RD&I	NHS University Hospitals Plymouth NHS Trust **STANDARD OPERATING PROCEDURE**

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Investigator's Brochure (IB)

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Page: **1** of **9**

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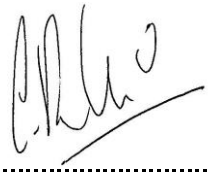
AUTHORISED BY

Name: Chris Rollinson

Job Title: Research Governance Manager

Signature: 

Date: 21st Jan 2019

1 Purpose and Scope

An Investigator's Brochure (IB) is part of the clinical trial authorisation (CTA) application. It documents all relevant information about the Investigational Medicinal Product (IMP), including chemical structure, non-clinical trials and clinical trials.

It should be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the IMP within it. It should also detail which adverse reactions are expected and their frequency of occurrence, giving valuable safety information and guidance to the investigator(s) to use for assessing expectedness and determining the expedited reporting requirements of any Suspected Unexpected Serious Adverse Reactions (SUSARs).

The IB is a key trial document required by the competent authority and the research ethics committee. It must be reviewed on at least an annual basis and updated if necessary. The process to be adopted by a Chief Investigator and Sponsor when producing an Investigator Brochure (IB) for a research study involving a medicinal product to be used in either a new indication or as a new compound. Production of this document may be completed in-house or contracted out to a vendor. It should be clear who has been assigned this function. The IB is relevant across multiple clinical trials using the same product.

If the IMP has a marketing authorisation and it is being use within its authorisation in the specified population, there may be no need to make use of an IB as a Summary of Product Characteristics (SmPC) may suffice as the reference safety information.

The outcome is that all research using Investigational Medicinal Products (IMPs) has a comprehensive document detailing all known safety reference data and that this data is reviewed on at least an annual basis. The trial master file must contain clear evidence the IB has been reviewed even when the review concludes that no update is required. This information has to be communicated to all relevant parties involved in the trial.

This SOP applies to all research studies that are using, or intend to use, IMPs that do not have a marketing authorisation and that are sponsored by the University Hospitals Plymouth NHS Trust (UHPNT). The Research, Development & Innovation (RD&I) Dept. acts on behalf of the Trust as study sponsors. This SOP does not apply where another organisation is responsible for creating and maintaining the IB.

Definitions

CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
EVCTM	Eudravigilance Clinical Trial Module
GCP	Good Clinical Practice
HRA	Health Research Authority
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
UHPNT	University Hospitals Plymouth NHS Trust
RD&I	Research And Development
REC	Research Ethics Committee
RO	Research Office
RSI	Reference Safety Information -
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

2 Who should read this document?

Chief Investigators (CI), Principal Investigators, Study co-ordinators, Research Governance Manager, Senior Research Facilitators, Clinical Trial Manager, Clinical Trial Pharmacist, Pharmacy Trial Support Manager and relevant Clinical Trial Administrative staff.

3 Procedure to Follow

3.1. Responsibilities

Responsibility		Undertaken by	Activity
1	RD&I Office	Research Governance Manager or delegate	Confirm an IB / SmPC is included within the Sponsor documentation submitted for review.
2	RD&I Office	Research Governance Manager or delegate /	Confirm with Pharmacy that a copy has been received to enable Pharmacy process to begin
3	Chief Investigator	Chief Investigator	Assign a responsible individual to ensure oversight of creation, regulatory approval and on-going maintenance of the IB.
4	Chief Investigator	Chief Investigator	Ensure that the annual review of IB/SmPC is undertaken, documented and distributed as required
5	Pharmacy	Clinical Trial Pharmacist	To review and sign off IB and review and sign off on annual review.
6	Pharmacy	Clinical Trial Pharmacist	Ensure that an up to date IB is maintained in the Pharmacy file
7	Chief Investigator / Sponsor	Chief Investigator / Research Governance Manager or Delegate	Ensure revisions to IB are sent for relevant approvals to MHRA & REC
8	RD&I Office	Chief Investigator / Study Co-ordinator or Delegate	Ensure IB is distributed to all sites including any updates; there must be documented evidence of receipt of the current IB by study sites.

3.2 Procedure

The Chief Investigator is responsible for coordinating the production of the IB. It is recommended that input from other relevant personnel (i.e. pharmacy) is sought, and that all review comments are retained. It is important that where comments have been submitted but not incorporated, a record is kept along with a brief explanation as to why the suggested changes were not made.

The IB or SmPC forms part of the essential documents for an IMP study, and must be included within the documentation submitted to the Sponsor to be reviewed as part of the Sponsor review process. Where there is no evidence to show input during the preparation and production of an IB, a final review and sign off from the Clinical Trials Pharmacist will be required. This will be requested by the Research, Development & Innovation (RD&I) Office.

The IB must not be forwarded to the competent authority (MHRA) or the Research Ethics Committee prior to Sponsor sign off.

Specific content of an Investigational Brochure will vary depending on whether the subject of investigation is a medicinal product, device or therapeutic intervention. The description below uses the case of a medicinal product. In the case of a device or therapeutic intervention the terms should be adapted appropriately and followed where applicable.

The Investigator's Brochure (IB) is a compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human participants.

Its purpose is to provide the investigators and others involved in the research project with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures.

The IB also provides insight to support the clinical management of the research project participants during the course of the clinical trial.

The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial.

As part of their written application to the Research Ethics Committee (REC), the investigator must provide the REC with a current copy of the Investigator's Brochure and if updated during the trial, the Investigator/institution should supply a copy to the REC in accordance with that REC's procedures.

In the case of a marketed product being studied, it may be acceptable to use the Product Information as a substitute for the Investigational Brochure. The ICH guidelines state:

"If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e. a new indication), an IB specific to that new use should be prepared."

3.3 IB content

Refer to ICH GCP E6 (R1), section 7, for guidance on the minimum information that should be included in an IB and suggestions for its layout. An IB template can also be located on the Trust intranet site "StaffNet" under RD&I Dept/documents.

3.4 Review / Updates to the Investigator's Brochure

The IB or SmPC as appropriate for each drug must be reviewed on at least an annual basis. The review and the decision to continue to use the existing version or to change the document must be documented. This process must be completed irrespective of whether changes were necessary. It is expected that the Clinical Trials Pharmacist be involved in the review / revision process of the IB.

More frequent review / revision may be appropriate, but this will depend on the stage of development of the drug or the generation of relevant new information. However, in accordance with GCP, relevant new information may be so important that it should be communicated to all Investigators, and possibly to the REC and/or regulatory authority before an IB revision has taken place.

A copy of the revised IB must be sent to the Sponsor for final sign off before it is sent to all sites. The Sponsor will send to the Clinical Trials Pharmacist for review and sign off at every revision / review unless evidence of their involvement can be provided. The IB template requires signatures from the Chief Investigator, Clinical Trials Pharmacist and the Sponsor for each version.

It is the responsibility of the CI to ensure that all sites have the most recent version of the IB once signed off by the Sponsor or the most recent version of the SmPC. Old version will be superseded by the site upon receipt of new version of the IB. It is expected that evidence be provided to show that the sites have received the latest version. An email trail will be acceptable evidence.

3.5 Submission of Revised Investigator's Brochures

Where an IB requires revision and not simply a review, amendments will be made to the document, which requires both regulatory authority and REC approval. It is important to include the following information in the submission:

- how the risk/benefit assessment of the study has been affected
- how these changes impact the trial
- what alterations to the protocol are proposed to take account of these changes?

Where revisions alter benefit/risk assessment of the study, the revised IB must be submitted as a substantial amendment. Where alterations to the protocol are required, all revised documents should be submitted in a single amendment.

3.6 Amendments Regarding Investigator's Brochure Safety Updates

The Reference Safety Information (RSI) is a list of medical events that defines which reactions are expected for the Investigational Medicinal Product (IMP) being administered to clinical trial subjects, and so do not require expedited reporting to the Competent Authority and Eudravigilance Clinical Trial Module (EVCTM) - if direct reporting is

performed by UHPNT (for the UK we report through the eSUSAR system the MHRA will forward the report onto EVCTM on our behalf).

The entire Investigators IB is not the RSI, but a clearly defined section of it. The same also applies for the SmPC.

The RSI for any IMPs involved in a clinical trial must stay consistent during each reporting period. At the end of the reporting period the Sponsor in collaboration with the Chief Investigator may assess the new safety information that has been generated and submit any proposed safety changes to the IB or RSI as a substantial amendment. This amendment should be supported by the Annual Safety Report/Development Safety Update Report and approved before the RSI is changed.

If you are a non-commercial sponsor using a IB provided by a Pharmaceutical company and they issue an update which contains RSI changes then you have two options. The first is to submit a substantial amendment to the MHRA to update your IB and change your RSI. The second option is to conduct and fully document a risk assessment of the changes and if you feel that you can justify not using the new RSI to again document it and continue with the old IB.

If you are using the SmPC for your RSI then the assessment should be made against the version of the SmPC that was submitted with your initial application as this is your approved RSI. If a new version of the SmPC is released then you should conduct an assessment of the changes and make a documented decision as whether you need to update your RSI or continue with the old version of the SmPC. If you decide you do wish to change to the new version of the SmPC then you will be required to submit a substantial amendment to the MHRA.

Changes to the RSI include the downgrading of reactions from unexpected to expected. Until the amendment justifying the downgrading has been approved the events must be treated as unexpected.

4 Document Ratification Process

The review period for this document is set as ***default of three*** years from the date it was last ratified, or earlier if developments within or external to the Trust indicate the need for a significant revision to the procedures described.

This document will be approved by the ***RD&I Manager or their Deputy***.

Non-significant amendments to this document may be made, under delegated authority from ***a senior RD&I manager***, by the nominated author. These must be ratified by the ***a senior RD&I manager***.

Significant reviews and revisions to this document will include a consultation with ***appropriately knowledgeable staff***. For non-significant amendments, informal consultation will be restricted to ***staff*** who are directly affected by the proposed changes.

Dissemination and implementation

4.1. Dissemination of this SOP

4.1.1. New SOPs and new versions of existing SOPs: The Research Governance Manager will be responsible for ensuring authorised SOPs are uploaded on the RD&I intranet site. Internal Trust Staff are expected to use the RD&I intranet site to access latest versions of SOPs and to check the website regularly for updates.

Notice of new or amended procedural documents that have undergone a major amendment will be given *via* the following routes:

• Inclusion in the Trust weekly e-bulletin Vital Signs

• Direct email to Trust Researchers and or teams

4.2. Training in this SOP

4.2.1. All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP.

5 Reference material

ICH GCP E6 (R1), section 7, can be located at:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

IB Template, can be located at:
http://staffnet.plymouth.nhs.uk/Departments/ResearchandDevelopment/Documents.aspx

6 Amendment History

Version Number:	1.1
Date of Issue:	Jan 2019
Details:	Update logo and Trust's name

Version Number:	1.0
Date of Issue:	Aug 2017
Details:	New SOP