Creation & Maintenance of Investigator Brochure

POLICY DETAILS	
Document Type	Standard Operating Procedure
Document name	KHP-CTO/CT/SOP10.0 Creation & Maintenance of Investigator Brochure
Version	v5.0 03Apr24
Effective from	8th April 2024
Review date	3rd April 2027
Owner	King's Health Partners Clinical Trials Office
Originally Prepared by	Jackie Pullen, Clinical Quality Manager
Reviewed by	Amy Holton, Quality Manager
Approved by	Ann-Marie Murtagh, Interim Director KHP-CTO
Superseded documents	Creation & Maintenance of Investigator Brochure v4.2 24Mar23
Relevant regulations/legislation/guidelines	Statutory Instrument 2004 no 1031 Statutory Instrument 2006 no 1928

CHANGE HISTORY			
Date	Version Number	Change details	Approved by
04 February 2013	Final v 2.0	Change to reflect re-branding of JCTO to KHP-CTO	Jackie Powell
24 June 2013	Final v 3.0	Minor amendment to wording of section 4.4	Jackie Powell
31st October 2016	Final v 4.0	Update of Glossary and scheduled review	Jackie Pullen
24th October 2018	Final v 4.1	Minor amendment to include trials managed by KHP-CTO	Jackie Pullen
17th December 2019	Final v 4.1	Scheduled review, no changes required	Jackie Pullen
24th March 2023	Final v 4.2	Scheduled review, minor formatting change	Jackie Pullen
3rd April 2024	Final v5.0	Updated as per MHRA Inspection findings: IB contents, Reference Safety Information, IB updates	Ann-Marie Murtagh

Table of Contents

1.0 GLOSSARY

Clinical Trial - Any investigation in human subjects, other than a non-interventional trial intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal product or to identify any adverse reactions to one or more such products and to study absorption, distribution metabolism and excretion in one of more such products with the object of ascertaining the safety or efficacy of those products.

European Economic Area (EEA) – consists of the countries of the EU and additionally Iceland, Lichenstein and Norway. Countries that are Contracting parties to the EEA Agreement and are bound by the EU Clinical Trials Directive (EC/2001/EC).

Good Clinical Practice (GCP) - as defined in the Regulations.

Investigational Medicinal Products (IMP) - means a pharmaceutical form of an active substance or placebo being tested, or used as a reference in a clinical trial. This includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial –

(a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation,
(b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or
(c) used to gain further information about the form of that product as authorised under the authorisation

Investigator Brochure (IB) – is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in humans.

King's Health Partners (KHP) - King's Health Partners Academic Health Science Center is a pioneering collaboration between one of the King's College London (University) and three of London's most successful NHS Foundation Trusts – Guy's & St Thomas'. King's College Hospital and the South London & Maudsley.

King's Health Partners Clinical Trials Office (KHP-CTO) – Established in 2006 by Kings College London, Guy's & St Thomas' NHS Foundation Trust and King's College Hospital NHS Foundation Trust to provide a streamlined approach for all aspects of trial administration.

KHP-CTO Quality Team - Comprises the Clinical Quality Manager, Clinical Research Associate(s), Clinical Trial Administrator(s), Systems Executive, Training Executive(s) and Training Assistant.

KHP-CTO Standard Operating Procedures (SOPs) - "detailed, written instructions to achieve uniformity of the performance of a specific function," SOPs are the base on which Quality Systems and Processes are conducted and monitored against.

Medicines & Healthcare products Regulatory Agency (MHRA) - UK competent authority responsible for regulation of clinical trials.

Medical Dictionary for Regulatory Activities (MedDRA) - A clinically validated international medical terminology dictionary (and thesaurus) used by regulatory authorities for the purposes of adverse event classification.

Reference Safety Information (RSI) – Defines which reactions are expected for the Investigational Medicinal Product (IMP) being administered to subjects participating in a clinical trial.

The Regulations – The Medicines for Human Use (Clinical Trial) Regulations 2004, transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031. This became effective on the 1st May 2004**.** An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928. As amended from time to time.

2.0 BACKGROUND AND PURPOSE

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 Investigator's Brochure at least once a year.

The IB is the Reference Information Document which 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 purpose of this SOP is to describe when an IB is required, the minimum content required and when to update the IB.

3.0 SCOPE

All clinical trials of IMPs that do not have a marketing authorisation within the EEA and that are sponsored by one or more of King's Health Partner Organisations, or clinical trials where the sponsor responsibilities are managed by the KHP-CTO.

4.0 PROCEDURE

4.1 General Considerations

An IB will be produced for each IMP that does not hold a marketing authorisation in the UK or EEA. An IB can also be used for licenced products if the IMP(s) is being used outside its marketing application and the SmPC information is not suitable for the new indication or if one RSI is to be used across a global trial.

The IB will list the name of the Sponsor; and/or the organisation or individual who owns the Intellectual Property relating to the IMP and the identity of the IMP (i.e. research number or name.

The IB will be version controlled.

4.2 Version Control

Each copy of the IB will be version controlled *(see Version Control Guideline in Related Documents section 6.1).*

Example 1

Edition Number: Copy Number:
Release Date:

Replaces Previous Edition Number:
Date:

4.3 Contents

Please refer to ICH GCP E6 (R1), section 7, for guidance on the minimum information that should be included in an IB and suggestions for its layout. The RSI section is to follow CTFG guidelines. The IB should contain the following sections, each with literature references where appropriate:

4.3.1 Table of Contents

(See suggested example IB Table of Contents in Related Templates section 5.1).

4.3.2 Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

4.3.3 Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product'(s') pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

4.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.
To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given. Any structural similarities to other known compounds should be mentioned.

4.3.5 Nonclinical Studies

Introduction:
The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
    - Nature and frequency of pharmacological or toxic effects
    - Severity or intensity of pharmacological or toxic effects
    - Time to onset of effects
    - Reversibility of effects
    - Duration of effects
    - Dose response

- Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

a. Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

b. Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

c. Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g., irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

4.3.6 Effects in Humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from clinical trials, such as from experience during marketing.

a. Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

b. Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a clear, separate section called the "Reference Safety Information" (see section 4.3.8).

c. Marketing Experience

The IB should identify countries where the IMP has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

4.3.7 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the Investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the Investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical Investigator on

the recognition and treatment of possible overdose and adverse drug reactions that are based on previous human experience and on the pharmacology of the investigational product.

A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

4.3.8 Reference Safety Information

. The Reference Safety Information (RSI) is used for the assessment of expectedness of all 'suspected' serious adverse reactions (SARs) that occur in clinical trials. Therefore, the RSI is a list of expected serious adverse reactions, which are classified using Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA).

The content of the RSI should include a clear list of 'expected SARs' to the IMP(s). The list of expected SARs should be based on 'suspected' SARs that were previously observed more than once, with reasonable evidence that a causal relationship exists between the event and IMP; and not based on what might be anticipated from the pharmacological properties of a medicinal product or the compound class.

The RSI should include the nature, frequency, and severity of the expected SARs.
Fatal and life threatening SARs should not be considered expected for IMPs, unless supported by a positive benefit-risk balance. Thus, Fatal and life-threatening SARs should usually be considered unexpected even if previous fatal and life-threatening SARs have occurred.

The RSI should be presented in the form of a table, where the nature of the 'expected SARs' must be listed by body system organ class and using MedDRA preferred terms (PTs), followed by the frequency and severity, which must be calculated on an aggregated level and based on previously observed 'suspected' SARs to the IMP.

If the IMP is under development in different medical conditions, separate tables of expected SARs by indication may be appropriate, if the expected SARs are different e.g. for oncology conditions and non-oncology diseases.

If there are no suspected SARs for the product, a clearly defined section of the IB called RSI should still be present, followed by a brief text stating that no SARs are considered expected by the sponsor for the purpose of expedited reporting and identification of SUSARs in the DSUR for the IMP.

4.4 IB Updates

The IB for each IMP will be reviewed and validated at least once a year.

If the IB is updated with new information, this **may** result in a substantial amendment to the regulatory competent authorities where the trial is being conducted. If the RSI section within the IB is amended this will **always** result in a substantial amendment. However, changes to the format of the table that do not affect the expected SARs or slight modification of exposure rates

that do not result in a change in the category of frequency without the addition of new expected SARs and/or new PTs classification are not considered substantial.

When information in the IB is updated, a new version/edition will be required. If updated and submitted as a substantial amendment, the new RSI version is to be implemented on the date of regulatory approval. The newly updated RSI can only be used for assessment of expectedness of 'suspected' SARs for the purposes of expedited reporting after the approval of the substantial amendments in all regions where trial(s) is ongoing. Thus, if additional SUSARs occur before the new RSI is approved, these should be reported as SUSARs in the usual expedited manner.

If no changes or updates are required or available, a statement signed by the CI stating this fact will be filed in the Trial Master File. An updated version/edition of the IB is not necessary if the information has not changed.

4.5 IB Tracking

Investigator Brochures are controlled documents and as such, their circulation must be tracked and receipted to ensure that all Investigators and recipients are in possession of the latest and most up to date version. The KHP-CTO IB receipt may be used to track this circulation in multi-centre studies.

5.0 RELATED TEMPLATES

5.1 IB Table of Contents *(suggested example)*

5.2 IB Receipt template

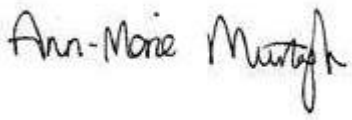
6.0 RELATED DOCUMENTS

6.1 Version control guideline

6.2 https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf

6.3 ICH GCP E6 (R1), section 7

7.0 APPROVAL and SIGNATURE



03/04/2024

Ann-Marie Murtagh
Interim Director
King's Health Partners Clinical Trials Office

Date