UCL

Standard Operating Procedure for creating and maintaining an Investigator's Brochure (IB) for UCL Developed Products

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Revision Chronology:			
SOP ID Number:	**Effective Date:**	**Reason for Change:**	**Author:**
JRO/SPON/S03/01	29/10/12	First version	Kim Champion
JRO/SPON/S03/02	30/10/15	Removal of reference to CTC as they now have their own SOP. Minor change of process evidencing IB review.	Kim Champion
JRO/SPON/S03/03	14/02/19	Revision Date Reached	Farhat Gilani

ACRONYMS:	
ATIMP	Advanced Therapy Investigational Medicinal Products
CI	Chief Investigator
CTC	Cancer Research UK & UCL Cancer Trials Centre (UCL affiliated Clinical Trials Unit)
CTIMPs	Clinical Trials of Investigational Medicinal Products
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IP	Intellectual Property
JRO	Joint Research Office http://www.ucl.ac.uk/jro/
MHRA	Medicines and Healthcare products Regulatory Agency
RM	Regulatory Manager
RSI	Reference Safety Information
SI	Statutory Instrument
SRA	Sponsor Regulatory Advisor
SOP	Standard Operating Procedure
TMF	Trial Master File
UCL	University College London

GLOSSARY	
UCL developed products	For the purpose of this SOP, UCL developed products refer to therapeutic agents developed by University College London (UCL) staff and manufactured in an UCL facility or on behalf of UCL.

Standard Operating Procedure for creating and maintaining an Investigator's Brochure

1. PURPOSE

This Standard Operating Procedure (SOP) describes the purpose, minimum content, creation and maintenance of an Investigator's Brochure (IB) for UCL developed products used in clinical trials of Investigational Medicinal Products (CTIMPs) sponsored by UCL and managed by the Joint Research Office (JRO)

2. JOINT RESEARCH OFFICE POLICY

All Joint Research Office (JRO) SOPs will be produced, reviewed and approved in accordance with the JRO SOP on SOPs.

The JRO acts as the representative of the Sponsor and will be the official name used on all SOPs.

3. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in Directives 2001/20/EC and 2005/28/EC (in the UK, these Directives were transposed into UK law by SI 2004/1031, SI 2006/1928) and subsequent amendments and when applicable Regulation 536/2014 and subsequent relevant SIs. Where applicable it incorporates elements of ICH GCP tripartite guidelines (E6).

The IB is a compilation of the clinical and non-clinical data on the Investigational Medicinal Products IMP(s) that are relevant to the study of the product(s) in human subjects as per Section 7.1 of ICH E6. The requirement for an IB is implemented into law through Article 2(g) of Directive 2001/20/EC and Article 8 of Directive 2005/28/EC in the European Union and Regulation 2 of SI 2004/1031 in the UK.

The amended Regulations (SI 2006/1928) state that the Sponsor of a clinical trial is responsible for the IB and shall ensure that the trial IB 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 shall validate and update the IB at least once a year.

The IB provides the investigators and others involved in the trial 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 study subjects during the course of the clinical trial.

The Detailed Guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3) declares that the IB contains the Reference Safety Information for the IMP against which the expectedness of an adverse reaction is determined.

4. SCOPE OF THIS SOP

This SOP relates to Investigational Medicinal Products (IMPs) developed by UCL, which are used as IMPs on trials sponsored by UCL.
This SOP does not apply to IMPs supplied to UCL for use in UCL clinical trials by drug suppliers other than UCL.

This SOP is applicable to Investigational Medicinal Products (IMP's) developed by UCL which do not have a marketing authorisation or are marketed products but being studied for a new indication.

5. RESPONSIBLE PERSONNEL

	Responsibility	**Undertaken by**	**Procedure**
5.1	Sponsor	JRO Clinical Trials Operations Manager	Assigning a responsible individual to ensure oversight of creation, regulatory approval and on-going maintenance of the IB, such as for example a JRO Sponsor Regulatory Advisor or Regulatory Manager (RM) (ATIMP).
5.2	Responsible individual (as per 5.1)	Chief Investigator (CI)	Creating and maintaining IB as per regulatory requirements and SOP, including the clinical sections of the IB. Reviewing the IB at least annually to ensure the clinical and non-clinical content of the IB is up-to-date and appropriate for the IMP in question. Provides clinical input for all reviews of the IB
5.3	Sponsor	Responsible individual (as per 5.1)	Coordinating internal reviews and sign off of the IB. Submitting the IB for regulatory approval (initial Clinical Trial Authorisation and amendments) as per applicable JRO SOP for approvals (**Associated SOP 1**) Distribution of the approved IB to applicable parties, such as to the CI or directly to the trial sites.

6. PROCEDURE

6.1	**Content of the IB**		
6.1.1	When drafting an IB refer to ICH GCP E6 (R2), section 7, for guidance on the minimum information that should be included in an IB and suggestions for its layout. See also **Associated Document 1** for guidance on information that should be included on the title page of an IB and for a suggested Table of Contents.		
6.1.2	In addition, for CTIMPs with Advanced Therapy Investigational Medicinal Products (ATIMPs) the following should be considered in relation to the content of the IB (as per European Commission Detailed guidelines on good clinical practice specific to advanced therapy medicinal products): (a) A description of the scope and sufficiency of existing information and its limitations; (b) Information obtained from on-going risk analysis based on existing knowledge of the type of product and its intended use including risk associated with the application method (e.g. surgery, concomitant medication, associated devices); (c) Information on the risk management plan (for marketed products); (d) Information on the risks due to product failure; (e) Information on the product safety handling, containment and disposal; (f) Information on short and long term safety issues particular to ATIMPs such as infections, immunogenicity/immunosuppression and malignant transformation as well as those related to medical devices for combined ATIMPs. Where necessary seek advice from the RM (ATIMP) and/or Pharmacovigilance Manager.		
6.2	**Review and finalisation of IB**		
	Responsibility	**Undertaken by**	**Procedure**
6.2.1	Sponsor	Responsible individual (as per 5.1)	Reviewing the IB to ensure inclusion of the required sections.
6.2.2	Responsible individual (as per 5.1)	JRO Pharmacovigilance Manager	Evidenced review of safety section of IB to ensure it contains expected side effects (RSI) and is appropriate with regards to SUSAR evaluation and Development Safety Update Report (DSUR) line listing evaluation. Acknowledgement, communication and filing of review as per JRO procedures. Note: Sufficient time must be allowed for review and for any requested changes to be made.
6.2.3	Responsible	Regulatory	Evidenced review of IB for CTIMPs with

	individual (as per 5.1)	Manager (ATIMP)	ATIMP to ensure the additional information as per section 6.1.2 has been appropriately addressed. Acknowledgement, communication and filing of review as per JRO procedures. Note: Sufficient time must be allowed for review and for any requested changes to be made.
6.2.4	Responsible individual (as per 5.1)	CI	Once the reviews are complete and the IB is finalized send to CI for signature.
6.2.5	Sponsor	Responsible individual (as per 5.1)	Submission of IB for Regulatory approval for use within the trial as per applicable JRO SOP for approvals (**Associated SOP 1**) Filing and distribution of the approved IB to applicable parties, such as to the CI or directly to the trial sites.
6.3	**Updates to IB**		
	Responsibility of	**Undertaken by**	**Procedure**
6.3.1	Responsible individual (as per 5.1)	CI	Annual review, and if applicable, revision of IB. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new clinical or safety information. However, in accordance with GCP, relevant new information may be so important that it should be communicated to the investigators, and possibly the Ethics Committee(s) and/or Regulatory Authority/ies before it is included in a revised IB. The timing of the annual review may be in line with the development International Birth Date (DIBD) of the IMP, since the IB is submitted to the MHRA as an Appendix alongside the DSUR. The revised/amended IB should be given a new version number and dated and must contain a revision history in either the IB or a separate summary of changes document indicating the changes that were made to the document.

			Where the review indicates there is no requirement to revise/amend the IB, the CI should sign a copy of the Annual Review of Investigator's Brochure form **Associated Document 2** and the IB version and date remains the same until next review.
6.3.2	Responsible individual (as per 5.1)	Pharmacovigilance Manager	Review of revised and amended safety sections of the IB before release of new version. Note: Sufficient time must be allowed for review and for any requested changes to be made.
6.3.3	Responsible individual (as per 5.1)	Regulatory Manager for Advanced Therapy Trials	For CTIMPS with ATIMP review of revised and amended IB before release of new version. Note: Sufficient time must be allowed for review and for any requested changes to be made.
6.3.4	Sponsor	Responsible individual (as per 5.1)	Evidence of all reviews (internal staff and CI) must be documented in the Trial Master File (TMF) and a copy/copies also filed in the Sponsor Trial File. Where the review indicates there is no requirement to revise/amend the IB the completed and signed **Associated Document 2** is filed in the TMF and a copy/copies also filed in the Sponsor Trial File.
6.3.5	Sponsor	Responsible individual (as per 5.1)	Submission of the revised and amended IB for regulatory and REC approval, as required. For further guidance see applicable JRO SOP for submissions of amendments (**Associated SOP 2**). Filing of the revised and amended IB in the TMF and also in the Sponsor Trial File. Only when approval from the MHRA and REC has been received - Distribution of the newly approved version IB to applicable parties, such as CI or directly to the trial sites can occur.

7. REFERENCES

https://www.ucl.ac.uk/jro

ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R2) (2016)

Directive 2001/20/EC OF the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No 1031), as amended.

COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

Detailed Guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3)

European Commission Detailed guidelines on good clinical practice specific to advanced therapy medicinal Products (ENTR/F/2/SF/dn D (2009) 35810)

8. ASSOCIATED SOPs

Associated SOP 1: JRO referenced SOPs for Regulatory Approvals

JRO	JRO/SPON/S29/ Standard Operating Procedure for Obtaining Research Ethics Committee and Clinical Trial Authorisation Approvals for Clinical Trials of Investigational Medicinal Products

Associated SOP 2: JRO/CTC/CTU referenced SOPs for Amendments

JRO	JRO/SPON/S13/ Standard Operating Procedure for the classification, review and submissions of clinical trial amendments

9. ASSOCITATED DOCUMENTS TO THIS SOP

Associated Document 1:	Guidance on information that should be included on the title page of an IB and a recommended Table of Contents for an IB.
Associated Document 2:	Annual Review of Investigator's Brochure form

10. SOP DISSEMINATION AND TRAINING

SOPs will be distributed to the relevant staff, by the named author on the front page of the SOP. Staff will sign the SOP training log (12. SOP Training Log) which is part of each SOP. The training will constitute of the person reading the SOP and being provided with the opportunity to ask specific questions to the author of the SOP.

11. SIGNATURE PAGE

Author and Job Title	Farhat Gilani, Clinical Trials Operations Manager
Signature:	
Date:	4/2/19
Authorised by: **Name and Job Title**	Helen Cadiou, Head of QA
Signature:	
Date:	04/02/19

12. SOP TRAINING LOG

	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	I confirm that I understand & agree to work to this SOP **SIGNATURE**	**Name of Trainer** (if training required)	**Signature**	**Date**
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	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	I confirm that I understand & agree to work to this SOP **SIGNATURE**	**Name of Trainer** (if training required)	**Signature**	**Date**
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