GUIDANCE DOCUMENT

PHARMACY CLINICAL TRIALS ACTIVITIES

covering

How to Procure An Investigational Medicinal Product
&
How to Set Up A Clinical Trial In A Dispensary

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Contents

This is one of the series of NHS national guidance documents issued by the NHS Pharmaceutical Quality Assurance Committee. Copies are available on www.portal.nelm.nhs.uk/qa/defalut.aspx or www.qcnw.nhs.uk

This guidance document has been produced on behalf of the NHS Pharmaceutical Quality Assurance Committee by the National Clinical Trials Working Group. Membership is shown below:-

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EXECUTIVE SUMMARY

The Clinical Trials Directive 2001/20/EC (CTD) was transposed into UK law through The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No.1031). This requires all manufacturing of clinical trials products to be carried out under an Investigational Medicinal Product Licence (MIA (IMP)).

The majority of NHS pharmaceutical manufacturing units (PMU) that have applied for and been granted the MIA(IMP) also have a Manufacturers' (Specials') Licence. This has required an overlaying of additional quality assurance system pertaining to IMP to the established Good Manufacturing Practices (GMP) for the Specials' licence. The GMP aspects of the CTD are reproduced as a reference material.

This guidance document is based on an information pack developed by the London & SE QA Group (QA Group) and guidance documents produced by Quality Control North West. This document is to be used as a reference source and to allow individual PMU and Dispensary personnel to enhance their existing Quality Systems.

For MIA(IMP) GMP aspects, the existing GMP system for Specials' manufacturing should suffice for the manufacturing activity. However, the training and coordination for obtaining the initial information and involvement of the Qualified Person (QP) are considered to be essential requirements for the setting up of processes such as development of the Technical Agreement, Confidential Agreement and Product File specification. The scripted templates in the Appendices could be adapted for these purposes. There may be occasions when the request is for investigations that may not be under the scope of the CTD such as those for physiological studies, and for such instances the PMU should apply, as best practice, the Quality System Framework in this pack.

For Dispensary Quality Systems, only the GCP aspects applicable to Pharmacy are covered in this document. Clinical GCP is the responsibility of the sponsor and clinical unit where the trial is being carried out.

This information pack is formatted as individual sections and appendices to allow each of these to be used as pull–out documents. The information is based on an understanding of the regulatory requirements and on sharing of best practices and is not to be considered as a policy document. The relevant document(s) will be revised provided there is/are any significant change(s).

This document has been split into the following sections:

- Glossary
- The regulatory requirements regarding the manufacture and assembly of investigational medicinal products.
- The requirements for the set up of a Clinical trial in a Pharmacy Dispensary.
- Example templates for the procurement of IMPs from licensed units.
- Example templates for the setup of a Clinical Trial in a Dispensary.
- Links and reference websites and documentation relevant to the clinical trials within the NHS.

The responsibility for the design of a trial.

Good Clinical Practice (GCP) as applied to departments outside pharmacy, and the regulatory requirements relating to the clinical evaluation of a Medical Device are outside the scope of this document.

SECTION 2: DEFINITIONS

2.1 Clinical trial

Any investigation in human subjects intended:

a) To discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more IMPs, and/or
b) To identify any adverse reactions to one or more IMPs, and/or
c) To study absorption, distribution, metabolism and excretion of one or more IMPs with the object of ascertaining its/their safety and/or efficacy of those products;

Essentially, if a study is not for the purpose of ascertaining the safety or efficacy of a product and the product is simply being used as an aid or tool in the study, for example to produce physiological effect, then manufacturing and handling of such products is not within the scope of the CTD.
Clinical studies involving only medical devices, food supplements or other non-medicinal therapies (such as surgical interventions) are not covered by the Directive.
The Regulations do not apply to non-interventional trials. In such trials, no additional diagnostic or monitoring procedure should be applied. Epidemiological methods should be used for the data analysis

The algorithm 'Is it a clinical trial within the scope of the CTD?' can be accessed from the European Commission Website

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/guidance-on-imp_nimp_04-2007.pdf

Reference could also be made to the Quality Control North West's guidance document on 'What is Manufacture?' that is reproduced as Appendix 2.

2.2 Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

2.3 Sponsor

An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

2.4 Investigator

A person responsible for the conduct of the clinical trial at the trial site. If a team of individuals at the trial site conducts a trial, the investigator is the responsible leader of the team and may be called the principal investigator.

2.5 Quality Assurance (QA)

This is the sum total of the organised arrangement made with the object of ensuring that medicinal products or services are of the quality required for their intended purpose.

2.6 Quality Control (QC)

This involves checking a service or process to make sure it is of the correct quality.

2.7 Qualified Person (QP)

A person who either satisfies the requirements of Articles 49 or 50 of Directive 2001/83 (as amended) or otherwise meets the definitions of a Qualified Person as stated in the Medicines for Human Use (Clinical trials) Regulations 2004, section 43.
In instances where an IMP is imported from third country, a QP release is required for procurement and supply for use in the clinical trial. Importation for IMP should be by holder of MA (IMP) [Import] and the release for procurement and supply for use in the clinical trial must be by QP of the import licence holder; there may be another QP for manufacturing.

2.8 Investigational Medicinal Product (IMP)

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.

2.9 Product Specification File (PSF)

A reference file(s) containing all the information necessary to draft the detailed written instructions on processing, packaging/labelling, quality control testing, batch release, storage conditions and shipping of an IMP. This document should be continually updated ensuring traceability between versions.

2.10 Protocol

This document should be present before any trials materials are manufactured and should contain the trial objectives, treatments, end points and details for any emergency procedures.

2.11 Assembly

In relation to an 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 trial, or
(b) Where the product (with or without other medicinal products of the same description) 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

2.12 Manufacture

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.

2.13 EudraCT

The Clinical Trial application and database, which is hosted by the EMEA

2.14 International Conference on Harmonisation (ICH)

This is specifically for technical requirements for registration of pharmaceuticals for human use. This is a group consisting of the US, Japan and the EU regulatory authorities and experts from the pharmaceutical industry.

2.15 Ethics Committee Opinion

Article 6 of the Directive requires an ethics committee to give an opinion before a clinical trial commences and sets out certain documents and particulars that it must consider in reaching that opinion. An ethics committee which has been established or recognised under the regulations and which receives a valid application for an ethics committee opinion from the chief investigator or the principal investigator in the case of a single site, would then give an opinion on the trial. Only if the opinion is favourable could the trial commence.

Article 7 of the Directive requires that Member States establish a procedure to obtain a single opinion for multi-centre trials. For multi-centre trials conducted inside the UK (irrespective of whether they are also being conducted in other countries), Regulation 13 would set out the ethics committee to which an application must be made in case of a multi-centre trial – i.e. to an ethics committee established or recognised for an area in which the chief investigator is "professionally based", or for the entire UK, and which is responsible for considering the type of clinical trial in question.

2.16 Application to the Competent Authority

Nobody is allowed to start a clinical trial until the trial has been authorised by the licensing authority. (The Medicines and Healthcare Products Regulatory Agency (MHRA) in the case of the UK.) To start or conduct a trial without authorisation (Regulations 11) is a criminal offence under the Regulations. In addition Regulation 12 controls the supply of medicinal products for use in clinical trials. In particular the product must not be sold or supplied to the investigator or other person conducting a trial, or a trial subject, unless the sponsor has been authorised 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 also amount to a criminal offence under the regulations.

Under Regulation 16 a request for an authorisation of a clinical trial would be made to the licensing authority by the sponsor in writing and signed by or on behalf of the applicant.

2.17 Studies in Healthy Volunteers

Under the legislation these studies are considered to be clinical trials and require authorisation.

2.18 Manufacturing Importation Authorisation for Investigational Medicinal Products [MIA (IMP)]

In accordance with the provisions of Article 13 of the Directive, all persons intending to manufacture, assemble and/or import IMPs are required to hold a manufacturing authorisation.

When applying for an MA(IMP) careful consideration should be given to whether authorisation to import is included (refer to section on Importation of Products For Use In Clinical Trials).

In order to determine if a product is to be manufactured under the terms of the MIA(IMP) or Manufacturing ‘Specials’ Licence refer to Appendix 2 for Quality Control North West’s guidance document on What is Manufacture?’ and MHRA’s algorithm ‘Is it a trial?’

2.19 Exemptions

In certain cases 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 study.

An exemption may be terminated where the hospital or health centre does not have the staff, premises, equipment or facilities to carry out changes to packaging or repackaging processes properly. It can also be terminated where it is considered that the IMP can no longer be safely administered or is not of satisfactory quality as a result of the changes in packaging or repackaging processes.

2.20 Good Manufacturing Practice (GMP)

This is a recognised standard for pharmaceutical processing and manufacture ensuring medicinal products are consistently produced and controlled

The holders of a Manufacturing Importation Authorisation for IMP are obliged to comply with the principles and guidelines of good manufacturing practice.

Particular attention should be paid to requirements of the current Annex 13 of EU-GMP. (Current version can be downloaded from
http://europa.eu.int/comm/enterprise/pharmaceuticals/eudralex/homev4.htm

2.21 Qualified Persons (QP)

(also refer to page 19 for QP's Role For Hospital Manufactured IMPs).

Article 13 (2) of Directive 2001/20/EEC requires that the holder of an MIA (IMP) must appoint at least one Qualified Person (QP), to be named on an MIA (IMP). The QP's duties are specific and are intended to ensure that every batch of an IMP has been manufactured and/or assembled and checked in accordance with:

- the requirements of Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice for medicinal products for human use,
- the product specification file
- any information notified in the application for a clinical trials authorisation.

A QP must satisfy the requirements of Article 49 or 50 of Directive 2001/83/EC (as amended) in respect of qualifications and experience.

SECTION 3: THE REGULATORY REQUIREMENTS REGARDING THE MANUFACTURE AND ASSEMBLY OF INVESTIGATIONAL MEDICINAL PRODUCTS.

3.1 Documentation

3.1.1 Ordering

Refer to Appendix 5 for Technical Agreement template

The order should request the processing and/or packaging of a certain number of units and/or their shipping and be given by or on behalf of the sponsor to the manufacturer. It should be in writing (though it may be transmitted by electronic means), and precise enough to avoid ambiguity. It should be formally authorised and refer to the Production Specification File and the relevant clinical trial protocol as appropriate.

3.1.2 Product Specification File (PSF)

The PSF is created by the PMU and should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. Any changes to the PSF must be subject to the Change Control Procedure.

The PSF should include or refer to the following GMP critical data:

- Specifications and analytical methods for starting materials, packaging materials, intermediate, bulk and finished product.
- Manufacturing methods.
- In-process testing and methods.
- Approved label copy.
- Relevant clinical trial protocols and randomisation codes, as appropriate.
- Relevant technical agreements with Contract Giver, as appropriate.
- Stability data.
- Storage and shipment conditions.

This list is not intended to be exclusive or exhaustive. The contents will vary depending on the product and stage of development.

A copy of the original trial application and approval should be included, as should any subsequent variations or amendments. Current version of the PSF must be available for the QP to release the manufactured IMP. The QP for importation of IMP would require copy of approved CTA.

3.1.3 Manufacturing Formulae and Processing Instructions

For every manufacturing operation or supply there should be clear and adequate written instructions and written records. Where an operation is not repetitive it may not be necessary to product Master Formulae and Processing Instructions.
Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the marketing authorisation is granted.

The information in the PSF File should be used to produce the detailed written instructions on processing, packaging, quality control testing, storage and shipping.

3.1.4 Packaging Instructions

IMPs are normally packed in an individual way for each subject included on the clinical trial. The number of units to be packaged should be specified prior to the start of the packaging operation, including units necessary for carrying out quality control and any retention samples to be kept. Sufficient reconciliation should take place to ensure that the correct quantity of each product required has been accounted for at each stage of the processing.

3.1.5 Processing, testing and packaging batch records

Batch records should be kept in sufficient detail for the sequence of operations to e accurately determined. These records should contain any relevant remarks that justify the procedures used and any changes made, enhance knowledge of the product and develop the manufacturing operations.

3.2 Production

3.2.1 Principles applicable to comparator product

If a product is modified, data should be available (e.g. stability, comparative dissolution, bioavailability) to demonstrate that these changes do not significantly alter the quality characteristics of the product.

The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been repackaged in a different container that may not offer equivalent protection, or be compatible with the product. A suitable use by date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article may be subjected, should be determined on or on behalf of the sponsor. Such a date should be justified and must not be later than the expiry date of the original package. There should be compatibility of expiry dating and clinical trial duration.

3.2.2 Blinding Operations

Where products are blinded, systems should be in place to ensure that the blind is achieved and maintained while allowing the identification of “blinded” products when necessary, including the batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency.

3.2.3 Randomisation Code

Procedures should describe the generation, security, distribution, handling and retention of any randomisation code used for packaging investigational products, and code-break mechanisms. Appropriate mechanisms should be maintained.

3.3 General

3.3.1 The procurement, preparation, and supply of IMPs must conform to the requirements of cGMP Controlled documentation of these processes is mandatory.

3.3.2 All documentation must take into account recommendations laid down in the following documents:-

a) Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004 No. 1031)
b) Good Clinical Practice Regulations (SI 2006 No. 1928)
c) Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007 (Orange Guide)
d) Orange Guide, Annex 13
e) Current professional Pharmacy standards
f) DoH Guidance Documents
g) Hospital and Departmental Health and Safety at Work documents.

3.4. Documents Required

The following example documents are required to initiate the manufacturing/ assembly process for a Clinical Trial

3.4.1 Quotation Request Form For An IMP

The sponsor, pharmacist, investigator or clinician who is organising the Clinical Trial will require to contact PMU and discuss requirements of the study along with obtaining a quotation for the work required to manufacture, assembly, test and release the required products for the study. An example form is attached in Appendix XX.

The PMU will then provide a quotation for the work.

3.4.2 Agreement To Supply An Imp/ Order Form

An order or agreement (an example form is attached in Appendix 4) will be completed by the relevant people and agreed by the Supplier and Quality Controller, who will each sign the document. It will be sent to the requestor who will countersign to show their agreement.

3.4.3 Clinical Trial Study File

Once the signed 'Agreement to Supply an IMP' or Order is received a Clinical Trial Study File will be set up by the PMU/Quality Controller.

This should be divided into 10 sections:

SECTION 1 – Request details
- Request for quotation form
- Quotation letter
- Any correspondence about quotation

SECTION 2 – Contract – IMP Agreement /Order
- Contract – IMP agreement to supply
- Any additional correspondence about order
- Delegation Log

SECTION 3 – Protocol + amendments
- Final Trial Protocol
- Amendments to protocol

SECTION 4 – CTA
- Copy CTA plus any substantial amendments
- MHRA CTA approval letter(s)
- IMPD section of CTA
- Simplified IMPD section of CTA
- Copy of approved label sent with CTA
- MHRA CTA approval letter – substantial amendment

SECTION 5 – ETHICS
- Ethics Committee application form (if available)
- Ethics Committee Favourable Opinion
- Trust Approval Letter

SECTION 6 – Product Specification File - Specifications
- Starting materials
- Packaging materials
- Intermediate bulk
- Finished Product

SECTION 7 – PSF – Manufacturing Details
Manufacturing Methods
In process testing and methods
Stability Data
Certificate of analysis for each material
Certificate of release within EU for each material if imported

SECTION 8 – PSF – Labelling & Randomisation
Final Approved label copy
Randomisation code
Storage and shipment conditions

SECTION 9a – Release certificate for Packaged Product
Certificate of release
Enquires/Complaints/Recalls

SECTION 9b– Proof of receipt
Proof of receipt at site(s)

SECTION 10 – Correspondence
Emails
Draft documents
Correspondence

3.5 Product Development

When the initial inquiry is received at PMU the Quality Controller should be informed so that specifications for starting materials (where applicable) and finished product can be begun, analytical investigations can be started, and stability studies planned, as soon as practicable.

This data may be required for the IMPD section of the CTA.

3.6 Packaging

Packaging and labelling of IMPs are likely to be more complex and more liable to errors (which are also harder to detect than of marketed products) when “blinded” labels are used. Supervision procedures such as label reconciliation, line clearance etc., and the independent checks by quality control staff should accordingly be intensified.

IMPs must be packed in an individual way for each patient included in the clinical trial. Packaging instructions are based on the order. Batches of investigational medicinal products may be subdivided into different packaging batches and packaged in several operations over a period of time.

The number of units to package should be specified prior to the start of the packaging operations, considering also the number of units necessary for carrying out quality controls and the number of samples to be kept. Reconciliation should take place at the end of the packaging and labelling process.

3.6.1 Labelling Instructions and Package Inserts

3.6.1.1 Labels should comply with Annex 13 of EU-GMP and include:

a) Name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information of the product, clinical trial and emergency unblinding.)
b) pharmaceutical dosage form, route of administration, quantity of dosage units
c) and in the case of open trials the name/identifier and strength/potency
d) the batch and/or code number to identify the contents and packaging operation;
e) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
f) the trial subject identification number/treatment number and where relevant, the visit number;
g) the name of the investigator if not included in a) or d)
h) directions for use; (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);
i) “for clinical trial use only” or similar wording;
j) the storage conditions;
k) the period of use (use-by date, expiry date or re-test date as applicable) in months/year and in a manner that avoids ambiguity;
l) k) “keep out of reach of children” except when the product for use in trials where the product is not taken home by subjects.

3.6.1.2 The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.

3.6.1.3 Particulars should appear in the official language(s) of the country in which the investigational medicinal product is to be used. The particulars listed in 3.6.1.1 should appear on the immediate container and on the outer packaging (except for immediate containers in the cases described in 3.6.1.4 and 3.6.1.5). Other languages may be included.

3.6.1.4 When the product is to be provided to the trial subject or the person administering the medication within an immediate container together with outer packaging that is intended to remain together, and the outer packaging carries the particulars listed in 3.6.1.1, the following information shall be included on the label of the immediate container (or any sealed dosing device that contains the immediate container):

a) name of sponsor, contract research organisation or investigator:
b) pharmaceutical dosage form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and in the case of unblinded trials, the name/identifier and strength/potency.
c) batch and/or code number to identify the contents and packaging operation; d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
d) the trial subject identification number/treatment number and where relevant, the visit number.

3.6.1.5 If the immediate container takes the form of blister packs or small units such as ampoules on which the particulars required in paragraph 3.6.1.1 cannot be displayed, outer packaging should be provided bearing a label with those particulars. The immediate container should nevertheless contain the following:

a) name of sponsor, contract research organisation or investigator;
b) route of administration (may be excluded for oral solid dose forms) and in the case of open label trials, the name/identifier and strength/potency;
c) batch and/or code number to identify the contents and packaging operation;
d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
e) the trial subject identification number/treatment number and where relevant, the visit number;

3.6.1.6 Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.

3.6.1.7 If

- the trial is conducted with materials that already have a marketing authorisation
- the patients participating in the trial have the same characteristics as those covered by the indications specified in the marketing authorisation
- the trial material does not require particular manufacturing or packaging processes, then the following particulars should be added to the original labelling:

i. name of sponsor, contract research organisation or investigator;
ii. trial reference code allowing identification of the trial site, investigator and trial subject.

3.6.1.8 If it becomes necessary to change the use-by date, an additional label should be affixed to the IMP. This additional label should state the new use-by date and repeat the batch number. It may be superimposed on the old use-by date, but for quality control reasons, not on the original batch number. This operation should be performed at an appropriately authorised manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other health care professional. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a second person. This additional labelling should be properly documented in both the trial documentation and in the batch records.

Although labels should comply with Annex 13 requirements listed above if absence can be justified this maybe acceptable. The Clinical trials tool kit includes a useful guidance document relating to abridged Annex 13 labelling. http://www.ct-toolkit.ac.uk/

3.7. Quality control

As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets its specification.

Quality Control should be performed in accordance to the PSF and in accordance with the information notified in the application to the competent authority.

Samples of each batch of IMP, including blinded product should be retained.

Consideration should be given to retaining samples from each packaging run/trial period until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results.

3.8. Release of Batches

Release of IMPs should not occur until the QP has certified the batch in accordance with a standard operating procedure.

The Quality Control Report should contain the statement that all procedures have been completed according to GMP and is signed by a Qualified Person (IMP). For PMUs example QP release forms in Appendix 9 should be completed to show release. For outside contractors the company release certificate should be received and then an internal QP release form completed.

SECTION 4 - IMPORTATION OF PRODUCTS FOR USE IN CLINICAL TRIALS

4.1 Introduction

The Clinical Trials Directive 2001/20/EC (CTD) cover the conduct, within the EEA, of clinical trials on medicinal products involving human subjects. This regulation also requires compliance to the importation of IMPs. If the product is imported from a third country and does not have an EEA licence it must be QP released; this is regardless of its destination.

Importation of licensed product from within 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.

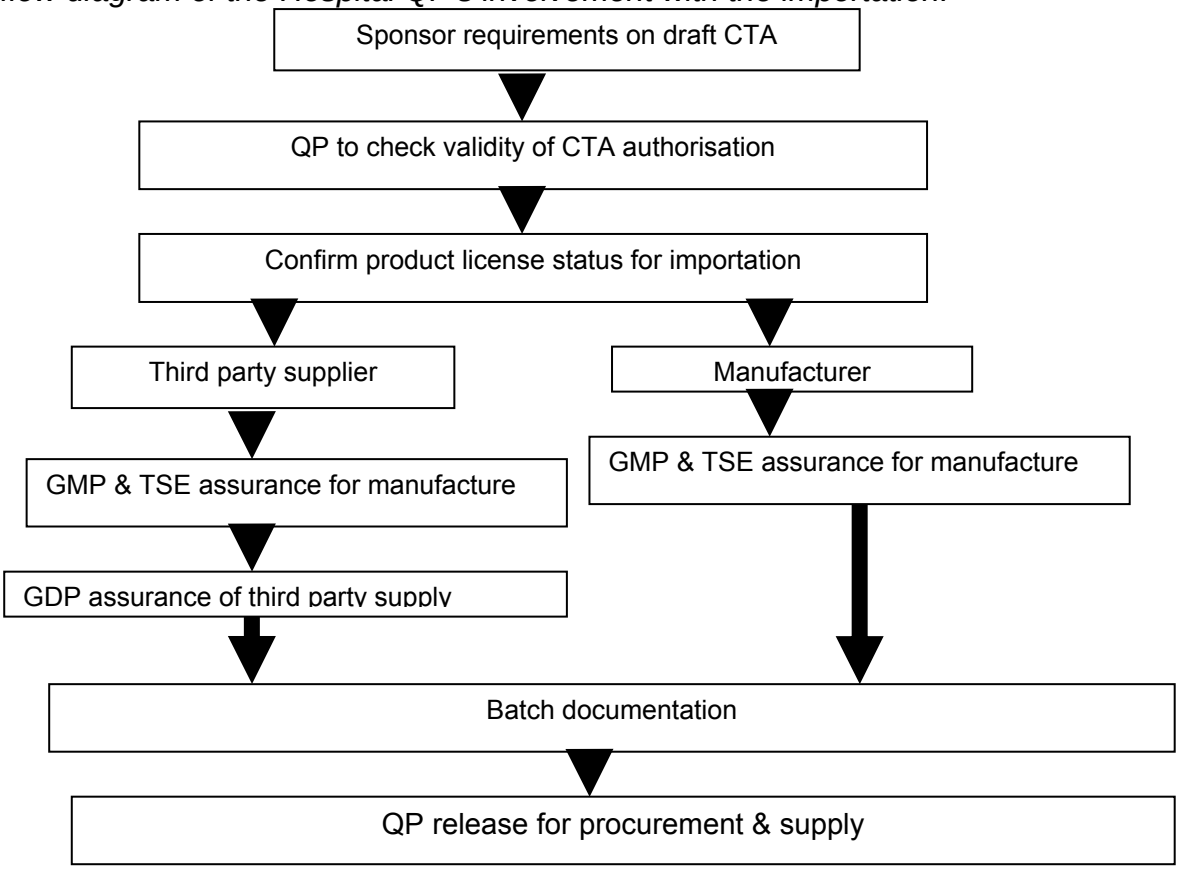
Importation of IMP from outside EEA - this activity needs to be performed by the holder of a MIA(IMP) and the QP must certify that the overseas manufacturing site operates in accordance with standards equivalent to EU GMP by filling in a QP declaration form which should accompany the CTA submission. The form is available on the MHRA website www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Forms

CTA and Hospital QP's involvement with the sourcing / importation

The trial sponsor will require product information in English for the CTA to the regulatory authority to conduct a clinical trial.

The Hospital QP will need to be assured of the legitimacy for the source of the supplier and obtain relevant information related to the product (such as SPC) in English in order to support the CTA.

The flow diagram of the Hospital QP's involvement with the importation.



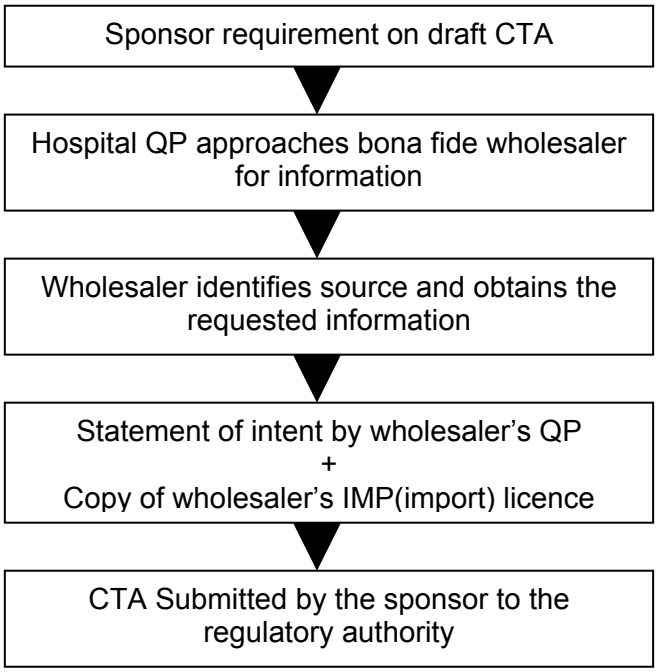
The MIA(IMP) Import licence holder can provide the necessary information required for sourcing / importation, for the CTA. When the Sponsor gains approval for the clinical trial the products can then be imported and the wholesaler's QP is required to release for procurement and supply for the clinical trial (note that this is not for release of the product for use in the trial) to the Hospital QP. It is the Hospital QP's responsibility to release the imported product for use in the clinical trial.

It is recommended that importation should be through commercial wholesaler that has (MIA (IMP) importer licence since that wholesaler uses network of established sources and provides assurance of the legitimacy of the supply chain. The wholesaler must hold an IMP Manufacturing Authorisation (import) that covers the product requested. The MIA(IMP) [Import] will specify the class of product allowed not the product name.

The Hospital QP should approach the commercial wholesaler with details in the draft CTA and obtain

- **A copy of IMP MIA (import)**
  Product information in English e.g. SPC
  A statement from the wholesaler's QP

The statement from the wholesaler's QP is to confirm the intent to supply product from a third country. The form published on the MHRA website should be used for the statement (Medicines and Healthcare products Regulatory Agency, Application form for a Manufacturer's Authorisation Investigational Medicinal Products (MA(IMP). Available at http://www.mhra.gov.uk/home/groups/comms-ic/documents/licensing/con026417.doc



When the Sponsor gains approval for the clinical trial then the brief description of the product required (or relevant part of the CTA) will be required by the wholesaler as evidence that the product is for the clinical trial. This information is required for batch documentation to enable release by the wholesaler's QP**. The wholesaler's QP release is for the procurement and supply of the product and is not the release of the product for the trial.**

SECTION 5 - FLOW CHART FOR THE MANAGEMENT OF MANUFACTURE AND ASSEMBLY OF IMP

Process		Documentation	Responsibility	
			Sponsor	Pharmacy
1	Enquiry to manufacture /assemble	e-mail/ telephone. Complete the Request Form (refer to Appendix XX for a template)	√	
		▼		
2	Set up an IMP folder with the Record & Communication Log sheet and log the details of the enquiry	Brief details of e-mail/telephone message in Log. Originals kept in file		√
		▼		
3	Complete the details required for PSF & Technical Agreement (refer to Appendix 5 and 6 for template)	Form should be formatted for completion of following: 1. Sponsor name & address 2. Sponsor contact details including telephone / fax/ email 3. Name & contact details of Qualified Person (QP) 4. Copy of study protocol 5. Copy of ethics approval for study 6. Outline of study and summary of manufacture / assembly required 7. Name of the IMP 8. Name & contact details of the company that manufactured and/ or assembled the IMP 9. Copy of IMP QP release document (if for assembly only) 10. Copy of the certificate of analysis for the IMP (if for assembly only) 11. Copy of Control of Substances Hazardous to Health (COSHH) data sheet 12. Anticipated time period for the study 13. Names and contact details for the clinical trial sites 14. Names and contact details for the principal investigators at each site 15. Batch and Pack size required 16. Known specification for storage / environmental conditions required during manufacture/ assembly operations and shipment 17. Known specification for primary packaging (Containers & closures) 18. Outline of labelling requirements 19. Randomisation method and codes to be used (for placebo controlled studies) 20. Known Shelf life / Expiry Period for IMP 21. Shipping & Distribution 22. Any other comments	√	
		▼		

Process		Documentation	Responsibility	
			Sponsor	Pharmacy
4	On receipt, sign and date when the form is received in the Department	Place the form in the IMP folder and pass the folder to the Lead GMP Trial Coordinator		√
		▼		
5	Assess the details for the request	Communicate on any details that need clarification and maintained logs for correspondence. Assess the details for need to comply with Manufacturing under IMP Licence.	√	√
		▼		
6	Assess charges. Forward costs charges and other service delivery times to Pharmacy Commercial Services	Pharmacy Commercial Services or authorised Pharmacy IMP leads to draw up Technical Agreement.	√	√
		▼		
7		Confirmation from Pharmacy Commercial Services for setting up the IMP documentation	√	
		▼		

Process		Documentation	Responsibility	
			Sponsor	Pharmacy
8	Prepare a draft Product Specification File (PSF)	Draft PSF should include: 1. Details of the following details provided by the Sponsor a. Copy of CTA b. List of raw materials, including name of supplier, grade, quantities c. Analytical specification(s) for raw material(s) d. TSE status of raw materials e. Specification for primary container(s) f. Specification for closure(s) g. Proposed batch size h. Proposed pack size i. Sample label(s) / packaging artwork j. Source of the randomisation method and codes used (for blinded trials) k. Proposed expiry period for batch l. Storage conditions for finished product m. Conditions for shipment 2. Draft Repack Worksheet (for Assembly operation) 3. Draft Production Worksheet (for Manufacturing operation) 4. Draft Quality Control Worksheet (for Analytical testing and/or QP final Release)		√
		▼		
9	Send the draft documents in PSF to Sponsor	Verify & amend if necessary	√	

Process		Documentation	Responsibility	
			Sponsor	Pharmacy
		▼		
10	On receipt, sign and date the returned documentation	Place the documentation in the IMP folder and pass the folder to the Lead GMP Trials Coordinator		√
		▼		
11	Receive and make appropriate amendments until all the documents have been mutually agreed	Maintain communication logs	√	√
		▼		
12	Final approved versions of all relevant documents compiled for the PSF	Use PSF checklist to ensure all relevant documents are approved	√	√
		▼		
13	Source and procure the raw material and other relevant materials from approved/authorised suppliers	QC testing / approval according to QC testing procedure in PSF in anticipation of order		√
		▼		
14	Manufacture/ assembly on receipt of confirmed order	Manufacture /assembly to documents in PSF		√
		▼		
15	Testing of finished product	QC testing of finished product. Quality Control Department to generate Certificate of Analysis		√
		▼		
16	QP release	Checklist for QP to 'certify' compliance to IMP manufactured in accordance to EU-GMP CTA (including any amendments) and current version of PSF		√
		▼		
17	Shipping & Distribution	Approved couriers and under suitable storage conditions	√	√

SECTION 6 - QP's ROLE FOR HOSPITAL MANUFACTURED IMPS

Process Map	Role functions
Trial initiation	Local Trust policy should have requirement to liase with Pharmacy. The Pharmacy Lead will involve the QP for any trials that requires manufacturing of any IMP.
Draft CTA	Review to assess • Copy of CTA • Sourcing of raw materials Assessment of supply chain for importation • Manufacturing/ labelling, etc Review the Technical Agreement – QP is one of the signatories for the Technical Agreement
CTA and any amendments	Approve all the information collated for the PSF such as • Specific training needs • Authorisation to manufacture • Manufacturing Instructions Packaging & Labelling instructions • QC Testing Specification
Manufacture	
Packaging and Labelling	
Deviation and Trend Reviews	To assess any variation and if significant to notify the Sponsor for the need to amend the CTA
Manufacturing Release	Certification of batch release
Complaints	Quality aspects of complaint • Liase with the sponsor for disposition of excess stock/returns/recalls
Post-trial use of IMP	• To be informed of Pharmacovigilance /SUSAR reports • To be informed of premature termination /suspension of the trial

SECTION 7 - THE REQUIREMENTS TO SET UP A CLINICAL TRIAL WITHIN A PHARMACY DEPARTMENT

7.1 Rationale

This document is to establish guidelines on the documentation for a Clinical Trial being undertaken in a hospital pharmacy under the Clinical Trials Directive and UK legalisation. This should be used in conjunction with the Institute of Clinical Research/Royal Pharmaceutical Society Practice Guidance on Pharmacy Services for Clinical Trials document, June 2005.

7.2 Regulators expectations

MHRA inspections will cover all relevant aspects of investigational medicinal product (IMP) handling e.g. manufacturing, assembling, packaging and labelling, preparation, randomisation, emergency code breaking, storage, destruction and accountability.

They will look for the following documents to be available:

A **SIGNED AGREEMENT** with the study sponsor.

This must clearly show the responsibilities of the pharmacy, sponsor and investigator in handling of the IMP.

STANDARD OPERATING PROCEDURES for all processes undertaken for the trial.

These include, but is not exhaustive

- Set up/initiation of a study within Pharmacy
- Receipt of study drugs
- Safe Handling and Storage of study drugs
- Dispensing of study drugs
- Drug accountability/Reconciliation
- Drug returns and disposal
- Emergency code breaking
- Security of randomisation codes
- Preparation and instructions
- Close down including archiving
- Training
- Maintaining a Pharmacy Study File

EVIDENCE OF COMPETENCE of staff dispensing e.g. CVs, qualifications, trials specific training records, dispensing and checking procedures

EVIDENCE OF SECURE, TEMPERATURE CONTROLLED STORAGE separate storage of returns etc

Accurate **DRUG ACCOUNTABILITY** from receipt to destruction or return of drug

7.3 Personnel

An individual from the Pharmacy department should be nominated as the co-ordinator of clinical trial materials within the pharmacy. The co-ordinator should be the contact person for any sponsor, research nurse or investigator.

7.4 Training

All staff who may be involved with clinical trials should receive basic training in departmental procedures for handling them. They will need to sign a log which will be retained for the sponsor. Staff involved in the dispensing should be familiar with the trial documentation, dispensing procedures and availability of information. Evidence of this training must be kept in the individual's CPD log.

7.5 Labelling

The exemption for hospital pharmacists allows for the assembly and repackaging of products as long as this is completed under the supervision of a Pharmacist. All medication must be labelled to comply with Annex 13 of the GMP guidelines. See Section3.6.1

7.6 Documents

All documents should be version controlled and approved for issue. This should be clearly visible on the document.

7.6.1 Clinical Trials Checklist

This should be a list detailing all the documents and references required in order to set up, run and complete a Clinical Trial. This should include the following information (see Appendix 7 for example):

Trial name
EudraCT number
Protocol number
Sponsor name
Sponsor contact details
Principal Investigator
Research Nurse
Copy of protocol and Amendments
Copy of Investigator brochure
MHRA Approval (Copy of letter)
Ethics Committee Approval (Copy of letter)
Trust Approval Letter (Copy of Letter)
NHS Clinical Trial Agreement (CTA) (Annex 5)
Confidentiality agreement
Technical Agreement
Drug information including storage conditions, packaging and labelling
Treatment code break details
Delegation of responsibility log
Pharmacy Fees and prescription charges agreed
Patient Identification records
Details of invoicing procedure

7.6.2 Clinical Trial Procedure Template

This should be set up at the start of a study and cover the following topics. This should be issued for all personnel involved in dispensing Clinical Trials.

Sample template is attached (see Appendix XX) and the following details should be included

Trial title
The protocol title should be written here including abbreviation and any acronyms etc.

Description
Include the type and phase of study including a brief description and a synopsis of the work required by Pharmacy

Sponsor Contact
Include the study contact from the sponsor running the study

Investigator
Include the Principal investigator at the site and any additional investigators.

Research Nurse
Include the Research Nurses involved in this study.

Pharmacy Personnel
Include the Pharmacy contact for this study and back up cover.

Start Date and length of study
Include the estimated starting date and the estimated time the study will be running at the site.

Patient numbers
Include the estimated number of patients to be recruited at the site.

Randomisation details
Include whether the numbers will be allocated in a sequential or random fashion and how this will be done, for example by Interactive Voice Recognition System (IVRS) and include who will do this.

Description of trial materials
Include the full description of a patient pack. If possible add a diagram or photograph

Dosage
Include the dosage to be taken in the study and any dose escalation that is required.

Also any of the following if applicable

- Dosage adjustments in event of toxicity's,
- Standard pre-treatment monitoring
- Additional therapies required
- Details of comparator arm
- Need for hydration fluids /pre-treatments
- Concomitant medications allowed /disallowed

Location of material
Include the exact location and storage conditions that will be used for the study material including any non drug material e.g. specific ancillaries being supplied by Pharmacy.

Dispensing Procedure
Include the step by step procedure to dispense each item for the study, including the location of labels and ancillaries that are needed, maximum dilutions/infusion rates of injectables and any other information such as storage, expiry once reconstituted/diluted. Include details of each dispensing visit, any counselling and advice that should be given to the patients

Receipt of Trial Material
Include any special requirements on receipt of each batch of material

Return of Trial Material
Include detail of how and when trial material which has been returned or unused is to be handled by Pharmacy.

Emergency Code Breaking Procedure
Include the precise procedure for breaking the randomisation code in the event of an emergency including all contacts and locations of files and envelopes.

Reordering Procedure
Include details of how and when drug supplies should be reordered.

Archiving
Include details of how and what is to be archived and for how long.

Communication details
Include the methods of notification for patients prematurely withdrawn as well as the standard exit procedure.

Additional Templates

This may be required for each study and may be provided by the sponsor or designed by the Pharmacy department depending on the responsibilities agreed for the specific study. Examples of such templates are (see Appendix 11):

Drug Accountability
Prescription
Receipt /return
Temperature Log
Signature Log
CVs for Clinical Trial Pharmacist/Technician in charge of study
Risk Assessment
Training Record

7.6.3 Retention of documentation

Clinical Trial documentation should be retained in Pharmacy for the life of the trial. Storage after that time is the responsibility of the Sponsor and should ideally be specified at the start of the study. Documentation should be stored for a minimum of 5 years by the sponsor.

7.6.4 Standard Operating Procedures

All processes should be described in departmental standard operating procedures, which should be suitably version controlled and regularly reviewed.

7.6.5 Storage and handling

All medication should be managed by the pharmacy. It is recommended that IMPs is kept separate and secure to ensure there is no confusion between trial materials but MHRA does not expect standard pharmacy stock items to be ring fenced and kept separate for clinical trials use. Product can be taken from standard pharmacy stock provided it is appropriately labelled once selected and accountability records are maintained.

The storage conditions should be appropriate for the IMP and the material should be dispensed against the appropriate prescription. Each prescription should contain the study title and protocol number.

The pharmacy will be involved in the reconciliation and return or disposal of the unused medication. This must be documented.

Records of the data showing compliance of the product storage conditions to their requirements must be kept.

7.6.6 Audit

The clinical trial process must be internally audited. This should include all aspects of the process from receipt of the submission in pharmacy to the administration of the product to the patient and its reconciliation.

7.6.7 Pharmacy Sign Off

The clinical trial requirements must be approved by the Pharmacy Department and a Checklist confirming the requirements are in place should be signed prior to dispensing the IMPs. (See Appendix 10 for an example sign off sheet.

Section 8 - Pharmacy Briefing on Research Networks

8.1. Architecture of Networks

The UK has a Clinical Research Network (UKCRN) infrastructure now called the National Institute for Health Research Clinical Research Network (NIHR CRN)**.**. There are topic-specific networks (TCRN) for cancer, diabetes, stroke, dementias and, degenerative diseases, mental health, and medicines for children In addition; Primary Care Research Networks also exist. Each network operates to broadly similar principles: each being governed by a coordinating centre, which in turn reports to the NIHR CRN. Each network is accountable through performance management and measures of success include accrual, study set-up times, use of resources etc. Each network works with constituent organisations within its geographical footprint, and these may include hospital trusts, primary care trusts, academic institutions and industry. Each TCRN has a clinical lead and a management structure.

The comprehensive local research networks (CLRN) form the national Comprehensive Clinical Research Network (CCRN) and are the latest of the NIHR CRN networks. There are 25 CLRNs across England. Each CLRN has a clinical lead. Each CLRN is bound by general principles set by the NIHR CRN, but the interpretation of these and the local operating procedures vary between each CLRN. The primary purposes of the CLRN are to provide research management and governance infrastructure and to provide 'service support costs' for research which is recognised within the NIHR CRN portfolio of studies. Service support is the additional cost to an organisation of conducting a research study and which will cease once the research activity itself terminates.

8.2. Network Funding

Each NIHR CRN network has funding for staffing and management costs. In addition, each network has some funding available for service support costs, but this varies considerably across TCRNs. In 2008/09, the majority of NHS trusts have an allocation of 'transitional R&D funding' which, in theory, is available to provide service support costs arising in NHS trusts as a consequence of participating in research studies. In reality this funding is locked into directorate budgets and not available on demand for research. TCRN budgets remain fairly static between years. CLRN budgets have been set for 2008/09 Within the CLRN budgets for 2008/09 is a defined amount for 'key service support' which is intended for overcoming local blocks to the delivery of NIHR CRN studies: locally and nationally pharmacy support has been identified as a priority for this funding. CLRN funding can only support research within the NIHR CRN portfolio of studies.

Each CLRN is managing the allocation of its budget slightly differently. There are a number of mechanisms to access and distribute funding:

- By direct approach from Chief Investigators/R&D offices to request study-specific service support costs

- Through business plans submitted by individual NHS trusts

- Through formulaic allocation by CLRNs

The potential is that CLRNs will be inundated with uncoordinated and unrealistic bids for funding. Therefore it is imperative that Pharmacists, network representatives and NHS trust R&D Managers collaborate to provide CLRNs with a coherent summary of pharmacy requirements.

8.3. Useful Websites

www.ukcrn.org.uk

www.nihr.ac.uk

8.4. Acknowledgement

This paper is based on a pharmacy briefing document prepared for the North West Chief Pharmacists by Dr. Matthew Peak, Co-Director of Cheshire, Merseyside and North Wales Medicines for Children Research Network.

APPENDIX 1 – REFERENCE SOURCES

[All sites accessed on 30/10/2008]

Regulatory

- 'European Union Clinical Trials Directive', Commission Directive 2001/20/EC, 'the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human us'. Available at

http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf

Statutory Instrument 2004 No.1031, The Medicines for Human Use (Clinical Trials) Regulations 2004.
Available at http://www.opsi.gov.uk/si/si2004/20041031.htm

Commission Directive 2005/28/EC, 8 April 2005, 'laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products' Available at
http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32005L0028:EN:HTML

Commission Directive 2003/94/EC, 8 October 2003' laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Available at
http://europa.eu.int/eur-lex/pri/en/oj/dat/2003/l_262/l_26220031014en00220026.pdf

European Commission Clinical Trials Directive 2004 Guidance Documents
http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/dir200120ec.htm

Statutory Instrument 2006 No. 1928
The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006
http://www.opsi.gov.uk/si/si2006/20061928.htm

Statutory Instrument 2006 No.2984
The Medicines For Human Use (Clinical Trials) Amendment (No.2) Regulations 2006
http://www.opsi.gov.uk/si/si2006/20062984.htm

Directive 2003/94/EC. Principles and Guidelines of GMP in Respect of Medicinal Products for Human Use and IMPs for Human Use
http://pharmacos.eudra.org/F2/eudralex/vol-1/DIR_2003_94/DIR_2003_94_EN.pdf

Volume 10 Clinical Trials The Rules Governing Medicinal Products in the European Union
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev10.htm

Helpful documents

Medicines and Healthcare products Regulatory Agency, 2004, Description of the medicines for human use (clinical trials) regulations 2004. Medicines and Healthcare products Regulatory Agency.

Medicines and Healthcare products Regulatory Agency, 2005, Final regulatory impact documents.

Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol

Available at
www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Legislationandguidancedocuments

GCP

ICH GCP guidelines
http://www.ich.org/LOB/media/MEDIA482.pdf

DECLARATION OF HELSINKI
This is attached as a separate document.

New Guidance for the notification of serious breaches of GCP or the trial Protocol
www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Legislationandguidancedocuments

GUIDELINE FOR STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST IN HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS
http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf

17. ABPI GUIDELINES FOR PHASE 1 CLINICAL TRIALS 2007 EDITION
http://www.abpi.org.uk/publications/pdfs/phase1_guidelines.pdf

Transitional arrangements

Medicines and Healthcare products Regulatory Agency, September 2005, Transitional Qualified Persons.

Manufacturer's Authorisation (MIA(IMP))

Medicines and Healthcare products Regulatory Agency, Application form for a Manufacturer's/Importation Authorisation Investigational Medicinal Products (MIA(IMP).

Medicines and Healthcare products Regulatory Agency, Notes for completing an application form for a manufacturer's/Importation Authorisation – Investigational Medicinal Products MIA (IMP).

Medicines and Healthcare products Regulatory Agency, October 2005, How to submit a Clinical Trial Authorisation (CTA). Medicines and Healthcare products Regulatory Agency.

Medicines and Healthcare products Regulatory Agency, Is it a Clinical Trial? (Algorithm)

All above available at
www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Legislationandguidancedocuments

Annex 13

European Commission, 2003, Volume 4, Good Manufacturing Practices, Annex 13 Manufacture Of Investigational Medicinal Products.
Available at
http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/anx13en030303Rev1.pdf

Importation

Medicines and Healthcare products Regulatory Agency, October 2005, Importation of Investigational Medicinal products from third world countries.

Available at
www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Legislationandguidancedocuments
(contains link to proposed QP declaration form).

IMP v NIMPs

Definition of Investigational Medicinal Products (IMPs) and definition of Non Investigational Medicinal Products (NIMPs)
http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27.pdf

MHRA contact for further information

For further information on Clinical Trials, please contact Clinical Trials Unit, 12-2, MHRA, Market Towers, 1 Nine Elms Lane, London SW8 5NQ,
telephone 020 7084 2327, fax 020 7084 2443 or e-mail the clinical trial helpline (clintrialhelpline@mhra.gsi.gov.uk) or via main website at www.mhra.gov.uk

Other

Institute of Biology, Royal Pharmaceutical Society of Great Britain, Royal Society Of Chemistry, 2000, Qualified Persons in the pharmaceutical industry. Royal Pharmaceutical Society of Great Britain.

The Institute of Clinical Research, Royal Pharmaceutical Society of Great Britain, 2005, Practice guidance on pharmacy services for clinical trials. Royal Pharmaceutical Society of Great Britain.

European commission, 2003, Detailed Guidance on the European clinical trials database (EUDRACT Database), Brussels, European Commission Enterprise Directorate-General. Available at http://dg3.eudra.org/F2/pharmacos/docs/Doc2004/april/cp%20and%20guidance%20eudract%20april%2004.pdf

Clinical Trial Tool Kit, 2004,
Clinical Trial Tool Kit, Available at http://www.ct-toolkit.ac.uk/

UKCRN costing tool,
http://www.ukcrn.org.uk/index/industry/costing.html

NCRN Chemotherapy & Advisory Service.
Link to follow

Department of Health, 2005, Report of the Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees, London, Department of Health.
Available at
http://www.dh.gov.uk/assetRoot/04/11/24/17/04112417.pdf

Websites

http://www.mhra.gov.uk
Medicines and Healthcare products Regulatory Agency

http://www.emea.eu.int
European Medicines Agency

http://europa.eu.int/eur-lex/lex/en/index.htm
EUR-Lex provides direct free access to European Union law. The system makes it possible to consult the Official Journal of the European Union and it includes inter alia the treaties, legislation, case-law and legislative proposals.

www.opsi.gov.uk
The Office of Public Sector Information is at the heart of information policy, setting standards, delivering access and encouraging re-use of public sector information].

http://pharmacos.eudra.org/F2/home.html
Latest news on Pharmaceuticals, Review of Pharmaceutical legislation, EudraLex Collection - Volumes 1 to 9 (The Rules Governing Medicinal Products in the European Union), The Community Register (Community Register of medicinal products for human use, Community Register of orphan medicinal products for human use, Community Register of veterinary medicinal products.).

Acknowledgement

This paper is based on a pharmacy briefing document based on documents written by Quality Control North West and Quality Assurance London, Eastern and South East Specialist Pharmacy Services

APPENDIX 2 – WHAT IS MANUFACTURE ?

DEFINITIONS OF MANUFACTURE AND ASSEMBLY, IN THE PREPARATION OF INVESTIGATIONAL MEDICINAL PRODUCTS.

Description of process	Manufacture /Assembly	Licence required
Reconstitute vial and transfer into syringe for immediate dosing on ward (syringe not labelled)	Dispensing Reconstitution	NO
Reconstitute vial and transfer into syringe/IV bag etc for dosing (syringe requires labelling with Subject number from randomisation code according to Annex 13) i.e. for prescription	Reconstitution and Assembly	NO
Reconstitute vial and transfer into syringes for dosing (syringe requires labelling with Subject number from randomisation code according to Annex 13)	Reconstitution and Assembly	NO
Dispensing from bulk containers for prescription into individual subject pack and labelled according to Annex 13	Assembly	NO
Dispensing from bulk containers into batch of subject specific bottles and labelled according to Annex 13	Assembly	NO
Dispensing from bulk containers into batch of non subject specific bulk bottles, labelled according to Annex 13 for bulk storage Subject specific information added at time of dispensing	Assembly Assembly	NO NO
Suppy from EU (not importation)	N/A	NO
Importation from outside EU	Importation	YES

Description of process	Manufacture /Assembly	Licence required
Filling of capsules with powder	Manufacture	YES
Over encapsulation of tablets or capsules	Manufacture	YES
Dilution of powder with water e.g. antibiotic (no additional labelling)	Reconstitution	NO
Weighing of IMP, Addition of water and adjustment of pH	Manufacture	YES
Mixing of IMP powder with other powders and dispensing into unit doses	Manufacture	YES
Preparation of liquids for Oral use	Manufacture	YES
Preparation of liquids for External use	Manufacture	YES
Filling of ampoules/vials	Manufacture	YES
Filling of large volume parenteral and irrigation solutions	Manufacture	YES
Filling of eye drops	Manufacture	YES
Mixing of creams/ointments	Manufacture	YES
Filling of aerosols	Manufacture	YES
Production of tablets	Manufacture	YES
Production of suppositories	Manufacture	YES
Medical gases	Manufacture	YES

APPENDIX 3 – EXAMPLE OF THE QUOTATION REQUEST FORM FOR MANUFACTURE/ASSEMBLY OF IMPs

Please complete the following with as much detail as possible to enable your request for a quotation to be processed efficiently and to avoid any unnecessary delays.

CLINICAL TRIAL DETAILS

EUDRACT Registration Number :			
Name of Study		Phase :	
Number of Patients :			
Recruitment period :			
Name of Investigator (s)			
Name of Sponsor (s)			
LREC approval YES/NO		if no when can this be expected	
Name of Ethics Committee			
MHRA approval YES/NO		if no when can this be expected	
Unit/Department where study to take place			

CLINICAL TRIAL MATERIAL REQUIREMENTS

Description of Product/Presentation Required (include pack size, quantity, strength etc.)	
Is manufacturing required	YES / NO*
Is packaging required	YES / NO*
Final product required by	
Pharmaceutical form	
Formulation Details – Active and placebo (if applicable)	
Source of active agent/placebo	
Is the active/placebo approved for Human use?	YES / NO*
If no, what steps have been taken to justify its use in this trials ?	

QUOTATION REQUEST FORM continued

If product to be supplied is ready for packaging please indicate the following :	
Dimension of primary product	
To be supplied as blister packs	YES / NO*
To be supplied as bulk supplies	YES / NO*
Labelling requirements	

Randomisation: Is this to be carried out by Stockport Pharmaceuticals ? YES/NO	
Will the randomisation schedule be supplied by the Investigator ? YES/NO	

CLINICAL DETAILS

Dosage	
Method/Route of Administration	
Precautions/Contraindications/Warning (if applicable)	
References	

ADDITIONAL REQUIREMENTS

Request initiated by :

Name (please print) _____
Signature _____
Status (please print) _____
Hospital (please print) _____
Date _____

Please attach the following if available

- Clinical Trial Protocol/Synopsis
- Draft label text

APPENDIX 4 – EXAMPLE OF THE INFORMATION REQUIRED FOR SETTING UP OF PRODUCT FILE SPECIFICATION & TECHNICAL AGREEMENT

[……. HOSPITAL NHS TRUST] PHARMACY MANUFACTURING UNIT ([PMU])
Details for the Manufacture of Investigational Medicinal Products

Clinical Trial No (if available).:
EudraCT No (if available):

[Contract Giver]: **Contract Number**

Requestors details:

Type of Study			
Number of Patients :			
Recruitment period :			
Name of Investigator (s)			
Name of Sponsor (s)			
LREC approval		if no when can this be expected	
Name of Ethics Committee			
Unit/Department where study to take place			
CTA approval		if no when can this be expected	

Name
Designation
Address (include the post code)
Tel. Number
Bleep number
Fax Number
e-mail address

Sponsor's details

Name
Designation
Address (include the post code)
Tel. Number
Bleep number
Fax Number
e-mail address
Brief details of the trial

Product details

Complete the following pages for each of IMPs / strengths required under same contract

Product Name	
Form: e.g. tablet, injection	
Strength: e.g. mg, mcg per ml, % w/v	
Pack Size:	
Route of Administration: e.g. intra-venous, oral	
Number of units required: **e.g. 100 capsules**	

Formulation

Please list ALL ingredients, with their grade (e.g. BP, USP) and approved supplier

Ingredient	Grade e.g. BP, EP, USP	Do you want PMU to purchase ingredient on your behalf? (Y/N)	Contact details of approved supplier (Postal / telephone/e-mail)

Packaging

Primary Container (including closure details) e.g. type 1 glass vial with silicone stopper

Primary container component	Grade e.g. Type I glass	Do you want PMU to purchase ingredient on your behalf? (Y/N)	Contact details of approved supplier (Postal / telephone/e-mail)

Secondary container: e.g. cardboard box

Component 1	
Specification	
Contact details of approved supplier(Postal / telephone/e-mail)	
Do you want PMU pharmacy to purchase component on your behalf? (Y/ N)	

Stability, Storage & Method of Manufacture

Shelf – life: e.g. 12 months	
Storage conditions: e.g. between 2 and 8 ^{o}C Room Temperature	
Source of information: for stability data (send copies if available or details of reference)	
Labelling: please list any particular details required on the labels	
Method of manufacture – include details of filter compatibilities etc where applicable	

Health & Safety

COSHH data sheets

Please supply hazard data sheets for **ALL** ingredients, except water. Supplied: Yes/No If No why not?	

Quality Control Testing

Do you want PMU quality control to undertake any product testing? (Y/N)	
If No please give details of the laboratory that will undertake this testing and who will approve the product as fit for purpose.	
Please list or attach details of analytical methods to be used and a full product release specification.	

In addition to any chemical analysis PMU will arrange for microbiological testing e.g. sterility test, microbial limit test, pyrogen/LAL test as appropriate.

APPENDIX 5 – EXAMPLE OF A TECHNICAL AGREEMENT

[……. HOSPITAL NHS TRUST] PHARMACY MANUFACTURING UNIT ([PMU])

Technical Agreement for the Manufacture of Investigational Medicinal Products

Clinical Trial No.:

EudraCT No.

[Contract Giver]: **Contract Number:**

Summary of manufacture / assembly required:

Checked by: **QP for *The [PMU]***
Checked by: **on behalf of [Contract Giver]**

General Arrangements

1. The *[Contract Giver]* will provide GMP relevant details from the original CTA dossier and any subsequent CTA amendments.

2. The *[PMU]* warrants that it is in possession of a current MIA(IMP) granted by the MHRA under requirements of EU Directive 2001/20EC. The licence number is MA(IMP) ……and this licence covers the scope of activities to be undertaken.

3. The *[PMU]* will advise *[Contract Giver]* of any results of any audit by any agency or company, which could prejudice the quality of any product or service provided.

4. The *[PMU]* will allow the *[Contract Giver]* reasonable access to its premises for the purpose of quality audit or inspection of ongoing processes.

5. The *[PMU]* will undertake to ensure that operations are in accordance with GMP and in particular, Annex 13 Manufacture of Investigational Medicinal Products Vol. 4 EC GMP.

6. In consultation with the *[PMU]* will set up a Product Specification File to detail the manufacturing, assembly and distribution processes required. The [PMU] shall provide all documentation pertaining to the manufacture, assembly and distribution of the IMP/placebo for approval by the [Contract Giver]; the approved documents will be held in the Product Specification File.

7. The *[PMU]* will be responsible for approval of the Standard Operating Procedures and Batch Manufacturing Records (BMR).

8. The *[PMU]* will only sub-contract any necessary product testing for which there is no in-house capability such as microbial testing.

9. The *[PMU]* will agree with the *[Contract Giver]* on the ordering process.

10. The *[PMU]* will inform the *[Contract Giver]* of the lead-time from order to delivery.

11. The *[PMU]* will agree with the *[Contract Giver]* any confidentiality arrangements.

Starting Materials (e.g. Drug, packaging components, product information leaflets)

1. Details and specifications for the Drug, excipients, and packaging components are specified and agreed by *[Contract Giver]* and the *[PMU]*. These will be filed in the Product Specification File (PSF). A copy of the PSF signed by both parties will form part of the technical agreement.

2. A freedom from TSE statement must be obtained for any liable materials used in manufacture or packaging.

Manufacture of active & placebo products

1. The *[PMU]* will agree the formulation & physical parameters for any placebo product, if required, with the *[Contract Giver]*. The formulation agreed upon will be specified in the PSF.

2. The *[PMU]* and the [Contract Giver] will agree the analytical testing of products to be undertaken. Microbiological testing will form part of the normal release criteria. The agreed testing protocols will be filed in the PSF.

Packaging

1. The *[Contract Giver]* will provide the *[PMU]* with details on pack size, labelling instructions, batch size and patient information leaflets. The *[PMU]* will then draft a Worksheet(s) complete with sample label(s), for comment and approval by the *[Contract Giver]*. A final version of the master repacking document(s) will be produced and a copy sent to the *[Contract Giver]* for approval. The signed copy will be filed in the PSF. Any subsequent amendments must be specified and/ or approved in writing.

2. The *[Contract Giver]* will provide the *[PMU]* with details of blinding and randomisation, where applicable.

3. The *[PMU]* and the [Contract Giver] will agree on the control, security and disclosure arrangements for the blinding and randomisation details.

Quality Control Testing

1. The *[PMU]* is responsible for sampling and quality control inspection of product in accordance with its own procedures (SOPs) unless requested otherwise by the *[Contract Giver]*.

2. The *[PMU]* is responsible for generating quality specifications for all raw materials and finished product unless requested otherwise by the *[Contract Giver].*

3. The *[PMU]* will advise the *[Contract Giver]* of any unplanned deviations that occur which are not in compliance with agreed specifications. The *[PMU]* and the *[PMU]* will agree any reworking of any out of specification product. Exception report forms will be filed in the clinical trial folder.

4. Details of all analytical testing to be undertaken will be agreed with the QP and all results must be made available to the QP.

Retained samples

The *[PMU]* will retain samples of final product for an agreed period.

Product release and QP certification

1. The *[PMU]* will provide QP approval that the product has been manufactured / assembled in compliance with GMP and the PSF.

2. The *[PMU]* will provide a certificate of conformity with each batch of product. The QP will sign the certificate of conformity.

Storage and Transport of Product

1. The *[PMU]* will store the finished product in suitable temperature conditions as specified in the PSF. Product will be stored in restricted access areas.

2. Product will be shipped under cold chain or ambient temperature as specified in the PSF.

Supply of Finished Product

The *[PMU]* will supply the product as directed in writing by *[Contract Giver]* when the process is complete and QP approval has been issued.

Disposal of Surplus or Reject Product

The *[PMU]* will arrange for disposal of any reject materials at the request of the *[Contract Giver]*.

Complaints and Defect Reports

1. The *[PMU]* will investigate all complaints within a reasonable time scale upon written request and will provide the *[Contract Giver]* with a written report. In the case of a potentially serious complaint The *[PMU]* will make an initial response within 24 hours.

2. The *[PMU]* will advise *[Contract Giver]* of any quality defect in the product that becomes known to them at any time.

3. The *[Contract Giver]* will advise the *[PMU]* of any defect in the product that becomes known to them at any time.

Pharmacovigilance

The *[PMU]* will advise *[Contract Giver]* of any suspected adverse events that are reported to them at any time.

Product Recall

The *[Contract Giver]* has responsibility for initiating a product recall. The *[PMU]* will provide all necessary information quickly and accurately in order to assist in the recall

Archiving

The *[PMU]* will agree the end-of-trial document archiving arrangements with the *[Contract Giver]*.

Supply of Product for Compassionate Use

The *[Contract Giver]* has responsibility for ensuring that product for compassionate use is available at the end of the trial; should this be necessary.

If additional product needs to be manufactured or imported to supply for compassionate use after the end of trial, the product must be made on a named patient basis by a unit holding a Specials licence or imported as an unlicensed medicine and notified to MHRA using the notification of intent to import form. The form and guidance on importation is available on the MHRA website www.mhra.gov.uk/Howweregulate/Medicines/Importingandexportingmedicines

[PMU] contacts:

Name:	Job title:
Address:	Email:
	Tel:
	Fax:

Name:	Job title:
Address:	Email:
	Tel:
	Fax:

Name:	Job title:
Address:	Email:
	Tel:
	Fax:

[CONTRACT GIVER] contacts:

Name:	Job title:
Address:	Email:
	Tel:
	Fax:

Name:	Job title:
Address:	Email:
	Tel:
	Fax:

Name:	Job title:
Address:	Email:
	Tel:
	Fax:

Technical Agreement Approval

Signature: ***On behalf of the [Contract Giver]***	
Date:	Job Title:

Signature: ***On behalf of the [PMU]***	
Date:	Job Title:

Signature: ***On behalf of The [PMU]***	
Date:	Job Title: Qualified Person

APPENDIX 6 – CONFIDENTIALITY AGREEMENT TEMPLATE

Clinical Trial No.:
EudraCT No.

THIS AGREEMENT dated xxxxxxx is made

BETWEEN:

(1) xxxxxxxx (the 'Supplier'); and

(2) xxxxxxx (the 'Recipient').

RECITAL

In order to allow Recipient to manufacture xxxxxxxx for the Supplier the Supplier is willing to disclose confidential information and proprietary materials**,** including formulation and production method, to the Recipient on and subject to the provisions of this Agreement ("The Project").

IT IS AGREED as follows:

1 Definitions

In this Agreement the following words shall have the following meanings:

1.1 'Confidential Information' shall mean

(a) in respect of Information provided in documentary form or by way of a model or in other tangible form, Information which at the time of provision is marked or otherwise designated to show expressly or by necessary implication that it is imparted in confidence;

(b) in respect of Information that is imparted orally, any Information that the Supplier or its representatives informed the Recipient or its representatives at the time of disclosure was imparted in confidence;

(c) in respect of Confidential Information imparted orally, any note or record of the disclosure;

(d) any copy of any of the foregoing; and

(e) the fact that discussions are taking place between the Supplier and the Recipient.

1.2 'Information' shall mean but shall not be limited to information and data concerning formulae, algorithms, sequences, chemical and biological compositions; knowledge of biological structures and functions in plants, soils, pests, humans, animals and the environment. Information also includes knowledge of the existence and activity of biological material not in the public domain as well as the biological or other materials. The research collaborations, commercial relationships, products, and corporate development strategies of the parties are also included in Information. Such Information is not dependent on how it is disclosed, whether expressed as technical information or otherwise and it includes that represented in intellectual property or know-how generally. And shall include but shall not be limited to; notes, letters, memoranda, reports,

contracts, registrations, licenses, tables, databases, data books, notebooks, computer prints, text and data stored in computer programmes, drawings, charts, illustrations, materials, samples, and all other documentation and materials prepared or made available pursuant to the Project

1.3 'Permitted Purpose' shall mean that the Confidential Information may only be used by the Recipient for the purpose of the manufacture of xxxxxxxx. Project shall have the meaning given above in the Recitals.

2 Obligations of the Receiving Party

For a term of 10 years from the date of this Agreement, except as provided for in clause 7, the Recipient undertakes to the Supplier to:

(a) receive and keep the Confidential Information secret and confidential and not disclose such Confidential Information to any third party;

(b) take all necessary precautions to ensure that such undertaking is enforced and is enforceable and take such action as to ensure that patentability is not destroyed through making information available to the public, for instance by written or oral description;

(c) use the Confidential Information only for the Permitted Purpose;

(d) only disclose the Confidential Information under binding obligations of confidence (which it undertakes to enforce and for which it is legally responsible) to; those of its subsidiaries, employees, sub-contractors, seconded staff, officers, agents, consultants and collaborators as need to have access thereto wholly necessarily and exclusively for the purposes of the Project whose identity the Recipient shall provide to the Supplier at their request;

(e) not without the Supplier's prior written consent make any commercial use of or make any commercial gain from the Confidential Information or seek to obtain any protection of the intellectual property contained in the Confidential Information;

(f) promptly notify the Supplier if it becomes aware that any of the Confidential Information falls within the provisions of clause 3.

3 Limitation of the obligations of Recipient

Clause 2 shall not apply to Confidential Information which:

(a) was known to the Recipient prior to its communication by or through the Supplier (as evidenced by the Recipient's records); or

(b) is or becomes in the public domain except by any default or fault of the Recipient or any person acquiring it from the Recipient; or

(c) becomes known to the Recipient by the action of another person not in breach of any obligation of confidentiality owed to the Supplier; or

4 Return of Confidential Information

4.1 Upon termination of this Agreement, in the event that the Recipient is in breach of any of the conditions of this Agreement, and at any other time on the written request of the Supplier, the Recipient will immediately return the Confidential Information and any copies thereof made by or in the possession of or under the control of the Recipient pursuant to this Agreement, and make no further use or disclosure of any of the Confidential Information. If the Supplier so dictates, the Confidential Information shall be destroyed under the above circumstances.

5 Limitation of transferred rights

5.1 The Recipient acknowledges and agrees that the property and copyright in Confidential Information disclosed to it by the Supplier, including any documents, files and any other items containing any Confidential Information, belongs to the Supplier. It will not be removed from the Recipient's address nor be given to any other person or parties.

5.2 This Agreement shall neither prejudice nor limit the rights of the Supplier in respect of any intellectual property rights in the Confidential Information.

5.3 Except as provided for herein the Recipient may not assign or transfer any rights or obligations hereunder without the prior written consent of the Supplier.

5.4 This Agreement shall not be construed to:

(a) grant the Recipient any license or rights other than as expressly set out herein in respect of the Confidential Information; nor

(b) require the Supplier to disclose any Confidential Information to the Recipient.

6 Foreground Intellectual Property

6.1 In the event that the Recipient makes or observes any new discovery, improvement or invention ('Invention') relating to the Confidential Information or as a direct result of the Project then the Recipient will bring this to the attention of the Supplier.

6.2 The Recipient shall not make or seek to make actual commercial gain from such an Invention, nor make any patent application or secure any other proprietary rights to legally protect any such Invention except with the prior written agreement of the Supplier.

6.3 The Supplier will, at all times, retain the right to use an Invention for non-commercial research purposes.

7 Publication

The Recipient shall not arrange nor permit the publication of any information regarding the results or outcome of the Confidential Information without the prior written consent of the Supplier, such consent shall not be unreasonably withheld.

8 Limitation of liability of Disclosing Party

The Supplier gives no warranties in relation to the Confidential Information disclosed by it hereunder and in particular (but without limiting the foregoing) no warranty or representation, express or implied, is given by the Supplier as to the accuracy, efficacy, completeness, capabilities or safety of any materials or information provided under this Agreement.

9 Notices

All notices required to be served pursuant to this Agreement shall be made in writing to the addresses at the head of this Agreement.

10 Law and disputes

The validity, construction and performance of this Agreement shall be governed by English law. Any dispute arising under or in connection with this Agreement shall be subject to the exclusive jurisdiction of the English courts to which the Parties to this Agreement hereby submit. **AGREED** by the Parties through their authorised signatories:

For and on behalf of xxxxxxxx	For and on behalf of xxxxxxxxx
signed	signed
print name	print name
title	title
date	Date

APPENDIX 7 – EXAMPLE OF A DISPENSARY CHECKLIST

Hospital Trust

PROCEDURE FOR INITIATING A CLINICAL TRIAL

CLINICAL TRIALS CHECKLIST

All information entered on the checklist must be initialled and dated.

	Item	Action/Details	Initials	Date
1	EudraCT number			
2	Protocol number			
3	Sponsor Name			
4	Sponsor contact details			
5	Principal Investigator			
6	Research Nurse			
7	Copy of protocol			
8	Amendments (list number)			
9	Copy of Investigator brochure			
10	MHRA Approval (Copy of letter)			
11	Ethics Committee Approval (Copy of letter)			
12	Trust Approval (Copy of Letter)			
13	Confidentiality /Clinical Trial Agreement(s)			
14	Drug information			
15	Treatment Code Break details			
16	Pharmacy Fees/Prescription Charges			
17	Invoices			
18	Patient ID records			
19	Responsibility Log			
20	Risk Assessment			
21	Pharmacy Training			
22	Date study started			
23	Date study completed			
24	Closedown			

Appendix 7 CLINICAL TRIAL PROCEDURE TEMPLATE

FULL TRIAL TITLE:		
DESCRIPTION:		
SPONSOR AND CONTACT:		Tel
		Fax
		Email
INVESTIGATOR:		Tel
		Fax
		Email
RESEARCH NURSE:		Tel
		Fax
		Email
PHARMACY PERSONNEL:		Tel
		Fax
		Email
START DATE	*LENGTH OF STUDY*	
PATIENT NUMBERS		
RANDOMISATION DETAILS		
DESCRIPTION OF TRIAL MATERIAL		
DOSAGE		

STUDY XXX version 01 Date approved _____ Approved by _____

LOCATION OF TRIAL MATERIAL
DISPENSING PROCEDURE:

STUDY XXX version 01 Date approved _____ Approved by _____

RECEIPT OF TRIAL MATERIAL:
RETURN OF TRIAL MATERIAL:
EMERGENCY CODE BREAK PROCEDURES:
REORDERING PROCEDURES:
ARCHIVING:
COMMUNICATION DETAILS:

STUDY XXX version 01 Date approved _____ Approved by _____

APPENDIX – 8 RECORD OF TRAINING

The personnel below have been trained in the dispensing procedure for this study.

Name	Job Title	Date Trained	Signature of trainee	Signature of trainer

SPECIFIC TRAINING NEEDS FOR MANUFACTURE/ASSEMBLY UNDER MA(IMP)

The following should be included in the training program of various staff groups (Note: This is not exhaustive list).

1. Senior Pharmacy management / Trust R&D

• Appreciation of GMP requirements under Clinical Trials Directive and local quality system.

This is for implementation of Trust policies and to ensure there is uniform approach for initiation of IMP manufacturing/assembly.

2. Senior Technical Services / QC

• GCP awareness training
• Trust policies for management of CTA
• Local Quality System for manufacturing/assembly of IMPs.

3. Other Technical Services / QC

• Confidentiality
• Control of randomisation codes
• Trials specific training such as labelling

APPENDIX 9 – EXAMPLE OF A CHECKLIST FOR QP RELEASE OF MANUFACTURE OF THE INVESTIGATIONAL MEDICINAL PRODUCTS

Clinical Trial No.: **EudraCT No.**

ITEM / ACTIVITY	Completed (If applicable)	Additional information
Study Approval		
Contract – IMP technical Agreement		
Contract- Confidentiality agreement		
Copy of CTA form		
IMPD or simplified IMPD		
MHRA Approval letter		
Ethics Committee favourable opinion		
Trust approval		
Final Protocol		
Amendments to protocol		
Product information		
Drug product name/ form		
Batch number		
Manufacturers details		
ML for marketed product		
Raw materials approval		
TSE status		
Components approval		
Batch Manufacturing record reviewed		
Batch manufacture according to GMP		
Detail of deviations (if any)		
Process validation status		
Quality Control Testing completed		
Sterility Assurance		
Stability Reports		
Labels compile with CTA		
For randomised studies – correct numbers used		
Expiry allocation		
Environmental monitoring compliant		
Other product specific items		

As per directive 2001/20/EC Article 13 I certify that this material has been manufactured and checked in accordance with [PMU] procedures and GMP, the product specification file and the approved relevant regulatory submission and is considered suitable for use.

***APPROVED/REJECTED BY: …… DATE:……**
PRINT NAME: QUALIFIED PERSON

*delete as appropriate and record reason if rejected

APPENDIX 10 – EXAMPLE OF A CHECKLIST FOR PHARMACIST

PHARMACY SIGN OFF FOR CLINICAL TRIALS

Protocol Name / Study Number

Initial box

	Activity	**Initials**	**Date**
1	I have all the documentation that Pharmacy require for this trial		
2	Relevant pharmacy staff are fully informed of the trial and can dispense the medicinal products according to the trial protocol		
3	I am satisfied that the trial can go ahead, in respect of all pharmacy issues		

Signature……. Date……..

Designation…….

Pharmacy copy
R&D (sponsor) copy
Trial Master File

APPENDIX 11 – EXAMPLE OF PHARMACY DOCUMENTS – Additional Templates

HOSPITAL TRUST Regulatory Green Light form

Name of study:

Study Number

Pharmacy sign off:

Name: _____

Job title: _____

Signature: _____

Date: _____

R&D sign off:

Name: _____

Job title: _____

Signature: _____

Date: _____

CI/PI sign off:

Name: _____

Job title: _____

Signature: _____

Date: _____

Curriculum Vitae Template

SUBMISSION OF CURRICULUM VITAE (CV) TO RESEARCH ETHICS COMMITTEES AND NHS R&D OFFICES

Guidance for applicants

Your CV needs to demonstrate that you are qualified by education, training and experience to conduct the research.

A standard template for an investigator CV is set out below. This template would be suitable for submission of CVs by:

- Chief Investigators (for submission with main REC application)
- Local Principal Investigators (for submission with the Site-Specific Information Form to RECs and NHS R&D offices)
- Academic supervisors (for submission with student applications).

The template is issued as guidance and is not intended to be prescriptive. Use of the template is not a requirement for a valid application.

The NRES Standard Operating Procedures state that CVs should be a maximum of 2 pages. This is also guidance and is not an absolute requirement.

It is important that experience relevant to the specific research project is fully summarised, but the overall document should be kept concise. It is not necessary to provide a complete record of the applicant's professional and academic background. In particular, CVs should not include lengthy lists of publications.

This template is recommended by NRES and the NHS R&D Forum for applications both for ethical review and R&D approval.

Curriculum Vitae Template (2)

Name:	
Present appointment: *(Job title, department, and organisation.)*	
Address: *(Full work address.)*	
Telephone number:	**Email address:**
Qualifications:	
Professional registration: *(Name of body, registration number and date of registration.)*	
Previous and other appointments: *(Include previous appointments in the last 5 years and other current appointments.)*	
Research experience: *(Summary of research experience, including the extent of your involvement. Refer to any specific clinical or research experience relevant to the current application.)*	
Research training: *(Details of any relevant training in the design or conduct of research, for example in the Clinical Trials Regulations, Good Clinical Practice, consent or other training appropriate to non-clinical research. Give the date of the training.)*	
Relevant publications: *(Give references to all publications in the last two years plus other publications relevant to the current application.)*	
Signature:	**Date:**

Curriculum Vitae Template (2)

Name:

Date of Birth:

Current Employment:

Job Title:

Trust

Start Date:

Academic Qualifications:

Qualification/Speciality	Year	College/University

Signature: **Initials:** **Date:**

Letter to accompany Curriculum Vitae

Trust details

DEPARTMENT OF PHARMACY
Tel: XXXXXXXXXXXXXXX Fax: XXXXXXXXXXXXXX

Our Ref. ZZZ/ Date:

STRICTLY PRIVATE AND CONFIDENTIAL

CRA,
Sponsor company address

Dear

re: study protocol no.

…….. you asked for my curriculum vitae (CV) as a key member of pharmacy staff responsible for this study at the XXXXXXXXXXXXXXXX.

I have worked in the present position as XXXXXXXXXXXXXXXXXXXXXX at the XXXXXXXXXXXXXXXXXX for over _____ years ***I.E. DESCRIBE AS APPROPRIATE*** .

Most recent training related to ICH Good Clinical Practice was received subsequent to implementation of the EU Clinical Trials Directive by me in XXXXX 200X. Details of my qualifications are given below.

Please note that information in this document is defined as personal data under European Union Directive 95/46/EC.

Also, please note that this CV is strictly private and confidential thus it is only to be used for this study and not for any other.

Yours sincerely,

XXXXXXXXXXXX
XXXXXXXXXXXXX
B. Pharm *YEAR*
M.R. Pharm.S *YEAR*
M.Sc *YEAR*

INVENTORY LOG TEMPLATE (1)

Protocol Number / Name of Study	Investigator:
Sponsor:	

Delivery Status

On receipt of Non-Commercial IMP please check that a Certificate of Analysis or QP release is present in the pharmacy file.
If not the delivery must be quarantined until the relevant documents are received.
This form must be used to confirm status of delivery

Date of delivery	Delivery Ref. Number	IMP	Batch Number	C of A / QP received Y / N	Quarantine delivery Y / N	Delivery approved for dispensing

INVENTORY LOG TEMPLATE (2)

Trust/CT/month year/study number

(Sponsor's protocol no. : _____)

SAMPLE Drug Dispensing and Accountability Record

Patient name : _____ Patient number : _____(use terminology to suit)

DISPENSED MEDICATION				**RETURNED MEDICATION**		
Date	**Visit number (if applicable)**	**Quantity dispensed**	**Dispensed by/ Checked by**	**Date**	**Quantity returned**	**Counted and sent for destruction (if applicable) by**

SIGNATURE & DELEGATION LOG

Study No.:				Investigator Name:			
Study Title:				REC Approval Number:			
Site Identification:				Eudract Number:			
Name (printed)	**Signature**	**Initials** Abbreviated signature or paraph	**Study function**	***This section to be completed by Investigator only***			
				Key delegated tasks If tasks change during the study, make a new entry on a new line (see codes)	***From*** **(dd-mmm-yyyy)** Completed at start of study participation	***To*** (dd-mmm-yyyy) Completed at site closure or departure from site	***Investigator*** **Initials** Abbreviated signature or paraph

CODING				
A = Decide on subject eligibility	**E** = Instruct subject on use of study drug	**I** = Prepare drug, if applicable	**M** = Authorized to break randomization code
B = Obtain informed consent	**F** = Store drug & drug codes	**J** = Handle dangerous goods, if applicable	**N** = _____
C = Medical care of subjects	**G** = Drug accountability & dispensing	**K** = Collect, prepare, & archive study documents	**O** = _____
D = Make CRF entries/corrections	**H** = Access IVRS, if applicable	**L** = Clinical assessment of SAEs & AEs (M.D.)	**P** = _____

I confirm that this list accurately reflects the delegation of responsibilities during the study:

Investigator Signature: .....

Date: | | | | | | 2 | 0 | 0 | |
d d m m m y y y y

FILING INSTRUCTIONS:

At Site initiation: File a photocopy in the Investigator File, section Agreement/Contracts, prior to enrollment of the first subject.
During the study: Maintain in the Trial Centre File, section Site Signature Log. If there is a change or addition, file a photocopy in the IF.
At site closure: File original in the Investigator File. File copy in the Trial Centre File.

TEMPERATURE MONITORING RECORD

Location	
Temperature range:	15°C to 25°C

MONTH:	
YEAR:	

Temperatures will only be recorded Monday to Friday.

In the event of a temperature excursion, quarantine drug supply and contact the Sponsor for advice.

Date	Day	Time of reading	Temperature		Initials	Action to be taken if appropriate
			Maximum	Minimum		
1st						
2nd						
3rd						
4th						
5th						
6th						
7th						
8th						
9th						
10th						
11th						
12th						
13th						
14th						
15th						
16th						
17th						
18th						
19th						
20th						
21st						
22nd						
23rd						
24th						
25th						
26th						
27th						
28th						
29th						
30th						
31st						

Senior Technician/Pharmacist's Signature:_____ Date:_____

PHARMACY DEPARTMENT
Address

PRESCRIPTION FOR STUDY MEDICATION

Please take this form to the Pharmacy

Study Title:-

Study Code: study number Sponsor protocol no. :

Please supply for :

Patient name : _____ Patient number : _____

Addressograph label:

Visit number (if applicable) :

Medication to be ready by : _____ (date) _____ (time)

Medication to be collected by : ☐ hospital staff or ☐ patient
(The allocated person must complete bottom of prescription)

Doctor's Signature: _____ Date: _____

Doctor's Name: _____ Ext. no/Dect no. : _____
(please print)

For Pharmacy Use Only

Dispensed by : _____ signature _____ (print name) _____(date)

Checked by : _____ signature _____ (print name) _____
(date)

Medication collected by

_____ signature _____ (print name) _____(date)

N.B. After collection, this prescription must be retained for filing in pharmacy by Clinical Trials staff.

Appendix 12 **Audit Aide Memoir for the Handling of Clinical Trials in Pharmacy Departments**

Trust		**Date**	
Auditors		**Designation**	

Other staff present:

RESULT RATINGS

Green = Compliance with Acceptance Criteria

Amber = Minor (where it is evaluated that the non-conformance has no effect on the legality of the operations or systems or procedures require minor alterations that can easily be accomplished)

Red = No such system/procedure currently in place

Glossary of terms used in connection with the checks required for each criterion:

Assess: Requires the auditor(s) to use their professional judgement in assessing whether the audit standard is complied with and, if not, attributing a non-conforming grade.

Examine: Generally relates to procedures and/or materials that need to be examined.

Procedure: Relates to written procedures which should be assessed for appropriateness and compliance with official guidelines.

References

1. Guidance Document Pharmacy Clinical Trials Activities
2. Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007 (“Orange Guide”)
3. Model Policy Template for the Safe Handling of Clinical Trial Medicines in NHS Trusts
4. Good Clinical Practice Directives 2005/28/EC and 2001/20/EC
5. Directive 91/356 /EEC as amended for the labelling of Investigational Medicinal Products
6. Medicines for Human Use (Clinical Trials) Regulations 2004 SI 2004/1031
7. Practice Guidance on Pharmacy Services for Clinical Trials. RPSGB June 2005
8. The Safe and Secure Handling of Medicines: A Team Approach. A revision of the Duthie Report March 2005
9. Clinical Trials: Management Issues – MRC/DoH Joint Project 2004
10. Labelling of Clinical Trials – MRC/DoH Joint Project 2004
11. Clinical Trials :What is Manufacture QCNW website

Audit Aide Memoir for the Handling of Clinical Trials in Pharmacy Departments

A Policy

Acceptance criteria		***Check required***	**Evidence**	***Audit result Green/Amber/Red***	**Observations and non-compliances**
1.	There is Trust policy for the handling of clinical trials, giving details of processes involved in setting up a trial and which staff are responsible for what within the Trust unless there is an agreed and documented change in an individual case.	**Procedure**			
2.	There is designated pharmacist/technician for clinical trials and this is documented in the Trust Policy.	**Assess**			
3.	There is pharmacy policy giving details of the responsibilities of the designated clinical trials pharmacist / technician and for the handling of clinical trials within the department.	**Procedure**			
4.	In-patient or in-clinic administration of trials is in accordance with local policy.	**Procedure**			

Audit Aide Memoir for the Handling of Clinical Trials in Pharmacy Departments

B Process control/documentation/records

Acceptance criteria		*Check required*	Evidence	*Audit result Green/Amber/Red*	Observations and non-compliances
1.	Manufacturing (Investigational Medicinal Product - IMP) activities are only carried out under the supervision of a QP(IMP).	Assess			
2.	Assembly (dispensing) tablet/capsule IMPs is carried out under the supervision of a pharmacist.	Assess			
3.	Any procedure involving dissolving, dispersing, mixing or diluting with some other substance as a vehicle is for one patient only at a time and under the supervision of a pharmacist.	Assess			
4.	All pharmacy related trial documentation is kept in separate individual folders/ separate sections of a larger folder.	Examine			
5.	There is a list of all trials undertaken, with start and finish dates.	Examine			
6.	A Clinical Trials Checklist or equivalent is completed for all trials.	Examine			
7.	A signed agreement with the study sponsor, giving clear responsibilities of the sponsor, the investigator and the pharmacy in handling the IMP is in place for all trials.	Examine			

B Process control/documentation/records

Acceptance criteria		***Check required***	**Evidence**	***Audit result Green/Amber/Red***	**Observations and non-compliances**
8.	All documentation directly involving the IMP including correspondence with the MHRA must be held in the pharmacy file for that trial.	Assess			
9.	There is an organogram in the pharmacy clinical trials file giving clear lines of responsibility.	Examine			
10	Standard Operating Procedures (SOPs) are in the standard Trust format, authorised, dated, version controlled with changes since the previous version highlighted in some way, and subject to documented review.	Examine			

B Process control/documentation/records

Acceptance criteria		*Check required*	Evidence	*Audit result Green/Amber/Red*	Observations and non-compliances
11	SOPs available for all processes involved in a trial. As a minimum this should include:- Initiation of study within pharmacy Procurement of IMPs for Trust sponsored studies Receipt/recording delivery of study drugs Safe Handling and Storage of study drugs Dispensing of study drugs Drug accountability/reconciliation Drug returns and disposal Emergency code breaking Security of randomisation codes Preparation(dispensing procedure) Closedown and archiving Training	Examine			
12	There is also an SOP covering deviations and errors (both pre and post issue) including records of corrective and preventative actions taken, and how it is permissible to correct documentation.	Examine			

Audit Aide Memoir for the Handling of Clinical Trials in Pharmacy Departments

B <u>Process control/documentation/records</u>

Acceptance criteria		***Check required***	**Evidence**	***Audit result Green/Amber/Red***	**Observations and non-compliances**
13	Labels must be in English and comply with the requirements of the latest "Orange Guide" (2007 Edition p.163 and summary on p.170)	Examine			
14	Expiry date labelling is done as per Annex 13 in Rules and Guidance for Pharmaceutical Manufacturers and Distributors.	Assess			
15	Clinical Trial Procedure/Guideline specific to each trial undertaken. This should at least include:- Title and description(type and phase of study) and a summary of the work required by pharmacy Principal Investigator Research Nurses Pharmacy personnel Sponsor contact Dates and length of study with patient numbers Randomisation type Description of trial supplies Dose and any potential adjustments Drugs to be given concomitantly Where supplies are stored Dispensing procedure Receipt and return of material (including recording) Emergency code break procedure	Examine			

Audit Aide Memoir for the Handling of Clinical Trials in Pharmacy Departments

B Process control/documentation/records

Acceptance criteria		***Check required***	**Evidence**	***Audit result Green/Amber/Red***	**Observations and non-compliances**
16	Superseded documents must be stored separately and not destroyed.	Assess			
17	Pharmacy should hold a copy of all patient information leaflets	Assess			
18	Records should be regularly audited by pharmacy staff.	Assess			
19	Records are retained according to a clear procedure.	Assess			

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C Training

Acceptance criteria		Check required	Evidence	Audit result Green/Amber/Red	Observations and non-compliances
1.	There must be documented evidence of the competency of pharmacy staff involved in the trial. E.g. Qualifications Trials specific training records Dispensing and checking authorisations	Examine			
2.	Staff sign for having read SOPs.	Examine			
3.	Training records and signature logs are kept with the relevant trial.	Examine			

D Security

Acceptance criteria		Check required	Evidence	Audit result Green/Amber/Red	Observations and non-compliances
1.	IMPs are stored under the same conditions as any other medicine according to the manufacturers labelled instructions.	Assess			
2.	Storage areas are clearly labelled and sufficiently spacious to allow easy selection of the correct product.	Assess			
3.	The identity of all involved in the receipt, dispensing, issue, administration and disposal of trial material is recorded.	Examine			
4.	IMPs are stored separately to non-trial materials and are clearly labelled as such.	Assess			

Audit Aide Memoir for the Handling of Clinical Trials in Pharmacy Departments

E Quality and Integrity

Acceptance criteria		Check required	Evidence	Audit result Green/Amber/Red	Observations and non-compliances
1.	The cold chain is maintained for all IMPs requiring refrigeration.	Assess			
2.	The temperature is monitored for all storage areas (including any elsewhere in the hospital), records kept and action taken according to a contingency plan if outside pre-defined limits.	Assess			
3.	Monitoring devices are calibrated and this is recorded.	Assess			
4.	Products are stored so as not to contaminate, or be contaminated by, other products.	Assess			
5.	Stock is rotated as appropriate according to procedure.	Assess			
6.	Materials are protected as necessary from inappropriate light/moisture/temperature.	Assess			
7.	Unlicensed medicines are not purchased for use in trials (eg.ready-made cytotoxics for chemotherapy trials) unless specifically released by a QP (IMP).	Assess			

F Safety Issues – staff and patients

Acceptance criteria		Check required	Evidence	Audit result Green/Amber/Red	Observations and non-compliances
1.	There must be a comprehensive recall procedure and emergency code break procedure in place.	Examine			
2.	The recall procedure and code break procedure are tested theoretically periodically and this documented.	Assess			
3.	Where possible samples are obtained prior to trial commencement to enable a risk assessment and preparation of extra labels to be carried out as applicable.	Assess			
4.	Code breaks may be held within the pharmacy department. There must be access to these at all times (including out-of-hours) and on-call pharmacists must be familiar with the procedure should the need arise.	Assess			
5.	There must be an SOP and specific patient information for the handling of spillage of the trial material as appropriate.	Examine			

Audit Aide Memoir for the Handling of Clinical Trials in Pharmacy Departments

G Responsibility/Accountability

Acceptance criteria		Check required	Evidence	Audit result Green/Amber/Red	Observations and non-compliances
1.	Where specific responsibilities for clinical trials are part of a job role this should be clearly stated in the relevant job description.	Examine			
2.	Responsibilities for each aspect of a trial are clearly documented in Trust policy and in the Clinical Trial Agreement	Examine			

Audit Aide Memoir for the Handling of Clinical Trials in Pharmacy Departments

H Removal/Destruction

Acceptance criteria		Check required	Evidence	Audit result Green/Amber/Red	Observations and non-compliances
1.	Expired stock is removed in a timely manner, clearly segregated from other stock and labelled as such.	Assess			
2.	Expired/returned/unwanted stock is disposed off according to the terms agreed in the trial protocol. Written authorisation is either obtained from the investigator prior to destruction of any clinical trial material or stocks may be returned to the sponsor. Records of destruction/sending for destruction are kept.	Assess			

AUDIT REPORT FOR THE HANDLING OF CLINICAL TRIALS IN PHARMACY DEPARTMENTS

Date of audit……

Report completed by……..Designation…….

Next audit date……

COMMENTS

The following points were noted during the audit, where possible this includes a suggested plan to action

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Please note below any other observations or difficulties experienced with the completion of the audit, referring to the appropriate section number where possible.
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Copies sent to: Chief Pharmacist…….Date…….

Relevant section manager……Date…….