Children's Brain Tumour Drug Delivery Consortium
Accelerating Progress in Drug Delivery

CHILDREN WITH CANCER UK

Roadmap for Preclinical to Clinical Translation: Introduction

In 2021, the Children's Brain Tumour Drug Delivery Consortium (CBTDDC), core funded by Children with Cancer UK, brought together a Clinical Trials Working Group to address the lack of translation of paediatric CNS drug delivery devices into clinical trials. Comprising researchers and clinicians from across the globe, this partnership highlighted four main challenges:

(1) a lack of specific funding for prototype development and/or scale-up for clinical trials;

(2) difficulties in navigating the regulatory landscape;

(3) lack of accurate preclinical models; and

(4) increased need for multi-centric working.

In response to this, we ran a workshop in November 2021 on 'Clinical Trial Readiness for CNS Drug Delivery'. During this meeting, the CBTDDC committed to producing a roadmap document outlining the sequence of main steps for preclinical to clinical translation of CNS drug delivery devices, linking to further advice and information.

The following pages contain this schematic roadmap and further information. Due to the complexity of the regulations, while most of the guidance given is applicable UK wide, a few specific steps are only relevant to England.

We recommend using this roadmap in conjunction with the NIHR's Clinical Trials Toolkit, with reference also to the HRA's research planning resource. In particular, this Health Research Authority (HRA) resource provides useful insight into the roles and responsibilities of key individuals in translational / clinical research. The HRA also provide free access to their Medical Devices course, which explains the regulations and considerations for clinical investigations of medical devices across the UK.

Flowchart (click on steps to jump to more information)

Do the 'right' preclinical work / start discussions around Intellectual Property and route to clinical adoption (includes patient engagement and funding)

Think through considerations for trial design and draft trial protocol (includes potential participating centres, risk assessment, sponsorship and patient engagement)

Secure funding for trial

Finalise trial protocol and supporting documentation (includes further liaison with participating centres)

Apply for trial approval

Next steps after approval (includes trial registration and UKCA/CE marking)

Section 1 - Preclinical study considerations

Plan your preclinical work with the future clinical trial in mind.

Seek advice from the MHRA as they can advise what preclinical tests will be needed.

Patient and public involvement/engagement (PPI/E) is important in research design and many funders now see this as a compulsory part of grant applications. See the UK Standards for Public Involvement in research.

Choice of model. You will need to show tolerability and survival benefit in one or more preclinical tumour model(s). Use models that best match the human disease, and that are amenable to the intended mode of drug delivery. Pharmacokinetic profiles and/or evidence of brain parenchyma drug penetration would be advantageous. The Experimental Design Assistant (EDA) is a web application which helps researchers improve the design of animal experiments: https://eda.nc3rs.org.uk/

Choice of drug to be delivered. Physico-chemical properties needed for the drug will depend on the mode of delivery to be used. More preclinical data will be needed for molecularly targeted drugs (including data on their mechanism of action and target specificity), than for non-targeted cytotoxic drugs. Also consider how you will get hold of drug if it's not off patent.

Expand your collaborations with drug delivery researchers working with other brain conditions to share knowledge about the most appropriate models for different delivery techniques.

Think about how you will measure the outcome and toxicities, and which endpoints to select (e.g., brain drug penetration; tolerability; maximum tolerated dose; overall survival benefit relative to standard-of-care) for evidence of tolerability and efficacy. Also think about how you will measure drug distribution, the levels of drug reaching the tumour, and drug metabolism and clearance.

Discuss Intellectual Property considerations with your University's Commercial Office / Technology Transfer Office.

Think about route to clinical adoption, and whether the device can be manufactured to scale. If possible, seek advice from organisations such as CHEATA (Nottingham), Devices 4 Dignity (Sheffield), TrusTech (Manchester), Health Tech Enterprise (Cambridge), and MD-TEC (Birmingham).

Consider using a Contract Research Organisation (CRO), identified through your local Research Design Service (RDS), to produce materials to necessary GLP / GMP standards.

Seek advice on relevant funding streams and on how to strengthen your funding application from your institution's research development managers, or from your local RDS. Some examples of funding streams to consider for preclinical work are listed on the next page.

Funding streams to consider:

NIHR i4i Connect

NIHR i4i Product Development

NIHR i4i Challenge

SBRI Competitions

Innovate UK biomedical catalyst

MRC Impact Acceleration Account

MRC Developmental Pathway Funding Scheme

Innovate UK

Biomedical Catalyst

Charity grants, such as those from Cancer Research UK (Therapeutic Catalyst, Drug Development Project).

Cancer Research Horizons Seed Fund

Section 2 - Trial considerations and draft protocol

Patient and public involvement/engagement (PPI/E) is critical to ensure that the question proposed is important and relevant to the people it directly affects and that the trial is practical and feasible. If possible, try to involved PPI/E members who have direct experience of the type and anatomical site of the brain tumour that your trial will focus on. The HRA and NIHR have more information on best practice for public involvement in trials here and here, respectively. Note, your local RDS may be able to provide a grant to support PPI/E activities during the protocol design stage.

2.1 Trial considerations include:

- Should be conceptually simple and tailored to the specific tumour type, tumour anatomical location, and patient group
- Address questions of clinical relevance where genuine uncertainties exist
- Address questions of local tissue delivery, clearance, tolerability and efficacy
- Avoid unnecessarily complex/restrictive entry criteria
- Avoid unnecessarily complex data requirements
- Ensure the most appropriate choice of control arm (e.g., standard-of-care)
- Choose appropriate outcome measure(s) for tolerability, toxicity and efficacy (including disability)
- Consider whether the protocol can be adapted during the trial if necessary
- Does the protocol enable you to learn as much from patients as possible, not just safety and feasibility (e.g. measure cognitive outcomes / long-term toxicity)?
- Can you use / adapt a trial design that has been successful before (more attractive to potential sponsors)?
- How will your intervention fit into current NHS patient pathways (more appealing for adoption into clinical practice)?
- National or international (international trials are easier if run between countries with compatible trial regulation; having a pharma sponsor will make international trials easier)?
- Single or multi centre? Choice of participating centres - expertise of using the technique at participating centres will be crucial, as will willingness to see the trial succeed. Considerations for selection and evaluation of investigator sites are highlighted here.

2.2 Draft Protocol Design

- Seek advice from your local Research Design Service (RDS).
- Consult the HRA protocol guidance, and template, which conform to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.
- There is also MHRA guidance for manufacturers of the device and investigators, as well as information on biological safety assessments, statistical considerations, and applying human factors and usability engineering to medical devices.
- Look at examples of P0/1 protocols in the Pilot and Feasibility Studies journal.
- You can also seek advice from registered Clinical Trials Units (CTUs). The UK Clinical Research Collaboration (UKCRC) provide a search tool for identifying CTUs with expertise in coordinating multi-site research in different disease areas or with different trial designs.
- The NIHR can offer support for setting up clinical research studies, both for commercially sponsored studies and for non-commercial studies. Some studies can apply for NIHR Clinical Research Network (CRN) support as part of their application for MHRA approval (see p8). However, for Clinical Trials of Investigational Medical Products (CTIMPs) and combined trials of an investigational medicinal product and an investigational medical device (IMP/Device trials), applicants must apply for NIHR CRN support through the Non-commercial Portfolio Application service in CPMS.
- Activities in the protocol must be costed - make sure to differentiate between research costs, NHS service support costs and treatment costs. Refer to the Department of Health's AcoRD guidance. INVOLVE's cost calculator can help account for public involvement/engagement costs.
- Explain how you will ensure that your technology is adopted into the NHS, making sure to include any barriers that might hinder adoption and how these will be overcome.
- Identifying potential participating clinical sites.

2.3 Risk assessment

While developing the protocol, you also need to undertake a risk assessment. The MHRA have implemented a scheme for defining the risks associated with each clinical trial. The risk assessment will be needed before you can secure a sponsor. Consult the NHS R&D Forum Sponsorship Principles document for guidelines on sponsor requirements. If your trial will include sites in the European Union (EU), you will need a sponsor from an EU member state. Your local CTU might be able to recommend a European sponsor.

2.4 Sponsorship

You will need to agree on a trial sponsor. The trial sponsor will then identify potential participating sites. Sites selected will need to do 'Capacity and Capability Assessments' to evaluate whether or not they can participate in your trial. The NHS R&D office at each site will need to approve site participation. You can find contact details for Research and Development (R&D) staff at NHS organisations on the NHS R&D Forum website here.

Section 3 - Secure funding for the clinical trial

Get advice on appropriate funding opportunities and how to strengthen your funding application from your local RDS and from your institution. It can be useful to try to use / adapt a trial design that has been successful before, and also to highlight the applicability of your intervention for multiple indications. You could also consider obtaining letters of support from appropriate organisations, such as the NCRI Childrens Group and the NCRI Brain Group.

The document 'Points to consider when assessing the feasibility of research', prepared by the Association of Medical Research Charities (AMRC) and NIHR Medicines for Children Research Network (MCRN), discusses considerations of potential funders when reviewing applications for funding clinical trials.

Funding streams to consider:

NIHR i4i Connect

NIHR i4i Product Development

NIHR i4i Challenge

Innovate UK biomedical catalyst

SBRI Competitions

P1-P3 AI in Health and Care Awards

NIHR Efficacy and Mechanism Evaluation (EME)

NIHR Health Technology Assessment (HTA)

NIHR Programme Grants for Applied Research

NIHR Health and Social Care Delivery Research

NIHR Global Health Research Programme

Wellcome Trust Discovery Awards

Charity grants, such as those from Cancer Research UK (Drug Development Project, Experimental Medicine Award, Clinical Trial Award)

It is also possible to enter into a funding partnership, but note that these routes may involve substantial contractual and commercial requirements, and some 'partners' may be viewed negatively upon peer review. Options include:

- Industry
- Business Angels
- Venture Capitalist / Philanthopy (The AntiCancer Fund; Cancer Horizons Seed Fund)
- Crowd Funding

Section 4 - Finalise trial protocol and supporting documentation

Once funding is secured, finalise the trial protocol and supporting documentation. MHRA guidance on compiling submissions for clinical investigations of medical devices can be found here. Further information on the documentation that you will need to submit with your MHRA application can be found here and here.

Once you have the final protocol, this must be sent to potential participating sites so that they can start their capacity and capability assessments. The UK Local Information Pack is the UK-wide mechanism for setting up participating NHS/Health & Social Care (HSC) organisations. More information on planning and working with participating sites can be found here, here and here.

Section 5 - Apply for Clinical Trial Approval

To find out whether your device study needs MHRA authorisation, use this online algorithm and flowchart. If the answer is yes, there is now is a single combined review service for applying for REC, HRA and MHRA approvals. This is initiated when you create an account via the Integrated Research Application System (IRAS) portal.

Before starting your application in IRAS, it is advisable to work through this checklist, and also to have a preliminary discussion with the MHRA to seek clarity on which regulations and standards are applicable to your intervention.

When you are ready to apply, login in to your IRAS account and you will be guided through the application process. There is also further step-by-step guidance on the HRA website. At present, all applications for IMP/Device trials will require applicants to complete information in both the standard and new parts of IRAS. See here for more information. Your trial sponsor and local NIHR Research Design Service can also offer advice, as can (if applicable) the regulatory consultant employed by the device manufacturer.

The MHRA will process the application based on the type of the trial (Type A, B or C) as described in the document Risk Adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products (PDF).

Through IRAS, you will be offered a slot for a REC meeting. Try to choose a date that you can attend (virtually), taking into consideration the RECs usually used by your CTU and also any specialities of each REC (the Research Ethics Service [RES]). Depending on your study, additional approvals might be needed from other bodies (e.g., Radiation Assurance, Pharmacy Assurance, Surgical Assurance, Gene Therapy Advisory Committee). Seek advice from the MHRA on which approvals you need for your trial.

Section 6 - Next steps after trial approval

Once approved, the HRA will automatically register the clinical trial with the ISRCTN clinical trial registry.

Do site initiation visits at all participating centres, and sign all contracts.

Before the trial begins, complete the Trial Master File (TMF) documentation as described here. Further guidance on the TMF can be found here and here.

If not already in place, secure either UKCA or CE marking for your device. See the guidance on UKCA and CE markings.

Section 7 - Further Information

Administration of Radioactive Substances Advisory Committee (ARSAC) - https://www.gov.uk/guidance/how-and-when-to-submit-research-applications-to-arsac

Confidentiality Advisory Group (CAG) - https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/confidentiality-advisory-group/

Decision tool to determine whether a study needs MHRA authorisation - https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949145/Algorithm_Clean__1_.pdf

EMA 'Guideline for good clinical practice E6(R2)' - https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf

EMA 'ICH E6 (R2) Good clinical practice - Scientific guideline' - https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline

European Forum for Good Clinical Practice - https://efgcp.eu/

European Medicines Agency (EMA) 'Good Clinical Practice' - https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice

Gene Therapy Advisory Committee (GTAC) - https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/gene-therapy-advisory-committee/

HRA 'Good Clinical Practice' - https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/good-clinical-practice/

HRA Approvals overview - https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/hra-approval/

HRA Informing participants and seeking consent - http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/

HRA Overview of Combined Review Process - https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/
HRA trial protocol guidance - https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/

HTMR (Hubs for Trials Methodology Research) Network - https://www.methodologyhubs.mrc.ac.uk/about/network/

Integrated Research Application System (IRAS) - https://www.myresearchproject.org.uk/

International Medical Device Regulators Forum - https://www.imdrf.org/about
MHRA guidance on risk adapted approaches in the management of CTIMPs - https://www.gov.uk/government/consultations/mhra-draft-guidance-on-randomised-controlled-trials-generating-real-world-evidence-to-support-regulatory-decisions/appendix-3-risk-adapted-approaches-to-the-management-of-clinical-trials-of-investigational-medicinal-product

MRC-NIHR Trials Methodology Research Partnership (TMRP) - https://www.methodologyhubs.mrc.ac.uk/about/tmrp/

NIHR clinical trials toolkit - https://www.ct-toolkit.ac.uk/; https://www.ct-toolkit.ac.uk/routemap/

NIHR document 'Planning a Randomised Controlled Trial: Points to Consider' - https://www.ct-toolkit.ac.uk/documents/planning-a-randomised-controlled-trial-rtc-points-to-consider/27168

NIHR INVOLVE - http://www.hra-decisiontools.org.uk/consent/index.html

NIHR Medtech and In vitro diagnostics Co-operatives (MICs) - https://www.nihr.ac.uk/partners-and-industry/industry/access-to-expertise/medtech.htm#two

NIHR Research Design Service - https://www.nihr.ac.uk/explore-nihr/support/research-design-service.htm

NIHR Study Support service - https://www.nihr.ac.uk/explore-nihr/support/study-support-service.htm

Research Ethics Committee Directory - https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/search-research-ethics-committees/

Resources to maximise PPI/E involvement - https://www.invo.org.uk/find-out-more/how-to-involve-people/information-for-researchers/

SPIRIT trial protocol guidance - http://www.spirit-statement.org/

The NHS Research & Development Forum: https://rdforum.nhs.uk/

Trial management overview - https://www.ct-toolkit.ac.uk/documents/summary-of-trial-management-systems-workstream-4-document-b/27247

UK Gov 'Good clinical practice for clinical trials' - https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials

UK Gov 'Guidance: Clinical trials for medicines: apply for authorisation in the UK' - https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk

UKRI 'Good research practice policies and guidance' - https://www.ukri.org/about-us/mrc/our-policies-and-standards/research/

UKRI Principles of Consent - http://www.hra-decisiontools.org.uk/consent/principles.html

WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects - https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/