Annual Review of the Investigator's Brochure

NJRO-REG-SOP-008

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1. Background/Introduction

As defined in Directive 2001/20/EC, the Investigator's Brochure (IB) is 'a compilation of the clinical and non-clinical data on the Investigational Medicinal Product (IMP) or products which are relevant to the study of the product or products in human subjects'. The IB should contain all relevant information about the IMP including which adverse reactions are expected for a given IMP and their frequency of occurrence. This provides valuable safety information to the Chief Investigator (CI) and will be used for assessing expectedness. This will determine the expedited reporting requirements of any Suspected Unexpected Serious Adverse Reactions (SUSARs).

The purpose of the IB is to provide those involved in a trial with information to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. Therefore it is essential that this information is periodically reviewed and updated accordingly.

In accordance with the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, it is the Sponsor's responsibility to:

(a) ensure that the IB for that trial, and any update of that brochure, presents the information it contains in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial; and

(b) validate and update the IB at least **once a year**.

2. Purpose

This Standard Operating Procedure (SOP) describes the procedure for reviewing and updating the IB for those Clinical Trials of Investigational Medicinal Products (CTIMPs) sponsored by The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH FT).

3. Scope of Document

This SOP is applicable to all Chief Investigators (CI) of NuTH FT sponsored CTIMPs and those personnel within the NuTH FT Research & Development (R&D) team (particularly the Regulatory Compliance Team) with responsibility for the review of updates to the IB.

4. Procedure

It is a legislative requirement that the IB is reviewed on an annual basis. For those CTIMPs sponsored by NuTH FT the responsibility for undertaking the annual update of the IB is delegated to the CI of the trial via a 'Delegation of Sponsor Duties Agreement'. The CI should ensure that the process begins in a timely manner prior to the one-year deadline, allowing time for consideration by the Sponsor. The timing of the update should be calculated from the date of the original Clinical Trial Authorisation (CTA) from the Medicines and Healthcare products Regulatory Agency (MHRA) and not the start date of the trial.

4.1. Reviewing and Updating the IB

If the trial is of a novel product then the CI should arrange appropriate input in to the review (e.g. pharmacological/toxicological) to ensure that the required expertise is applied to the process of reviewing the current knowledge of the IMP. If the IMP is manufactured within NuTH FT then Newcastle Specials Pharmacy Production Unit must be involved in this review. The accumulated safety information, as prepared for the Developmental Safety Update Report (DSUR), should be used to determine if there has been a change to the risk/benefit profile of the IMP. This review must be documented, even if it was decided that no updates to the document were necessary. This can be in the form of Trial Management Group (TMG) meeting minutes, file notes and/or via the 'IB/Summary of Product Characteristics (SmPC) Review Template Form' (applicable to studies managed by the Newcastle Clinical Trials Unit (NCTU), all of which should be contained within the Trial Master File (TMF). Changes to the relevant safety section of the IB may also be documented via a file note or TMG minutes as the RSI only represents one component of the IB.

Once a full IB review has been completed, the CI should submit the following documents to the Regulatory Compliance Team (via the safety reporting inbox: mailto:tnu-tr.safetyreporting@nhs.net) for consideration:

- A revised IB with an associated risk assessment; or
- A statement that a full review has been performed and there is no requirement to update the IB
- IB/SmPC Review Template Form (Trials managed by NCTU)
- Documented changes to RSI if the relevant safety section (RSI) has been updated.
- Any relevant file notes or TMG minutes documenting this review

The revised IB and risk assessment or statements of 'no change' should be signed by all who have been involved in the review. The Regulatory Compliance team will confirm whether the Sponsor considers that the risk/benefit assessment for the study has changed and independent advice may be sought if required.

If the IMP is manufactured externally (e.g. by a pharmaceutical company) then it is the CI's responsibility to obtain the most up to date IB from the IMP supplier. Should the CI encounter difficulties in obtaining this information then NuTH FT Pharmacy should be contacted as the provision of this information is included in the contract between Pharmacy and the IMP manufacturer.

4.2. Updating a Summary of Product Characteristics

The SmPC may be used instead of the IB in trials of IMPs that already have marketing authorisations. In such cases care should be taken to adopt, as soon as possible, any updated versions of this document that may be produced by the manufacturer. In addition there should be a documented annual check that the most current version is in use. When any updated SmPC is being adopted, care should be taken to ensure that the study will still be using the product strictly within the terms of its marketing authorisation.

4.3. Submission for Regulatory Approval

If the risk/benefit assessment for the study has changed the IB should be submitted to MHRA and the main REC for approval, as a substantial amendment (see NJRO-REG-SOP-009: Amendments to Sponsored CTIMP, ATMP or Device Trials). Otherwise details of the update should be sent to the regulatory authorities for information.

5. Review and Monitoring

This SOP will be reviewed every 2 years or in the event of a change to the appropriate regulations.

6. References

6.1. European Commission (2010/C 82/01) - Detailed Guidance on the Request to the Competent Authorities for Authorisation of a Clinical Trial on a Medicinal Product for Human Use, the Notification of Substantial Amendments and the Declaration of the End of the Trial (CT-1)
6.2. Statutory Instrument 2006/1928: The Medicine for Human Use (Clinical Trials) Regulations 2006
6.3. ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R2)
6.4. MHRA Good Clinical Practice Guide (2016)

7. Appendices

N/A