1. Introduction

This Standard Operating Procedure (SOP) describes the process to be adopted by a Chief Investigator (CI) when producing or amending an Investigator's Brochure (IB), Investigational Medicinal Products Dossier/ simplified Investigational Medicinal Products Dossier (IMPD/sIMPD) or sourcing an Summary of Product Characteristics(SPC), for a research study involving an Investigational Medicinal Product (IMP).

The outcome is that all research using IMPs has a comprehensive document incorporating all known Reference Safety Information (RSI) and that this document is reviewed on at least an annual basis.

RSI is mandatory for IMP trials and must be identifiable, approved and consistent.

2. Scope

This SOP applies to all research studies that are using, or intend to use IMPs, and that are sponsored by the University Hospitals of Leicester NHS Trust (UHL).

3. Procedure

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

3.1 Investigational Medicinal Product Dossier (IMPD/Simplified Investigational Medicinal Product Dossier (sIMPD)

The IMPD contains data on the quality of any IMP (including placebo), it provides a summary of information related to the quality, manufacture and control of the IMP. A full IMPD is required where little or no information on the IMP has been submitted to the MHRA before and does not have a Marketing Authorisation (MA) for the product in Member States (MS). This provides information on the quality of the IMP (including placebo), including summaries of information related to the quality, manufacture and control of the IMP.

A simplified version of the IMPD (sIMPD) may be submitted if information has been assessed previously as part of MA or a clinical trial to the competent authority.

3.2 Summary of Product Characteristics (SPC/SmPC)

This is a document approved as part of a marketing authorisation of a medicine, containing a definitive description of the product both in terms of its chemical pharmacological and pharmaceutical properties and the clinical use to which it can be put. All SmPCs are available on www.medicines.org.uk

3.3 Investigator's Brochure

An IB 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.

3.4 When Is a Full Investigator's Brochure Required?

3.4.1 When conducting an IMP study using a product that has not yet been granted a licensing authorisation (non- approved compound) a fully comprehensive IB is required. It is likely that this type of study will be categorised as Type C in accordance with the Medicines for Healthcare Regulatory Agency (MHRA) Risk-adapted approach to IMP studies. However, this will be confirmed on a case-by-case basis at Sponsor Green Light Process risk assessment.

3.4.2 In cases where a licensed product is to be used outside of the licensed indication, or in a different subject population, it is not necessary to complete a full IB. A summary of relevant data that complements the existing Summary of Product Characteristics (SPC) to support the use of the IMP in the study will be required instead. As Sponsor, UHL recommend that the summary is included within the protocol, and that a SPC is appended to this document. It is likely that this type of study will be categorised as Type B in accordance with the MHRA Risk-adapted approach to IMP studies. However, this will be confirmed on a case-by-case basis at Sponsor Green Light Process risk assessment.

3.4.3 In cases where a licensed product is being used within the terms of its license an IB will not be required. The SPC, (Section 4.8), as published by the product manufacturer will be appropriate to use as RSI for assessments of expectedness. It is likely that this type of study will be categorised as Type A in accordance with the MHRA Risk-adapted approach to IMP studies. However, this will be confirmed on a case-by-case basis at Sponsor Green Light Process risk assessment.

3.5 When is an IMPD / SIMPD Required?

When applying for a clinical trial authorisation, a full IMPD is required where little or no information about an IMP has been previously submitted to the Competent Authorities, when it is not possible to cross-refer to data submitted by another Sponsor and/or where there is no MA in the community.

However there are situations where a simplified IMPD will be sufficient. A simplified IMPD may be submitted if information has been previously assessed as part of a MA in any member state or a clinical trial to the Competent Authority.

4. Preparation of the IB / IMPD / sIMPD

The CI is responsible for coordinating the production of the IB/IMPD/sIMPD. It is recommended that input from other relevant personnel (i.e. pharmacy) or the manufacturer of the IMP 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/IMPD/sIMPD or SPC 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 approval process. Where there is no evidence to show input during the preparation and production of an IB/IMPD/sIMPD, a final review and sign off from the Clinical Trials Pharmacist will be required. This will be requested by the Research Office.

The IB/IMPD/sIMPD must not be forwarded to the competent authority (MHRA) or the Research Ethics Committee prior to Sponsor sign off. Guidance on the requirements for an IB/IMPD/sIMPD can be found on the MHRA website. https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#reference-safety-information--updated-guidance

5. Review / Updates to the IB / IMPD / sIMPD

The IB/IMPD/sIMPD or SPC 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 using the UHL IB/IMPD/sIMPD/SPC review template (Appendix 2). 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/IMPD/sIMPD.

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/IMPD/sIMPD revision has taken place.

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

It is the responsibility of the CI to ensure that all sites have most recent version of the IB/IMPD/sIMPD once signed off by the Sponsor or the most recent version of the SPC. It is expected that evidence be provided to show that the sites have received the latest version. An email trail will be acceptable evidence.

5.1 Submission of Revised IB / IMPD / sIMPD

Where an IB/IMPD/sIMPD requires revision and not simply review, amendments will be made to the document, which may require 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 may have been affected
- How these changes impact the trial
- What alterations to the protocol are proposed to take account of these changes?

Where alterations to the protocol are required, it is advisable to submit all revised documents in one amendment.

5.2 Amendments Regarding Investigator Brochure Safety Updates

Where revisions to the RSI are required the revised IB must be submitted as a substantial amendment. (General new safety data that does not impact the risk to benefit ratio can be added without a substantial amendment).

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 C I must assess any new safety information that has been generated and submit proposed changes as a substantial amendment. This amendment should be supported by the Annual Safety Report/Development Safety Update Report and approved before the revised RSI is implemented.

Changes to the RSI can include the downgrading of reactions from unexpected to expected, but until the amendment justifying the downgrading has been approved such events must be treated as unexpected. Updating of RSI does not allow previously reported events to be downgraded.

6. Responsibilities

	Responsibility	Undertaken by	Activity
1	Sponsor	Head of Research Operations or delegate	Confirm an IB / SPC is included within the Sponsor documentation submitted for review.
2	Sponsor	Head of Research Operations or delegate	Confirm with Pharmacy that a copy has been received to enable Pharmacy review process to begin.
3	Chief Investigator	Chief Investigator	Generate IB or provide copy of existing SPC to the Sponsor as part of the Sponsor review documentation requirements.
4	Chief Investigator	Chief Investigator	Ensure that the annual review of IB/SPC is undertaken, documented and distributed as required.
5	Pharmacy	Clinical Trial Pharmacists	Ensure that an up to date IB is maintained in the Pharmacy file. Review and approve revisions.
6	Chief Investigator / Sponsor	Chief Investigator / Head of Research Operations or delegate	Ensure revisions to IB are sent for relevant approvals to MHRA & REC and are not implemented until approved.

7. Supporting Documents and Key References

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8. Key Words

Research, Innovation, Volunteers, Participants, CTIMPS, Trials, ICH GCP, IB, IMPD, sIMPD, SPC

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This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

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