Investigator’s Brochure (IB) TEMPLATE

***(Version 2.0, 02-Mar-2022)***

**Guidance Notes for UCL JRO IB Template**

This IB template should be used to draft an IB for a Clinical Trial of an Investigational Medicinal Product (CTIMP) or Advanced Therapy Investigational Medicinal Product (ATIMP).

The IB should contain a summary compilation of the clinical and non-clinical data relating to an Investigational Medicinal Products (IMP) which are relevant to the study of the product in human subjects.

This template is written in line with the minimum information stipulated in Section 7 of ICH GCP (E2), refer to this guidance for more information:

<https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf>

In addition, for CTIMPs with Advanced Therapy Investigational Medicinal Products (ATIMPs) refer to European Commission Detailed guidelines on good clinical practice specific to advanced therapy medicinal products:

<https://ec.europa.eu/health/system/files/2019-10/atmp_guidelines_en_0.pdf>

Ensure information provided in the ‘Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions’ section is compliant with the Clinical Trial Facilitation Group (CTFG) Q&A document – Reference Safety Information (Nov 2017):

<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>

**General notes on using the IB template:**

The IB must be consistent with the trial protocol, IRAS form, Clinical Trial Authorisation (CTA) application, and any other relevant trial documentation, and should be cross checked prior to finalisation. The JRO will carry-out a review of the draft IB and provide advice and guidance prior to approval.

1. **Text in blue is guidance and/or instruction and should be deleted once addressed**
2. **Suggested text given in red should be included/adapted/expanded/amended if appropriate (otherwise this can be deleted)**
3. **Section names given in black should not be amended**

**Guidance notes on Style and Formatting:**

1. Abbreviations should be written in full on first appearance and a list of abbreviations should be included in the Abbreviations section of the IB.
2. Use bullet point lists or tables where appropriate rather than long passages of prose

**Logos** - please ensure all appropriate and relevant logos are added to the front page, and that bodies represented have agreed to the use of their logo.

**This covering page should be deleted once the IB has been drafted.**

Investigator’s Brochure

*Add Clinical Trial Logo (if applicable)*

**IMP Name/Number:**

**EudraCT / ISRCTN Number:**

**Sponsor: University College London**

**Sponsor Project ID Number:**

**Effective Date:**

**Version Number:**

This IB should be reviewed at least annually. More frequent revision may be appropriate depending on the stage of development and/or the generation of relevant new clinical or safety information.

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Signature page

**Chief Investigator Name:**

|  |  |  |
| --- | --- | --- |
| **Signature** |  | **Date** |

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ABBREVIATIONS

Define all unusual or ‘technical’ terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE Adverse Event

ADR Adverse Drug Reaction

ATIMP Advanced Therapy Investigational Medicinal Product

CI Chief Investigator

CTCAE Common Terminology Criteria for Adverse Events

CTIMP Clinical Trial of Investigational Medicinal Product

FTIM First Time in Man

GLP Good Laboratory Practice

IB Investigator’s Brochure

IMP Investigational Medicinal Product

IMPD Investigational Medicinal Product Dossier

MedDRA Medical Dictionary for Regulatory Activities

RSI Reference Safety Information

SAR Serious Adverse Reaction

SODA Summary of Drug Arrangements

SUSAR Suspected Unexpected Serious Adverse Reaction

IB VERSION HISTORY

|  |  |  |
| --- | --- | --- |
| **Version Number** | **Version Date** | **Reasons for Update** |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

# 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.*

# INTRODUCTION

*The Introduction should aim to provide a high-level overview of the IMP and the setting in which it is being investigated.*

*Briefly state the IMP chemical name, generic name (if approved) and trade name (if approved). List the active ingredients and confirm which pharmacological class the IMP is in. Briefly discuss its expected position within this class (i.e., the advantages it is expected to have over other products in that class).*

*Identify the anticipated prophylactic, therapeutic or diagnostic indication(s) that the IMP is being developed to address.*

*Briefly discuss the rationale for performing research with the IMP,* *identifying anticipated prophylactic, therapeutic, or diagnostic indications. Provide information on the general approach to be followed in developing/evaluating the IMP.*

*If appropriate, discuss other treatment options.*

# PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION

*This is a brief section describing 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.*

*The section should aim to provide the investigator with 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 of the dosage form(s).*

## Physical, Chemical and Pharmaceutical Properties

*Describe the IMP substance. Briefly describe the physical and chemical properties of the product, and give a brief summary of the relevant pharmaceutical properties.*

## Formulation Including Excipients

*Describe the formulation to be used including the excipients. Justify the use of this formula if clinically relevant. Provide information on structural similarities to other known compounds.*

## Storage and Handling

*Provide instructions for the storage and handling of the IMP in its dosage form.*

# NON-CLINICAL STUDIES

*The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. The study design and animal species or tests systems used should be stated. When a large number of non-clinical studies are available, it can be beneficial to provide the details of each study in a tabulated format, often in an Appendix, and then provide focused summaries of results and interpretations, supported by tables and figures, within the non-clinical section.*

*This section includes the results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies in a summary form. Examples of the information are:*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *Species tested* | *Number/ sex of animals per group* | *Unit dose* | *Dose interval* | *Route of administration* | *Duration of dosing* | *Duration of post-exposure follow-up* |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *Type of Study* | *Construct(s)* | *Test System* | *Administration Method* | *No./Group/Dose(s)* | *GLP Compliance* | *Testing Facility* |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

*Discuss the results of these studies including the following information:*

* *Nature and frequency of pharmacological or toxic effects.*
* *Severity or intensity of pharmacological effects.*
* *Time to onset of effects.*
* *Reversibility of effects.*
* *Duration of effects.*
* *Dose response.*

*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 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.*

## Non-clinical Test Material

*State what material was used in the non-clinical studies and what form that material took.*

## Good Laboratory Practice

*Specify which studies were conducted to GLP. Where studies have not been conducted to GLP explain the justification for this and whether the studies were conducted in the spirit of the principles of GLP/GLP like conditions.*

## Non-clinical Pharmacology

### Non-clinical Pharmacology Studies Performed

*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)).*

### 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.*

*Biodistribution and vector shedding studies may be discussed in this section.*

## 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 Toxicology Studies

### Repeated Dose Toxicology Studies

### Carcinogenicity Studies

### Reproductive and Developmental Toxicity

### Genotoxicity (mutagenicity) studies

### Other Toxicity Studies

# EFFECTS IN HUMANS

*This section should include a thorough discussion of the effects of the Investigational Medicinal Product in humans. A summary of each completed clinical trial should be provided as well as any additional information obtained through alternative methods e.g., experience during marketing.*

*If clinical data from studies with similar products is relevant the data can be presented in this section.*

*ICH E6 specifies that information should be summarised on the ‘pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities’.*

*This section may be very brief if this is a First Trial in Man (FTIM) trial with little clinical data available.*

## Clinical Overview

*Provide a summary of clinical studies conducted to date (if applicable)*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *Title / reference* | *Product* | *Dose range and route of administration* | *No. of subjects* | *Sponsor / study Identifier* | *Safety summary* |
|  |  |  |  |  |  |

## Clinical Studies Conducted with IMP/ATIMP

### Pharmacokinetics and Product Metabolism in Humans

* + *Summary of metabolism, absorption, plasma protein binding, distribution and elimination.*
  + *Bioavailability of the IMP (absolute and/or relative).*
  + *Differences in pharmacokinetic profile in population subgroups such as the elderly, renal impairment etc.*
  + *The effect of food on the pharmacokinetic profile.*
  + *The effect of other drugs on the pharmacokinetic profile. It is particularly important to investigate drugs known to affect the cytochrome P450 (CYP) pathway as well as drugs commonly co-prescribed for the condition being investigated.*

### Safety and Efficacy

* + *Summary of the safety profile of the IMP and its metabolites.*
  + *Pharmacodynamics profile of the IMP and its metabolites.*
  + *Summary of the efficacy of the IMP and its metabolites.*
  + *Dose response summary.*
  + *Tables to summarise adverse drug reactions (ADRs).*
  + *Discuss the important differences in ADR incidence and patterns across subgroups or indications.*
  + *Describe the possible risks and anticipated ADRs in future studies based on the current experience with the IMP.*
  + *Describe any precautions that should be taken or special clinical monitoring that should be performed.*

### Marketing Experience

* *List those countries where regulatory approval has been granted or rejected. List those countries where the IMP is currently being marketed and has been withdrawn from the market. Discuss any additional information gained through the marketing process. 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.*

*If there have been no clinical studies conducted to date with the ATIMP/IMP state….*

There have been no clinical trials with [name of product] to date.

## Existing Clinical Data from Other Clinical Studies

*Where there is little or no clinical experience with the IMP this section can be included to add any data available from other relevant clinical studies using a similar IMP/ATIMP. Provide details on the IMP/ATIMP and how it differs from the IMP to be tested.*

# SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

*For first-time-in-man IBs, state that no data are available on the relationship of AEs to administration of the IMP, because no studies have yet been conducted in human subjects. For IMPs in early phase development, state that limited data are available on the relationship of AEs to administration of the IMP, because clinical experience is limited. In this case, state that the guidance for the investigator is based on non-clinical data and on the results of any Phase I/II studies.*

*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 IMP. 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.*

*This section should include risks related to the IMP, as well as critical raw materials, excipients, conditioning regime, procedures related to the IMP and its administration.*

*The following subheadings may be helpful, but do not all need to be included if not relevant.*

## Summary of pre-clinical and clinical data

## Dosage and Method of Administration

## Special Warnings and Special Precautions for Use

*Please state:*

[Name of product] is intended for investigational use only by selected Investigators familiar with information in this Investigator’s Brochure and experienced in conducting clinical studies.

## Interactions

## Use during Pregnancy and Lactation

## Undesirable Effects

*Detail significant known and potential risks with the product and discuss how this is being mitigated.*

*For ATIMPs the following should be included:*

* *risks associated with the administration procedure and/or upstream interventions on subjects, and information on short and long-term safety issues particular to ATIMPs such as infections, immunogenicity/immunosuppression and malignant transformation.*
* *Where appropriate, information should be provided in the IB on the measures that should be put in place to protect clinical trial subjects from identified risks.*

## Overdose

*Include any guidance to the clinical investigator on the recognition and treatment of possible overdose that is based on previous human experience and on the pharmacology of the investigational product.*

*Possible wording for First Time In Man (FTIM) Trial….*

No data from clinical studies are available regarding overdose of [name of product].

## Drug Abuse and Dependency

*Possible wording for FTIM Trial….*

No studies have been conducted to evaluate the potential for abuse and dependence. Based on the mechanism of action and pharmacological activity, however, there is no evidence to suggest that [name of product] has potential for abuse or dependence.

## Use and Handling

*For ATIMPs provide information on the product safety handling, containment and disposal. It is acceptable that detailed instructions are laid down in a separate document available at the site (e.g. handling instructions and/or pharmacy instructions), which can be attached as Annex to the IB.*

*The reconstitution of the ATIMP (where applicable) should be described. It is acceptable that the detailed instructions are laid down in a separate document available at the site (e.g. handling instructions and/or pharmacy instructions), which can be attached as Annex to the IB.*

*Example of wording for GM material…*

This IMP contains genetically-modified material. Local biosafety guidelines applicable for gene therapy products should be followed. Instructions for the preparation of the infusion solutions will be provided in the IMP management plan.

## Reference Safety Information (RSI) for Assessment of Expectedness of Serious Adverse Reactions

* *This safety section should contain a clear list or table of expected serious adverse reactions (SARs) indicating severity and frequency for each listed SAR. The expected SARs should be listed using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms or Common Terminology Criteria for Adverse Events [CTCAE] terms.*
* *This section should be limited to expected SARs only. All observed adverse reactions including non-serious adverse reactions, suspected SARs that have occurred only once, and fatal and life-threatening SARs that are considered unexpected should not be included in this section but described in the Summary of data and guidance for the investigator section.*
* *Example Expected Serious Adverse Reactions tables shown below.*
* *The frequency of adverse reactions reported as in the table below are derived from previous clinical trials and are defined using the following convention: very common (>1/10), common (> 1/100 to <1/10), uncommon (> 1/1,000 to <1/100), rare (> 1/10,000 to <1/1,000), very rare (< 1/10,000) not known. Use this convention where sufficient numbers of subjects have been exposed to the IMP/ATIMP.*
* *During the early stages of product development, the number of observed ‘suspected SARs’ for each ‘expected SAR’ should be provided, together with the number of patients exposed, see example below:*

Table of Serious Adverse Reactions for [Product Name] considered expected for safety reporting purposes.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *System Organ Class (SOC)* | *SARs* | *Number of subjects exposed (n) = 328* | | |
| *All SARs* | *Occurrence of fatal SARs* | *Occurrence of life-threatening SARs* |
| *n\* (%)* | *n (%)* | *n (%)* |
| *Gastro-intestinal disorders* | *Diarrhoea* | *25 (7.6)* | *0 (0.0)* | *0 (0.0)* |
| *Hepatobiliary disorders* | *ALT increase* | *12 (3.6)* | *0 (0.0)* | *0 (0.0)* |
| *AST increase* | *9 (2.7)* | *0 (0.0)* | *0 (0.0)* |
| *Cardio vascular disorders* | *Myocarditis* | *33 (10.0)* | *0 (0.0)* | *2 (0.6)* |

*n = number of subjects who have experienced the SAR*

*If there are expected life-threatening or fatal SARs listed in this RSI section, the number of suspected life-threatening and fatal suspected SARs that have occurred should be included as in the table above.*

*Where there are no expected SARs listed, please state:*

No SARs are considered expected by the sponsor for the purpose of expedited reporting of SUSARs and identification of SUSARs in the “Cumulative summary tabulation of serious adverse reactions” in the DSUR for the IMP [Product Name].

## Other Potentially Clinically Relevant Information for the Investigator

# References