Standard Operating Procedure			***Enter SOP Number***
Sponsor IB Assessment			**55.016**
Version	***1.0***		
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1. SOP Category
NHS GG&C Sponsor Pharmacovigilance

2. Staff Category
Sponsor Pharmacy
Pharmacovigilance and Safety Manager
Project Managers
Chief Investigators (CIs)

3. Scope
This procedure applies to NHS GGC staff with sponsor responsibilities.

4. Purpose
The purpose of this Standard Operating Procedure is to outline how Investigator's Brochures (IBs) provided by partner organisations such as a pharmaceutical company, should be assessed for content and quality during set up and at each forthcoming update for clinical trials either sponsored or co-sponsored by NHS Greater Glasgow & Clyde (GG&C). This SOP should be read alongside SOP 55.005[1] and SOP 55.006[2]. This SOP does not cover development or review of an IB prepared by NHS GG&C or their co-sponsors.

5. Procedures

5.1 Background
All clinical trials must have a source document relating to the clinical use of the Investigational Medicinal Product (IMP). Where an IMP is an unlicensed medicine within the European Union (EU) member states, an IB may be the source document. Responsibility for provision of an IB for a drug that is at the pre-licensing or post-licensing stages is usually delegated via contractual responsibilities to the partner who owns the rights to the IMP. IBs require to be submitted to the MHRA for approval in their own right.

Where an IB has been used in support of a clinical trial sponsored by either the partner or by organisations other than NHS GG&C/GU the IB should have regulatory approval in place as it will usually have been submitted to the MHRA by the commercial pharmaceutical company for their own trials. Even if the IB already has regulatory approval, the IB must still be submitted by NHS GG&C as Sponsor to the MHRA for regulatory approval as part of the initial clinical trial application, for approval to use the appropriate section of the IB as the Reference Safety Information (RSI) for the study.

For any version of an IB which has not yet had regulatory approval, the Sponsor must submit on behalf - and with permission – of the partner organisation. There is therefore a risk that if the IB does not meet regulatory standards, it will not be approved and the entire CTA submission rejected. This can be costly both financially and in terms of delay to the study.

Therefore, whilst the final responsibility for the content of the IB will usually contractually lie with the partner, assessment and review by sponsor representatives may identify potential issues pre-submission.

5.2 IB content

The sections below delineate the minimum information that should be included in an IB and clearly defined when the Sponsor Pharmacist performs their review. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. The IB must include sufficient reference to relevant reports, literature etc to justify the statements provided. Before a review of an IB can be conducted, it is important that the structure and the purpose of the IB is understood. There are 6 main sections within the IB:

1. Summary – This should provide a high-level overview of all the subsequent sections, providing a profile of 'physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information'.

2. Introduction – This should provide a high-level overview of the IMP and the setting in which it is being investigated.

3. Physical, Chemical and Pharmaceutical Properties and Formulation - This is a brief section describing the chemical, physical, and pharmacological properties of the drug. This section should provide sufficient information on the investigational product so that potential risks associated with either the drug itself or any excipients can be assessed. This section should also provide information on storage and handling, including preparation steps needed prior to administration, such as reconstitution or dilution.

4. Non-clinical studies – This section provides the sole evidence upon which benefits and risks can be assessed before first administering the drug in humans.

5. Effects in humans – This section should summarise the results obtained in all clinical studies conducted with the drug to date. If the drug has already been marketed anywhere at the time of preparing the IB, then the post-marketing safety information obtained by the pharmaceutical company will also need to be summarised.

6. Summary of data and guidance for the investigator – This section is important for clinical trials of IMPs (CTIMPs) and it is here that the totality of the non-clinical and clinical experience is summarised and interpreted. The information contained in this section will be utilised for the use of the investigational drug in future clinical trials. The subheadings in this section of the IB are generally also used in prescribing information e.g. 'therapeutic indications', 'contraindications' and 'warnings and precautions for use'. This section should provide clear understanding of the possible risks and adverse reactions of the drug and of the specific tests, observations and precautions that may be needed for a clinical trial. This section will also include the 'Clinical Experience' of the IMP in licensed use, where relevant. Information from this section is usually also incorporated in to the protocol directly.

Reference Safety Information (RSI):

There should be a clearly defined section of the IB that contains the RSI. This location of the RSI section may vary between different IBs, particularly those that belong to different pharmaceutical companies. Often, it may be found in Section 5 or 6 or included as an appendix within the IB. This will be a list of serious adverse events derived from clinical trials where causality for that event has been attributed to the IMP. The RSI defines those serious adverse reactions that are considered expected for the IMP. The RSI should take the form of a table of Serious Adverse Reactions listed by system organ class and preferred terms followed by the frequency of those reactions. The RSI determines those Serious Adverse Reactions (SARs)

considered expected for the IMP and therefore not subject to expedited reporting to the MHRA. For products early in their development cycle this section may simply state that no SAEs are to be considered expected. Its purpose is **not** to clarify in one place all the safety information of the IMP for investigators.

5.3 Review of IB during clinical trial set-up

When a clinical trial is in set-up, a partner organisation will normally supply Sponsor with the current IB for the IMP. This is the IB that should be submitted with the Clinical Trial Authorisation (CTA) to the MHRA for approval to use as the RSI for the trial. The pharma company should confirm that this IB has regulatory approval (See SOP 21.017[3] if the IB does not have regulatory approval). The Sponsor Pharmacist will review the IB, paying particular attention to Section 6: Summary of data and guidance for the investigator. The information contained in the IB will guide the study drug content and clinical management of patients to be included and detailed in the study documents, including the protocol and Patient Information Sheet and unless adequately justified as part of the submission any restrictions in IMP use must be mirrored in the protocol etc. The Sponsor Pharmacist will review the following for inclusion:

- Dose/ Administration of study drugs. It must be clear what the dose, frequency/interval, maximum daily dose, methods of administration and safety monitoring procedures of the study drug are. For oral drugs, how should the drug be taken e.g. in fasted state or with a meal? Section 5 (Effects in Humans) of the IB should be checked for the 'effect of food' on the study IMP. For other methods of administration e.g. IV, is it clearly documented how the drug should be administered? It should also be clear what the maximum intended duration of treatment of the IMP is and its safety in repeated dosing, both as monotherapy and in combination with other drugs. Management of toxicity should be clearly defined and, where relevant, the management and symptoms of overdose. The use of the IMP in specific populations, such as extremes of age, pregnancy, hepatic impairment and renal impairment should also be clearly defined.

- Adverse Drug Reactions. Section 5/ Effects in humans should be reviewed for the adverse drug reactions. These need to be included in the 'side effects' section of the PIS where 'Very common' (will occur in more than 1 in 10 participants) and 'common' (will occur in up to 1 in 10 participants) side effects must be included, along with rarer but serious side effects. The information can often be found in the section on emerging safety profile and the associated table with the tabulated list of adverse drug reactions from clinical trials. This section should also include any rescue or preventative therapies that may be required for safety or tolerability purposes.

- Contra-indications – These can usually be found in Section 6/ Summary of data and guidance for the investigator of the IB and, where relevant, these must be included in the exclusion criteria of the study protocol.

- Warnings and precautions – Again, these can usually be found in Section 6/ Summary of data and guidance for the investigator of the IB. This information should be reviewed to ensure all pregnancy, lactation and contraceptive requirements are included in the protocol. The review should include:
    - Are hormonal methods of contraception permitted?
    - Are males required to use barrier contraception methods to prevent potential exposure to partners via semen?
    - How long after the last dose of study treatment should contraception be used by female and males?
    - Are contraception requirements in line with current CTFG guidance?
    - Is combined contraception required e.g. Highly effective methods such as oral combined contraception and barrier methods?

- Are males permitted or not to donate sperm while on study treatment?
- Are photosensitivity reactions expected?
- Will the IMP cause prolongation of the QT interval?
- All other relevant warning and precautions should be included in the protocol.

- Interactions with other drugs – The effect of the IMP on other medicines and the effects of other medicines on the IMP can usually be found in Section 6 / Summary of data and guidance for the investigator of the IB, with more detailed information provided in Section 5 / Effects in humans. The IB should provide clear guidance as to what concomitant meds are prohibited and what should be used with caution. The drug-drug interaction section in Section 6 / Summary of data and guidance for the investigator should be in line with the pharmacokinetics/drug metabolism/ clinical impact of drug-drug interaction data wording in Section 5.

The Sponsor Pharmacist and the relevant Pharmacovigilance Manager will review the following section to determine its suitability as per guidance issued by the clinical trial facilitation group[4]

- Reference Safety Information. The location of this can vary from IB to IB but it must be clearly defined. Where the product is used for multiple indications, then it may be more appropriate for the RSI to be divided into distinct cohorts.

Where provided to the sponsor, the Investigational Medicinal Product Dossier should be reviewed to ensure that information contain within is consistent with that in the IB. As with the IB, responsibility for preparation and submission of the IMPD for MHRA approval will generally be contracted to the partner organisation.

5.4 Review of IB at each update

The IB should be reviewed at least annually and each update should be reviewed in line with SOP 55.006[2]. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new clinical or safety information. If more than 12 months have passed since the last IB update, the Sponsor Pharmacist should request the IB update from the partner organisation. On receipt of the IB, it should be ascertained if regulatory approval has yet been granted for the updated IB. Otherwise, see SOP 21.017 [3].

The revised/ amended IB should have a new version number and date. It is imperative that a revision history, such as a 'Summary of Changes' section, has been included with the IB update. This may be included at the front of the IB or supplied as a separate document. Otherwise, this must be requested this from the pharma company. The Summary of Changes should also detail which changes are thought to be substantial and which are regarded as 'other changes'. It may be helpful to request a tracked version of the updated IB also particularly if the IB does not have regulatory approval as a tracked and clean version of the IB will be required to be submitted with the MHRA submission for approval in this scenario. The pharma company should also provide guidance along with the IB in order to state whether or not they think the updated IB should be submitted as a substantial amendment or not.

A review of the changes should be performed to ascertain which changes are relevant to the study. Attention should be paid to Section 6 (Summary of data and Guidance for the Investigator) in particular. Please see section 5.3 of this SOP for those sections which should be closely reviewed for any updates or changes. The implications of the updated IB for any changes to the protocol or the Patient Information Sheet must be considered. The changes should be assessed to see if consideration needs to be given to the re-consenting patients currently on treatment.

If the updated IB has changed the RSI of the study drug, then this IB will be submitted for approval to use as the RSI in the next DSUR reporting period. Please refer to SOP 55.005 for more detail.

On completion of the review of the updated IB, the relevant changes are collated for the Investigator who will then be requested to perform a review of the updated IB to assess if the risk-benefit of the study or clinical management of patients has changed with the update (see SOP 55.006[2])

5.5 IB review deems content not satisfactory

If the IB review is performed and not found to be of a sufficient quality to be approved by the MHRA e.g. RSI information does not follow CTFG Guidance or there are inconsistencies within the IB e.g. guidance regarding concomitant drug interactions in Section 6/ Summary of data and guidance for the investigator is not supported or consistent with IMP pharmacokinetic profile in Section 5 / Effects in humans, then the pharmaceutical partner must be informed. If it is thought that the IB will not receive regulatory approval in its current form, an amended IB should be requested from the partner. If the inconsistencies or errors are deemed not sufficient for an immediate update to the IB, the pharma partner should confirm that these will be addressed at the next IB update.

It is the responsibility of the pharma partner, who own the rights to the IMP, for the correct and accurate content of the IB.

6. Referenced documents

1. SOP 55.005 Management of Updates to Reference Safety Information V3.0
2. SOP 55.006 Management of IBs and SmPCs in CTIMPS V3.0
3. SOP 21.017 Regulatory Approval of IBs not submitted for Approval by Commercial Partner V1.0
4. Clinical Trial Facilitation Group (CTFG) Q&A document – Reference Safety Information. November 2017

7. Related documents

1. EUDRALEX Volume 10 Clinical trials guidelines http://ec.europa.eu/health/documents/eudralex/vol-10/ (Accessed 30.09.2020)
2. http://www.ct-toolkit.ac.uk/ (Accessed 30.09.2020)
3. Medicines and Healthcare products Regulatory Agency, Good Clinical Practice Guide, UK: TSO, 2012.
4. The Medicines for Human Use (Clinical Trials) Regulations (UK SI 1031) and amendments

8. Document History

Version	Date	Description
1.0	09/05/2022	First Release