York Foundation Trust R&D Unit
Standard Operating Procedure
Pharm/S43

How to procure an Investigational Medicinal Product

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&D Unit's website and R&D Newsletter for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

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This SOP will normally be reviewed every 2 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of significant changes
1.0	16th May 2013	Minor changes only
2.0	14th September 2015	

Contents

1 Introduction, Background and Purpose

Clinical Trials sponsored by York Teaching Hospital NHS Foundation Trust (or those co-sponsored with the University of York) may require the Pharmacy department (at either York or Scarborough hospital) to arrange for the manufacturing and procurement of Investigational Medicinal Product to be used within the trial.

This SOP is written to describe the process of procuring Investigational Medicinal Product (IMP) for use in Clinical Trials of Investigational Medicinal Products (CTIMPs) sponsored or co-sponsored by York Teaching Hospital NHS Foundation Trust. It is necessary to ensure that the manufacture of IMP as part of this process complies with The Medicines for Human Use (Clinical Trials) regulations 2004 (SI 2004 No 1031) and European Union Good Manufacturing Practice (EU – GMP).

This SOP:

- Describes the responsibilities and requirements of York Teaching Hospital NHS Foundation Trust in its role as Sponsor for clinical trials involving manufacture of IMP.
- Is necessary to ensure that the required contracts or Technical Agreements are in place to describe the responsibilities of each party (Sponsor and Manufacturer) in such instances.
- Describes the key considerations in selection of an IMP provider and the key steps and documentation that are required to be kept to provide an audit trail of what has taken place.
- Describes the role of Pharmacy in reviewing and advising the design of a protocol for those trials sponsored by York Teaching Hospital NHS Foundation Trust to ensure that Pharmacy have oversight and input into the IMP management arrangements.

The guidance document entitled ‘Pharmacy Clinical Trials Activities’ produced by the NHS Pharmaceutical Quality Assurance Committee (1st edition, April 2009) has been used extensively to inform this procedure. In addition to this, the ‘Good Clinical Practice Guide’ released by the MHRA in September 2012 has been used to produce this SOP and should act as a reference when procuring IMP within the Trust.

For the purposes of this SOP, Investigational Medicinal Product is defined as;
A Pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or used for an unauthorised indication, or to gain further information about the authorised form.

The term ‘MIA (IMP)’ is used throughout this document. This is used to describe the Manufacturing Authorisation for Investigational Medicinal Products.

2 Who Should Use This SOP

This SOP is aimed at:

- Members of the Clinical Trials Team within Pharmacy at York Teaching Hospital NHS Foundation Trust, and is applicable at both York and Scarborough hospital.
- Members of the Research and Development (R&D) Unit within York Teaching Hospital NHS Foundation Trust.
- Chief Investigators (CI) of clinical trials sponsored or potentially sponsored by York Teaching Hospital NHS Foundation Trust, or co-sponsored with the University of York or other organisation.

3 When this SOP Should be Used

This SOP should be followed when doing the following:

- Discussing with contractors, manufacturers and R&D, arrangements for the manufacture and supply of IMP for a CTIMP sponsored or co-sponsored by York Teaching Hospital NHS Foundation Trust.
- Writing or agreeing a Technical Agreement to cover the manufacture of IMP for use in a clinical trial sponsored or co-sponsored by York Teaching Hospital NHS Foundation Trust.
- Ordering IMP for use in a Trust sponsored or co-sponsored clinical trial from the manufacturer or contractor.
- Reviewing and advising on arrangements for IMP management for a trial sponsored or co-sponsored by York Teaching Hospital NHS Foundation Trust as part of the protocol design stage.

4 Procedure(s)

4.1 Pharmacy input into protocol design of York Sponsored CTIMPs

It is important that the source, supply and management of IMP to be used within the trial is considered in the early stages of a trial set up, as part of the design of the protocol. The protocol should provide clear and unambiguous instructions for the management of IMP at each site involved in the study.

It is the responsibility of the Sponsor or Chief Investigator to consult with the Clinical Trials team within Pharmacy at York Teaching Hospital NHS Foundation Trust (including York or Scarborough hospital) to achieve this purpose. This will involve discussion between the Research Advisor within the York Hospital R&D Unit and the Clinical Trials Manager, Pharmacist or Senior Pharmacy Technician within Pharmacy at York and/or Scarborough hospital.

It is the responsibility of the Pharmacy Clinical Trials Team at either site to provide advice to the Sponsor/Chief Investigator on the following matters:

A. Sourcing

- What drugs are to be used and where will they come from
- Is there a requirement to purchase them or are there other arrangements for supply
- Is there a need to do anything else with them e.g. blinding or over encapsulation
- How will they be presented e.g. blister packs, loose etc
- What paperwork is required e.g. MIA (IMP), Qualified Person (QP) certification
- Who will undertake the manufacturing steps required
- How will they be stored

B. Supply

- How will the IMP be transported to site (temperature control etc)
- Initial supply and re supply arrangements
- IMP management (stock levels, expiry dates, accountability and tracking documentation)
- Dispensing
- What happens in the event that supplies of IMP are limited

C. Other

- Code breaks
- IMP recall arrangements
- Management of temperature deviations
- Expiry date extension and re labelling
- Returned medication and destruction
- Changes to safety data
- Changes to IMP presentation

R&D/S02 details the stages at which Pharmacy will be notified of and involved in this process.

It is advisable for Pharmacy input to be requested at the earliest possible opportunity during the protocol design stage. It is expected that Pharmacy will be involved significantly during ‘stage 2: Full trial development’ as described in the above SOP to advise on arrangements for ‘randomisation of participants, manufacture, packaging, supply, storage and dispensing of IMP (including placebo substances)’.

Pharmacy has a responsibility as an external reviewer of ‘Sponsorship in principle applications’. This will include, but is not limited to, review of the following documents as part of this application:

- The protocol including IMP management arrangements
- Clinical trial risk assessment
- Any relevant draft contracts that investigators have received from other parties
- Copy of Summary of Product Characteristics (SmPC), Investigator Brochure (IB) and/or Investigational Medicinal Product Dossier (IMPD);

In addition to this, before making regulatory submissions the Investigator must incorporate/consider all protocol and related document amendments, as specified during the sponsor review process. This provides reassurance that Pharmacy has the required oversight of the IMP arrangements as part of the sponsorship application and Clinical Trials authorisation (CTA) application.

4.2 Selection of an IMP provider for CTIMPs sponsored by York Teaching Hospital NHS Foundation Trust

When selecting an IMP provider/manufacturer, consideration should be made as to what activities constitute manufacturing or assembly. This will help to understand what activities can be conducted at the Investigator site and/or what will require the services of an external provider when making the decision on the source of the IMP. This will be done as part of the protocol design process and the following definitions should help with this:

- Manufacturing, in relation to an IMP, includes any process carried out in the course of making the product, but does not include dissolving or dispersing the product in, or diluting it or mixing it with, some other substance used as a vehicle for the purpose of administering it.
- Assembly, in relation to IMP, means:
  (a) Enclosing the product (with or without other medicinal products of the same description) in a container which is labelled before the product is sold or supplied, or used in a clinical trials or
  (b) Where the product is already contained in the container in which it is to be sold or supplied and is 'over-labelled' before the product is sold or supplied, or used in a clinical trial

For more detail of what constitutes manufacturing or assembly refer to Appendix 2 of the guidance document on clinical trials activities published by the NHS Pharmaceutical Quality Assurance committee (1st edition, April 2009). Reference should also be made to chapter 6.8 of the MHRA Good Clinical Practice Guide 2012.

When responsible for selecting a suitable IMP provider or manufacturer, Pharmacy must ensure compliance with the following (in relation to manufacturing, assembly and importation processes being conducted by the IMP provider as applicable):

- *Article 13 of the clinical trials directive 2001/20/EC , transposed into UK law through The Medicines for Human Use (Clinical Trials) regulations 2004 (statutory instrument 2004 no. 1031), requires all persons intending to manufacture or assemble IMP's to hold a manufacturing authorisation or*

MIA (IMP) (It should be noted that this may be authorised and identified differently in EU countries by the relevant competent authority)

A register of UK holders of manufacturer's authorisations for Investigational Medicinal Products (MIAIMP) can be found on the MHRA website (www.mhra.gov.uk). A register of EU holders of manufacturer's authorisations for Investigational Medicinal Products (MIAIMP) can be found on the EudraGMDP website (http://eudragmp.ema.europa.eu/inspections/mia/index.do). The proposed IMP provider can be confirmed as being present on this register by York Teaching Hospital NHS Foundation Trust when acting as Sponsor for a clinical trial. In all cases however, a copy of the MIA(IMP) should be requested from the IMP provider selected and the requirement for the IMP manufacturer to have this should be clearly stated in the Technical Agreement. This is the responsibility of the Pharmacy department.

- *The regulatory requirements regarding the role of the QP are met*

Article 13 (2) of the directive 2001/20/EEC requires the holder of a MIA (IMP) to appoint at least one Qualified person (QP), to be named on a MIA(IMP). The QP has a specific role to ensure that each batch of an IMP is manufactured and/or assembled and checked in accordance with:

1. The requirements of commission directive 2003/94/EC which describes the principals of Good Manufacturing Practice for medicinal products for human use
2. The Product Specification File
3. Any information notified in the application for Clinical Trials Authorisation/Investigational Medicinal Product Dossier

A QP must also satisfy the requirements of article 49 or 50 of directive 2001/83/EC in respect of their qualifications and experience. Pharmacy must be aware of who the QP is and ensure their responsibilities are clearly indicated in the Technical Agreement for the trial (see section 4.3). QP certification must be provided by a QP named on the MIA(IMP) authorisation specified in the CTA application as responsible for manufacturing and importation of the IMP.

- If importation of IMP is required, the manufacturing authorisation holder also requires authorisation to import. It is the responsibility of Pharmacy to ensure that the manufacturer chosen to import IMP (if required) has this authorisation.

The clinical trials directive above also requires compliance with respect to the importation of IMP's as follows:

- *Importation of licensed product from within the EEA* – this activity can be performed by a commercial wholesaler that holds a wholesale dealers licence (WL). There is no requirement for WL holders to have a QP.
- *Importation of IMP from outside the EEA* – this activity needs to be performed by the holder of an MIA (IMP) and the QP must certify that the overseas manufacturing site operates in accordance with standards equivalent to EU GMP as part of required QP release. The QP will need to declare this as part of the CTA submission and the Trial Sponsor must request Product information in English for the CTA to the MHRA.

This must therefore be considered as part of the protocol design stage of a trial.

This SOP may not contain all the information required to cover all possible circumstances relating to the manufacture and/or importation of IMP's and the relevant requirements, therefore reference should be made to Chapter 6.3 of the Good Clinical Practice Guide produced by the MHRA in 2012 during any process of procuring IMP for use in a Trust sponsored trial.

In particular, the Sponsor must ensure that both 'technical release' and 'regulatory release' are completed prior to authorising commencement of a clinical trial. This two-step IMP release process is detailed in the guide and should be referred to during the process of procurement of IMP for use in a Trust sponsored trial.

Exemptions from the need for an MIA (IMP)

It is important to note that there are exemptions from the need to hold an MIA (IMP). These exemptions apply where assembly or other changes to the packaging of an IMP is done in a hospital or health centre by a Doctor, Pharmacist or Person acting under the supervision of a Pharmacist and where the IMPs are for use in the hospital or health centre or another hospital or health centre taking part in the same trial.

The above exemption allows York Teaching Hospital NHS Foundation Trust to assemble products to be used in trials sponsored or hosted by the organisation.

Manufacturing of IMP's within Pharmacy at York Teaching Hospital NHS Foundation Trust is not permissible as the department does not hold the required manufacturing authorisations for Investigational Medicinal Products. Therefore, an external provider must be sought.

Process of selection of a Manufacturer

Usually it is the responsibility of Pharmacy (on behalf of the Sponsor) to identify a suitable contractor to provide or manufacture the IMP for use within a trial sponsored by York Teaching Hospital NHS Foundation Trust. In some circumstances, an IMP manufacturer may have been already been identified by the Chief Investigator or Sponsor (by virtue of an existing relationship e.g. Grant collaboration with the organisations involved). In these circumstances, Pharmacy has the responsibility to ensure that the manufacturer meets all the required standards as detailed in this SOP and that this is detailed in a Technical Agreement to cover the manufacture of IMP for the study (See Section 4.3). Any deviations from the requirements set out in this SOP, and the rationale for these, should be explained by the Sponsor through a file note.

If required to identify a suitable manufacturer, Pharmacy will approach an NHS Pharmaceutical Manufacturing Unit to assess the viability of them providing IMP for use in the clinical trial. The rationale for this is NHS Pharmaceutical Manufacturing Units will usually be more cost effective.

If for any reason agreement cannot be reached with an NHS Pharmaceutical Manufacturing Unit, a commercial provider will be approached. Pharmacy can provide advice on commercial companies that provide this service.

4.3 Agreements with IMP providers for CTIMPs sponsored by York Teaching Hospital NHS Foundation Trust

The manufacture and supply of an IMP must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product of an unsatisfactory quality. There should be a written contract in place which defines the duties of each party (Contract Giver and Contract Acceptor) prior to manufacture of IMP for use in the trial. The Contract Giver will be the Sponsor of the trial, in this case, York Teaching Hospital NHS Foundation Trust, or the University of York, or the study may be co-sponsored by both organisations. The Contract Acceptor will usually be the Pharmaceutical manufacturing unit or other IMP provider chosen by the Sponsor to manufacture the IMP.

The contract will usually take the form of a **Technical Agreement** as it covers the technical details of manufacture, packaging and testing. More than one Technical Agreement may be required for a trial depending on the arrangements for manufacture, supply and procurement of each IMP involved in the trial.

The Technical Agreement should clearly describe the standard of work expected and who is responsible for a given task. It should describe arrangements and responsibilities for the following activities:

- Documentation
- Production
- Quality control
- Release
- Shipping
- Complaints
- Recalls and returns
- Destruction

To provide the detail required in a Technical Agreement (under those headings) it may be useful to refer to Annex 13 of EU-GMP relating to the manufacture of IMP as a guide as to what to include in the Technical Agreement. The key characteristics of a Technical Agreement are also included in Appendix 2 and can be used as a guide to ensure the required contents of a Technical Agreement are met. The Trust's preferred template for a Technical Agreement can be found in Appendix 1. This is designed to accommodate a Co-Sponsored study so may require adaptation to suit a study individually sponsored by the Trust.

York Teaching Hospital NHS Foundation Trust will use this template when 'drawing up' a Technical Agreement for use within a Trust sponsored or co-sponsored CTIMP. In some circumstances, it may be considered appropriate that the Technical Agreement provided by the Contract Acceptor is used. In these circumstances, this agreement should be checked by Pharmacy, against our preferred template, to ensure that all the required elements are covered before the agreement is accepted.

Further guidance on Technical Agreements can be found in Chapter 7 of the EU-GMP guide.

It is important that the following requirements are also met:

- All agreements for the supply of an IMP for a particular trial must be in place prior to NHS permission for the trial being granted.
- It is important that Technical Agreements are completed prior to the project being progressed and manufacture of IMP being initiated.
- It is the responsibility of the CI to discuss contracts/Technical Agreements that are required with the Head of R&D once Sponsorship in Principle is agreed. The Pharmacy Department at York Teaching Hospital NHS Foundation Trust will input to this process.
- When a Technical Agreement is in place, the relevant section of the pharmacy checklist should be updated, by a member of the clinical trials team, with the date that the agreement was signed to provide a clear audit trail of this activity in relation to the dates of issuing Pharmacy readiness and subsequent NHS permission (See Pharm/F32 – Clinical Trials Pharmacy checklist). The use of the checklist is designed to ensure Pharmacy readiness is not issued prior to a Technical Agreement being in place.

4.4 Process of procuring IMP from an IMP providers for CTIMPs sponsored by York Teaching Hospital NHS Foundation Trust and required documentation

Section 5 of the guidance document on clinical trials activities published by the NHS Pharmaceutical Quality Assurance committee (1st edition, April 2009) contains a flow chart which summarises the process of manufacture and assembly of an IMP for use within a clinical trial and shows responsibilities of the Sponsor and the Pharmaceutical Manufacturing Unit (PMU) as part of this.

The procedure shown in the table below considers the responsibilities of the Clinical trials team within Pharmacy (acting on behalf of the Sponsor) when required to procure an IMP which requires manufacturing by a PMU or other external service provider, and should be used as a guide by Pharmacy staff in clinical trials at York Teaching Hospital NHS Foundation Trust when required to do this.

It highlights what actions are required and what documentation is required to be kept or is an important part of the process. It also details where this documentation should be stored in the Pharmacy clinical trial file (Pharm/F52 – Pharmacy clinical trial file contents).

The procedure assumes it has already been identified what IMP's are required for the purpose of a trial (during the protocol design phase) and that a suitable Pharmaceutical Manufacturing Unit or other IMP Service Provider has been identified as a potential source of the IMP.

Action required	Documentation
Make an enquiry to manufacture/assemble the required IMP(s). This would usually follow discussion of the requirements for the study between the Manufacturer and the Clinical trials manager. The Manufacturer may send you a form to complete and return	File a copy of the enquiry and relevant correspondence in the Pharmacy study file section 23 plus any forms completed at the request of the Manufacturer.

Provide information to the Manufacturer upon request to support completion of the Product Specification File and Technical Agreement. Liaise with Head of R&D and Research Adviser as required. See Section 5 of the guidance document on clinical trials activities published by the NHS Pharmaceutical Quality Assurance committee (1st edition, April 2009) for more details on what the PSF contains and what may be requested.	File copies of correspondence and any forms required to be completed by the Manufacturer.
Liaise with the Manufacturer to obtain a quote for the work and a draft Technical Agreement. Initiate a Technical Agreement if the Manufacturer does not provide one. Use Template in Appendix 1 as guidance.	File copies of draft Technical Agreements and quotations provided by the Manufacturer in section 23. File all correspondence in section 23.
Liaise with the Head of R&D and Research adviser regards acceptability of the Technical Agreement and quote received from Manufacturer	File copies of correspondence regarding amendments made.
If everything is acceptable, or following required amendments, sign Technical Agreement (on behalf of sponsor). A Technical Agreement should be in place prior to the project being progressed further.	This is the agreement to supply the IMP and is an Essential document. Please file in the Pharmacy study file section 23.
Review and amend draft product specification file provided by the Manufacturer	File all correspondence in section 23.
Receive and make appropriate amendments until the PSF documents have been mutually agreed. Once PSF is finalised, the manufacturer will proceed to source raw materials for manufacture	File all correspondence in section 23.
Once PSF is finalised, place order for the IMP with the Manufacturer. *(The order (which should refer to the protocol and PSF) should request the processing and shipping of a specified number of units and be given on behalf of the sponsor to the manufacturer. It should be in writing although can be submitted via electronic means).*	File a copy of the completed order form or relevant documentation in section 23 of the Pharmacy file.
The manufacturer will assemble product on receipt of a confirmed order according to the PSF. Manufacture will be followed by appropriate product testing and QP release in accordance with EU-GMP and the current PSF. They will then ship the product to site.	
IMPORTANT – The IMP order should be placed following execution of a Technical Agreement and following NHS permission for the study from R&D – the amber light.	

4.5 Supply of IMP to the Investigator site

Regulation 12 of the UK clinical trials regulations controls the supply of medicinal products for use in clinical trials. In particular, the IMP must not be sold or supplied to the Investigator or other person conducting the a trial, or a trial subject, unless the Sponsor has been authorised (by the UK competent authority – the MHRA) to conduct a trial with that product (unless It is sold or supplied in accordance with a marketing authorisation relating to that product) and the product has been manufactured or imported by a person holding a manufacturing authorisation in the UK or EEA. To supply a product otherwise would amount to a criminal offence under the regulations.

4.6 Location of the Technical Agreement

During the conduct of the clinical trial, in which the procured IMP is being used, the final executed Technical Agreement will be located in the Sponsor file, a copy being placed within section 19 of the Pharmacy site file.

5 Related SOPs and Documents

Royal Pharmaceutical Society of Great Britain, Practice Guidelines for Pharmacy Services, 2005.

Professional Guidance on Pharmacy Services to Clinical Trials, National Pharmacy Clinical Trials Advisory Group, Version 1.0, October 2013.

R&D/S02 – Application to an Alliance trust for sponsorship of a CTIMP.

Guidance document on clinical trials activities published by the NHS Pharmaceutical Quality Assurance committee (1st edition, April 2009).

Pharm/F52 – Pharmacy Clinical Trial File Contents.

Pharm/F32 – Clinical Trials Pharmacy Checklist.

The Medicines for Human Use (Clinical Trials) regulations 2004 (statutory instrument 2004 no. 1031).

MHRA Good Clinical Practice Guide, 2012.

EU GMP guide – Eudralex volume 4 Annex 13 (Manufacture of IMPs).

6 Appendix 1 – Technical Agreement template

TECHNICAL AGREEMENT

among

York Teaching Hospital NHS Foundation Trust,
(hereinafter referred to as the "**Trust**");

and

(Insert name of Sponsor/Co-Sponsor*)*
(hereinafter referred to as the "**insert name of Sponsor/Co-sponsor**");

and

(Insert name of IMP manufacturer)
(hereinafter referred to as "**insert name of IMP manufacturer").**

(individually a "**Party**" and together the "**Parties**").

WHEREAS:

A. The **[insert name of Co-Sponsor]** and the Trust are leading the Study in the United Kingdom for which they have together taken on the role of Sponsor;

B. The **[insert name of Co-Sponsor]** and the Trust together shall be referred to as "Co-Sponsors"; and

C. **[insert name of IMP manufacturer]** has agreed to supply the Investigational Medicinal Product to the Co-Sponsors, for use in the Study, in accordance with this Agreement.

1. Definitions

1.1. In this Agreement (including the recitals) the following words and phrases shall, unless the context otherwise requires, have the meanings set out opposite them:

"**Agreement**"	means this Technical Agreement;
"**Arising IPR**"	means all Intellectual Property Rights arising out of the Study, including Data;
"**Chief Investigator**"	means **[insert name of Chief Investigator],** an employee of the **[insert name of Sponsor],** who will take primary responsibility for the conduct of the Study;
"**Consideration**"	means **[insert amount of money]** (the total amount payable by the [insert name of Sponsor] to **[insert name of IMP manufacturer]** for the manufacture and supply of the IMP).
"**CTA**"	means the clinical trial authorisation issued by the MHRA in respect of the Study as such clinical trial authorisation may be amended by the MHRA from time to time;
"**Data**"	means together the Raw Data and the Summary Data;
"**Delivery Date**"	means the date for delivery specified by the Co-Sponsors in any written request issued under Clause 3.4;
"**Delivery Location**"	means the Pharmacy Stores, York Hospital, Wigginton Road, York, YO31 8HE, UK (for the attention of Clinical Trials Manager);

"**Effective Date**"	means the last date of signature of this Agreement;
"End of Study Report"	the report prepared by the Co-Sponsors at the end of the Study for submission to the MHRA;
"Freedom of Information Act"	The Freedom of Information Act 2000, of England & Wales, any subordinate legislation made under that Act from time to time, the Environmental Information Regulations 2004 No. 3391, and any guidance or codes of practice issued by the Information Commissioner.
"GCP"	means Good Clinical Practice as defined in the regulations.
"GMP"	means Good Manufacturing Practice as defined the regulations.
"IPR"	means "**Intellectual Property Rights**" which are defined as all patents, design rights (whether registered or unregistered), trade marks, service marks, domain names, trade and business names, publicly available and registered applications for any of the foregoing, copyrights, inventions, information, trade secrets, know-how and registered database rights including all applications for the same, all extensions and renewals to any of them and publicly available and registered applications for any of them and any right or form of protection of a similar nature and having equivalent or similar effect to any of them which may subsist anywhere in the world;
"IMP"	means "**Investigational Medicinal Product**" defined as **[insert name of the IMP]** as described in section **[insert relevant section of the IMPD]** of the IMPD;

"IMPD"	means the Investigational Medicinal Product Dossier for **[insert name and description of IMP]**
"MA (IMP)"	means Manufacturing Authorisation for an Investigational Medicinal Product
"**MHRA**"	means the Medicines and Healthcare products Regulatory Agency or any successor body;
"**Participating Site**"	means the **[Insert name and address of participating site]**
"Product Specification File"	means file containing all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release, storage conditions and/or shipping of the Investigational Medicinal Product
"**Protocol**"	means the protocol for the Study entitled **[Insert study protocol title] [insert version number of the protocol]**
"QP"	means a Qualified Person as defined in the regulations.
"**Raw Data**"	means the primary data first collected by the Chief Investigator from the Study, together with the output of any analyses thereof;
"**REC**"	means a National Research Ethics Service Research Ethics Committee established in any part of the UK;
"Reference/Retention Samples"	means samples of each batch of product retained under the responsibility of the

	manufacturer which released the batch for use in the EEA. These should be kept in the primary container used for the study or in a suitable bulk container for at least one year beyond the final shelf-life or two years after completion of the clinical trial whichever is the longest. If the sample is not stored in the pack used for the study, stability data should be available to justify the shelf-life in the pack used
"**Regulations**"	means the EU Study Directive (2001/20/EC) which is incorporated into the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), Directives 2003/94/EC and 2005/28/EC, any guidelines adopted by the European Commission or any other regulatory authority or REC pursuant to any such directives; legislation or binding guidance governing the use in clinical research, control, handling or destruction of medicinal products; and relevant professional standards or guidance;
"**RGF**"	means the *Department of Health* Research Governance Framework for Health and Social Care (second edition 2005) and any subsequent revisions;
"**Study**"	means the clinical study described in the Protocol;
"**Study Participant**"	means any person who is recruited by a Participating Site to take part in the Study;
"**Summary Data**"	means a summary of the Raw Data.

"SUSARs" means Suspected Unexpected Serious Adverse Reactions as defined in the regulations and in the Protocol.

1.2. Words denoting the singular include the plural and vice versa, words denoting a gender include all genders, and words denoting persons include corporations and all other legal entities.

1.3. Unless the context otherwise requires, references in this Agreement to any Clause will be deemed to be a reference to a clause of this Agreement.

1.4. The headings are inserted for ease of reference and will not affect the interpretation or construction of this Agreement.

1.5. A reference to a statute, statutory provisions or subordinated legislation is a reference to it as it is in force as at the date of this Agreement, taking account of any amendment or re-enactment and includes any statute, statutory provision or subordinate legislation which it amends or re-enacts; provided that, as between the Parties, no such amendment or re-enactment shall apply for the purposes of this Agreement to the extent that it would impose any new or extended obligation, liability or restriction on, or otherwise adversely affect the rights of the Parties.

2. Commencement and Duration

2.1. This Agreement shall come into force on the Effective Date and shall continue in full force and effect until the date upon which the End of Study Report is submitted to the MHRA or unless terminated earlier in accordance with the terms of this Agreement.

3. Duties of [insert name of IMP manufacturer]

3.1. **[insert name of IMP manufacturer]** shall provide such assistance to the Co-Sponsors as the Co-Sponsors shall reasonably request from **[insert name of IMP manufacturer]** from time to time in relation to the Study and in achieving CTA and MA(IMP), including in particular preparing and updating the IMPD. The reasonable direct costs of **[insert name of IMP manufacturer]** for such assistance shall be borne by the Co-Sponsors, unless otherwise agreed in writing by the Parties.

3.2. Each Party shall promptly forward to the other Parties copies of any written communication received by such Party from the REC, MHRA or under any Regulations that may be reasonably expected to affect the manufacture or supply of the IMP, and shall confer with the other Parties with respect to the best means to respond to any such communication.

3.3. In the event that the Co-Sponsors are required by the REC or MHRA or under Regulations to change the Protocol, CTA or MA(IMP) or in the event that the Co-Sponsors wish to change the Protocol, CTA or MA(IMP), **[insert name of IMP manufacturer]** shall use all reasonable efforts to accommodate any written request from the Co-Sponsors relating thereto.

3.4. The Co-Sponsors shall notify **[insert name of IMP manufacturer]** in writing of:

3.4.1. Partial loss: partial loss, damage, defects or non-delivery of a shipment within ten Business Days from the Delivery Date, provided, however, that if the loss, damage, defects or partial non-delivery are not evident immediately to the Co-Sponsors at the Delivery Date, such notification shall be made no later than ten (10) Business Days after it becomes evident.

3.4.2. Entire loss: an entire non-delivery within five (5) Business Days from the Delivery Date

and the Parties will cooperate to ensure that notification and follow-up with the involved ground and air carriers and customs or other warehouses is made in order to determine if such missing delivery can be located. **[insert name of IMP manufacturer]** shall be responsible for replacing and shipping any damaged or missing product at its cost.

3.5. Upon request of the Co-Sponsors, **[insert name of IMP manufacturer]** shall store any unshipped Product for a minimum period of five (5) years from the applicable Delivery Date against payment of **[insert name of IMP manufacturer]** standard storage fees. At the end of the five (5) years period, upon the Co-Sponsor's request, **[insert name of IMP manufacturer]** agrees to extend the storage for a duration to be determined by the Co-Sponsors in consultation with **[insert name of IMP manufacturer]** ("Extension Period"). Upon request of the Co-Sponsors **[insert name of IMP manufacturer]** shall label, pack and ship the stored Product in accordance with Section 3.5.

3.6. **[insert name of IMP manufacturer]** will supply **[insert quantity of IMP]** of the IMP to the Delivery Location to administer to the Study Participants in accordance with the Protocol and labelling/shipping instructions provided in writing by the Co-Sponsors.

3.7. **[insert name of IMP manufacturer]** shall deliver the IMP to the Delivery Location on the appropriate Delivery Date notified by the Co-Sponsors. The Co-Sponsors will confirm receipt of the IMP to **[insert name of IMP manufacturer]**

3.8. **[insert name of IMP manufacturer]** shall ensure:

3.8.1. that it supplies the IMPD which will be used for the purposes of the Study and the MHRA application and will include, without limitation information on the manufacture, ingredients, stability and storage requirements of the IMP. For the avoidance of doubt, **[insert name of IMP manufacturer]** has no approval to, and is not responsible for, dispensing the IMP to Study Participants.

3.8.2. that the IMP is manufactured in accordance with the Protocol, all relevant laws and Regulations and in accordance with GMP and GCP.

3.8.3. that a MA (IMP) is in place for the activities required to undertake the study.

3.8.4. that adequate premises, equipment, knowledge and experience are made available to carry out the work required by the Co-Sponsors as set out in this agreement. The work shall be carried out at the following address; **[insert address of IMP manufacturer]**

3.8.5. that staff involved in the manufacture of the IMP are adequately trained

3.8.6. that it keeps an up to date Product Specification File and other required records containing all relevant documents pertaining to the specification, assembly, manufacture, testing, labelling, stability and storage/shipment of the IMP as well as a copy of the Protocol and CTA , and makes the same available for the purposes of auditing or

otherwise. It should be continually updated, ensuring appropriate traceability to the previous versions.

3.8.7. that a QP is available to release the manufactured batch, that he or she is named on the MA(IMP) and is familiar with the Study and the contents of the Product Specification file

3.8.8. that Product release is only undertaken after all batch documentation and any QC test results have been reviewed and deemed satisfactory

3.8.9. that only raw materials complying with all relevant regulatory requirements are used in the manufacture of the IMP.

3.8.10. that all activities, materials and components associated with the IMP are documented to allow full traceability

3.8.11. that all current data regarding stability collected according to **[insert relevant section of IMPD]** of the IMPD is provided to the Co-Sponsors within two weeks of collection.

3.8.12. that the IMP is properly addressed to the Delivery Location, packed, secured and transported in such manner as to enable it to reach the Delivery Location in good condition. The IMP should be shipped and stored at **[insert storage conditions of the IMP]**. This should be evidenced through the use of a temperature monitoring device (which accompanies the shipment) or a validated controlled packing system.

3.8.13. that clear instructions are provided to the Delivery Location to allow analysis of the temperature during shipment to be made upon receipt of the IMP to allow the Co-Sponsors to authorise use of the IMP for the Study.

3.8.14. that if, following receipt of IMP at the Delivery Location, the Co-Sponsors report any temperature deviation(s) during shipment that **[insert name of IMP manufacturer]** will assess and confirm suitability of IMP for continued use in the Study.

3.8.15. that Reference/Retention samples are kept within **[insert name of IMP manufacturer]** Reference Store which will allow timely access by **[insert name of IMP manufacturer]** and/or the MHRA.

3.8.16. that they notify the Co-Sponsors in advance of any Regulatory Authority inspections, or if the work is subject to any inspection

3.9. **[insert name of IMP manufacturer]** acknowledges and agrees that the IMP will be packaged and labelled by **[insert name of IMP manufacturer]**, in accordance with current Eudralex Volume 4 Annexe 13 labelling requirements and in accordance with written information provided by the Co-Sponsors. **[insert name of IMP manufacturer]** shall provide any and all such information regarding the IMP as each of the Co-Sponsors may reasonably require in order to obtain and maintain the CTA and to use the IMP in accordance with the Protocol and all applicable Regulations.

4. Duties of Co-Sponsors

4.1. The Co-Sponsors shall have the sole responsibility for filing all documents with the MHRA, for obtaining and maintaining the CTA and for carrying out the Study.

4.2. The Co-Sponsors shall ensure that:

4.2.1. An order in respect of the IMP is in the form of a signed order

4.2.2. the IMP is assessed upon receipt and that any temperature deviations are reported to **[insert name of IMP manufacturer]** in a timely manner.

4.2.3. the IMP is used only in the Study

4.2.4. Any surplus IMP remaining at the end of the Study will be disposed of in accordance with the Co-Sponsor's SOP Pharm/S57 (Destruction of Clinical Trial Medication)

5. Payment Provisions

5.1. The **[Insert name of Sponsor/Co-sponsor]** shall pay **[insert name of IMP manufacturer]** the Consideration in accordance with this Clause 5.

5.2. **[insert name of IMP manufacturer]** shall invoice the **[Insert name of Sponsor/Co-sponsor]** for the Consideration and the **[Insert name of**

Sponsor/Co-sponsor] shall pay **[insert name of IMP manufacturer]** within thirty (30) days of receipt of the invoice.

6. Guidelines, Regulations and Approvals

6.1. The Parties acknowledge that the **[Insert name of Sponsor/Co-sponsor]** and the **[Insert name of Sponsor/Co-sponsor]** have entered a Co-Sponsorship Agreement and that together the **[Insert name of Sponsor/Co-sponsor]** and the **[Insert name of Sponsor/Co-sponsor]** are the Co-Sponsors of the Study.

6.2. The Co-Sponsors shall:

6.2.1. ensure that all relevant regulatory requirements, REC and other necessary approvals have been obtained for the Study before the Study commences and provide these to **[insert name of IMP manufacturer]** as appropriate;

6.2.2. comply with the terms of such institutional, regulatory and REC approvals for the Study; and

6.2.3. conduct the Study in accordance with the RGF, the Regulations, the Protocol and the principles of GCP.

6.3. The Co-Sponsors will notify **[insert name of IMP manufacturer]** immediately in writing of any revocation or amendment to an institutional, regulatory and/or REC approval, which concern **[insert name of IMP manufacturer]** or the IMP, and will provide copies of any revocations or amendments to **[insert name of IMP manufacturer]**.

7. Protocol

7.1. The Co-Sponsors will provide **[insert name of IMP manufacturer]** with a copy of the Protocol and any relevant associated documents.

7.2. The Co-Sponsors will notify **[insert name of IMP manufacturer]**, and provide **[insert name of IMP manufacturer]** with a reasonable opportunity to review and comment upon, any proposed changes to the Protocol, which may modify

the intended use of the IMP or the IMP itself. However, the Co-Sponsors shall have full and final discretion over changes to the Protocol and will notify **[insert name of IMP manufacturer]** when any changes have been finalised.

8. Recall of Products and Results

8.1. **[insert name of IMP manufacturer]** will formally notify the Co-Sponsors by fax [insert fax number of Co-Sponsors] within 24 hours of becoming aware of a potential recall of products or results already given to the Co-Sponsors.

8.2. The Co-Sponsors will formally confirm receipt of the notification described in clause 8.1 above to **[insert name of IMP manufacturer]** by e-mail or fax of any recall of the IMP within 24 hours of becoming aware of such notification. The Co-Sponsors will also formally inform the MHRA of any recall of the IMP within 24 hours after becoming aware of it.

8.3. **[insert name of IMP manufacturer]** shall execute any recall and shall obtain from the Co-Sponsors all necessary information required to perform the recall. All information has to be collected within 24 hours after request. The alert should be classified from 1 to 3 depending upon the expected risk presented to the public health by the defective product as reported in Doc. Ref. EMEA/INS/GMP/23020/2007:

Class	Description
1	The defect presents a life threatening or serious risk to health
2	The defect may cause mistreatment or harm to the patient, but it is not life threatening or serious
3	The defect is unlikely to cause harm to the patient, and the recall is carried out for other reasons such as non compliance with the MA or specification

.

8.4. **[insert name of IMP manufacturer]** shall conduct an investigation to determine the cause of the potential recall and will provide the Co-Sponsors with interim and final written reports as and when requested by the Co-Sponsors.

9. COMPLAINTS

9.1. **[insert name of IMP manufacturer]** will be responsible for the investigation of complaints relating to the service provided to the Co-Sponsors.

9.2. The Co-Sponsors will inform **[insert name of IMP manufacturer]** of any complaints concerning the quality of the service provided.

9.3. The Co-Sponsors will communicate all complaints relating to **[insert name of IMP manufacturer]** which implicate the quality of the IMP. The investigation and report of the findings will be completed within 30 days unless otherwise agreed, based on the severity of the problem. A documented response will be issued to the Co-Sponsors, where necessary.

10. Reporting

10.1. In order to allow the Parties to fulfil their general reporting obligations in connection with the IMP, the Co-Sponsors shall report all SUSARS within the legally required timescale to MHRA and to **[insert name of IMP manufacturer]**.

11. Liability and Indemnity

11.1. **[insert name of IMP manufacturer]** is responsible for the pharmaceutical quality of the IMP and agrees to maintain appropriate product liability insurance.

11.2. **[insert name of IMP manufacturer]** shall at all times indemnify, and keep indemnified the Co-Sponsors against all costs, damages, expenses, liabilities and losses incurred by the Co-Sponsors, or for which the Co-Sponsors may become liable, arising out of or in connection with any claim or proceedings brought against the Co-Sponsors (for damages to property, death, personal injury, or otherwise) arising out of or in connection with any defects or alleged defects in the IMP or to the use of the IMP by the Co-Sponsors.

11.3. No Party shall be liable for any loss of business or business interruptions, loss of profit, loss of revenue regardless of a Party's negligence.

11.4. Nothing in this Clause 11 shall purport to exclude or limit the liability of a Party in respect of liability which cannot, by law, be excluded or limited, including death or personal injury caused by a Party's negligence or fraudulent misrepresentation.

12. Arising IPR, Data and Reports

12.1. IPR in the IMP is the subject of a separate agreement between the [insert the names of the parties involved in the agreement and when this was executed].

12.2. All arising IPR shall belong to the Co-Sponsors. **[insert name of IMP manufacturer]** shall have no right to the Arising IPR.

12.3. **[insert name of IMP manufacturer]** recognises that the Co-Sponsors have a responsibility under the RGF to ensure that results of scientific interest arising from the Study are appropriately published and disseminated. **[insert name of IMP manufacturer]** agrees that the Co-Sponsors shall be permitted to present at symposia, national or regional professional meetings, and publish in journals, theses or dissertations, or otherwise of their own choosing, Arising IPR subject to the publication policy provided in this Agreement and the Protocol.

13. Confidentiality

13.1. In the event that one Party (the "**Disclosing Party**") makes available to an other Party (the "**Receiving Party**") under this Agreement information that is marked as "confidential" or has about it the nature of confidence (in whatever format) during the course of the Study ("**Confidential Information**"), the Receiving Party shall not use nor disclose any Confidential Information except for the purposes of the Study or the proper performance of this Agreement without the prior written consent of the Disclosing Party. Each Party shall ensure that each of its employees or other individuals who have rightful access to the Confidential Information have agreed to be bound by equivalent obligations of confidentiality and non-use as apply to the Parties in terms of this provision.

13.2. The obligations in clause 13.1 shall not apply to Confidential Information that the Receiving Party can show:

(a) is in, or has become part of, the public domain other than as a result of a breach of these obligations of confidentiality by the Receiving Party;

(b) 'was independently developed by the Receiving Party without reference to the Confidential Information

(c) was in its written records prior to entering into this Agreement;

(d) was independently disclosed to the Receiving Party by a third party entitled to disclose the same; or

(e) is required to be disclosed under any applicable law; or by order of a court or governmental body or authority of competent jurisdiction, provided that the Receiving Party gives the Disclosing Party sufficient prior notice of such disclosure to allow the Disclosing Party to take precautionary measures.

13.3. No term of this Agreement, whether express or implied, shall preclude the Co-Sponsors from making public under the Freedom of Information Act 2000, and any codes applicable from time to time relating to access to public authorities' information, details of matters relating to this Agreement unless such details constitute a trade secret; the disclosure of such details would or would be likely to prejudice substantially the commercial interests of any person (including but not limited to any of the Parties hereto) or such details fall within such other exemption as may be applicable at the discretion of the Co-Sponsors. **[insert name of IMP manufacturer]** will facilitate the Co-Sponsors' compliance with their obligations under these provisions and comply with any request from the Co-Sponsors for that purpose.

13.4. The Co-Sponsors agree to adhere to the principles of medical confidentiality in relation to all personal data relating to the Study Participants. The Co-Sponsors shall not disclose the identity of the Study Participants to **[insert name of IMP manufacturer]** or to any other third party without the prior written consent of the Study Participants in accordance with the requirements of the Data Protection Act 1998, principles set out in the Report of the Caldicott Committee on the review of patient identifiable information dated December 1997 and any other applicable legislation and industry codes concerning collection and processing of personal data.

13.5. Except as expressly provided in this Agreement no Party to this Agreement shall use another Party's name, corporate identifier, crest, logo, registered name, trade mark or the name of any of its employees for any purpose whatsoever without the prior written consent of that Party or individual.

14. Termination

14.1. This Agreement may be terminated by a Party immediately by notice in writing to the other Parties in the event that:

14.1.1. a Party (in the reasonable opinion of the terminating party) is in material breach of any of its obligations under this Agreement or the Protocol, which if it can be remedied remains unremedied on the expiry of twenty-eight (28) days after receipt by the Party in breach of written notice from the other Party specifying the breach and the action required to remedy same;

14.1.2. a Party has a receiver, administrative receiver, or administrator appointed to itself or any of its assets and undertakings, should go into liquidation (or any analogous proceedings) or be unable to pay its debts as they fall due;

14.1.3. a Party is unable to permanently continue the Study for reasons beyond its control including (but without prejudice to the generality of the foregoing) the loss of funding or withdrawal of ethical approval;

14.1.4. the regulatory permissions and approvals previously granted to perform the Study are withdrawn;

14.1.5. interim analysis of the Data from the Study (or the data of another study) supersede the necessity for completion of the Study;

14.1.6. continuing the Study poses, in the opinion of the Co-Sponsors an unacceptable risk to the rights, interests, safety or wellbeing of the Study Participants.

14.2. A Party shall be entitled to terminate this Agreement on six (6) months prior written notice to the other Parties. For the avoidance of doubt, where the Party

requesting early termination under this Clause 14.2 is **[insert name of IMP manufacturer]**, **[insert name of IMP manufacturer]** agrees to fulfil its commitments under this Agreement for all Study Participants enrolled up to and including the date of termination.

14.3. The Parties agree that if the Study is terminated for any reason whatsoever then this Agreement will be deemed to have terminated effective as of the effective date of termination of the Study, but termination of this Agreement shall not relieve any party for any obligation accrued as at or relating to the period prior to termination..

14.4. The provisions of Clause 1 (Definitions), Clauses 3.4., 3.5, 3.7 and 3.8 (Supply of the IMP), Clause 6 (Guidelines, Regulations and Approvals), Clause 10 (Reporting), Clause 11 (Liability and Indemnity), Clause 12 (Arising IPR, Data and Reports), Clause 13 (Confidentiality) Clause 14 (Termination) and Clause 16 (Governing Law) shall survive termination or expiry of this Agreement.

15. Miscellaneous

15.1. Nothing in this Agreement and no action taken by a Party pursuant to this Agreement shall constitute or be deemed to constitute a partnership between the Parties or shall constitute a Party as an agent, employee or representative of the other.

15.2. No variation of this Agreement shall be valid unless it is in writing and signed by or on behalf of each Party.

15.3. Failure by a Party to enforce at any time or for any period any term of this Agreement does not constitute and shall not be construed as a waiver of such term and shall not affect the right later to enforce such term and any other term herein contained.

15.4. If any provision of this Agreement is held to be void or unenforceable by any legislation or judicial or administrative authority, such provision shall be deemed to be severable and shall not affect the validity of the remaining portion of this Agreement which shall remain in force and effect as if this Agreement had been granted with no such provision and it is hereby declared the intention of the

Parties that they would have executed the remaining portion of this Agreement without including therein any provision.

15.5. Any notice under this Agreement shall be in writing and delivered personally, by courier, by recorded delivery post, or by facsimile, providing evidence of receipt if posting to the following addresses.

For **[insert name of Sponsor/Co-Sponsor]**:
[Insert address and fax number of the Sponsor/Co-Sponsor]
For the attention of the **[insert title of person to whom this should be sent]**

For the Trust:
York Teaching Hospital NHS Foundation Trust
Wigginton Road, York, YO31 8HE
Fax: **[insert fax number to which this should be sent]**
For the attention of the **[insert title of person to whom this should be sent]**
with a copy to the Clinical Trials Manager, Pharmacy Department

For **[insert name of IMP manufacturer]**:
[Insert address and fax number of the IMP manufacturer]
For the attention of **[insert title of person to whom this should be sent]**,

16. GOVERNING LAW

This Agreement shall be governed and construed in accordance with the laws of England and Wales and the Parties hereby submit to the exclusive jurisdiction of the Courts of England and Wales.

IN WITNESS WHEREOF, these presents consisting of this and the preceding (12) pages are executed by the Parties in duplicate as follows:-

For and on behalf of the **[insert name of Co-Sponsor]**
Signed by

……

Print Name

……

Date

……

For and on behalf of the Trust

Signed by

……

Print Name

……

Date

……

For and on behalf of **[insert name of IMP manufacturer]**

Signed by

……

Print Name

……

Date

……