CERSI-AT
Centre of Excellence in Regulatory Science and Innovation for Advanced Therapies

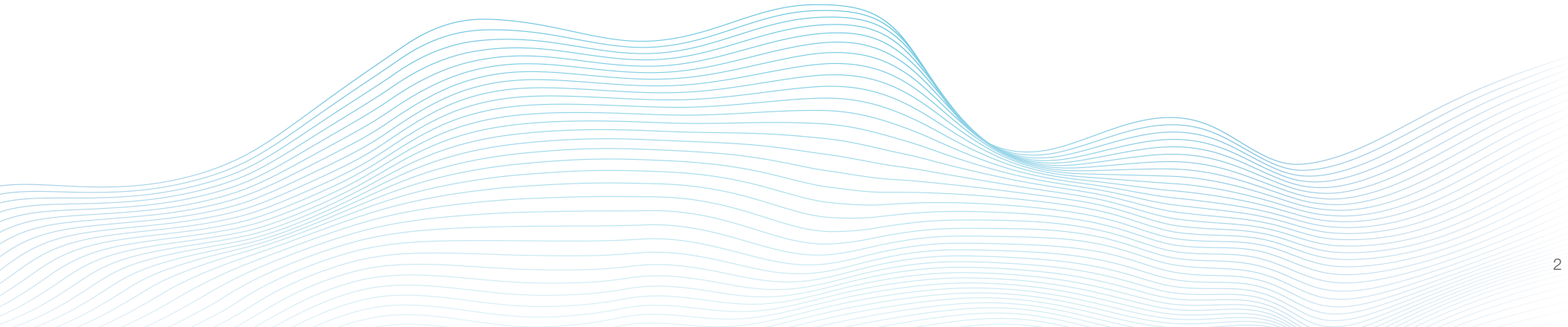
CATAPULT
Cell and Gene Therapy

Clinical trial start-up tool for ATMPs in the UK

Introduction

This tool sets out to collate the various regulatory guidance documents and processes encountered along your pathway to an active ATMP clinical trial. It aims to highlight efficiencies that may support progress towards making the UK government's goal of 150 days from clinical trial submission to first patient applicable to ATMPs.

A glossary of the review bodies involved in trial site start-up across the United Kingdom is provided, and the scope and underlying assumptions are defined. An interactive pathway then cross-links to relevant cheat sheets aligned to each process step. Information has been reviewed by the relevant regulatory bodies.



Commitment to Expedited Development

The UK is committed to being the fastest and most supportive environment globally for the clinical development of ATMPs. The UK government has strategically re-engineered the regulatory landscape to match the pace of your innovation, ensuring that breakthrough cell and gene therapies reach patients with unparalleled speed.

Integrated Approvals:

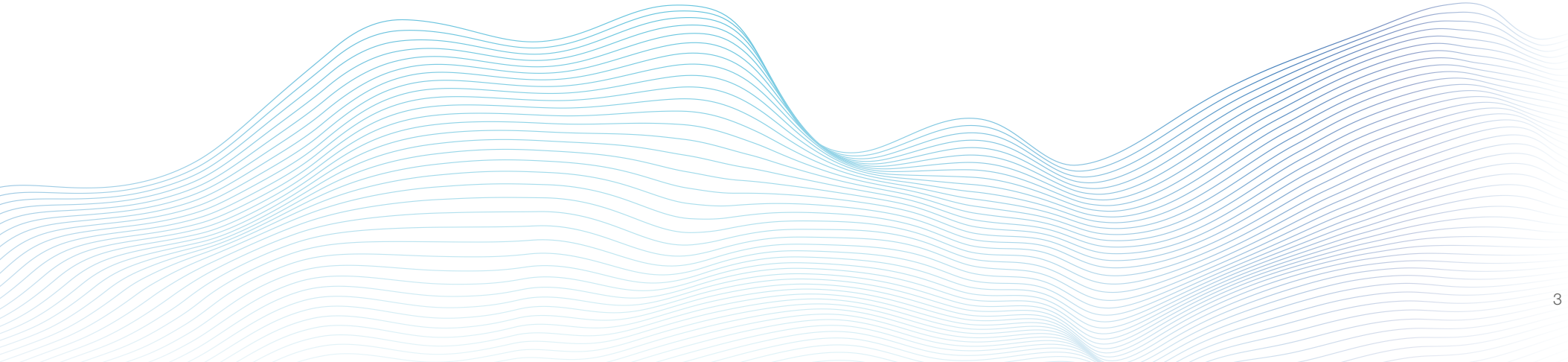
The UK has eliminated duplicative reviews. The Combined Review service, delivered by the MHRA and Research Ethics Committee (REC), provides a single, streamlined application and a unified decision.

Expertise and Pragmatism:

UK regulators are world leaders in ATMPs and offer early and ongoing engagement through dedicated pathways, providing clear, solutions-focused advice to de-risk your development and accelerate your path to approval. UK regulators understand the unique complexities of ATMP manufacturing and logistics and have built a flexible framework to support this.

A National Commitment to Speed:

The national ambition is to make the UK the most attractive destination for complex clinical trials backed by an end-to-end ecosystem of world-class research infrastructure and specialist NHS sites. Choose the UK for partnering with a regulatory system built to faster deliver the next generation of medicines to patients.



Glossary of Start-Up Related Organisations*

***This tool focuses on the regulatory process in England, although major variations in devolved nations are noted where relevant. (NI = Northern Ireland, S = Scotland, W= Wales)**

defra
Department for Environment Food and Rural Affairs

Issues deliberate release consents for GMO products in England.

Devolved nation competent authorities will not receive a separate application but are joint reviewers if the respective nation is part of the research.

NI: Department of Agriculture, Environment and Rural Affairs (DAERA)

S: Science and Advice for Scottish Agriculture (SASA)

W: Welsh Government

HSE Health and Safety Executive

Administers the contained use regime for GMO products. Class 1–2 products (low risk) require notification to HSE. Class 3–4 (higher risk) require full HSE approval.

Devolved nation competent authorities will not receive a separate application but are joint reviewers if the respective nation is part of the research.

NI: Health and Safety Executive for Northern Ireland (HSENI)

S: Scottish Government

W: Welsh Government

HTA Human Tissue Authority

Licenses and inspects establishments that procure human tissues or cells that are used as ATMP starting materials, or which carry out associated donor testing in England, Wales and Northern Ireland. The Human Tissue (Scotland) Act 2006 is administered separately under Scottish legislation via NHS Research Scotland.

The import, storage, processing and export of starting materials may also be regulated by the HTA if these activities take place prior to the commencement of manufacturing.

MHRA Regulating Medicines and Medical Devices

MHRA acts as the UK's competent authority, reviewing clinical trial applications to ensure scientific validity and participant safety. It conducts Good Clinical Practice and Good Manufacturing Practice inspections.

NHS Health Research Authority

The HRA oversees the research ethics service and issues approval for research taking place in the NHS in England.

Devolved nation competent authorities issue research governance reviews for their respective jurisdiction:

NI: HSC Public Health Agency (R&D)

S: NHS Research Scotland (NRS)

W: Health and Care Research Wales (HCRW) - joint with HRA

NHS **Local Genetic Modification Safety Committees**

Review examines containment measures, including product handling, staff training and waste disposal protocols.

NHS **Local NHS organisation**

Local NHS organisation will require the UK Local Information Pack (LIP) which contains relevant contracts and documents to support site set up and applies UK-wide. Confirmation of capacity and capability is required from the local R&D office (R&D Permission in Scotland).

NIHR | National Institute for Health and Care Research

NIHR hosts the interactive Costing Tool (iCT), needed to complete the National Contract Value Review (NCVR) – standardised way of costing and contracting of trial sites.

NIHR work in partnership with delivery infrastructure across the UK:

NI: HSC Public Health Agency (R&D)

S: NHS Research Scotland (NRS)

W: Health and Care Research Wales (HCRW)

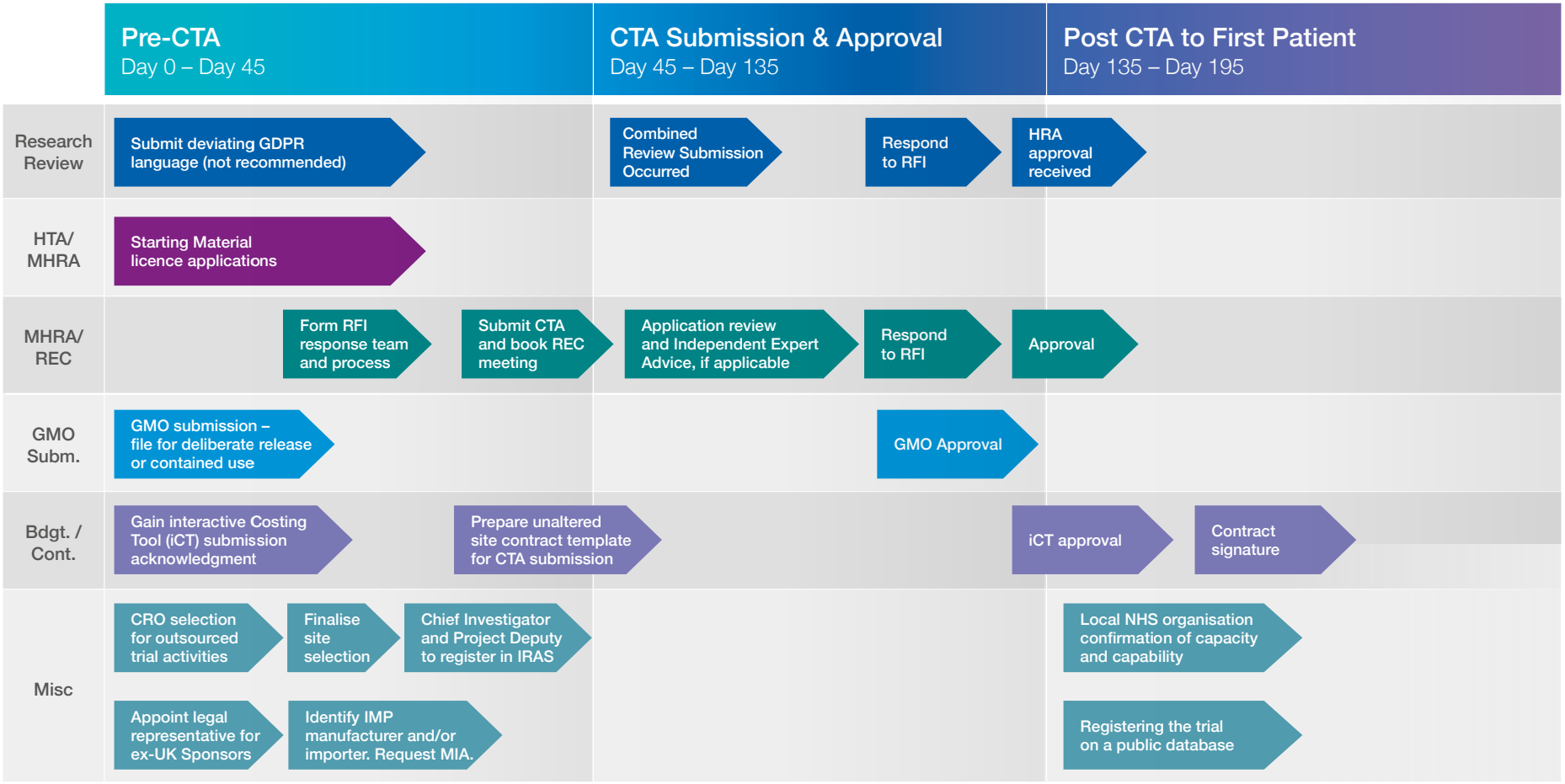
UK ATMP Start-Up Pathway Tool

Scope and Assumptions:

- This tool addresses the regulatory pathway transparency barrier identified in various reports.
- It amalgamates all regulatory pathways for potential ATMPs in one graphic. Specifically, should your product not be classed as a GMO, you may need to exclude some regulatory steps, e.g. HSE approval.
- The graphic does not consider the medical device regulatory pathway for Combination Products.
- The tool allows for a 45-day window for activities ahead of a CTA.
- Timelines are an informed estimate and may vary for your product.

UK ATMP Start-Up Pathway Tool

Click the links within the interactive pathway tool to access specific cheat sheets relevant to the linked process step. The timeline is designed to support progress towards making the UK government's 150-day timeline applicable to ATMPs, but may vary depending on the product and chosen clinical sites.



Cheat Sheet 1:
HRA GDPR Language Template

Return to pathway →

Link to Process

Mandatory Template:

- From **1 April 2025**, all new research applications submitted via IRAS must use the HRA's official GDPR transparency wording template, developed on behalf and applicable to all four UK nations. Adopting the HRA template is the most direct path to compliance. Creating custom wording requires significant justification and public involvement efforts.

Purpose:

- Provide participants with comprehensive information about their data rights and usage.
- Align Participant Information Quality Standards and principles of meaningful public involvement.
- Improve transparency on international data transfers.

Using Bespoke Wording:

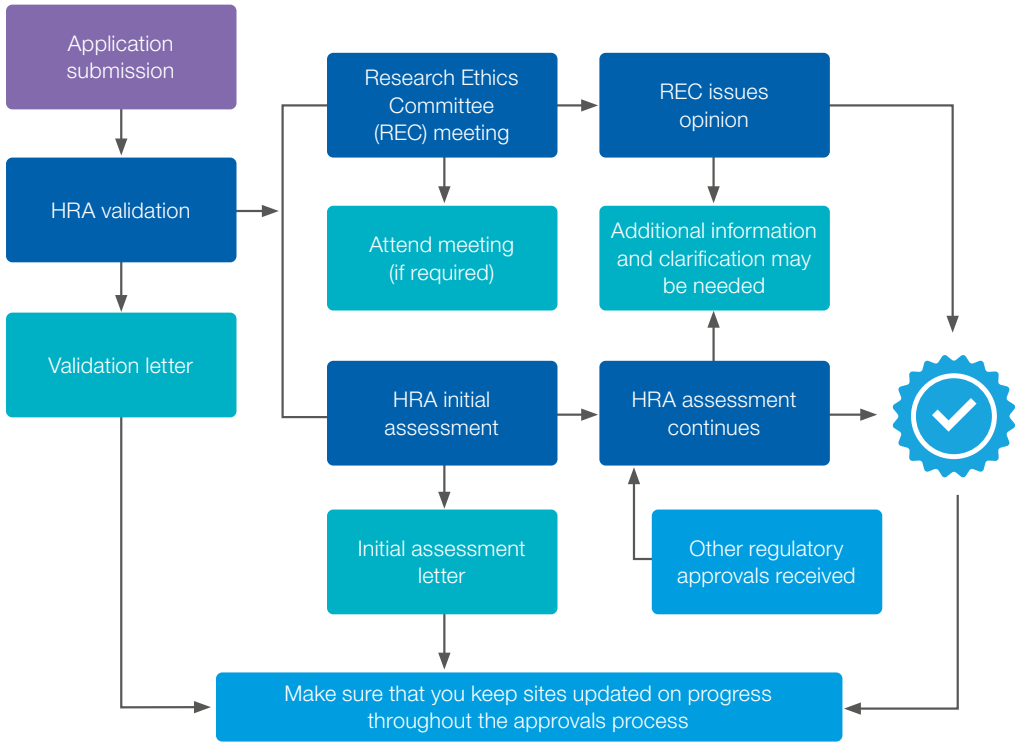
- Using bespoke wording should be exceptional and is not encouraged.
- Sponsor wording must demonstrate how it meets the HRA's four principles of meaningful public involvement.
- This requires sponsors to conduct and document their own public involvement work to justify their custom text.

Cheat Sheet 2:
Research Review and Approval

Return to pathway

Link to Process

- The "UK study-wide governance criteria" detail the standards that research stu dies must meet to receive HRA Approval.
- The submission happens as part of the Combined Review through IRAS (same submission goes to MHRA, REC and HRA).
- HRA queries will be received in IRAS.
- The MHRA database links with the REC and HRA/ HCRW database. If no other outstanding criteria are to be addressed, HRA & HCRW Approval is issued alongside the REC and MHRA outcomes.
- HRA & HCRW Approval covers England and Wales – other arrangements to provide governance oversight apply in Scotland and Northern Ireland. More details can be found here.
- For studies involving Scottish sites, you must obtain permission from NHS Research Scotland (NRS) rather than HRA Approval. If a study is led in England (HRA Approval) and includes Scottish sites, the HRA shares its review with NRS, removing the need for a full re-review.



Source: HRA, "HRA Approval" (2025)

Cheat Sheet 3:
Starting Material Licences

Return to pathway

Link to Process

The HTA licence ensures human tissues and cells are used safely, ethically, and with proper consent. A site will likely need an HTA licence if it engages in the following activities with patient tissues/cells intended for human application.

- **Procurement:** Collecting the tissues/cells.
- **Testing:** Any testing on the tissues/cells.
- **Processing:** Any manipulation, including separation, concentration, or purification.
- **Storage:** Storing the tissues/cells (for more than 48h) before they are processed into the ATMP or used for other research.
- **Distribution:** Sending the tissues/cells to another location (e.g., the manufacturing site).

The procurement and testing of human tissues or cells used as starting materials in the manufacture of ATMPs may only be carried out by establishments holding an appropriate HTA licence or by individuals, or organisations working under the authority of a third-party agreement with an establishment holding an appropriate HTA licence. This applies to all tissues and cells which are covered by the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended).

Blood may also be used as a starting material. In this case, the Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for procurement, testing, processing, storage, and distribution under the Human Blood Safety and Quality Regulations 2005.

The HTA and MHRA have also established a joint position whereby the collection of blood as a starting material for an ATMP can be carried out under either a HTA tissues and cells licence or an MHRA blood establishment licence.

Ideally, the need for a licence is established before clinical trial site selection. As it is issued without directly being linked to a specific indication, it could be that your site does already has a licence in place. The already received licence / knowledge of the application process should form part of the site feasibility questionnaire. The process can begin ahead of the Combined Review submission. The HTA licence is needed prior to site activation.

Return to pathway

Cheat Sheet 4:
Submitting Clinical Trial Application

Link to Process

Preparation & Account Setup

- Finalise Documents: Ensure documents are final, version-controlled, and clearly named.
- Access System: Log in to the new part of IRAS. New users must create an account; existing users may use their standard login.
- Define Roles: Identify the Chief Investigator (CI), Project Deputy (who can edit the form), and Sponsor Delegate.

Project Creation & Team Assignment

- Create Project: Select “New Project” in IRAS and complete the filter questions (identifying the study as a CTIMP or combined trial).
- Assign Users: Add the CI and Sponsor organisation. The CI must log in and “accept” their role for the project to proceed.

Completing the Application

- Data Entry: Fill in the Project Details, Study Information, and Clinical Trial Dataset.
- Uploads: Upload all required supporting documentation. An indicative list of documents can be found here.
- REC Booking: Use the integrated booking tool to reserve a Research Ethics Committee (REC) meeting slot. REC meeting dates can be previewed in this calendar.

Authorisation & Submission

- Sponsor Review: Electronically “share” the application with the Sponsor/Delegate for review.
- Authorisation: The Sponsor must verify and authorise the application within the system.
- Submit: Once authorised, and the CI has accepted the project, click Submit. The application is sent simultaneously to the MHRA and REC for parallel review.

Return to pathway

Cheat Sheet 5:
Combined Review Steps

Link to Process

Step 1

Confirmation of validation can take up to 7 days. If valid, the 30 day assessment period commences. If not valid then the sponsor will have the remaining of the 7 days to rectify the validation issues. The assessment may be extended by up 90 days if the MHRA decides to consult a relevant committee (e.g. the Commission on Human Medicines (CHM)/Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG)). A guide to avoid common validation issues can be found here. A collection of relevant clinical trial guidance can be found here.

Step 2

If the MHRA/REC requests further information (Requests for Information(RFI)), the sponsor has 60 days to respond, but they may request an extension. The extension is not limited in number of days.

Step 3

The MHRA shall consider a valid amended request for approval within 10 days from receipt of the RFI response. The 10 day period may be extended by a further 30 days. If an ATIMP and if the MHRA/REC consults with a relevant committee or specialist group, it can be extended by 60 days.

Cheat Sheet 6:
Clinical Trials Expert Advice Guidance

Return to pathway

Overview

Link to Process

- Guidance accompanies the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025.

When is Expert Advice Required?

- High-Risk: First-in-human trials, novel compounds with significant safety concerns, or “cascade system” effects.
- Complex Mechanisms: Compounds acting via the immune system, novel engineered structures, or targets with insufficient biological data.
- Species Specificity: When animal models may not predict human activity.

Application Process

- Pre-Submission: Assess against criteria; email MHRA (clintrialhelpline@mhra.gov.uk) 28 days before submission to book review.
- Submission: Submit via IRAS four weeks before the expert meeting.
- Documentation: Provide a separate document detailing target function, dose rationale, and safety mitigations.

Impact on Timelines

- Initial Approval: Decision timeline extends by 90 days (Total: 120 days).
- Modifications: If advice is needed on RFI responses, timelines extend by 30 days (60 days for ATMPs).

Cheat Sheet 7:
Responding to Requests for Information (RFI)

Return to pathway →

1. Form a Rapid Response Team

- A pre-formed team eliminates the “scramble” to find experts, enabling you to meet strict timelines and ensuring all new responses align with previous filings and the target product profile.
- Establish a protocol where the core team meets within one hour of receiving a query to triage and assign owners.
- If this is your first submission, have a mock run of the RFI process to test if your email chains and document access permissions work.
- Generate a list of Anticipated Regulatory Questions for your specific product and therapeutic area.

2. Receiving a RFI

- If reviewers need more information, they will raise a RFI.
- This is sent as a task in IRAS to the submitting person.

3. Timelines & Extensions

- Standard Deadline: You have 60 days to respond.
- Need More Time? Email the MHRA at clintrialhelpline@mhra.gov.uk to formally request an extension (N.B. extension affects review timeline).
- Final Decision: Issued 10 days after your RFI response is received.

4. How to Respond in IRAS

- Access RF: Go to My Tasks > My Personal Tasks. Select Project.
- Provide Your Response:
  - Review comments and reply directly in the on-screen text box.
  - For very long responses or those with images/tables, you can upload a separate document and clarify this in the text box.

Upload Documents:

- Add new/updated documents via the Project Dashboard.
- Return to the RFI screen by selecting Update RFI Details.

5. Submitting Your Response

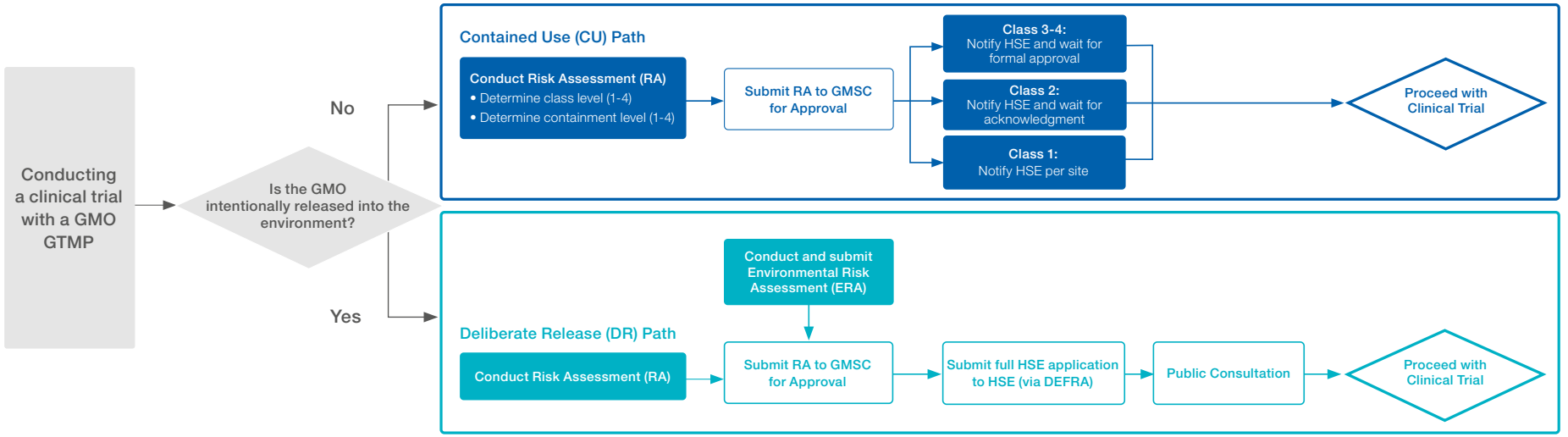
- Applicant: Once complete, select Request review.
- Sponsor/Delegate: The task is routed to the appropriate person under My Tasks > My Organisational Tasks. They perform the final submission to the assessors.

6. Follow-Up Queries

- If assessors have further questions after your response, they will raise a “request for clarification”.
- This will appear as a new task in your My Personal Tasks section.

Cheat Sheet 8:
GMO Submission Flowchart

Return to pathway



These submissions can run in parallel or ahead of the clinical trial application. Approval needs to be secured for site activation.

Contained Use (CU) Path

- Submission Guide
- Forms (CU1/CU2) Genetically Modified Organisms (GMO) forms
- Premises Notification (Class 1): If site has never worked with GMOs before (GMO(CU)), must submit form CU1. If premises already notified, only need GMSC approval.
- Activity Notification (Class 2-4): Higher risk classes must submit form CU2 (Notification of Intention) unless they already hold a relevant class 2-4 approval under which the new class 2 activity can also be undertaken.
- Class 2: Must notify HSE and can proceed after 45 days for new class 2 activities, or upon receipt of acknowledgement letter for subsequent class 2 activities; requests for additional information ‘stop the clock’.
- Class 3-4: Must receive written approval (up to 90 days); requests for additional information ‘stop the clock’.
- Submit forms, GM risk assessment and fee to: bioagents@hse.gov.uk. Clock starts upon receipt of acknowledgement letter, that is issued after payment clears and application received.

Deliberate Release (DR) Path

- Submission Guide
- The Deliberate Release application is a dossier submitted to Defra (gm-regulation@defra.gov.uk). It consists of two main parts found in the public register of applications.
- Part A (A1-A6): Full technical dossier and environmental risk assessment (ERA).
- Part B: Application summary to be placed on the public register for the Public Consultation phase.
- Defra’s statutory period (90 days) to review the application, including the Public Consultation (60 days) where the public comments on the Part B summary.
- Defra issues a “Consent to Release” letter if approved, outlining strict conditions to follow during the trial.
- Devolved nations are responsible for granting their own GMO (deliberate release) consent.

Return to pathway

Cheat Sheet 9:
Interactive Costing Tool (iCT) & National Contract Value Review (NCVR)(RFI)

Link to Process

The iCT is a mandatory digital system to calculate standard pricing for commercial clinical trials in the UK NHS. It replaces local site-by-site price negotiations with a single national price validation, known as the National Contract Value Review (NCVR).

Submission & Review Process:

- Sponsor creates a project in the Central Portfolio Management System (CPMS) and inputs study resource requirements into the iCT.
- Proof of submission needs to be part of the submission package for the Combined Review.

National Review (Study Resource Reviewer):

- A designated “Lead NHS Site” or National Reviewer validates the resource requests against the protocol. The review focusses on resources (time/procedures) rather than prices (which are fixed by the national tariff).
- Outcome: A validated “Master Costing” is locked for the whole of the UK.

Site Implementation (Local Sites):

- Sponsor shares the “Master Costing” with participating sites via CPMS. Sites cannot negotiate the prices generated by the iCT (except for specific pass-through costs).
- Sponsor uses iCT to generate the finance schedule which is copied into the site contract.
- Drastically reduces contract setup time (averaging ~35 days).

Advice for ATMP Trials:

- Use the “ATMP & Early Phase Costing Guidance” when filling out the iCT. ATMP trials often require complex pharmacy setup or extended observation times that standard templates do not capture. Manually add these as “itemised costs” to reimburse sites.

Return to pathway

Cheat Sheet 10:
Model Agreement for ATMPs

Link to Templates

The National Contract Value Review (NCVR) now applies to ATMP studies. To support this scope expansion, specific templates were released which are updated biannually.

ATMP-mCTA: Model Clinical Trial Agreement for ATMPs (Sponsor-to-Site).

CRO-ATMP-mCTA: Model Agreement for ATMPs (CRO-to-Site).

All new templates contain a locked financial appendix. Sponsor must insert the iCT-generated Finance Schedule directly into this appendix. The templates contain quality and apheresis appendices which are not templates.

Sites are mandated to accept the national iCT-validated price without local re-negotiation.

Cheat Sheet 11:
Miscellaneous Considerations

Return to pathway

Early CRO selection	Early selection allows leveraging the CRO's operational expertise to "pressure test" the protocol and submission dossier, identifying practical or regulatory pitfalls that may trigger avoidable queries.
Appointing UK Legal Representative	Appointing a UK Legal Representative is a mandatory regulatory requirement for non-UK sponsors, ahead of a clinical trial application. It is the official point of contact for the MHRA and assumes legal liability for the trial's conduct. The Legal Representative's details and signature are required for submission.
Finalise site selection	A finalised site selection allows for concluded feasibility checks and for contract negotiations to run in parallel with the regulatory review. Having locked-in sites ensures that the recruitment projections and logistics described in the protocol are feasible, reducing the risk of immediate amendments post-approval.
Chief Investigator selection	Robust selection is strategically critical as the CI acts as the "face" of your study to the Research Ethics Committee (REC). Their early input ensures your protocol aligns with UK NHS standard of care, avoiding practical pitfalls that often trigger rejection. Their presence at the REC meeting is a supporting factor in securing a Favourable Opinion.
Registering the trial on a public database	While the HRA now facilitates automatic registration for the ISRCTN registry, the legal responsibility remains with the sponsor to ensure the trial is visible on a WHO-recognised registry before before recruitment of the first participants or within 60 days of the REC/MHRA approval, whichever is first. Sponsors are required to upload a summary of the results to the registry within 12 months of the global study end date.
Identify IMP manufacturer and/or importer. Request MIA.	IMP manufactured outside the UK must secure a partner who holds a UK Manufacturer's Import Authorisation (MIA(IMP)). The MIA holder acts as legal gatekeeper for the supply chain, employing a UK-based QP who must verify that the product was manufactured in accordance with GMP standards. The QP Declaration, signed by the QP named on the MIA license, is a core submission document.
Confirmation of capacity and capability	Confirmation of Capacity and Capability (R&D Permission in Scotland) is an operational assessment at each local NHS organisation. The review timeline differs between sites. This step concludes with the execution of the site agreement. There is no need to share the LIP in Scotland, since NRSPCC do that on behalf of the Sponsor. Sponsor remains responsible for sharing with research teams.

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