Standard Operating Procedure:

Medicinal Product Management

# Purpose:

This standard operating procedure (SOP) describes the product management processes for the use of medicinal products in clinical research, including Clinical Trials of Investigational Medicinal Products (CTIMPs) and Advanced Therapy Investigational Medicinal Products (ATIMPs). It covers arrangement, ordering, labelling, shipment, storage, monitoring, accountability, and reconciliation procedures. By following this SOP researchers can help to ensure the quality and safety of the medicinal products used in their research.

# Scope:

This SOP is applicable to all clinical research projects where the University of Birmingham (UoB) is the sponsor or takes on the sponsor’s responsibilities for the management of medicinal products. Where clinical research is sponsored by another institution, this procedure should be followed as far as possible, and in line with the contractual agreement between the UoB and other institution. This SOP also applies to clinical research approved by a UoB Research Ethics Committee (REC), which is required to follow UoB-GCP-POL-001 UoB Principles of Good Clinical Practice (GCP) for Clinical Research. This SOP may be used as a guidance document in all other cases.

# Implementation plan:

This SOP will be implemented in line with this document’s effective date for all CTIMPs, ATIMPs and any other clinical research still in set up. For active clinical research that is already in the recruitment phase (or further) at the time of implementation, this SOP will be implemented within 3 months of the effective date.

# Stakeholders:

Where the UoB takes on the sponsor’s responsibility for medicinal product management, the UoB will delegate the majority of these duties to the chief investigator (CI) and/or a clinical trials unit (CTU). All delegation of duties will be documented using e.g. the CI declaration and/or the clinical trials task delegation log (see UoB-CLN-CTM-QCD-002 Clinical Trial Task Delegation Log).

* Chief investigator (CI): the CI may delegate some activities to members of their research team, however evidence of CI oversight and approval is still required. It is highlighted within this SOP where activities are, and are not, appropriate to delegate to a team member. For clinical research approved by a UoB REC, the role of CI may be referred to as the UoB principal investigator (UoB PI), or the supervisor for postgraduate research students.
* Principal Investigator (PI): an individual responsible for the conduct of the research at a research site. There should be one PI for each research site. In the case of a single-site research project, the chief investigator and the PI will normally be the same person.
* UoB CTU.
* UoB Research Governance Team.

# Background and rationale:

The management of medicinal products used in research projects is critical in clinical trials and studies to safeguard the participant. The sponsor must ensure and guarantee both the quality and the safety of any products and substances used in research projects. It is critical to maintain any medicinal product’s traceability in order for its movement and administration to be tracked. In order to facilitate an accurate audit trail, researchers must implement an accountability procedure to correctly record all data on medicinal products used within the research project; this should include actual-use data received from participants. Researchers should require all participants, for the duration of their involvement in the research project, to accurately record all medicinal products taken.

Investigational Medicinal Products (IMPs) are pharmaceutical forms of an active substance, or placebo, being tested or used as reference in clinical trials. This covers products with an existing marketing authorisation that are being used or assembled (formulated or packaged) in a different way to their authorised form. It also includes products being used for an unauthorised indication, or when products are being used to gain further information about their authorised form. Legislation relating to IMPs requires the product to be of sufficient quality, and to be manufactured and labelled in accordance with the terms of the Clinical Trial Authorisation (CTA). This ensures both the safety of the participant, and the quality of the data. CTIMPS have additional requirements contained within [The Medicines for Human Use (Clinical Trials) Regulations 2004](https://www.legislation.gov.uk/uksi/2004/1031/contents/made). Where CTIMPs also use non-investigational medicinal products (NIMPs), the IMP procedures stated within this SOP will apply. Where research only involves authorised NIMPs, please follow the procedures for medicinal products. Advanced Therapy Medicinal Products (ATMPs) are those which are prepared or manufactured, fully or partially, by a method involving an industrial process. ATMPs fall into three categories: gene therapies, somatic cell therapies and tissue engineered products. ATMPs that are tested or used in clinical trials are called ATIMPs. ATIMPs fall under the same regulations as all other clinical trials, but there are some additional factors that should be considered when developing a research project and these are clearly indicated within this SOP. The term ‘medicinal product’ will be used within this document to refer to all medicinal products including IMPs, NIMPs and ATMPs as appropriate, unless otherwise stated. There are a number of key considerations that should be addressed as early as possible when setting up a research project in order to avoid funding shortfalls, and to facilitate the most appropriate medication procedure. For further information on IMP considerations, see the [Clinical Trials Toolkit: Trial Supplies](http://www.ct-toolkit.ac.uk/routemap/trial-supplies/).

## Arranging the supply of medicinal products

There are various supply sources for medicinal products. They may come directly from a standard commercial supplier, may be provided to the investigator by a pharmaceutical company, or could be supplied by another marketing authorisation holder (MAH). A third-party vendor may be contracted to undertake medicinal-product management. Each of these scenarios involves different degrees of risk.

### Commercial supply

If the medicinal product is an authorised product within the UK, medicinal-product management is relatively straightforward as products can be dispensed from general pharmacy stock or from contracted external commercial suppliers. Commercial suppliers may supply medicinal products for a research project, either free of charge or at a cost.

### Generic vs. branded products

Many medicinal products have two names because more than one version is available.

The brand name is the name given to a medicinal product by the patent holder, usually the originating pharmaceutical company. This is also called the "proprietary name". Generics is the term used for non-branded medicinal products. Names of these non-branded products are generic or scientific names derived from a product’s characteristics such as active ingredients and use. The generic name is agreed by an expert committee and is understood internationally. This is also called the "non-proprietary name". For example, sildenafil is the generic name of a medicine used to treat erectile dysfunction. Pfizer, the company that makes sildenafil, sells it under the brand name Viagra.

If the medicinal product is a branded product that has only one supplier and one standard formulation, there is no risk of a site sourcing an incorrect product. When generics or multiple formulations are available, there is a risk of the site sourcing an incorrect product. This risk is further compounded by different National Health Service (NHS) Trusts across the United Kingdom (UK) having their own local supply contracts. These contracts are usually renewed annually, therefore the supplier or brand may change during the course of a research project.

## Manufacture and assembly of an IMP: the need for MIA(IMP) authorisation

An IMP will always need to go through a manufacturing and/or importation step, irrespective of its source. Within the UK, any organisation engaged in manufacturing and/or importation activities must hold a manufacturer’s/importer’s authorisation for IMPs, known as a MIA(IMP). The definition of ‘manufacturing’ in this context includes any manipulations performed on an IMP. Manipulations include assembly (i.e. packaging and labelling), re-packaging, and additional labelling of products with marketing authorisations. Each batch of IMP must be certified by a qualified person (QP) after manufacture/assembly, and prior to its release for use in a clinical trial (for exemptions, see “Exemptions from MIA(IMP)” below).

The definition of “importation” in this case means the bringing of an IMP into Great Britain from outside the UK. This may be from a country on the ‘approved country for import list’ (which initially includes all European Union (EU) and European Economic Area (EEA) countries). IMPs imported into Great Britain from outside the UK that have been QP certified in a listed country will not require recertification in Great Britain. If the exporting country is not on the ‘approved country for import list’ the IMPs will require QP certification in the UK by the MIA(IMP) holder upon importation, in a manner equivalent to IMPs manufactured in the UK. The QP will also need to know whether EU GMP has been followed throughout the supply chain. If the IMP is an existing authorised medicine either within the EEA, or within an International Council on Harmonisation (ICH) country (e.g. United States of America (USA) or Japan) it is accepted that EU GMP, or an equivalent standard, has been followed. For further information please see Schedule 3, Part 2 (7-8) of the [Medicines for Human Use (Clinical Trials) Regulations 2004](https://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf) and Article 13 of [Directive 2001/20 EC](https://ec.europa.eu/health/system/files/2016-11/dir_2001_20_en_0.pdf).

### Labelling

Regulation 46 of the [Medicines for Human Use (Clinical Trials) Regulations 2004](https://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf) applies to CTIMPS and ATIMPs and covers the requirements for clinical trial labelling. Clinical trial labels must abide by the requirements in Articles 26 to 31 of [Annex 13: Manufacture of IMP](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf) (Volume 4 of The Rules Governing Medicinal Products in the EU: GMP Guidelines (hereon referred to as ‘Annex 13’)). Labelling of an IMP is an assembly activity, it is required to be performed by an MIA(IMP) holder, unless exemptions apply as stated in Regulation 37 of the [Medicines for Human Use (Clinical Trials) Regulations 2004](https://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf).

### Exemptions from MIA(IMP)

A specific exemption from the need for an MIA(IMP) applies to hospitals or health centres engaged in assembly activities only (e.g. labelling). Such institutions do not require an MIA(IMP) if the assembled IMP is to be used within that specific hospital or health centre, or another hospital or health centre named as an investigator site within that same trial. The assembly must be carried out by a doctor or pharmacist, or a person under the supervision of a pharmacist. For more detail see Regulation 37 of the [Medicines for Human Use (Clinical Trials) Regulations 2004](https://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf).

Note: No IMP manufacture/assembly/importation activities may be carried out by a CTU, or an independent investigator, unless they specifically hold a MIA(IMP).

# Process map:

# Procedure:

## Project classification

1. The CI (or delegate) will determine whether the medicinal product is an IMP and whether the clinical research project is classified as a CTIMP or ATIMP. Refer to the UoB-CRG-POL-002 UoB Clinical Research Definitions.

## During trial setup:

### Research project design and protocol development

1. The CI (or delegate) will design the research project and develop the protocol for medicinal-product management, covering the aspects listed below.
* Details of all medicinal products being used.
* A description of the medicinal product (including components) and justification for its choice.
* Clear instructions with respect to dose, dose schedules and dose regime.
* A description of the delivery method (e.g. tablet, liquid), and mode of administration.
* The packaging and labelling of the medicinal product.
* Medicinal-product ordering.
* The transportation and storage of the medicinal product.
* Where relevant, the medicinal product’s brand name. This is to ensure the same medicinal product is tested throughout the research project, as different brands of certain drugs can exhibit different bioavailability (e.g. ciclosporin).
* Information, or reference to pre-existing information (e.g. pharmacy manual), regarding:
* medicinal-product accountability,
* implementation and maintenance of blinding (if applicable, see UoB-RND-SOP-001 Randomisation and Blinding)
* plan for compliance monitoring.
* The end of the research project is clearly defined as well as the follow-up period for the participants especially if this is to continue after the end of the research project. See UoB-CLN-PRO-QCD-002 Protocol Template CTIMP for further details.
* For CTIMPs and ATIMPs only: a list of IMPs, ATMPs and NIMPs with a statement on the authorised status of each product, along with their proposed use, as included in the trial’s CTA application. For unauthorised NIMPs, a justification for use in the trial will be included.
1. The CI (or delegate) will document medicinal-product management in the risk assessment (see UoB-POS-SOP-001 Project Oversight and Quality Management and UoB-CLN-TQM-QCD-001 Risk Assessment Report). When carrying out the risk assessment, the CI (or delegate) will have a number of issues to consider.
* How will the medicinal product be sourced?
* Does the medicinal product have any special handling restrictions?
* Does the medicinal product require temperature monitoring?
* What transport and storage arrangements are in place for the medicinal product?
* What medicinal-product management experience and qualifications do research staff have?
* Where will the medicinal product be administered to participants?
* Is the research project running in the EU?
* Is the research project running in Northern Ireland (NI) and importing medicinal products from Great Britain or from outside of the EU?
* If yes, follow the Northern Ireland Protocol regarding importing medicinal products.
* In addition, the following issues should be considered for CTIMPs and ATIMPs.
* Is the IMP licensed, is it licensed for use within the UK, and is it being used in accordance with the license?
* Will an approved list of brands be created?
* Will generics be used?
* Is IMP management achievable locally, or will a vendor be appointed?
* What level of IMP accountability will be used? Refer to the joint paper from the Medical Research Council (MRC) / Department of Health (DH) / Medical Healthcare Regulatory Agency’s (MHRA) ‘[Risk-adapted approaches to the management of clinical trials of investigational medicinal products](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf)’.
* What level of compliance review will be conducted to ensure participants take their prescribed medicinal products?
* For ATIMPs also consider the:
* need for, duration and nature of any follow-up with participants
* disposal of waste products
* need to perform an environmental risk assessment if viral vectors are used.
1. The CI (or delegate) will ensure that individuals working on activities relating to medicinal-product management are appropriately trained and qualified. See also UoB-TRN-SOP-001 Training.
* Where ATMPs are used the medical care given, and the medical decisions made, must be by a medically qualified doctor or dentist.
1. The CI (or delegate) will obtain the summary of product characteristics (SmPC) if the medicinal product is being used in accordance with the terms of the marketing authorisation. When the conditions of use in the research project significantly differ from those authorised, it is expected that the SmPC will be complemented with a summary of relevant data. The summary should support the use of the medicinal product in the research project, and may be incorporated into the protocol. It is expected that any additional information to support the medicinal product’s use will be included within the protocol (as detailed in point 2).
2. For CTIMPs and ATIMPs, where required the CI (or delegate) will create an investigator’s brochure (IB). See also UoB-ESD-SOP-001 Essential Documents Development and Maintenance.
3. The CI (or delegate) will ensure a process is established for obtaining and documenting any medicinal-product alerts, or updates to the SmPC or IB, as appropriate. See also UoB-AES-SOP-001 Adverse Event Reporting.
* Where the medicinal product is being supplied by the manufacturer, it is expected that it will be the responsibility of the medicinal-product supplier (as outlined in a contractual agreement) to notify the CI/CTU of any updates to the SmPC/IB.
* Where the above is not applicable, the CI (or delegate) will develop a process to ensure checks for updates to the SmPC/IB are made with evidence of at least yearly checks being conducted. For CTIMPs/ATIMPs, checks will be made at least quarterly.
1. For ATIMPs, the CI (or delegate) will ensure that an alert card for participants is developed. The CI (or delegate) will obtain approval from both the sponsor and the Research Ethics Committee (REC) prior to use. As a minimum, the alert card will contain:
* the participant’s name
* the investigator’s contact number
* information regarding the medical treatment being received.

### Responsibilities and contracts/agreements

1. The CI (or delegate), in collaboration with the Research Governance Team (RGT), will define the division of responsibilities between the medicinal-product supplier and the sponsor. The agreement will include details of a number of relevant considerations.
* Costs of the trial medication (e.g. percentage reduction, free).
* Provision of advice to the sponsor regarding the medicinal product’s stability, the potential for an extension to the expiry date and associated relabelling.
* Responsibilities for decision making on product stability in the event of a temperature excursion.
* Responsibilities for QP release/certification; medicinal-product labelling, ordering and shipment; product recalls and defect reporting.
* Where the supplier is the MAH, provision of safety information to the sponsor.
* Responsibilities for medicinal-product accountability, reconciliation, and destruction.
* Provision of documentation from the supplier for filing in the Study/Trial Master File (S/TMF), including drug shipment forms/overviews, certificates of analysis, QP certificates (if applicable).
* The required standards of service (all applicable laws, guidance, and procedures to be adhered to e.g. GMP), and the procedures for informing the sponsor of any incidence of protocol non-compliance/ serious breaches.
* Any other expectations from the medicinal-product supplier.
* For ATIMPs only, the manufacturer will provide a 30-year guarantee for the maintenance of traceability systems.
1. For blinded CTIMPs and ATIMPs only, the CI (or delegate) will ensure the IMP is provided to the trial in a final blinded format. The CI (or delegate) will:
* assign the IMP supplier/MAH the responsibility of blinding the IMP
* appoint a third-party vendor to blind the IMP if the IMP supplier/MAH is unable to blind the IMP themselves.
1. If a vendor is required for (elements of) medicinal-product management, the CI (or delegate) will perform a vendor assessment as detailed in UoB-CPR-SOP-001 Compliance Review.
* A technical agreement will be put in place between the sponsor and the vendor to document respective responsibilities and must include the quality standards that will be adhered to (e.g. GMP).
1. The CI (or delegate) will ensure that all contracts and technical agreements are signed and in place before related work begins. Signed copies will be shared with the RGT.
* Contracts and agreements with the UoB must not be signed by the CI (or delegate); the appropriate signatures may be arranged by the [UoB Contracts Team](https://intranet.birmingham.ac.uk/finance/RSS/Research-Support-Group/Contracts/index.aspx). If the terms of the contracts and agreements follow standard models and have no unusual terms, the following may apply:
* ‘normal’ technical agreements may be signed by the CTUs Director of Operations
* organisation information document (OID) and participant information centre (PIC) agreements may be signed by RGT unless there are any unusual terms which must be flagged to the contracts team.
1. The CI (or delegate) will ensure oversight and maintenance of all contracts/agreements throughout the research project. They will inform the [UoB Contracts Team](https://intranet.birmingham.ac.uk/finance/RSS/Research-Support-Group/Contracts/index.aspx) if any amendments are required, or where there is a breach of contract.

### Medicinal-product labelling

1. The CI (or delegate) will ensure that medicinal-product labels include, as a minimum, the project reference code. This allows identification of the project and participant (and if applicable the project site).
2. Where prescription only medicines (POM) are used, the CI (or delegate) will ensure that the prescribed labelling remains visible. See also [Schedule 5, Article 3 of The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994](https://www.legislation.gov.uk/uksi/1994/3144/schedule/5/made).
3. Where appropriate, the CI (or delegate) will provide the participants with the following information in relation to the medicinal product:
* name of medicine
* route of administration
* posology (detailing the dosage and quantity required)
* name and contact details for the CI (or delegate)
* any applicable warnings.
1. Where appropriate, the CI (or delegate) will ensure the labelling protects the blinding of the medicinal product.
2. For CTIMPs and ATIMPs, the CI (or delegate) will design the trial-specific labels and submit the designs to the MHRA (as the competent authority (CA)) on application for a CTA. Trial-specific labels will be designed in accordance with Articles 26 to 31 of [Annex 13](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf), except where conditions listed below are met.
* Adaptive labelling requirements as specified in Article 32 of [Annex 13](https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-4/2009_06_annex13.pdf) applies where Article 14 (2) of Direction 2001/20/EC is met, i.e.:
* the product does not require particular manufacturing or packaging processes
* the product has a market authorisation in the UK
* the product is being used within the terms of its marketing authorisation.
* No additional clinical trial-specific labelling (including Article 32 of Annex 13) is required where Regulation 46 (2) of the Medicines for Human Use (Clinical Trials) Regulations 2004 is met, i.e.:
* the product does not require particular manufacturing or packaging processes
* the product has a market authorisation in the UK
* the product is being used within the terms of its marketing authorisation, and
* the product is dispensed in accordance with a prescription given by a healthcare professional and a dispensing label is applied. See Schedule 5, Article 3 of The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994.

### Medicinal product ordering, shipment, storage, and accountability

1. The CI (or delegate) will set up the medicinal-product ordering process for sites and ensure that each site (e.g. pharmacy) has the correct equipment (e.g. fridge) and space to accommodate the medicinal product for the duration of the research project.
2. The CI (or delegate) will develop and implement a process for medicinal-product shipment, including a process for monitoring conditions during shipment (if necessary).
* If the research project is running in Northern Ireland (NI) and importing medicinal products from Great Britain or a country outside of the EU, the CI (or delegate) will follow the Northern Ireland Protocol regarding importing medicinal products.
* If the research project is running in the EU consider using local medicinal-product suppliers and follow EU legislation for medicinal-product shipment.
1. As per the risk assessment (and also to allow future reconstruction of the research project), the CI (or delegate) will set up medicinal-product accountability procedures (e.g. through drug accountability logs) to document the following:
* the medication received by the site
* the medication received by each participant, and when and where this was received
* the medication returned and/or destroyed.

For ATIMPs, where human cells or tissues are used, the CI (or delegate) will ensure it is possible to link anonymously the donor/source to the donation, to link the donation to the product and then to link the product to the participant. Traceability has to work in both directions, e.g. from source to participant and from participant to source.

1. The CI (or delegate) will develop and implement procedures for monitoring medicinal-product compliance (e.g. drug accountability logs, or participant diaries for take-home medication).
* The plan for monitoring medicinal-product compliance may be discussed as part of the research project-specific risk assessment, and the procedures put in place may be detailed in the research project-specific monitoring plan. See also UoB-POS-SOP-001 Project Oversight and Quality Management.
1. The CI (or delegate) will ensure that the participant is trained according to the protocol where the medicinal product is self-administered by the participant at home. Participants will be trained in:
* storage
* reconstitution
* administration method
* record keeping (e.g. subject diary)
* retention of used receptacles (e.g. bottles)
* the use of any equipment provided.
1. The CI (or delegate) will have procedures in place to monitor the medicinal product’s storage conditions (e.g. temperature, humidity, protection from light etc.) both at site and at coordinating centres (where applicable) in accordance with the IB/SmPC and risk assessment.
2. The CI (or delegate) will set up a documented process to assess the effect on the medicinal product should a deviation from these storage conditions occur (e.g. a temperature deviation). This will include:
* the extent of the deviation (e.g. 1ᵒC vs 20ᵒC, 1-minute deviation vs 2-day deviation)
* contacts details of the person(s) responsible for making the final decision about action required in the event of a deviation (e.g. medicinal product supplier, sponsor or CTU director of operations).
1. The CI (or delegate) will decide and document whether research project-specific or hospital-standard prescriptions will be used for prescribing the medicinal product. Where required, create research project-specific prescriptions in accordance with [UK prescribing law](https://bnf.nice.org.uk/guidance/prescription-writing.html). The prescription should identify the research project, the name of the PI and the participant’s research project number.
2. The CI (or delegate) will assess and document the suitability of site (pharmacy) processes and storage facilities at (each) site. Note that this may form part of the pharmacy assurance process. See the Health Research Authority (HRA) for more details on [Pharmacy Assurance](https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/technical-assurances/pharmacy-assurance/).
3. The CI (or delegate) will train site staff (investigators and pharmacy staff, as appropriate) in the research project-specific medicinal-product management procedures.
4. Where medicinal products require shipping to sites, the CI (or delegate) will ensure the following is clearly documented and retained in the S/TMF, prior to the release of medicinal products to sites.
* Appropriate contract/agreement in place with the IMP supplier.
* Technical release: certification by a QP that the medicinal product is suitable for use in the research project. For off-the-shelf drugs this will already be in place.
* Regulatory release: required approvals and agreements are in place to allow recruitment to begin. As a minimum, a favourable REC opinion is required. For CTIMPS and ATIMPs a CTA is needed.
1. The CI (or delegate) will refer to UoB-SMA-SOP-001 Investigator Site Management. They will inform the site(s) in writing of the regulatory green light and confirm that recruitment can begin.

### Medicinal product recalls

1. The CI (or delegate) will document a process for use in the event of a medicinal product’s recall.
* For CTIMPs and ATIMPs, the CI (or delegate) will set up a process for identifying IMP recall notifications from the [MHRA](https://www.gov.uk/drug-device-alerts).
1. Where the medicinal product is manufactured specifically for the research project, the CI (or delegate) will ensure that the agreement between the manufacturer and the sponsor documents a requirement for the manufacturer to inform the CI (or delegate) of the medicinal product’s recall.
* The CI (or delegate) will liaise with the CA prior to any recall being initiated.
* For CTIMPS, they will contact the CA’s Clinical Trials Unit.
* For ATIMPS, they will contact the CA’s Defective Medicines Report Centre.
1. The CI (or delegate) will document and maintain up-to-date contact details for each site in order to manage a medicinal product’s recall (e.g. pharmacy etc.).
2. In the event of a medicinal product’s recall, the CI (or delegate) will contact sites as soon as possible with instructions for the recall, as per research project-specific processes.
3. The CI (or delegate) will document the decisions made and actions taken; they will retain all relevant documentation in the S/TMF and relevant site files as applicable.

### Medicinal product temperature deviations

1. Upon assessment, the PI (or delegate) will report any medicinal product’s temperature deviations to the CI (or delegate).
2. The CI (or delegate) will liaise with the medicinal product’s manufacturer for advice on the impact of the deviation. For UoB-sponsored clinical research outside of a CTU, and in the event that the medicinal product’s manufacturer cannot give any conclusive advice, the CI (or delegate) will contact the RGT as the sponsor. The RGT will contact an expert in that area and confirm the conclusive advice to the CI. See also UoB-CRG-SOP-001 Sponsor Oversight of Clinical Trials.
* UoB CTUs, will escalate temperature deviations, as per their local processes to an appropriately trained person. Where this is not possible, the UoB CTU will contact RGT as the sponsor.
1. The CI (or delegate) will document the decisions made and actions taken, and will retain all relevant documentation in the S/TMF and relevant site files as applicable.

### Transfer of medicinal product between sites

1. The CI (or delegate) will have a formal process in place prior to the transfer of any medicinal product between the research project’s sites. The following will be clearly documented:
* details of the medicinal products that have been transferred (including batch numbers and quantities))
* evidence that the medicinal product’s storage conditions were maintained both by the originating site, and during shipment to the receiving site (as per the risk assessment).
1. For CTIMPs and ATIMPs only: the transfer of IMPs between sites is only allowed in exceptional circumstances (as per Article 47 of [Annex 13](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf)). Where transfer of an IMP between sites is required, the CI (or delegate) will have a formal process in place, with the following clearly documented:
* details of the IMP that has been transferred (including batch numbers and quantities)
* evidence that the IMP’s storage conditions were maintained both by the originating site, and during shipment to the receiving site (as per the risk assessment).
* Prior to the transfer of IMP between sites, the CI (or delegate) for UoB-sponsored clinical research outside of a UoB CTU will obtain approval from the RGT as the sponsor.

## During the trial:

1. Where stock is delivered to site for the research project, the CI (or delegate) will:
* ensure the receipting site (e.g. pharmacy) checks and documents the quantity and condition of any medicinal products /treatment packs at the time of arrival
* monitor the expiry dates of medicinal products
* for CTIMPs and ATIMPs, relabel the IMP in accordance with Article 33 of [Annex 13](https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-4/2009_06_annex13.pdf),where it becomes necessary to change the use-by date.
1. The CI (or delegate) will maintain oversight of stock levels and expiry dates, and will ensure that the medicinal product is restocked in a timely manner throughout the trial.
2. The CI (or delegate) will maintain an up-to-date list of research project-specific contacts (e.g. research project-specific pharmacists) at each site for use in the event of an emergency.
3. The CI (or delegate) will ensure that the site has the ability to unblind a participant immediately in the case of a medical emergency, see UoB-RND-SOP-001 Randomisation and Blinding.

## After the trial:

1. The CI (or delegate) will ensure medicinal-product reconciliation is performed as per the research project-specific monitoring plan (where appropriate).
2. The CI (or delegate) will ensure any remaining medicinal product is destroyed (where appropriate) and retain documentation of its destruction. It is recommended that, where possible, the medicinal product is only destroyed after the research project report has been written.
* Under some circumstances it is possible to re-use medicinal products, see section ‘Use of research project material after project completion’ below for details.
1. The CI (or delegate) will archive documentation relating to the medicinal product’s management (including pharmacy documentation) with the S/TMF and relevant site files at the end of the research project, in accordance with UoB-ARC-SOP-001 Archiving.

### Use of research project material after project completion (if appropriate)

1. For licenced products with no modifications, the CI (or delegate) will remove any research project-specific labelling without damaging the underlying package and instructions. They will then transfer the stock to the pharmacy, and retain documentation of the transfer.
2. For CTIMPs and ATIMPs only: for material manufactured as an IMP, the CI (or delegate) will ensure the protocol allows for extended use outside of the specific research project before re-use. The CI (or delegate) will amend the IMP labelling (if required) and will retain documentation of the transfer of stock to the pharmacy.
* For continued use of the IMP to treat patients after the research project has been completed, or terminated early, the product is no longer an IMP and becomes an unlicensed relevant medicinal product and the responsibility of the prescriber.
* For transfer of the surplus IMP to another trial, the IMP must be appropriately re-labelled and prepared for re-assessment for QP release against the new CTA(s).

# List of expected outputs:

* Evidence of the medicinal product’s management and appropriate justification detailed in the protocol.
* Evidence of the medicinal product’s management documented in the risk assessment.
* Evidence of staff training on activities relating to medicinal-product management.
* Evidence of an SmPC, with appropriate notification systems in place for updates.
* Evidence of all required contracts and agreements to be in place e.g. between sponsor and the medicinal product’s supplier.
* Evidence of appropriate medicinal-product labelling, and relevant information about the medicinal product being made available to the participant.
* Evidence of documented procedures for medicinal-product ordering, shipping, storing and destroying.
* Evidence of clear medicinal-product accountability and monitoring of medicinal-product compliance.
* Where appropriate, evidence of technical and regulatory release prior to shipping the medicinal product to sites and recruiting participants.
* Evidence of procedures to monitor and act in response to a medicinal product’s recall.
* Evidence of temperature monitoring and a documented procedure to follow in the event of a medicinal product’s temperature deviation.
* Evidence of a documented procedure for a medicinal product’s transfer between sites.
* Evidence of medicinal-product reconciliation and destruction/reuse of any remaining medicinal product.
* Evidence that the documentation related to IMP management has been stored at the end of the trial as per UoB-ARC-SOP-001 Archiving.

Additional requirements, for CTIMPs and ATIMPs.

* A list of IMPs, ATMPs and NIMPs with a statement on the authorised status of each product in the protocol.
* CTIMP and ATIMP considerations documented in the risk assessment.
* Evidence of IB (if needed).
* For blinded CTIMPs or ATIMPs, evidence that the IMP is provided in a final blinded format.
* Trial-specific labels designed, and any necessary changes to the label made, in accordance with [Annex 13](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf).
* Where appropriate, evidence of documentation regarding extended use of an IMP outside the research project.
* Evidence of a process for an IMP’s recall notification from the [MHRA](https://www.gov.uk/drug-device-alerts).
* Evidence of a documented process of an IMP’s transfer between sites (if applicable), with evidence of the RGT’s approval of the transfer.

Additional requirements for ATIMPs only.

* Evidence that all medical decisions are made by a medically qualified doctor or dentist, and evidence that they are also responsible for the medical care given.
* Evidence of an alert card, with sponsor and REC approval.
* Evidence in the contract/agreement that the manufacturer will guarantee the maintenance of traceability systems for 30 years.

# Related documents:

* UoB-AES-SOP-001 Adverse Event Reporting
* UoB-ARC-SOP-001 Archiving
* UoB-CLN-CTM-QCD-002 Clinical Trial Task Delegation Log
* UoB-CLN-PRO-QCD-002 Protocol Template CTIMP
* UoB-CLN-TQM-QCD-001 Risk Assessment Report
* UoB-CPR-SOP-001 Compliance Review
* UoB-CRG-POL-002 UoB Clinical Research Definitions
* UoB-CRG-SOP-001 Sponsor Oversight of Clinical Trials
* UoB-ESD-SOP-001 Essential Documents Development and Maintenance
* UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research
* UoB-POS-SOP-001 Project Oversight and Quality Management
* UoB-RND-SOP-001 Randomisation and Blinding
* UoB-SMA-SOP-001 Investigator Site Management
* UoB-TRN-SOP-001 Training

Note the UoB QMS documents can be found on the [CRCT website](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/index.aspx). Internal work instructions can be obtained from the CRCT (crct@contacts.bham.ac.uk) and/or from the RGT (researchgovernance@contacts.bham.ac.uk).

# References and frameworks:

* Annex 13: Manufacture of IMP. Volume 4 of The Rules Governing Medicinal Products in the EU: GMP Guidelines: <https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf>
* Directive 2001/20 EC: <https://ec.europa.eu/health/system/files/2016-11/dir_2001_20_en_0.pdf>
* Clinical Trials Toolkit: Trial Supplies: <http://www.ct-toolkit.ac.uk/routemap/trial-supplies/>.
* European Commission. Definition of Investigational Medicinal Products (IMPs). Definition of Non Investigational Medicinal Products: <https://www.erasme.ulb.ac.be/sites/default/files/files/documents/2016/draft_guidance_definition_imp_2006_07_27_2.pdf>
* HRA Guidance on Pharmacy Assurance: <https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/technical-assurances/pharmacy-assurance/>.
* MRC/DH/MHRA joint paper: ‘[Risk-adapted approaches to the management of clinical trials of investigational medicinal products](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf)
* MHRA alerts and recalls for drugs and medical devices: <https://www.gov.uk/drug-device-alerts>.
* MHRA. Good Clinical Practice Guide, London: The Stationery Office, 2012.
* National Institute for Health and Care Excellence. Prescription Writing: <https://bnf.nice.org.uk/guidance/prescription-writing.html>
* NI Protocol: <https://www.gov.uk/guidance/supplying-authorised-medicines-to-northern-ireland>
* The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031): <http://www.legislation.gov.uk/uksi/2004/1031/contents/made>
* UoB Contracts Team: <https://intranet.birmingham.ac.uk/finance/RSS/Research-Support-Group/Contracts/index.aspx>

# Abbreviations and definitions:

| Term | Description |
| --- | --- |
| Advanced Therapy Investigational Medicinal Product(ATIMP) | Advanced Therapy Investigational Medicinal Products (ATIMPs) are ATMPs that are tested or used in a clinical trial. ATIMPs are used in accordance with the same regulations that govern all other clinical trials. There are some additional factors that should be considered when developing an ATIMP trial and these are clearly indicated. |
| Advanced Therapy Medicinal Product(ATMP) | Advanced Therapy Medicinal Products (ATMPs) are medicinal products that are prepared industrially or manufactured, fully or partially, by a method involving an industrial process. ATMPs fall into three categories: gene therapies, somatic cell therapies and tissue-engineered products.  |
| Alert card | Participant alert cards inform medically qualified doctors treating the participant about the medicinal product being used. It may also contain information about any independent registries or other sources of available data in case of safety/efficacy issues. In the event of certain serious adverse reactions, they instruct the medically qualified doctors to inform the CA, the sponsor and the investigational sites. |
| Auxiliary Medicinal Product (AMP) | See ‘Non-Investigational Medicinal Product’. |
| Blinding | Blinding is the practice of keeping one or more parties involved in a trial (for example, the sponsor, the investigator team, and/or the subject) unaware of which treatment is being administered to which participant. In relation to an Investigational Medicinal Product, blinding is the deliberate disguising of the product’s identity in accordance with the sponsor’s instructions. |
| Branded product | The brand name is the name given to a medicine by the originating pharmaceutical company that owns the patent. This is also called the "proprietary name". |
| CI | Chief investigator |
| Clinical trial authorisation (CTA) | The regulatory approval for a clinical trial of an investigational medicinal product, issued by the MHRA |
| Competent authority (CA) | A body with authority to act on a government’s behalf to perform a designated function. In the case of clinical trials, the CA ensures that requirements of the Clinical Trials Directive are transposed into national law and applied. The Medicines and Healthcare Products Regulatory Agency (MHRA) is the ‘competent authority’ in the UK. |
| CTIMP | Clinical Trial of an Investigational Medicinal Product. |
| Generic product | The generic or scientific name of a drug product is the agreed term given to non-branded medicinal products by an expert committee and is internationally understood. The generic or scientific name is derived from a product’s characteristics, such as active ingredients and use. This is also called the "non-proprietary name". |
| GMP | Good Manufacturing Practice |
| HRA | Health Research Authority |
| Investigational Medicinal Product (IMP) | A pharmaceutical form of an active substance, or placebo, being tested or used as a reference in a clinical trial. This includes products that already have a marketing authorisation but are used or assembled (formulated or packaged) in a different way to the authorised form, when used for an unauthorised indication, or when used to gain further information about the authorised form. |
| Investigator brochure (IB) | A document containing a summary of the clinical and non-clinical data, relating to an investigational medicinal product, that are relevant to the study of the product in human subjects. |
| Marketing authorisation (MA) | A product licence issued for a medicinal product by the medicine’s regulator (i.e. MHRA in the UK) before the product can be placed legally on the market. |
| Marketing authorisation holder (MAH) | A company or other legal entity that has been granted a marketing authorisation to allow them to market a specific medicinal product. |
| Medicinal product | Substances, or a combination of substances, which either prevent or treat disease in humans or, are administered to humans with a view to making a medical diagnosis or restoring, correcting or modify physiological functions. |
| Medicinal product accountability | Medicinal product accountability allows the reconstruction of the research project. It documents what medicinal products were received by the site and the participant, includes the when and where, and states what medicinal products were returned to the sponsor or destroyed. It facilitates the reconstruction of the disposition of the medicinal product to demonstrate that participants received the correct medication, in the correct form and strength, according to the protocol. |
| MHRA | Medicines and Healthcare Products Regulatory Agency. |
| MIA(IMP) | Authorisation for the manufacturer/importation of investigational medicinal products. |
| Non-Investigational Medicinal Product(NIMP) | Medicinal products supplied to subjects participating in a trial, used in accordance with the protocol, which do not fall under the definition of IMPs in Directive 2001/20/EC. Also known as auxiliary medicinal product (AMP).Examples include:Medicinal products used to minimise anticipated adverse reactions e.g. corticosteroids and/or antihistamines (NIMP) treatment given to reduce the risk of expected adverse reactions before the administration of a new anti-neoplastic agent (IMP).Medicinal products used as a rescue medication e.g. opioid pain relief treatment (NIMP) given as a rescue medication when administration of a new IMP painkiller (IMP) is found to provide inadequate pain relief.Medicinal products used as challenge agents e.g. a skin prick test (NIMP) used to identify subjects with allergic responses as part of the inclusion/exclusion criteria for a clinical trial.Medicines used to assess primary endpoints in the clinical trial e.g. PET radiopharmaceuticals (NIMP) administered to a clinical trial population to measure organ function before and after the subject has been given an IMP, whose effects in this organ are the primary endpoint.Concomitant medicinal products systematically prescribed to study patients e.g., anti-cancer treatment (NIMP) in the trial of a new anti-sickness drug (IMP), where the objective of the trial is to assess the anti-sickness effect of the new drug by testing the new drug against the gold standard anti-sickness drug (NIMP) in patients treated with the same anti-cancer treatment (NIMP).Background treatment administered to each clinical trial subject in a study e.g. adjuvant chemotherapy (NIMP) given to all patients in the development of a new indication for a licensed medicine (IMP).Standard-of-care medicines that are already being administered by a subject but are continued during a research project are generally considered to be NIMPs.Detailed and useful examples of NIMPs can be found in the European Commission ‘[Definition of Investigational Medicinal Products (IMPs). Definition of Non-Investigational Medicinal Products](https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/imp_03-2011.pdf)’. |
| PI | Principal investigator. |
| Qualified person(QP) | The qualified person is legally responsible for certifying that each batch of IMP has been manufactured and checked in compliance with the requirements of UK/EU GMP, the product specification file, and the CTA. |
| RGT | Research Governance Team. |
| SOP | Standard operating procedure. |
| Summary of product characteristics (SmPC) | Summary of product characteristics (SmPC) describes the properties and conditions for use of a particular medicinal product, and is the basis of information for health professionals on how to use the medicinal product safely and effectively. It includes the composition, pharmaceutical form and strength, approved indications, side effects, warnings and precautions for use, shelf life, storage conditions and the name of the marketing authorisation holder. The summary of product characteristics (SmPC) replaces the IB if the IMP is authorised in any EU member state and it is used according to the terms of the marketing authorisation. |
| TMF | Trial master file. |
| UoB | University of Birmingham. |

See also the [Glossary of Terms](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/Glossary-of-Terms.aspx).