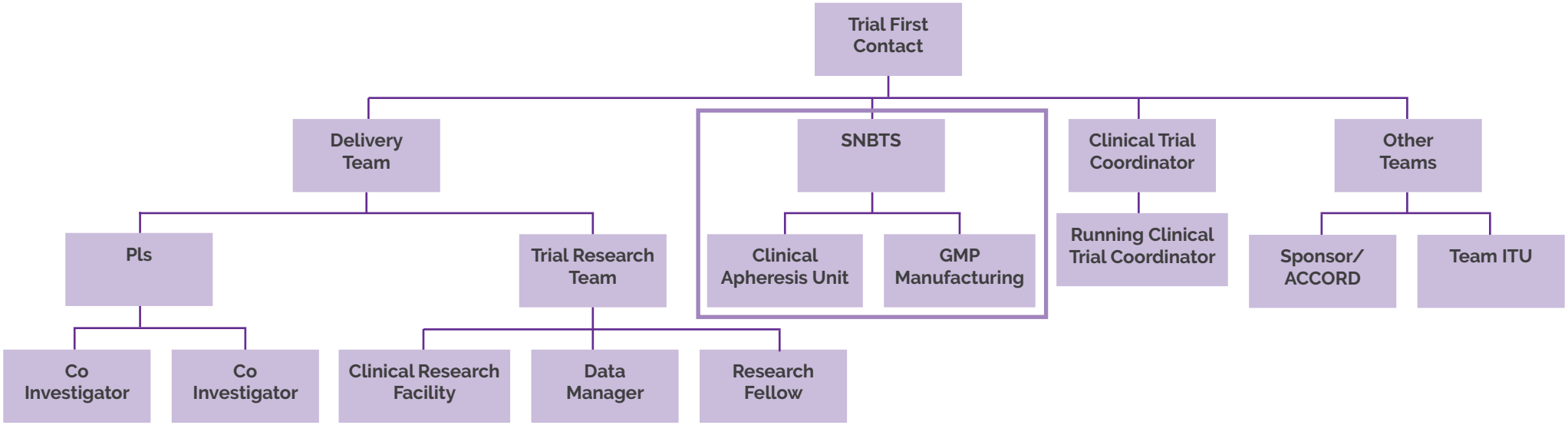
NHS Lothian ATIMP portfolio:

- **Experience within Liver Cirrhosis, Cancer (Haematology), Ophthalmology, Cardiovascular and Paediatrics**
- **Experience of commercial and non-commercial ATIMPs**

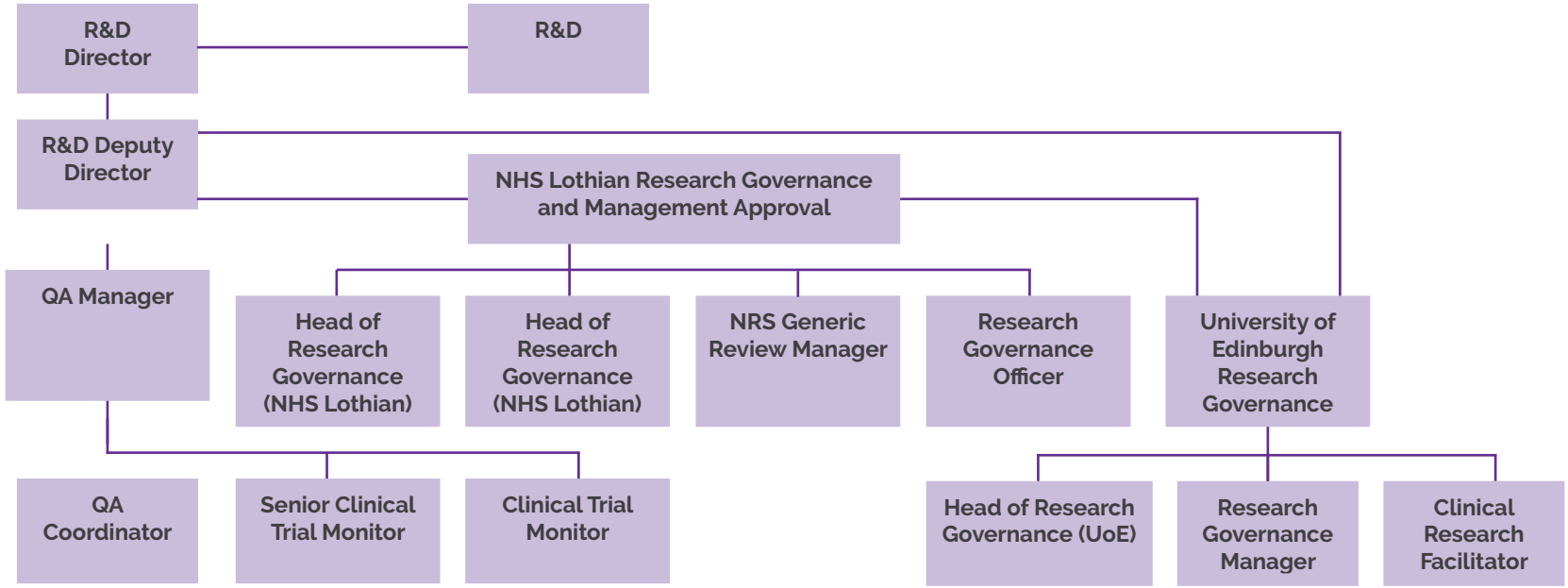
NHS Lothian ATIMP specific additional approval committees:

- **Combined Advanced Therapy and Genetic Modification Safety Committee with links to ACCORD and Board Level Committees**

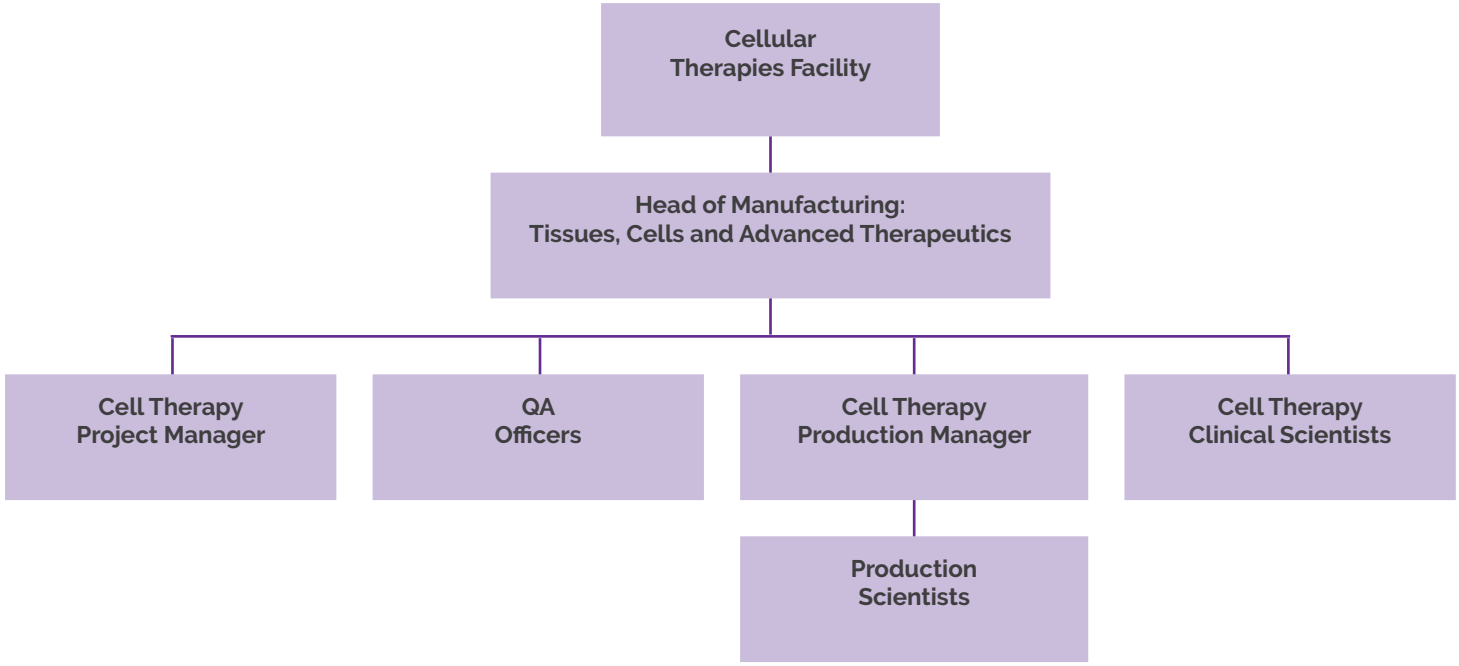
NHS Lothian / University of Edinburgh
Trial Delivery Structure



NHS Lothian / University of Edinburgh R&D Department Structure



NHS Lothian / University of Edinburgh Cellular Therapies Facility



NHS Greater Glasgow and Clyde (NHS GGC)

NHS Greater Glasgow and Clyde is the largest health board in Scotland, delivering services in 25 major hospitals, 10 specialist units and >50 health centres and clinics.

The GGC R&D region, also referred to as NHS Research Scotland (NRS) West Node, covers the NHS Greater Glasgow and Clyde, NHS National Waiting Times, NHS Lanarkshire, NHS Ayrshire & Arran and NHS Dumfries and Galloway areas. It is managed by the R&D office in NHS Greater Glasgow and Clyde. The West Node leads on the IT infrastructure for NRS by hosting the Scottish Research Management Database (SReDa) and the National Databases Coordinator.

NHS Greater Glasgow and Clyde and the University of Glasgow have a long-standing and close collaboration in clinical research. This collaboration is overseen by the Glasgow Health Science Partnership (GHSP) which ensures oversight and appropriate delegation of responsibilities between the two organisations. GHSP supports clinical research by bringing together world-leading clinical academics and state-of-the-art facilities with access to the West of Scotland NHS patient base of 2.8 million (52% of the Scottish population).

Facilities include Western Europe's largest acute hospital (the Queen Elizabeth University Hospital), one of Europe's largest cancer centres (the Beatson West of Scotland Cancer Centre), the largest non-commercial diagnostics laboratory in Europe and a plethora of world-leading research laboratories within Glasgow University and the CRUK Beatson Institute. The Experimental Cancer Medicines Centre (ECMC) provides a unique infrastructure linking the world-leading early phase drug development programme with the NHS biorepository and analytical laboratories in Glasgow and elsewhere in the UK ECMC network.

The Royal Hospital for Children, Glasgow is also based on the Queen Elizabeth University Hospital campus and has 244 paediatric beds and the neonatal unit for the Royal Hospital for Children and the Queen Elizabeth University Maternity Unit. The hospital provides a large number of specialist services to the West of Scotland and the wider population of Scotland in addition to the full range of secondary care services to people of Greater Glasgow and Clyde. Specialist services include: cardiology and cardiac surgery, renal and bone marrow transplantation. For a number of these services, the children's hospital is recognised as the sole provider in Scotland.

GGC support our researchers and partners throughout the clinical research process with a range of services designed to ensure scientific integrity, fast approvals, effective governance, proactive project management and robust data management and reporting processes. The GGC support function also includes developing a 'fit for purpose' translational research infrastructure within the NHS. The partnership's research expertise includes world-class strength in Cancer; Cardiovascular and Medical Sciences; Infection, Immunity and Inflammation; Neuroscience and Psychology; Paediatric Medicine; Social Sciences and Health Economics. GGC have state-of-the-art research imaging capabilities including CT, 3T MRI and has been strengthened with the addition of a 7T MRI scanner **(http://www.nhsresearchscotland.org.uk/research-in-scotland/nodes/west).**

NHS Greater Glasgow and Clyde (NHS GGC)

NHS GGC ATIMP capabilities:

- Haematopoietic Stem Cell Lab and Paul O'Gorman Leukaemia Research Centre (POG-LRC) are located in the Gartnavel General Campus
- Dedicated LN2 storage facility for ATMP products
- Apheresis Unit located in the Gartnavel General Campus
- Dedicated Gene Therapy Isolator within Beatson West of Scotland Cancer Centre Dept of Pharmacy
- JACIE accreditation
- Previous experience in delivering both cellular therapies and gene therapy clinical trials
- HTA licence(s) in place for apheresis products as starting materials
- HTA licence in progress for tumour tissue as starting material

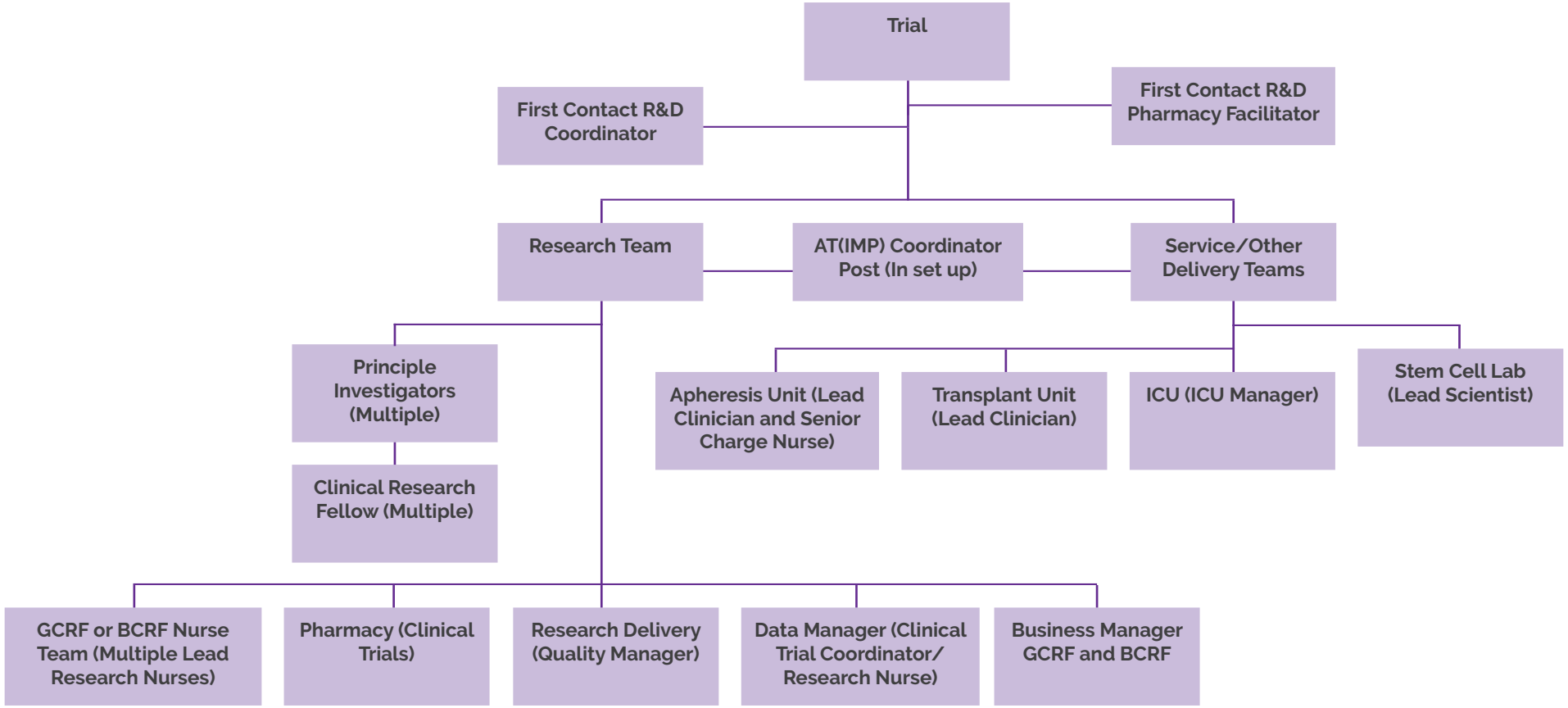
NHS GGC ATIMP specific additional approval committees:

- GM Safety Committee
- First in human phase I committee

NHS GGC ATIMP portfolio:

- Experience in running clinical trials of cellular products for indications including GI, Oncology-Haematology and Stroke
- Experience of running clinical trials of GMO products within Oncology-Haematology
- Selected for accreditations as a centre to deliver licensed CAR T Cell products
- Several clinical trials in set up with ATIMPs, e.g. TILs, CAR T cells, stem cells and T cells with enhanced TCRs in set-up as well as multiple trials involving GMO products
- Experience in delivering treatment with unlicensed cellular therapies, e.g. Cytotoxic Lymphocytes and Mesenchymal Stem Cells

NHS GGC Research Structure



Costing Guideline for Advanced Therapy Clinical Trials

ATIMP Costing Guideline

The sections detailed below provide guidance for the costing of clinical trials of Advanced Therapy Investigational Medical products (ATIMPs). This guideline identifies key stakeholder costs that can be considered for inclusion in the budget template when costing an ATIMP trial that are crucial to a realistic assessment of activity deliverable costs and may differ from those of a traditional Clinical Trial of an Investigational Medicinal Product (CTIMP). Where the study is industry sponsored, it is assumed the NIHR industry costing template is used and this guideline aids completion.

The document is for information purposes only and it is the responsibility of the research team, R&D and finance teams within each institution to accurately cost the study in line with the requirements of the study protocol.

1) Set-up, management and close down tasks

Item	Description	Comment
R&D management fee	Incorporates the local processes involved in the confirmation of capacity and capability which is required by the HRA. The management of close down activities locally in line with sponsor requirements.	Routinely under costed. Need to consider the level of activity at a local level. For example, organising Advanced Therapy review committees, liaising with non-traditional departments (e.g. Intensive Care Unit, waste management).
Site initiation fee	Includes the time taken for investigator and research staff to be trained regarding the requirements of the clinical trial protocol.	Due to the complexity of ATIMP trials additional training of research and support department staff is often required. Also increased level of staff required at Site Initiation Visit (SIV) and activity pre SIV. The standard cost used for CTIMP trials does not come close to covering SIV cost alone.
Chief Investigator Principal Investigator fee	Fee for all principal investigator activities.	The NIHR costing tool includes chief investigator fee. Principal investigator fee is not routinely included. This should be considered.
Archiving fee per box	The study specific archiving duration as defined by the MHRA.	In line with GCP requirements, ATIMP clinical trial records must be stored for a minimum of 30 years.
Apheresis unit set-up fee	Chargeable for departments who provide study support.	Requirement of support department for procurement of starting material. Unique to ATIMP clinical trials. Nationally agreed tariffs within National Blood Service may apply.
Cellular therapy lab set-up fee	Chargeable for departments in proportion to scheduled activities for the study and ongoing activities within the cell therapy lab.	The handling of starting material and then the IMP is unique to Advanced Therapy trials.
Biochemistry/ Haematology Lab set-up	Chargeable for departments who provide study support.	Check requirements detailed in study protocol.

ATIMP Costing Guideline

B) Other costs

Item	Description	Comment
Amendment Fee	Category A or B amendment fee, chargeable per amendment.	Currently £500 for Phase 1 study amendments, however this should undergo R&D committee review.
Screen failure	Pro rata for visits and investigations perform.	Very high screen failure rates typical in these studies. Suggest including no cap (to avoid re-negotiation of contracts). Also funding should be front loaded so it covers this activity. Also consider cost implications of bringing patients back to explain why they failed screening.
Clinical Trial Patient Travel	Recommended up to £250 per visit for adults, any costs in excess of this to be agreed by the sponsor before incurring the cost.	Sites delivering ATIMP trials often serve a large geographical area requiring patients to travel a substantial distance. Also given the intensive visit schedule that is required for such complex studies, it is important to consider covering all reasonable travel expenses. Paediatric patients: Costs would need to cover both the patient and a carer travelling. Some families may wish for 2 parents/ carers to accompany a child - to be agreed by the study sponsor.
Clinical Trial Patient Refreshments	Up to £20.00 per subject visit for adults. For paediatric patients consider up to £40.00. Any costs in excess of this to be agreed by the sponsor before incurring the cost.	For paediatric patients the cost would need to cover both the patient and their carer.
Disposal of Genetically Modified Waste	Disposal of any items that have contained a genetically modified product (e.g. giving set) after ATIMP has been administered.	Consult waste management team at your institution for specific instruction on the disposal of GM waste. Also need to factor in autoclaving, single use of equipment, sharps bins. Administration materials - the giving set is one element but cost of protective equipment etc. not generally considered at present. Paediatric patients: Depending on the age of the child and the type of ATIMP, special precautions may need to be taken with disposal of nappies and for parents to wear gloves when handling nappies.
Upfront Cost	Payment from sponsor for member of staff to work on the clinical trial	This would need to be appropriately justified on the costing template to show how much of a Whole Time Equivalent member of staff the total time entered for study assessments amounts to. This can be found on the Per Patient tab, in the 'Per Visit Time allocations for research staff (minutes per visit)' table (this is located under the 'Study Research Procedures and Related Activities' table), under the 'WTE for study' column. Once a WTE is determined, you should then obtain a quote from your Finance department for the relevant staff salary so that the full request can be submitted to the Sponsor. In the first instance, a request for upfront costs should be made by the study Principal Investigator (PI) to Sponsor. If agreed, the associated per patient timings for that member of staff should be removed from the per patient budget and a lump sum cost for the staff salary be entered into the costing template (speak to your Finance team to agree the best place to put this on the costing template). The payment schedule for these upfront costs should be properly set out in the costing template and the contract (i.e. if the salary is required to be paid in full upon receipt of the Green Light to begin the study). This expectation should be clearly stated in the costing template and the contract.

ATIMP Costing Guideline

2) Per Patient Costs

In this section standard timings have been included for assessments commonly included in the budget. This is not intended to replace a formal costing review and the protocol.

Assessment	Clinical time (minutes)	Nurse time (minutes)	Admin time (minutes)	Comment
Informed consent (study)	75	30		
Informed consent (Leukapheresis)		30		Due to the complexity of ATIMP trials, consider allowing more time to complete informed consent. Paediatric patients: Assent may be required dependent on the age of the child. For an early phase trial this would take 15 minutes in addition to parental consent.
Informed consent (chemotherapy)	10			Required in addition to the study informed consent Paediatric patients: As above.
Re-consent (sponsor lead amendment)	20	10		Required in addition to the study informed consent Paediatric patients: As above.
Eligibility Criteria Revie	30	60		
Medical History/ Demographics	45	30		
Physical Exam (incorporating neurological exam)	30	20		
Neurocognitive Assessment	15			Included for safety purposes to monitor potential neurotoxicity following CAR T-cell therapy.
Performance Status	5			
Concomitant Medication check (Screening)	5	15		
Vital Signs (Temp, BP, Pulse, respiration)	10 (Adult) 20 (Child)	10 (Adult) 20 (Child)		Paediatric patients: It is important to consider that this may take longer in children.
Concomitant Medication check (On study)	5	15		
Review of laboratory results	10			
Administer study drug in clinic (Preconditioning)		90		
Blood sample Collection only		10 Adult 30 Child		Paediatric patients: This could take 30 minutes or more in children especially if peripheral access/cannula is required.
Blood sample processing		30-90*		*Dependent on the processing requirements- consult study protocol for further information.

ATIMP Costing Guideline

2) Per Patient Costs continued

Assessment	Clinical time (minutes)	Nurse time (minutes)	Admin time (minutes)	Comment
Specimen dispatch by post/courier		60		
Prescription Pre-Conditioning Medication	10	10		
ATIMP Infusion		*		*Consult protocol and consider route of administration to accurately. Identify the time take for the ATIMP infusion.
CRF/eCRF training	60	60	60	Training will be required particularly if the study is using eCRF.
CRF/ eCRF completion including data transfer and query resolution	5	30	20	
Review/reporting AEs	30	60		
Study Coordination- site file maintenance			30	Per patient visit.
Monitoring (on site visit/ remote monitoring communication)	*	*	*	*This item should be costed on an hourly basis, so cost as an additional item rather than a core cost. Visits usually include clinical, nurse and admin time. The monitor will usually want to spend some time with the study PI (30-60 minutes) and the Data Manager/Nurse will need to be available during the entire visit to answer queries. Depending on organisation, the monitor will also visit pharmacy and/ or the cell handling facility. Additionally, remote monitoring calls should be charged at an hourly rate for the staff involved.
Protocol Amendment training	*	*	*	*Consider adding an hourly cost to the additional Itemised costs tab for staff training on Amendments/ study up-dates.
Teleconference communication with sponsor	60	60		Consider including time for teleconferences and remote communication with sponsor (e.g. safety review calls, patient updates).
Consultant specialist review (Neurology, respiratory. Gastro, surgical, microbiology)	60			Consider the potential toxicities associated with specific ATIMP being studied and include specialist clinical review as required.

ATIMP Costing Guideline

3) Study Investigations

Investigation	Description	Comment
Starting material collection *Doesn't always have to include Apheresis	E.g. apheresis or surgical collection of starting material.	ATIMPs often involve the collections of a starting material for manufacture. This can need 2 specially trained staff and can account for a day's work per patient.
Overnight stay - Inpatient ward	Charged per night for a bed in an inpatient ward or CRF.	Refer to study protocol regarding the recommended inpatient stay. For paediatric patients consider the need for a guest bed or accommodation for parents/ guardians.
Overnight stay - Clinical Research Facility (CRF)	Charged per night for a bed in CRF, including the cost of staffing.	In CRF, must charge for the cost of staffing for 12 hours for 2.5 nurses as per local policy (check with CRF for spe-cific cost). Also consider additional costs to the unit for paying staff 5pm-8pm and weekends.
Overnight stay Critical Care	Charged per night for an inpatient bed in critical care	Due to toxicity profile of ATIMPs consider the possible need for a critical care bed.
Cytokine release syndrome (CRS)	Consider treatments for CRS associated with CAR T therapy	Consult pharmacy regarding cost of Tocilizumab or other medications for CRS associated with CAR T therapy.
Viral Screen	Standard screen for communicable viruses	Consult study protocol for specific study requirements. For example, with CAR T therapy a viral screen performed within 30 days of the starting material entering the manufacturing facility is often required. A second viral screen performed within 7 days of procurement of the starting product is also required for product release.
Central venous catheter	Hickman line/PICC. Central administration may be required, consult protocol.	May be required if study incorporates a preconditioning chemotherapy regimen. To promote safety when administering preconditioning chemotherapy, a central venous catheter could be used instead of a peripheral cannula. If a central line is used, also remember to include consumable and staff time when costing. Consult clinical team responsible for administering preconditioning chemotherapy for their preference. Paediatric patients: It is standard practice for central venous devices to be inserted under general anesthetic therefore consider cost implication on theatre lists/anesthetics.
Platelet transfusion	Consider incorporating supportive therapies, which can be charged per unit.	Consider including supportive therapies that will be provided to patients during enrolment.
Group and Save (blood group check)	Consider incorporating supportive therapies	Consider including supportive therapies that will be provided to patients during enrolment
Blood transfusion	Consider incorporating supportive therapies	Consider including supportive therapies that will be provided to patients during enrolment
Unscheduled visits	Occasionally unscheduled visits need to take place e.g. to repeat an assessment or take an additional blood sample	This should be addressed in the Additional Itemised Costs with a statement to request that assessments that are conducted as part of an Unscheduled Visit will be costed as they appear in the Per Patient costs.
Biopsy	Including tumour, lymph node or bone marrow biopsy	Paediatric patients: It is standard policy that biopsies are performed under general anaesthetic. Consider cost implications on theatre lists/ anaesthetics.

ATIMP Costing Guideline

4) Local Research Governance Process

This may include establishing new committees if those already in existence are not appropriate. It also includes the cost for taking a study to existing committees within an organisation for review. Often meetings are held on an ad hoc basis but can involve 8-10 staff members required to review the study. It is important to liaise with your local R&D department to determine the number of staff required for the review, the amount of time taken and also grades of staff involved so costs can be recovered appropriately. Nomenclature may vary between organisations but examples of committees include: Genetic Modification Safety Committee, New Interventions Committee, Drugs and Therapeutic Committee.

Local Site Level Approval Process for Advanced Therapy Clinical Trials

Local Regulatory Approval Process for Advanced Therapy Trials - NuTH

Key regulatory approval considerations when setting up an ATIMP study in The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH)

An overview of the ATIMP study set-up process is provided in an earlier section of this toolbox.

Genetic Modification Safety Committee

The Genetic Safety Modification Committee (GMSC) performs the assessment and approval of gene therapy medicinal products (e.g. somatic cell and gene therapy products).

The sole statutory purpose of the GMSC is to advise the Trust whether the risk assessments undertaken on activities related to the use of GM products are adequate. Prior to the commencement of any project involving the use of GM material, the full risk assessment must be completed and reviewed by the Committee. Prior to submission of the risk assessment, appropriate approvals (e.g. MHRA, HRA, GTAC) should be obtained. A meeting of the GMSC will be convened as soon as possible following submission of the risk assessment form. Once reviewed, the final decision of the Committee is conveyed by email to the Principal Investigator (PI) following the meeting. The PI must ensure that copies of the local Standard Operating Procedures (SOPs) are forwarded to the chair of the GMSC prior to commencement of the study.

New Interventional Procedures Committee

The New Interventional Procedures Committee (NIPC) develops and monitors strategies for the introduction of new clinical procedures within the Trust. This also applies to any new high risk interventional procedure which has not been performed as part of a clinical trial, including those which have been approved by the Trust's R&D Department. It is the responsibility of the PI to complete the New Interventional Procedure Registration Form and the completed form is required to be sent to the NIPC secretary 14 days in advance of the next meeting.

Confirmation of Capacity and Capability (CofC&C) to deliver research

The Health and Research Authority (HRA) approval process for NHS England comprises a centralised risk assessment undertaken by the HRA and reviewed by an NHS England Research Ethics Committee. NHS organisations are responsible for confirming their capacity and capability to deliver the study. In NuTH the PI and the research delivery team are responsible for assessing their capacity and capability to deliver a research study, as well as seeking assurance of any support departments. Assurance of PI/delivery team capacity and capability is achieved by completion of the Capability form which is then submitted to R&D for full review. An overview of the R&D Confirmation of Capacity and Capability review process is detailed as follows;

- **An R&D officer assesses the submitted documents including the capacity and capability form for accuracy.**
- **All studies that include pharmacy also undergo a separate pharmacy review.**
- **All studies also require a finance review, this is facilitated by the R&D officer. The allocated officer will liaise with the research delivery team and sponsor regarding any queries related to finance, other departments and the contracting process.**
- **Once all queries are resolved, the R&D Officer will liaise with the sponsor regarding the contract review/finalisation/signatures.**
- **Partially executed contracts are requested from the sponsor and are sent to signature by the Trust Secretary.**
- **Once returned, the R&D Officer will issue a CofC&C email with the contract attached, addressed to the PI with all the parties involved copied in.**

Clinical Trial Risk Assessment for ATIMPs

All ATIMP clinical trials are classed as 'high risk' when requesting sponsorship from NuTH. The Regulatory Compliance Team act on behalf of NuTH in response to requests for sponsorships for ATIMP trials. It is the responsibility of the Sponsor (Regulatory Compliance Manager) to complete a risk assessment with this task often delegated to the Chief Investigator with input from the trial management team. Despite the completion of the risk assessment being an ongoing collaborative process, the final decision with regards risk categorisation lies with the Sponsor.

Further information regarding the study set-up and approval processes in NuTH can be found on the Newcastle Joint Research Office website **https://newcastlejro.com/**

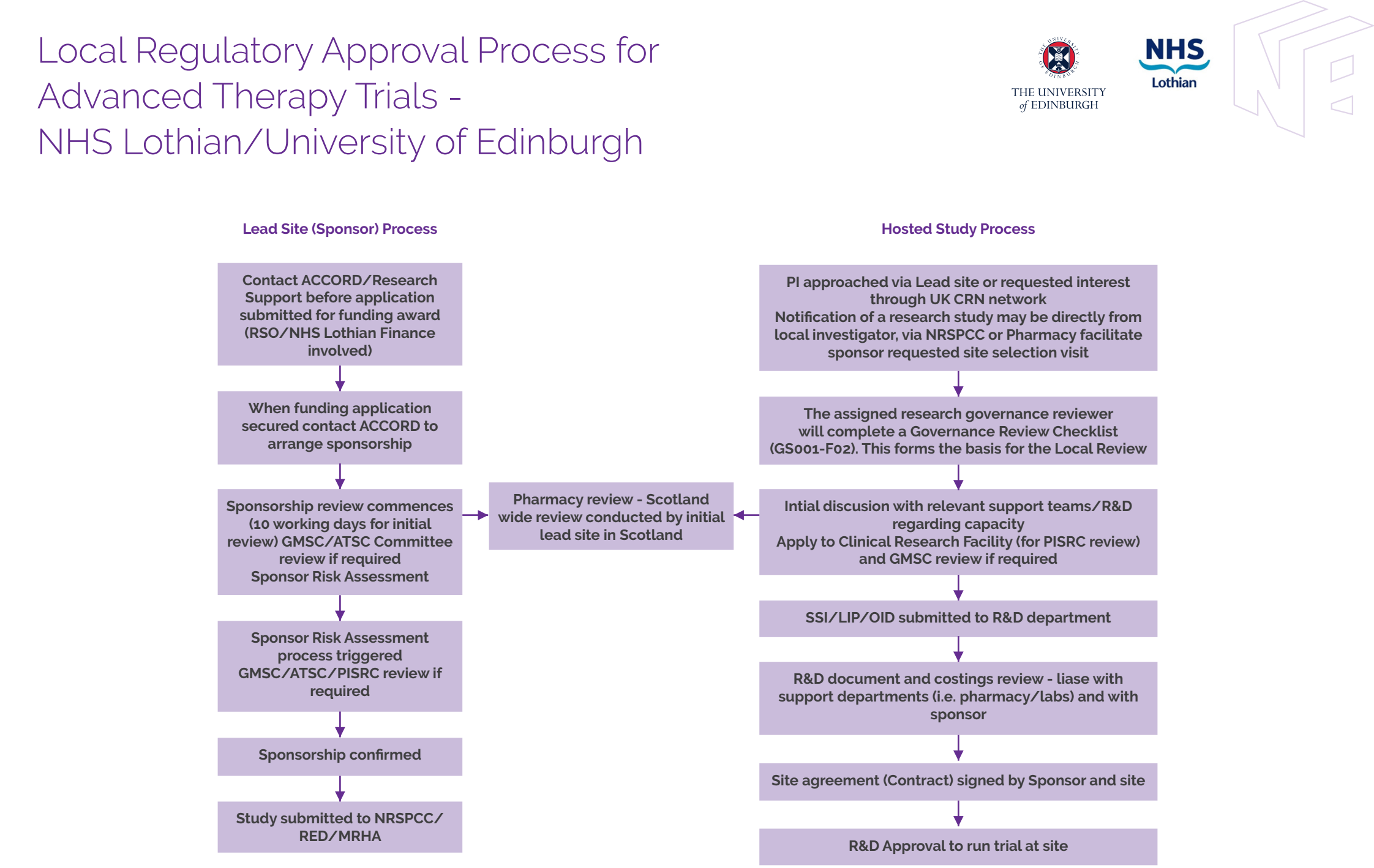
Local Regulatory Approval Process for Advanced Therapy Trials - NuTH

Clinical Trial Sponsor	Clinical Trial Co-ordinator & Principal Investigator	Joint Research Office	New Interventions Commitee	Genetically Modified Organism Safety Commitee	Pharmacy
The sponsor will send the local document pack to the research team. The NIHR 40 day metric will only start once the site is in receipt of a complete document pack as per HRA requirements. The local document pack should include the following documents: 1. HRA, GTAC approval 2. IRAS submission 3. MHRA approval 4. Protocol 5. Costing template 6. CTA 7. Patient documents	2a) Upon receipt of the document pack the trial Coordinator will register the study with R&D. 3a) The trial Coordinator notifies pharmacy that the trial set up process has started. 4a) PI completes documentation to submit to the New Interventional Procedure Committee and the Genetically Modified Organism Safety Committee. 5) It is the responsibility of the research delivery team to assess their capacity and capability (C&C) to deliver the study. Assurance of C&C is achieved through the completion of a C&C form which must have sign off from the study PI and the Research Clinical Lead. This phase of the set up process should include the actions described in this diagram (2a-4c) and the following: • Communication with sponsors to agree local recruitment targets and study timelines • Support departments (e.g. Apheresis Unit, Labs, Pharmacy) assurance of their ability to accommodate the research • Caldicott approval • IRMER/ARSAC approval • HRA/GTAC favourable opinion • MHRA approval	2b) The study is registered with R&D and assigned a reference ID. C of C&C 6) Once R&D are in receipt of a full document pack the confirmation of C&C process can begin. The R&D Officers will review the capability form and associated documents for completeness and accuracy. Once the confirmation of C&C review is completed the research team will be notified by email. On receipt of the C&C email it is the responsibility of the research team to notify the sponsor before participant recruitment begins.	4b) Assessment and approval processes performed by the committee of somatic stem cell therapies/tissue engineered products to be used by patients.	4c) Assessment and approval processes performed by the committee for gene therapy medicinal products.	3b) Pharmacy begins set up process. Completed documents are then sent back to the trial coordinator, who will facilitate the R&D Confirmation of Capacity and Capability review process.

Local Regulatory Approval Process for Advanced Therapy Trials - NHS Lothian/University of Edinburgh

THE UNIVERSITY of EDINBURGH

NHS Lothian



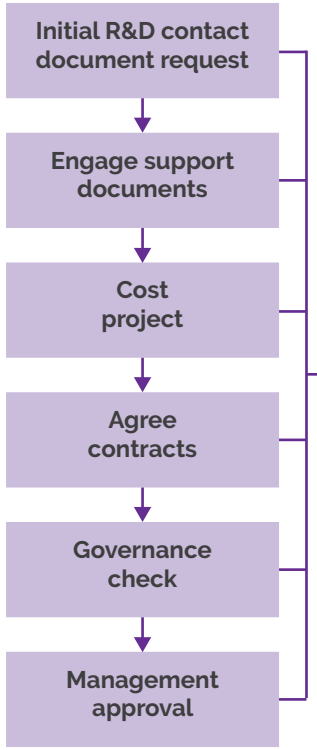
Local Regulatory Approval Process for Advanced Therapy Trials - NHS GGC

1) The Research Coordinator manages the approval process from start to finish and is the first point of contact for both the Principal Investigator and Sponsor when setting up a study within NHS GGC.

2) If the clinical trial is a phase 1 ATIMP it must go to the Phase 1 Committee for approval before management approval can be granted.

3) All ATIMP trials must be reviewed and receive approval from the Genetic Safety Committee.

4) In order to gain R&D approval as quickly as possible, the Coordinator is advised to submit documents to R&D as early as possible. At the very minimum a copy of the protocol and proposed budget is required to start the review process. An overview is provided opposite;



Checklist of documents required for R&D submission:

- **IRAS – R&D form fully signed**
- **IRAS SSI form fully signed**
- **Protocol**
- **CV (all personnel listed on the SSI)**
- **GP/ Consultant Information Sheet**
- **Letters of Invitation to participants**
- **Investigator Brochure**
- **Participant Information Sheet**
- **Consent Form**
- **Questionnaire**
- **Funding Application (for GG&C sponsored studies)**
- **Funding Award Letter**
- **ARSAC Authorisation**
- **MHRA Clinical Trial Authorisation**
- **If Phase 1 study– approval from Phase 1 Committee**
- **Genetic Modification Safety Committee approval**
- **REC (GTAC) favourable opinion and all correspondence**
- **Trial Agreements**
- **Evidence of Insurance or Indemnity**
- **REC(GTAC) favourable opinion for any substantial amendments**

Visit the NHS GGC Research and Development webpage
https://www.nhsggc.org.uk/about-us/

Local Regulatory Approval Process for Advanced Therapy Trials - LTHT

The Leeds Teaching Hospitals NHS Trust

How to get Confirmation of Capacity and Capability at Leeds Teaching Hospitals NHS Trust

1) Submission of the local information pack to enable R&D to begin the review process.

The study documents detailed below are required for a commercial study:

- **IRAS application form (combined REC and R&D form)**
- **Protocol and any amendments as submitted for HRA approval**
- **Participant information and consent documents (without local headers)**
- **Relevant model agreement**
- **NIHR costing template**
- **Delegation log (including research staff names but no signatures)**
- **HRA initial assessment letter (if issued) or HRA approval letter**

The study documents detailed below are required for a non commercial study:

- **IRAS application form (combined REC and R&D form)**
- **Protocol and amendments as submitted for HRA approval**
- **Participant information sheet and consent documents (without local headers)**
- **Statement of activities and schedule of events. These must be validated by the HRA (i.e. date and version number added by HRA**
- **Relevant model agreement**
- **HRA initial assessment letter if issued or HRA approval letter**

2) Arrange for Key Service Support Approval

Service support approval from any service departments that are required to provide support to the research study should be sought. This includes R&I finance approval.

3) New Interventional Procedures Group

If the study will involve testing of an interventional procedure which is new to LTHT, you must obtain the approval of the New Interventional Procedures Group (NIPG).

4) Genetically Modified Organism Committee

All ATIMP studies should be submitted for review by the Genetically Modified Organism Committee and approval granted before confirmation of capacity and capability can be issued.

For further information, visit the Leeds Teaching Hospitals Research and Development website **https://www.leedsth.nhs.uk/research/**