BU RDS SOP 025 V1

Title: Investigator Brochure, Summary of Product Characteristics and Investigational Medicinal Product Dossier	
Effective Date: 19/11/2019	Review Date: 19/11/2021
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Approver: University Research Ethics Committee	

1. Scope

1.1 This Standard Operating Procedure (SOP) applies to all staff working on research studies using Medicinal Product(s) (MP), sponsored or co-sponsored by BU.

1.2 Research involving Medicinal Product(s) include:

Clinical Trials of Investigational Medicinal Products (CTIMPs) – these trials fall under the Medicines for Human Use (Clinical Trials) Regulations 2004, and any subsequent amendments to the guidelines.

Clinical Trials of Medicinal Product(s) (MP) – these do not fall under the above regulations.

1.3 The Summary of Product Characteristics (SmPC/SPC), Investigator Brochure (IB) and Investigational Medicinal Product Dossier (IMPD) are classed as 'regulatory documents', and as such, should contain the Reference Safety Information, used to assess adverse reactions (see BU RDS SOP 011).

2. Responsibilities

The *Chief Investigator (CI)/Researcher* in conjunction with the *Sponsor*, is responsible for preparing and updating the regulatory documents, as applicable to their trial.

3. Procedure

3.1 Definitions (*document structures may be found in the appendix*)

3.1.1 The *SmPC/SPC* is a legal document approved as part of the marketing authorisation of a medicine, therefore this document will only be provided for **licensed medications**, regardless of whether the study is a CTIMP or not. This document contains a definitive description of the product, covering its chemical, pharmacological and pharmaceutical properties, as well as how the product can be used for specific conditions and the benefits and risks of the medicine. The information within the SmPC/SPC is updated as new data becomes available, throughout the life-cycle of the product.

3.1.2 The *IB* is compiled of both clinical and non-clinical data on the Investigational Product(s) (IP), relevant to the study of the product(s) in human participants. This document will only be provided for **unlicensed medication**. The IB should support the justification for

the proposed clinical trial, and the safe use of the medicinal product(s). One of the main goals of the IB is to provide the Investigator with a clear understanding of any possible risks and adverse reactions that may arise from administering the Investigational Product (IP), as well as any specific tests or precautions etc. that may need to carried out for a clinical trial. This information is provided by demonstrating the previous results from any human experience of the IP, and by outlining the pharmacology, toxicology, physicality, chemistry and clinical information of the IP(s).

3.1.3 The *IMPD* is the document that gives information on the quality of the IP, *including placebo*, and also summarises information regarding the manufacturing and control of the IP. The IMPD is one of the documents required whenever a clinical trial is intended to run in one or more European Union Member States. (imp-dossier.eu, 2018)

3.2 The CI/Researcher, or appropriate delegate should prepare the applicable regulatory documents and should then submit to the Sponsor, (via Research Development & Support (RDS)), alongside all the other required documents seeking approval. Once the documents have been reviewed and validated, the CI/Researcher or delegate, should submit all the required documentation to the NHS Research Ethics Committee (REC), NHS Research & Development (R&D), Health Research Authority (HRA)[1] and Medicines and Healthcare products Regulatory Agency (MHRA) (if applicable), for their approval/authorisation.

3.3 Any correspondence from the above bodies should be forwarded to the Clinical Governance Advisor (CGA), RDS, for filing, and within the Sponsor's study file. Likewise, the approved regulatory documents and approval letter should be forwarded to other relevant parties (e.g., manufacturer, Clinical Trials Pharmacies, co-Investigators etc.).

3.4 In relation to point 3.2, the CI/Researcher should also forward revised documents to the Sponsor (via RDS) before submission for approvals. The documents will be reviewed and any changes requested, before confirming ongoing sponsorship of the study and giving the go ahead for submission to regulatory bodies. The correspondence for this process should be filed within the Trial Master File (TMF).

3.5 The CI/Researcher, or appropriate delegate should review the regulatory documents annually, at the very least. For studies with MHRA authorisation, this review should be done at the time as preparing the Development Safety Update Review (DSUR) (see BU RDS SOP 014). If there are no changes to be made, then this should be recorded in the DSUR. If there are changes to be made, then this will most likely require a substantial amendment (see BU RDS SOP 002).

3.6 For studies exempt from MHRA review, then the regulatory documents should be reviewed at the time of preparing the Annual Progress Report (APR). If there are no changes to be made, then this should be recorded in the TMF via file note. If updates are required, then this will most likely require a substantial amendment (see BU RDS SOP 002).

3.7 Despite the requirement for annual reporting, should any new information of significance be made available during outside of this reporting, then the research team should seek advice from the Sponsor.

[1] Please note, as of June 2018, HRA approval is now HRA and Health and Care Research Wales (HCRW) approval

4. Abbreviations and definitions

APR	Annual Progress Report
CGA	Clinical Governance Advisor
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSUR	Development Safety Update Review
HRA	Health Research Authority
IB	Investigator Brochure
IMPD	Investigational Medicinal Product Dossier
IP	Investigational Product
MHRA	Medicines and Healthcare products Regulatory Agency
MP	Medicinal Product
R&D	Research & Development (NHS Research Governance)
RDS	Research Development & Support
REC	Research Ethics Committee
SmPC/SPC	Summary of Product Characteristics
TMF	Trial Master File

5. Related documentation and references

BU RDS SOP 002 – Amendments

BU RDS SOP 011 – Safety Reporting

BU RDS SOP 014 – Study Progress Reporting

ema.europa.eu. (n.d.). [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/05/WC500127919.pdf [Accessed 20 Jun. 2018]

imp-dossier.eu. (2018). IMP Dossier. [online] Available at: http://www.imp-dossier.eu [Accessed 20 Jun. 2018]

imp-dossier.eu. (2018). IMP Dossier » IMPD Headings. [online] Available at: http://www.imp-dossier.eu/impd-headings/ [Accessed 20 Jun. 2018]

Appendix:

Document Structures

- The *SmPC/SPC* has a predefined structure (ema.europa.eu, n.d.), with cross-referencing to avoid duplicate information:

1. Name of the medicinal product	
2. Qualitative and quantitative composition	
3. Pharmaceutical form	
4. Clinical particulars	4.1 Therapeutic indications 4.2 Posology and method of administration 4.3 Contradictions 4.4 Special warnings and precautions for use 4.5 Interactions with other medicinal products and other forms of interaction 4.6 Fertility, pregnancy and lactation 4.7 Effects on ability to drive and use machines 4.8 Undesirable effects 2.9 Overdose
5. Pharmacological properties	5.1 Pharmacodynamic properties 5.2 Pharmacokinetic properties 5.3 Preclinical safety data
6. Pharmaceutical particulars	6.1 List of excipients 6.2 Incompatibilities 6.3 Shelf life 6.4 Special precautions for storage 6.5 Nature and contents of container 6.6 Special precautions for disposal and other handling of the product

- The *IB* likewise has a predefined structure (ich.org, 1996):

1. **Title page** – including the Sponsor's name, identity of the Investigation Product(s) (IP), release date, edition number and date of edition

2. **Confidentiality statement** – the IB is a confidential document intended for use by the Investigator's team and the REC

3. **Table of contents**

4. **Summary** – a brief summary should be included that highlights the available information surrounding the significant physical, chemical, pharmaceutical, toxicological, pharmacokinetic, metabolic and clinical information of the IP.

5. **Introduction** – an introductory statement should be provided, identifying the chemical name (and generic and trade name(s) once approved), of the IP, all its active ingredients, the IP's pharmacological class, and its expected position within this class (e.g. advantages), the justification for initiating the clinical trial investigating the IP(s), and the expected prophylactic, therapeutic, or diagnostic indication(s). The introductory statement should end on the general approach to be followed in assessing the IP.

6. **Physical, Chemical, and Pharmaceutical Properties and Formulation** – the IB should include a description of the IP's substances, including its chemical and/or structural formula(e), alongside a succinct summary outlining its relevant physical, chemical and pharmaceutical properties.
This section should likewise include a description of the formulation(s) to be used in the trial, including excipients, and any clinical justifications for use. This section should set out instructions for storage and handling and identify any structural similarities to other known compounds.

7. **Nonclinical Studies** – within this section there should be a summary of all the nonclinical studies carried out previously, to assess the pharmacology, toxicology, pharmacokinetic and metabolism of the IP. The summary should likewise acknowledge the methods used, the results, and discussion of the relevance of the findings from these studies to the IP, and any possible adverse and unintended effects in humans (see section 7.3.5 of the ICH Guideline for Good Clinical Practice for other applicable sections to include, referenced in section 5 of this SOP).

8. **Effects in Humans** – this section should provide the known effects of the IP(s) on humans, including information surrounding pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities. The section should likewise summarise each previous clinical trial, if possible, and also information regarding the results of the IP(s) from outputs other than clinical trials, e.g. marketing (see section 7.3.6 of the ICH Guideline for Good Clinical Practice for the specifics of each category of data referenced above (*pharmacokinetics to marketing, inclusive)*, referenced in section 5 of this SOP).

9. **Summary of Data and Guidance for the Investigator** – this section should provide an overall summary of the nonclinical and clinical data available, and likewise a summary of the information from various sources on the varying aspects of the IP(s), where available. By providing this information, the Investigator is provided with the most comprehensive interpretation of the available data, and any possible implications of the information for future clinical trials.

The appendix of the ICH Guideline for Good Clinical Practice lays out a template title page and table of contents for a model IB document.

- The *Investigational Medicinal Product Dossier* (IMPD) may use the following section headings; however this is not an obligatory format for the document. You can see the suggested section headings on the following link - http://www.imp-dossier.eu/impd-headings/