INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

**Clinical electronic Structured Harmonised Protocol**

**(CeSHarP)**

**M11 Template**

Draft version

Endorsed on day/month/year

*Currently under public consultation*

*At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.*

**M11 Template**

**Document History**

|  |  |  |
| --- | --- | --- |
| **Code** | **History** | **Date** |
| M11 | Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation (document dated day/month/year). | day/month/year |

**Interventional Clinical Trial Protocol Template**

**0** **Foreword**

**0.1 Template Revision History**

| **Date** | **Description of Revision** |
| --- | --- |
| (To be determined) | Initial template |

**0.2 Intended Use of Template**

This template is intended for interventional clinical trials. The template is suitable for all phases and therapeutic areas of clinical research. Interventional trials may include but are not limited to human pharmacology, exploratory, confirmatory and post-approval studies. The template is designed to enable modification suitable for the particular trial. Refer to the sections below for additional details and conventions related to flexibility.

Existing ICH Guidelines were considered in its development. Where guidelines are cited, please refer to the most current version.

As a reminder, protocols often become public through transparency requirements in various regions/countries.

**0.3 Template Conventions and General Instructions**

**Text Structure and Flexibility**

This template uses the typefaces described in the table below to distinguish between their intended use and applicability. Use of consistent font sizes throughout the document is recommended, but not required.

| **Type of Text (Applicability)** | **Typeface Details** | **Description (Intended Use)** |
| --- | --- | --- |
| Universal text | Black Times New Roman font | Text (including headings) that should appear in all protocols |
| Conditional universal text | Black Times New Roman font in {braces} | Text that should appear in all protocols if applicable to trial. In some cases, a choice between options. |
| Optional text | Blue Arial font  Restyle to Black Times New Roman for final document | Text (including optional headings) that may be modified, deleted, or replaced according to the specific aspects of the trial |
| Controlled terminology | [Square brackets] in the prevailing typeface with grey shading  Populate field from available choices, or with free text if indicated; remove brackets and restyle text to match other text in the final document | Brackets with grey shading are used to indicate variable text modelled as a field in the electronic manifestation of the protocols |
| Text insertion point | <Chevrons> in the prevailing typeface with grey shading | Chevrons are used to indicate where to insert text. Any text within chevrons is intended to be replaced by applicable content. |

**Heading Structure and Flexibility**

This template uses the typefaces and numbering conventions described in the table below to distinguish between heading levels. To ensure consistency and predictability for all readers, the heading numbering conventions should be strictly observed. However, **fonts, font sizes, and colour are not intended to be fixed requirements**, and can be adapted as specific situations may dictate, or per country or regional requirements.

| **Example Heading** | **Heading Level** | **Typeface in this Template** | **Modification or Deletion** | **Addition** |
| --- | --- | --- | --- | --- |
| **1** | **LEVEL 1 (L1)** | 14 point Times New Roman Bold Black  ALL CAPS | **Do not delete or modify** L1 or L2 headings  Retain heading and indicate “Not Applicable” | **Do not add** L1 Headings |
| **1.1** | Level 2 (L2) | 14 point Times New Roman Bold Black | Add L2 headings, if needed, at the end of the higher-level section to preserve the established L1 and L2 heading structure |
| **1.1.1** | Level 3 (L3) | 12 point Times New Roman Bold Black | **Do not delete or modify** L3 headings that appear in black text  Retain heading and indicate “Not Applicable”  L3 headings that appear in blue text are optional and may be retained, deleted or modified as applicable to the study. | Add L3 headings, if needed, at the end of the higher-level section to preserve the established L1, L2 and L3 heading structure |
| **1.1.1.1** | Level 4 (L4) | Delete heading or modify as needed | Insert where needed |
| **Additional Non-Numbered Heading** | Non-numbered heading |

**Table and Figure Numbering**

Tables and figures should be numbered and include a title or caption, respectively. No numbering convention is specified by this template, but a consistent approach should be applied throughout the document.

Page orientation can be modified from portrait to landscape as needed.

**Word Usage in Template**

The following word usages have been selected for use within this template and are considered to be appropriate for all phases, trial populations, and therapeutic areas:

* Because the scope of this protocol template is focused on interventional clinical trials, the term clinical trials is used rather than clinical studies when referring to interventional clinical trials.
* Participant is used rather than subject, healthy volunteer, or patient when referring to an individual who has consented or was adequately/legally represented to participate in the clinical trial. Patient or individual is used to distinguish the population represented by the trial participants, when necessary.
* Trial intervention refers to any therapeutic, prophylactic, or diagnostic agent including pharmaceuticals, biologics, vaccines, cell or gene therapy products (when applicable), and drug-device combination products when registered as a drug. Trial interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices or other interventions intended for the participants during the trial. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.
* While blinding is the more commonly used term, masking is an alternative term which may be used in certain situations.

**Suggestions for Finalising Document:**

Various formatting, typefaces, and instructional elements are used in this template to inform preparation activities, but these should not appear in final protocols. Specific recommended steps for finalisation are as follows:

* Delete Section 0 and all its contents
* Update the Table of Contents (TOC).
* Confirm that the Level 1, Level 2 and Level 3 headings are visible in the navigation pane or bookmark view.
* Delete unneeded or non-applicable optional Level 3 or lower headings and ensure remaining Level 3 and lower headings are numbered appropriately
* Delete any unused optional text, unused text insertion points and related prompts
* Restyle any optional text to match the regular text
* Remove all instructional text, and
* Remove brackets after making appropriate selections.

**0.4 Abbreviations Used in this Template**

| **Abbreviation or Acronym** | **Definition** |
| --- | --- |
| AE | Adverse Event |
| AESI | Adverse Events of Special Interest |
| AxMP | Auxiliary Medicinal Product |
| COAs | Clinical Outcome Assessment(s) |
| CRF | Case Report Form |
| DREs | Disease-Related Events |
| ECG | Electrocardiogram |
| EU | European Union |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials Database |
| IB | Investigator’s Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IDE | Investigational Device Exemption |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IxRS | Interactive Response System where x refers to modality |
| jRCT | Japan Registry of Clinical Trials |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N/A | Not Applicable |
| NCT | National Clinical Trial |
| NIMP | Non-Investigational Medicinal Product or Auxiliary Medicinal Product |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| SAE | Serious Adverse Event |
| SoA | Schedule of Activities |
| TOC | Table of Contents |
| WHO | World Health Organization |

**This is the end of the instructional section, and the protocol content begins with the next page.**

|  |  |
| --- | --- |
| The order of the title page elements should be preserved. | |
| **Sponsor Confidentiality Statement:** | <Enter Sponsor Confidentiality Statement>  Insert the Sponsor’s confidentiality statement, if applicable, otherwise delete. |
| **Full Title:** | <Enter Full Title>  The protocol should have a descriptive title that identifies the scientific aspects of the trial sufficiently to ensure it is immediately evident what the trial is investigating and on whom, and to allow retrieval from literature or internet searches. |
| **Trial Acronym:** | <Enter Trial Acronym>  Acronym or abbreviation used publicly to identify the clinical trial, if any. Delete this line from the table if not applicable. |
| **Sponsor Protocol Identifier:** | <Enter Sponsor Protocol Identifier>  A unique alphanumeric identifier for the trial, designated by the Sponsor, is a standard part of trial data, and should be included for most trials. |
| **Original Protocol:** | [Yes/No] |
| **Version Number:** | <Enter Version Number>  An optional field for use by the Sponsor at their discretion. |
| **Version Date:** | <Enter Version Date>  An optional field for use by the Sponsor at their discretion. |
| **Amendment Identifier:** | {[Amendment Identifier]}  Enter the amendment identifier (e.g., amendment number). If this is the original instance of the protocol, leave blank. |
| **Amendment Scope:** | {[Amendment Scope]} {[Country Identifier] or [Region Identifier] or <Enter Site Identifier>}  Leave blank for original protocol.  If an amendment applies to all sites in the trial, enter “global” and delete the Country, Region and Site Identifier fields. If amending a single-country study, enter “global”.  If the amendment does not apply to all sites in the trial, select “Not Global” and utilize one of the identifiers based on amendment scope. Use the ISO-3166 region or country identifier (for example, DE or EU). |
| **Compound Code(s):** | <Enter Compound Code(s)>  Enter the Sponsor’s unique identifier for investigational compound(s) in the trial. Add fields as needed. |
| **Compound Name(s):** | <Enter Nonproprietary Name(s)>  <Enter Proprietary Name(s)>  Omit nonproprietary name fields if a nonproprietary name has not yet been assigned. Omit proprietary name fields if not yet established. |
| **Trial Phase:** | [Trial Phase] {<Enter Description of Trial Phase Other>}  For trials combining investigational drugs or vaccines with devices, classify according to the phase of drug development. |
| **Short Title:** | <Enter Trial Short Title>  Short title should convey in plain language what the trial is about and is suitable for use as “Brief Title” or “Title in Plain Language” in global clinical trial registries. It can also be suitable for use with informed consents and ethics committee submissions. |
| **Sponsor Name and Address:** | <Enter Sponsor Name>  <Enter Sponsor Legal Address>  <Enter Co-Sponsor Name>  <Enter Co-Sponsor Legal Address>  Provide the legal name of the individual or pharmaceutical or medical device company, governmental agency, academic institution, private organisation, or other organisation who takes primary responsibility for and initiates a clinical investigation. If more than one Sponsor, list the Primary Sponsor in this field.  Local Sponsor Name and Address:  <Enter Local Sponsor Name>  <Enter Local Sponsor Address>  In some countries, the clinical trial Sponsor may be the local affiliate company (or designee). In such cases, indicate in the Sponsor Local Name and Address Field. |
| **Manufacturer Name and Address:** | <Enter Device Manufacturer Name>  <Enter Device Manufacturer Address>  Manufacturer name and address information is required only for protocols that include investigational device(s) and should not be included for other protocols. Include the manufacturer address only if the manufacturer is different than the Sponsor listed above.  Add additional fields as needed if multiple investigational devices will be used in the trial. Delete this line if not applicable. |
| **Regulatory Agency Identifier Number(s):** | <EU CT Number>  <IDE Number>  <FDA IND Number>  <jRCT Number>  <NCT Number>  <NMPA IND Number>  <WHO/UTN Number>  <Other Regulatory Agency Identifier Number>  Include all numbers that are applicable for the trial and available at the time of protocol or amendment finalisation. Delete prompts for numbers not available at the time of document finalisation. Delete unused fields. Add fields for “other” if more than one is needed. |
| **Sponsor Approval:** | [<Enter Approval Date> or <State location where information can be found>]  All versions should be uniquely identifiable. Use the CDISC date format (dd/mmm/yyyy, for example 07/JUN/2015) to indicate the date the protocol (or amendment) was approved by the Sponsor. |

Sponsor Signatory:

Include either the sponsor signature or the statement below.

[{<Enter sponsor signature block (name and title of sponsor signatory and signature date)>}

or

{This protocol was approved via <describe method>.}]

**Medical Expert Contact:** <Enter contact information for Medical Expert (as designated by sponsor) orstate location where information can be found>

**SAE Reporting Method:** Report Serious Adverse Events to the sponsor <Enter SAE reporting method(s)> Refer to Section 9.4 for detailed reporting instructions.

Amendment Details

Choose the applicable statement below. For an original protocol that has not been amended, retain the first sentence below and delete the remainder of this entire section.

{Not applicable. This protocol has not been amended.}

Or include the below as applicable.

{This protocol has been amended previously. Details of prior amendments are presented in Prior Protocol Amendment(s).}

{Current Amendment}

The table below describes the current amendment.

|  |  |  |  |
| --- | --- | --- | --- |
| **Approximate <#/%> Enrolled at time of Sponsor Approval:** | Approximate <#/%> enrolled <Globally/Locally/Cohort>  Enter the approximate number or percentage of participants enrolled as a percentage of the expected total. If the number of expected participants is changing as a result of the current amendment, use the updated number of expected participants to estimate the current percent of enrollment. Estimates are adequate, as precise enrollment figures will likely be changing while an amendment is being prepared.   * For a global or single-country amendment, provide the estimated total enrollment at the time of the Sponsor approved the amendment. * For global amendments providing (consolidating?) only country/region-specific requirements, list approximate local enrollment total or percentage at the time of the amendment and select “locally”. * If consolidating a series of local amendments, the status of all the relevant locations can be listed   For a country/regional amendment, provide the estimated local or regional enrollment at the time the Sponsor approved the amendment. | | |
| **{Reason(s) for Amendment:}** | Primary: {[Primary Reason for Amendment] or <Enter “Original”>} \* | | Secondary: {[Secondary Reason for Amendment] or <Enter “Original”>}\* |
| **{Amendment Summary:}** | <Amendment Summary>  Describe key changes briefly. Changes which are included in the amendment but unrelated to the key changes do not need to be described here. | | |
| {Is this amendment likely to have a substantial impact on the safety or rights of the participants?} | | [Yes/No]  {If yes, briefly explain} | |
| {Is this amendment likely to have a substantial impact on the reliability and robustness of the data generated in the clinical trial?} | | [Yes/No]  {If yes, briefly explain} | |

\* Choose from the available categories as the primary reason and secondary reason(s) for the amendment. Select the closest match among the choices. Changes to primary estimand, endpoints, or related measures should be listed as a change of strategy. If none of the choices apply, choose “other” and provide a description. If no secondary reason, indicate “not applicable” for the secondary reason.

**{Overview of Changes in the Current Amendment:}**

Instructions for the Overview of Changes.

* If an Overview of Changes already exists from a prior amendment, move it to Section 12.3, Prior Protocol Amendment(s), and populate a clean overview table for the current amendment.
* List the changes that apply to the current amendment. Provide a brief description of the change(s) and a concise scientific rationale for specific changes (for example, change to individual inclusion/exclusion criteria).
* If the same change affects multiple parts of the protocol, it is acceptable to list multiple locations in the right column.
* Table can be sorted in any order preferred by the sponsor.
* Minor edits such as clarifications and corrections to typographical errors do not need to be itemized in this table.
* The changes in the table do not need to be detailed in revision marks, as these can be provided in a separate supporting document.
* Tabular presentation is common but not required. The page can be changed to landscape orientation if necessary.

| {Description of Change} | {Brief Rationale for Change} | {Section # and Name} |
| --- | --- | --- |
| <Enter Description of Amendment Change> | <Enter Rationale for Amendment Change> | <Enter Section of Amendment Change> |
| <Enter Description of Amendment Change> | <Enter Rationale for Amendment Change> | <Enter Section of Amendment Change> |
| <Enter Description of Amendment Change> | <Enter Rationale for Amendment Change> | <Enter Section of Amendment Change> |

(Add lines as needed)

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1. Protocol Summary

No text is intended here (header only).

* 1. Protocol Synopsis

The protocol synopsis is a short summary of the key points of the trial. In order to keep the synopsis brief, cross-references to full details in the main body of the protocol are acceptable.

No text is intended here (header only).

* + 1. Primary and Secondary Objectives and Estimands

Summarize the primary and secondary objectives and any associated estimands. Consider including a copy of the table describing the estimands from Section 3 of the protocol and follow all the same instructions.

<Enter Primary and Secondary Objectives and Estimands>

* + 1. Overall Design

Key aspects of the trial design are summarised below.

|  |  |  |  |
| --- | --- | --- | --- |
| **Intervention Model:** | [intervention model] | **Population Type:** | [population type] |
| **Control Type:** | [control type] | **Population Diagnosis or Condition:** | [population diagnosis or condition] |
| **Control Description:** | {[Nonproprietary name] or [INN] or <Enter “N/A”>} | **Population Age:** | Minimum: <numeric> [units of age] Maximum: <numeric> [units of age] |
| **Intervention Assignment Method:** | [intervention assignment method] | **Site Distribution and Geographic Scope:** | [site distribution] [site geographic scope] |
| **Adaptive Trial Design:** | [Yes/No]  {If Yes: [Adaptive Trial Design Type]} | **Master Protocol Design:** | [Yes/No]  {If Yes: [Master Study, Sub-Study]} |
| **Drug/Device Combination Product Indicator:** | [Yes/No] |  |  |

Further clarification:

* Control description - if active comparator or low dose, pick nonproprietary name or International Nonproprietary Name, indicate N/A if not applicable
* Intervention assignment method - Do NOT state block size.
* Population Diagnosis or Condition - SNOMED or MedDRA
* Population age range - For trials in which multiple age ranges may be eligible (for example, a younger cohort and an older cohort), indicate the minimum and maximum ages for the trial overall, with an additional comment for any excluded age ranges.

**Number of Arms:** [Number of Arms]

Enter the numeric value for the number of arms in the trial. For trials with a different number of arms in different periods, populate this field based on the total number of arms.

**Trial Blind Schema:** [Trial Blind Schema]

For designs in which these details may differ in one or more trial periods, answer according to the portion of the trial in which the highest number of blinded roles occurs. More details can be provided in Section 6.8.3 of the protocol.

**Blinded roles:** The following roles indicated will not be made aware of the treatment group assignment during the trial: [blinded roles]

“Not applicable (No blinding)” indicates an open-label trial.

**Number of Participants:**

State the expected number of participants to be assigned to trial intervention/enrolled. Indicate whether the number provided is the target or maximum number of individuals to be randomly assigned to trial intervention/enrolled.

A [Target/ Maximum] of <Enter Number of Participants> participants will be [randomly assigned to trial intervention/ enrolled].

**Duration**

Select one of the two options for total planned duration of trial intervention and trial participation for each participant. Note that the total duration of trial participation should include any washout and any follow-up periods in which the participant is not receiving trial intervention. When duration will vary, provide a short explanation (for example, “event-driven” or “adaptive design”.

Total planned duration of trial intervention for each participant:

{<Enter number> [unit of time]}

or

{<Enter alternate description of planned duration of trial intervention if duration will vary>}

Total planned duration of trial participation for each participant:

{<Enter number> [unit of time]}

or

{<Enter alternate description of planned duration of trial participation if duration will vary>}

If necessary, include any clarifications or cross-references to detail in the main body of the protocol in the optional field below.

<Enter Additional Description of Duration>

**Committees:**

Indicate whether any committee(s) will be reviewing data while the trial is ongoing, and the type of committee. Common examples include Data Monitoring Committee, Dose Escalation Committee, or Endpoint Adjudication Committee; describe others, if applicable. List independent committees in the space indicated. Other committees may be included in the separate space provided. Committees listed here should be fully described in Section 11.4.

Independent Committees: <Enter Independent Committees>

Indicate “N/A” if no independent committees will be involved in the trial.

{Other Committees: <Enter Other Committees>}

Delete “Other Committees” if not applicable.

* 1. Trial Schema

The purpose of this section is to provide a visual depiction of the trial design, orienting users of the protocol to the key features of the design. The schema depicts the trial arms, the flow of individual participants through the progression of trial period(s)/epochs (such as screening, washout/run-in, intervention, and key milestones [for example, randomisation, cross-over, end of treatment, end of study, post-treatment follow-up]). For complex trials, additional schemas may be added to describe activities or trial periods in greater detail.

<Enter Trial Schema>

<Enter Schema Notes>

* 1. Schedule of Activities

The schedule of activities must capture the procedures that will be accomplished at each trial visit, and all contact with participants, for example, telephone contacts. This includes any tests that are used for eligibility, participant randomisation or stratification, or decisions on trial intervention discontinuation. Allowable windows should be stated for all visits and procedures. A tabular format is recommended.

When applicable for studies with extensive sampling, for example serial PK sampling, a separate table may be added.

<Enter Schedule of Activities>

1. Introduction

No text is intended here (header only).

* 1. Purpose of Trial

Explain why the trial is needed, and why the research questions being asked are important. Do not restate the objectives or estimands. Do not restate the IB, but may cross-reference to the IB as applicable to the description.

<Enter Purpose of Trial>

* 1. Summary of Benefits and Risks

Include an assessment of known and potential risks and benefits, if any, from the perspective of an individual participant, including the basis of the risk (for example, nonclinical studies or prior clinical trials). Optional level 3 subheadings are provided to assist with organization of the section; alternatively, the section may be summarized in a single section utilizing the overall benefit-risk entry point.

* + 1. Benefit Summary

The benefit summary should describe any physical, psychological, social, or any other potential benefits to individual participants as a result of participating in the trial, addressing immediate potential benefits and/or long-range potential benefits. Clearly state if no benefits to an individual participant can be anticipated, or if potential benefits are unknown. For early clinical trials such as Phase 1, benefits for an individual participant (other than those of altruism) are expected to be minimal.

Benefits to society in general may also be included but should be described separately from the individual participant perspective.

<Enter Benefit Summary>

* + 1. Risk Summary and Mitigation Strategy

**Trial Intervention** – Describe risks related to trial-specific treatments and interventions. For the protocol, focus on the relevant key risks for THIS trial. Provide a brief description of strategies to mitigate identified risks or provide a cross-reference to the relevant protocol section.

<Enter Trial-specific Intervention Risks and Mitigations>

**Trial Procedures** – Consider risks associated with the design (for example, placebo arm) and procedures specific to THIS trial (for example, biopsies), and any measures to control or mitigate the risks. Provide a brief description of strategies to mitigate identified risks or provide a cross-reference to the relevant protocol section. This is not intended to be an exhaustive list of all possible risks associated with trial procedures but should focus on the unique risks inherent in the design or less common or high-risk procedures. As above, provide a brief description of strategies to mitigate identified risks or provide a cross-reference to the relevant protocol section.

<Enter Trial-specific Procedure Risks and Mitigations>

**Other** – Consider risks associated with other items (for example, challenge agents, imaging agents, medical devices). This could include discussion of risk mitigation for special populations, if not described elsewhere. Insert a line for each, as needed.

<Enter Trial-specific Other Risks and Mitigations>

* + 1. Overall Benefit:Risk Conclusion

Provide a succinct, concluding statement on the perceived balance between risks that have been identified from cumulative safety data, protocol procedures, and anticipated efficacy/benefits within the context of the proposed trial.

<Enter Overall Benefit:Risk Conclusion>

1. Trial Objectives and aSSOCIATED Estimands

In this section, precisely define each trial objective and refine each trial objective into a precise clinical question of interest by defining the associated estimand. For considerations on estimands, see ICH E9(R1). Ensure alignment with every other section of the protocol.

Include additional level 2 headers (e.g. for secondary objective(s) and associated estimands) as needed.

No text is intended here (header only).

* 1. Primary Objective(s) and Associated Estimand(s)

For all trials, precisely state each primary trial objective by providing a meaningful and concise description of the treatment effect of interest using natural, non-technical language for clear understanding of sponsors, investigators, clinical site personnel, trial participants, ethics committees, and regulators.

For trials intended to estimate a treatment effect or test a hypothesis related to a treatment effect, use the table to precisely describe the associated estimand(s). This includes specification of the target population, the treatment condition(s), the endpoint (or variable), the population-level summary, and each intercurrent event and the associated strategy for handling it. For other types of trials not intended to estimate a treatment effect or test a hypothesis related to a treatment effect, describe additional information relevant to the clinical question(s) of interest (e.g., the endpoint(s) associated with each objective). For these trials, including the table is not required.

| **Estimand Characteristic** | **Description** |
| --- | --- |
| **{Population}** | List of key characteristics, such as demographic characteristics (e.g., age, sex) and clinical characteristics (e.g., prior therapies, symptoms, severity, biomarker status)  {<Enter Population>} |
| **{Treatment}** | List of key aspects of treatment regimens in each study group, including at least investigational agents, dosage, and administration route  {<Enter Treatment>} |
| **{Endpoint}** | Definition of the endpoint  {<Enter Endpoint>} |
| **{Population-Level Summary}** | Description of the population-level summary (e.g., mean difference, relative risk)  {<Enter Population Level Summary>} |
| **{Intercurrent Event}** | **{Strategy}** |
| {<Enter Description of Intercurrent Event 1>} | Description of the strategy to address the intercurrent event (e.g., a treatment policy strategy); cross-reference the justification in Section 4  {<Enter Intercurrent Event 1 Strategy>} |
| {<Enter Description of Intercurrent Event 2>} | Description of the strategy to address the intercurrent event (e.g., a treatment policy strategy); cross-reference the justification in Section 4  {<Enter Intercurrent Event 2 Strategy>} |

* + 1. {Primary Objective}

<Enter Primary Objective>

{<Enter Table of Estimand Characteristics>} or {<Enter Estimand Characteristics Relevant to the Objective>}

* 1. Secondary Objective(s) and Associated Estimand(s)

Describe the secondary objective(s) and associated estimand(s) as outlined in Section 3.1. Use the same approach as above and consider including a table for a precise estimand description.

<Enter Secondary Estimand Description>

* + 1. {Secondary Objective}

{<Enter Secondary Objective>}

{<Enter Table of Estimand Characteristics>} or {<Enter Estimand Characteristics Relevant to the Objective>}

* 1. Exploratory Objective(s)

State each exploratory objective. This should generally include documentation of associated exploratory endpoints. It may be helpful in some cases to describe precise estimands to provide clarity on what is being estimated.

* + 1. {Exploratory Objective}

{<Enter Exploratory Objective>}

{<Enter Endpoint>} or {<Enter Table of Estimand Characteristics>} or {<Enter Estimand Characteristics Relevant to the Objective>}

1. Trial Design

No text is intended here (header only).

In the sub-sections below describe the trial design with specific mention, as applicable, of the components of an adequate and well-controlled trial and reflect the principles of Quality by Design. The description of the design should be concise and consistent with Section 1.1, Protocol Synopsis and Section 1.2, Trial Schema. The trial design should align with objectives/estimand(s) described in Section 3.

This section is intended to provide a description for the important aspects of the trial design and rationale for its key attributes. Operational details needed to implement the trial design should be covered in more detail in subsequent sections.

* 1. Description of Trial Design

Describe the trial intervention model (for example, single group, parallel group, cross-over, factorial, sequential), the expected number of participants, and the control method (for example, placebo, active comparator, low dose, historical, standard of care, sham procedure, or none [uncontrolled]). If there are any key aspects of the investigational trial intervention that inform the selection of intervention model, this should be described.

If applicable, indicate other design characteristics (for example, superiority, non-inferiority, dose escalation, or equivalence).

If the trial will have an adaptive or novel design (for example, the trial will be conducted under a master protocol), provide a summary of these design aspects.

If applicable, describe within-trial transition rules, for example, transitions involving cohorts or trial parts. Dose escalation or dose-ranging details should also be described.

<Enter Description of Intervention Model>

Describe the trial duration with reference to Section 1.2, Trial Schema. Explain what the overall duration for an individual participant is anticipated to be and why, including the sequence and duration of trial periods (for example, screening, run-in, randomisation, treatment [fixed dose/titration], follow-up/washout periods). Where applicable, include discussion of sentinel dosing (or lack thereof), dose escalation, and cohort expansion. If dose modification decisions are dependent upon review by a committee, include details in Section 11.4, Committees.

<Enter Description of Trial Duration>

State the method of assignment to trial intervention the level and method of blinding that will be used with reference to Section 6.8.

<Enter Method of Assignment to Trial Intervention>

<Enter Description of Level of Blinding and Method of Blinding>

Describe any other important aspects of the design, for example:

* Geographic scope of trial (for example, single-centre, multi-centre, or multi-centre and multi-national)
* Use of decentralised processes, tools, or features in the trial
* Planned use of a Data Monitoring Committee, or similar review group and cross-reference Section 11.4, Committees, for details,
* Whether an interim analysis is planned and, if so, refer to details in Section 10.9, Interim Analysis, and/or
* Any planned extension trial, long-term follow-up/registry, planned future use of samples or data, or post-trial sample analysis or other data-related activities.

<Enter Additional Description of Trial Design>

Or

<Enter Overall Description of Trial Design> if not using above optional subheadings.

* + 1. Stakeholder Input into Design

If applicable, describe any stakeholder (for example, patient, healthcare professional and patient advocacy groups) involvement in the design of the trial and any suggestions implemented.

<Enter Stakeholder Input into Design>

* 1. Rationale for Trial Design
     1. Rationale for Intervention Model

Provide a rationale for the trial intervention model described in Section 4.1, Description of Trial Design with a cross-reference to Section 6.3, Rationale for Investigational Intervention Dose and Regimen. Rationale for choice of comparator, if applicable, should be described separately in Section 4.2.5, Rationale for Control Type. A rationale for the choice of trial population should be described separately in Section 5.1, Description of Trial Population and Rationale.

<Enter Rationale for Intervention Model >

* + 1. Rationale for Duration

Provide a rationale that the trial duration is appropriate for a reliable and relevant evaluation of the trial intervention per the trial objective(s).

<Enter Rationale for Duration>

* + 1. Rationale for Estimands

When estimands are applicable, provide a rationale for those associated with the Primary and Secondary Objectives described in Section 3. This should include a rationale that the selected endpoint(s) are clinically relevant and provide a reliable and valid measurement of the intended intervention effect. It should also include a rationale for the selected strategies for handling intercurrent events.

<Enter Rationale for Estimands>

* + 1. Rationale for Interim Analysis

If applicable, provide a rationale for any interim analysis planned with respect to its purpose (for example, stopping the trial early for efficacy or futility) and timing.

<Enter Rationale for Interim Analysis>

* + 1. Rationale for Control Type

If applicable, provide a rationale for the type and choice of control selected for the trial (for example, placebo, active drug, combination, historical). Describe any known or potential problems associated with the control group selected in light of the specific disease and intervention(s) being studied. If comparators will differ by region, describe. The rationale for dose/dose regimen is explained in Section 6.3.

<Enter Rationale for Control Type>

* + 1. Rationale for Adaptive or Novel Trial Design

If applicable, provide a rationale for the use of an adaptive or novel design.

<Enter Rationale for Adaptive or Novel Design>

* + 1. Rationale for Other Trial Design Aspects

Discuss rationale for any additional aspects of the design not addressed above.

<Enter Rationale for Other Design Aspects>

Or

<Enter Overall Rationale for Trial Design> if not using above optional subheadings.

* 1. Trial Stopping Rules

If applicable, describe any trial-specific stopping rules, including guidance on when the trial should be stopped for efficacy or safety reasons, when a cohort or dose escalation should be terminated, and/or when a given treatment arm should be terminated. If applicable, describe any rules that may result in a temporary pause of dosing and/or enrollment into the trial and criteria for restarting enrollment. Ensure that the trial stopping rules are aligned with the specifications that are described in Section 10.9 for Interim Analyses.

<Enter Trial Stopping Rules>

* 1. Start of Trial and End of Trial

Define key timepoints in the trial, including trial start and end timepoint definitions. For example, a key timepoint definition for start of trial might be when the informed consent is signed by the first participant and a key timepoint definition for end of trial might be when participants are no longer being examined or the last participant’s last trial assessment has occurred. If applicable, consider local regulatory requirements for these and other definitions (for example, the first act of recruitment).

If appropriate, provide a cross-reference to Section 11.10

<Enter Start of Trial>

<Enter End of Trial>

* 1. Access to Trial Intervention After End of Trial

If applicable, describe any possibilities for access to trial intervention, if any, beyond completion of the trial. Planned extension trials, if described above in Section 4.1 do not need to be repeated.

<Enter Access to Trial Intervention after End of Trial>

1. Trial Population

No text is intended here (header only).

In the sub-sections below, describe the trial population: inclusion and exclusion criteria, contraception requirements and lifestyle restrictions. The trial population should generally be aligned with the population attribute of the primary estimand that was defined in Section 3. Consider the following when developing participant eligibility criteria to be listed in Section 5.2, Inclusion Criteria, and Section 5.3, Exclusion Criteria.

* List the criteria necessary for participation in the trial. Ensure that each criterion can be easily assessed definitively and answered with yes/no responses.
* Criteria should be written to avoid protocol waivers or exemptions.
* If participants require screening, distinguish between screening vs enrolling participants.
* Identify specific laboratory tests or clinical characteristics that will be used as criteria for inclusion or exclusion. If permitting existing medical diagnosis, imaging, genetic tests, or laboratory results, state any required window or acceptable test type.
* If measures to enrich the trial population for pre-specified subgroups of interest are used, these should be described.
  1. Description of Trial Population and Rationale

Describe the population selected (for example, healthy participants, adult participants, paediatric participants) and how the enrollment criteria reflect the populations that are likely to use the drug if approved. Specify the population age range (for example, ≤3 months, ≥18 to ≤80 years old) including the time point at which qualification for age criteria is determined (for example, at time of screening vs randomization for paediatric trials). Specify any key diagnostic criteria for the population (for example, “acute lung injury”, or a specific biomarker profile). If applicable, describe similar conditions or diseases and their differential diagnosis. If the target population is based on a subset of the entire trial population defined by a particular characteristic measured at baseline (e.g., a specific biomarker), this subset should be defined and justified in this section.

Provide a rationale for the trial population ensuring that the population selected is well defined and clinically recognisable. Describe how the selected population can meet the trial objectives and how the enrollment criteria reflects the targeted populations.

Justify whether the trial intervention is to be evaluated in paediatric participants, in adults unable to consent for themselves, other vulnerable participant populations, or those that may respond to the trial intervention differently (for example, elderly, hepatic or renally impaired, or immunocompromised participants).

<Enter Description of Trial Population and Rationale>

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

* 1. Inclusion Criteria

Inclusion criteria are characteristics that define the trial population, for example, those criteria that every potential participant must satisfy, to qualify for trial entry.

To be eligible to participate in this trial, an individual must meet all the following criteria:

* <Inclusion Criterion>
* <Inclusion Criterion>

Add criteria as needed. Number the criteria sequentially.

* 1. Exclusion Criteria

Exclusion criteria are characteristics that make an individual ineligible for participation.

An individual who meets any of the following criteria will be excluded from participation in this trial:

* <Exclusion Criterion>
* <Exclusion Criterion>

Add criteria as needed. Number the criteria sequentially.

* 1. Contraception

No text is intended here (header only).

* + 1. Definitions Related to Childbearing Potential

Specify the definitions of:

* Participant of childbearing potential
* Participant of non-childbearing potential

<Enter Definitions Related to Childbearing Potential or state Not Applicable>

* + 1. Contraception Requirements

Specify the:

* Contraceptive methods required
* Duration of use

<Enter Contraception Requirements or state Not Applicable.>

* 1. Lifestyle Restrictions

In the following subsections, describe any restrictions during the trial pertaining to lifestyle and/or diet, intake of caffeine, alcohol, or tobacco, or physical and other activities. If not applicable, include a statement that no restrictions are required.

{<Enter Lifestyle Restrictions>}

* + 1. Meals and Dietary Restrictions

If applicable, describe any restrictions on diet (for example, food and drink restrictions, timing of meals relative to dosing).

<Enter Meals and Dietary Restrictions>

* + 1. Caffeine, Alcohol, Tobacco, and Other Restrictions

If applicable, describe any restrictions on the intake of caffeine, alcohol, tobacco, or other restrictions.

<Enter Caffeine, Alcohol, Tobacco, and Other Restrictions>

* + 1. Physical Activity Restrictions

If applicable, describe any restrictions on activity (for example, in first-in-human trials, activity may be restricted by ensuring participants remain in bed for 4 to 6 hours after dosing).

<Enter Physical Activity Restrictions>

* + 1. Other Activity Restrictions

If applicable, describe restrictions on any other activity (for example, blood or tissue donation, driving, heavy machinery use, or sun exposure).

<Enter Other Activity Restrictions>

* 1. Screen Failure and Rescreening

Describe screen failure and indicate how screen failure will be handled in the trial, including conditions and criteria upon which rescreening is acceptable. If applicable, indicate the circumstances and time window under which a repeat procedure is allowed for screen failure relating to specific inclusion/exclusion criteria for the trial.

<Enter Screen Failure>

<Enter Rescreening>

1. Trial Intervention And Concomitant Therapy

No text is intended here (header only).

Trial interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices or other interventions intended for the participants during the trial.

Any regional requirements should be noted in the appropriate sub-sections.

* 1. Overview of Trial Interventions

Table of Trial Interventions

| **Arm Name** | **Arm Type** | **Intervention Name** | **Intervention Type** | **Dose Formulation** | **Unit Dose Strength(s)** | **Dosage Level(s)** | **Route of Administration** | **Regimen/‌Treatment Period/‌Vaccination Regimen** | **Use** | **IMP/NIMP**  **(AxMP)** | **Sourcing** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| <Enter Arm Name> | [Select Arm Type] | Enter Intervention Name | [Select Intervention Type] | [Select Dose Formulation] | <Enter Unit Dose Strength(s)> | <Enter Dosage Level(s)> | [Select Route of Administration] | <Enter Regimen/Treatment Period/Vaccination Regimen> | [Select Use] | [Select IMP or NIMP/AxMP] | [Select Sourcing] |

IMP=investigational medicinal product; NIMP/AxMP=non-investigational/auxiliary medicinal product.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

* 1. Description of Investigational Trial Intervention

The investigational trial intervention is the product used in the trial as part of trial objectives. Other trial interventions that are not part of trial objectives (not an investigational role in this trial) are described in Section 6.10 Description of Non-investigational trial interventions. For IMP, NIMP, AxMP designations based on local legislation, please refer to Table of Trial Interventions above.

Describe the investigational trial intervention to be administered in each arm of the trial and for each period of the trial including route and mode of administration, dose, dosage regimen, duration of intervention, use, packaging and labelling.

Refer to approved regional labelling, as appropriate.

For drug/device combination products, include details on the configuration and use of the device and device manufacturer. A device user manual may be referenced in this section.

<Enter Description of Investigational Trial Intervention>

<Enter Additional Text, if Needed>

* 1. Rationale for Investigational Trial Intervention Dose and Regimen

Provide a rationale for the selection of the dose(s) or dose range, pharmaceutical dose form, the route of administration, and dosing regimen of the investigational trial intervention, as applicable. This rationale should include relevant results from previous nonclinical studies and clinical trials that support selection of the dose and regimen. Discuss impact of differences in study population characteristics (for example, age, sex and/or race) which could lead to differences in pharmacokinetics and pharmacodynamics in this study as compared to previous studies. If applicable, justify any differences in dose regimen or therapeutic use relative to approved labelling. Describe prior trials and other information that support the dose and/or dose regimen of the investigational intervention.

Include a rationale for prospective dose adjustments incorporated in the trial, if any.

<Enter Rationale for Investigational Trial Intervention Dose and Regimen>

* 1. Investigational Trial Intervention Administration

Describe the detailed procedures for administration of each participant’s dose of each investigational trial intervention. This may include the timing of dosing (for example, time of day, interval), the duration (for example, the length of time participants will be administered the investigational trial intervention), and the timing of dosing relative to meals.

Include any specific instructions to trial participants about when or how to prepare and take the dose(s) and how delayed or missed doses should be handled.

Dose escalation or cohort expansion as part of the overall design should be covered in Section 4.1 Description of Trial Design.

<Enter Investigational Trial Intervention Administration>

* 1. Investigational Trial Intervention Dose Modification

For each participant, describe any dose modifications allowed, including conditions for such dose modifications, particularly regarding failure to respond or safety concerns. State any minimum period required before a participant’s dose might be raised to the next higher dose or dose range. Include whether it is permissible to start and stop treatment and how dose reductions (if permitted) are to be managed.

Information on stopping investigational trial intervention for participants due to safety/other reasons should be detailed in Section 7 Participant Discontinuation of Trial Intervention and Discontinuation or Withdrawal from Trial.

<Enter Investigational Trial Intervention Dose Modification>

* 1. Management of Investigational Trial Intervention Overdose

Describe what is meant by investigational trial intervention overdose. Provide any available information on managing the overdose and ensure it is consistent with the Investigator’s Brochure or product labelling. Cross-references these documents as applicable.

<Enter Management of Investigational Trial Intervention Overdose>

* 1. Preparation, Storage, Handling and Accountability of Investigational Trial Intervention(s)

No text is intended here (header only).

* + 1. Preparation of Investigational Trial Intervention(s)

Describe any preparation of the investigational trial intervention, and when necessary, by whom. When applicable, describe the maximum hold time once thawed/mixed before administration. Include thawing, diluting, mixing, and reconstitution/preparation instructions. For drug/device combination products, include any relevant assembly or use instructions and reference the package insert that is provided separately.

If the instructions are lengthy or complicated, it is acceptable to reference the package insert (if applicable) or include instructions in a separate document(s) provided to the site (for example, a pharmacy manual). If the latter, reference the separate documents.

<Enter Preparation of Investigational Trial Intervention >

* + 1. Storage and Handling of Investigational Trial Intervention

Describe storage and handling requirements (for example, protection from light, temperature, humidity) for the investigational trial intervention(s). For trials in which multi-dose vials are utilised, provide additional information regarding stability and expiration time after initial use (for example, the seal is broken).

State how the investigational trial intervention(s) will be provided to the Investigator. If applicable, describe the kits, packaging, or other material of the investigational trial intervention for blinding purposes.

If the instructions are lengthy or complicated, it is acceptable to reference the package insert (if applicable) or include instructions in a separate document(s) provided to the site (for example, a pharmacy manual). If the latter, reference the separate documents.

<Enter Storage and Handling of Investigational Trial Intervention>

* + 1. Accountability of Investigational Trial Intervention

Describe the accountability method, including how the investigational trial intervention will be distributed and related details, including:

* how and by whom the investigational trial intervention will be distributed
* participation of a drug storage repository or pharmacy, if applicable,
* plans for disposal or return of unused product,
* if applicable, plans for reconciliation of investigational trial intervention.

<Enter Accountability of Investigational Trial Intervention>

* 1. Investigational Trial Intervention Assignment, Randomisation and Blinding

No text is intended here (header only).

* + 1. Participant Assignment to Investigational Trial Intervention

Describe the method of assigning participants to investigational trial intervention without being so specific that blinding or randomisation might be compromised. If assignment to investigational trial intervention is by randomisation, describe when randomisation occurs relative to screening. State that at enrollment, participant identification codes should be assigned.

If adaptive randomisation or other methods of covariate balancing/minimisation are employed, include a cross-reference to the methods of analysis in Section 10 Statistical Considerations. As applicable, details regarding the implementation of procedures to minimise bias should be described.

<Enter Participant Assignment to Investigational Trial Intervention>

* + 1. {Randomisation}

Describe the randomisation procedures (for example, central randomisation procedures), the method used to generate the randomisation schedule (for example, computer generated), the source of the randomisation schedule (for example, sponsor, investigator, or other), and whether IxRS will be used. To maintain the integrity of the blinding, do not include the block size.

{<Enter Randomisation>}

* + 1. {Blinding}

Describe efforts to ensure that the investigational trial intervention(s) are as indistinguishable as possible. Plans for the maintenance of randomisation codes and appropriate blinding for the trial should be described. Procedures for planned (e.g., Interim Analysis), and unintentional (e.g., breach of procedure) breaking of randomisation codes should be provided. For unplanned but intentional actions (e.g., safety events), see Section 6.8.4.

If the trial allows for some investigators or other designated staff to remain unblinded (for example, to allow them to adjust investigational trial intervention), the means of maintaining the blinding for other investigators or staff should be explained. Measures to prevent unblinding by laboratory measurements or while performing study assessments, if used, should be described.

{<Enter Blinding>}

* + 1. {Emergency Unblinding at the Site}

Describe the criteria for breaking the trial blind or participant code. Describe the circumstances in which the blinding would be broken for an individual or for all participants and who has responsibility. Include the procedure for emergency unblinding such as via IxRS or code envelopes as well as documentation of unblinding. Indicate to whom the intentional and unplanned unblinding should be reported.

{<Enter Emergency Unblinding at the Site>}

* 1. Investigational Trial Intervention Compliance

Describe the measures to monitor and document participants’ compliance with investigational intervention (e.g., study intervention accountability records, diary cards, or investigational intervention concentration measurements).

List what documents are mandatory to complete (for example, participant drug log) and what source data/records will be used to document investigational intervention compliance.

<Enter Investigational Trial Intervention Compliance>

* 1. Description of Non-Investigational Trial Intervention(s)

As stated in Section 6, non-investigational interventions are products used in the trial but are not part of trial objectives and hence, are not investigational trial interventions.

The non-investigational trial intervention(s) may be described concisely in a table or in the following sections as applicable.

<Enter Description of Non-Investigational Trial Intervention>

* + 1. {Background Intervention}

Describe permitted background intervention(s), including administration and any conditions for use.

{<Enter Background Interventions>}

* + 1. {Rescue Therapy}

List all permitted rescue medications, treatments, and/or procedures, including any relevant instructions about administration and any conditions for use.

If administration of rescue therapy leads to the temporary discontinuation of trial intervention or a participant’s withdrawal from the trial, refer to Section 7 Participant Discontinuation of Trial Intervention and Discontinuation or Withdrawal from Trial.

{<Enter Rescue Therapy>}

* + 1. {Other Non-investigational Intervention}

If applicable, describe the use of any other non-investigational intervention, for example, challenge agents or diagnostics.

{<Enter Other Non-investigational Intervention>}

* 1. Concomitant Therapy

Describe the concomitant medications, supplements, complementary and alternative therapies, treatments, and/or procedures which are prohibited or permitted during the trial and include details about when the information will be collected (for example, screening, all visits).

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria.

When appropriate to separate the content, subheadings may be used.

<Enter Concomitant Therapy>

* + 1. {Prohibited Concomitant Therapy}

If applicable, describe any prohibited concomitant therapy.

{<Enter Prohibited Concomitant Therapy>}

* + 1. {Permitted Concomitant Therapy}

If applicable, describe any permitted concomitant therapy.

{<Enter Permitted Concomitant Therapy>}

1. Participant Discontinuation of Trial Intervention and Discontinuation or Withdrawal From trial

This section must align with the intercurrent events and their handling strategies introduced in Section 3 Trial Objectives and Estimands, and the investigational trial intervention described in Section 6 Trial Intervention and Concomitant Therapy.

No text is intended here (header only).

* 1. Discontinuation of Trial Intervention for Individual Participants

No text is intended here (header only).

* + 1. Permanent Discontinuation of Trial Intervention

Describe the criteria for discontinuation of a participant from any trial intervention, carefully evaluating which are appropriate for the trial population and therapy being studied.

Specify whether participants who discontinue trial intervention can or cannot continue the trial (continue trial visits). Depending on the chosen intercurrent event handling strategy, it will be important to continue to follow and ascertain outcomes in participants who discontinue treatment through the end of the trial to prevent missing data in important analyses. Refer to the Section 1.3 Schedule of Activities for assessments to be performed at the time of and following discontinuation of trial intervention.

Explain the process for collecting and recording the detailed reasons for discontinuing trial intervention(s) if not described elsewhere.

<Enter Criteria for Permanent Discontinuation of Trial Intervention>

* + 1. Temporary Discontinuation of Trial Intervention

Describe

* the criteria for temporary discontinuation or interruption of trial intervention for an individual participant
* what to do and which restrictions still apply if the participant needs to temporarily discontinue or interrupt trial intervention
* whether they will continue in the trial, and
* whether all, or specify which, assessments will be performed for the stated duration of the trial.

Details of any rechallenge or restart after a safety-related event should be included in Section 7.1.3, Rechallenge.

<Enter Temporary Discontinuation of Trial Intervention>

* + 1. Rechallenge

Describe the criteria for rechallenge/restarting trial intervention, how to perform rechallenge, number of rechallenges allowed during the trial, and whether all, or specify which, assessments will be performed for the stated duration of the trial.

If rechallenge is not allowed, state this.

<Enter Rechallenge>

* 1. Participant Discontinuation or Withdrawal from the Trial

Describe the criteria for participant discontinuation or withdrawal from the trial.

Describe the reason for withdrawal and the type and data to be collected for the final assessments with reference to the schedule of activities for the participant end of study visit unless provided in another section.

In many cases, the only reason for a participant being considered withdrawn from the trial should be a participant’s withdrawal of consent to continue to participate in the trial. All other participants, including those who discontinue treatment, should remain in the trial and continued to be followed to prevent missing data in important analyses. Please refer to Section 10 about the data that need to be collected for the trial estimands.

<Enter Participant Discontinuation or Withdrawal from Trial>

* 1. Lost to Follow-Up

Describe how the trial will define how participants are lost to follow-up. In general, participants should be considered lost to follow-up only if they cannot be reached despite multiple attempts at contact. Also describe approaches that will be used to minimize loss to follow-up, such as multiple, diverse methods to remain in contact with participants (e.g., telephone calls, texts, and emails to the participant) and how contacts will be recorded.

<Enter Lost to Follow-Up>

1. Trial Assessments and Procedures

No text is intended here (header only).

* Describe the assessments and procedures required during each phase of the trial that are relevant to the stated endpoints and related intercurrent events (e.g., surgery or use of rescue therapy). Provide details that are not already presented in the SoA, taking care not to duplicate information.
* Ensure alignment with every other section of the protocol. In particular, this section must align with the intercurrent events and associated strategies for handling them described in Section 3, trial intervention and therapies outlined in Section 6, the discontinuation and withdrawal procedures in Section 7, and the statistical analysis that is defined in Section 10.
* Reference the literature for the validation of scales/instruments/questionnaires/assays.
* Instructions or protocols for specialised tests and scales/instruments/questionnaires/assays may be presented in an appendix or a separate document and cross-referenced.
* If the trial includes qualitative interviews, describe these evaluations.
* If COA measures are utilised, include instructions for the investigators per local guidance. All descriptions related to COA parameters should be fully integrated into the appropriate sections of the protocol; separate COA sections should not be created in the protocol.
* Include minimums and limits for procedures (for example, number of imaging procedures/biopsies, radiation exposure, etc.) if appropriate to the trial.
  1. Trial Assessments and Procedures Considerations

Describe general considerations applicable across trial assessments and procedures.

<Enter Trial Assessments and Procedures Considerations>

* 1. Screening/Baseline Assessments and Procedures

Describe any assessments and procedures that are unique to screening/baseline (for example, collection of data on participant characteristics, assessments/procedures performed for the purpose of determining eligibility or for stratification) in this section. Describe screening and baseline assessments and procedures separately if screening and baseline are performed at different visits.

<Enter Screening Assessments and Procedures>

{<Enter Baseline Assessments and Procedures>}

* 1. Efficacy Assessments and Procedures

Describe efficacy assessments and procedures in this section. Cross-refer to Section 8.7 if immunogenicity assessments are used in efficacy determination.

<Enter Efficacy Assessments and Procedures>

* 1. Safety Assessments and Procedures

No text is intended under the main 8.4 header only. Describe safety assessments and procedures utilizing the following subsections as applicable. Add Level 3 headings as needed.

* Identify any non-investigator party responsible for evaluation of laboratory or other safety assessments (for example, Sponsor or external Independent Data Monitoring Committee; cross refer to Section 11.4 for details as applicable).
* Include guidelines for the medical management of relevant laboratory or other safety assessment abnormalities.

<Enter Safety Assessments and Procedures>

* + 1. {Physical Examination}

Include any specific instructions for the collection and interpretation of physical examinations.

{<Enter Physical Examination>}

* + 1. {Vital Signs}

Include any specific instructions for the collection and interpretation of vital signs.

{<Enter Vital Signs>}

* + 1. {Electrocardiograms}

Include any specific instructions for the collection, interpretation, and archiving of ECGs.

{<Enter Electrocardiograms>}

* + 1. {Clinical Laboratory Assessments}

Include any specific instructions for the collection and interpretation of clinical laboratory assessments.

* Type of laboratory (central/local/hybrid)
* acceptability of additional tests deemed necessary by the investigator or local regulations
* instructions for situations in which central laboratory results are not available in time for trial intervention and/or response evaluation, or in the event of a severe disruption (for example, a pandemic or natural disaster)
* treatment algorithms for results out of normal range
* Cross-refer to Section 12.1 Clinical Laboratory Tests for lab assessment panels

{<Enter Clinical Laboratory Assessments>}

* + 1. {Pregnancy Testing}

Optional section to specify pregnancy testing requirements.

{<Enter Pregnancy Testing>}

* + 1. {Suicidal Ideation and Behaviour Risk Monitoring}

If the trial meets any of the criteria requiring suicidal ideation and behaviour risk monitoring by the guidance/guideline in each region, include justification for the need for suicidal ideation and behaviour risk monitoring in the study and add any specific instructions for the collection and interpretation of the assessment. In case this is an AESI in the study, justification will also need to be provided in the appropriate subsection of Section 9.3.2.

{<Enter Suicidal Ideation and Behaviour Risk Monitoring>}

* 1. Pharmacokinetics

Include any specific instructions for the collection and assay of samples and interpretation of PK assessments.

* Describe the biological sample(s) collected, the handling of samples, and the assay method.
  + Specific sample collection and processing instructions can be described in an appendix or a separate document and cross-referenced.
* Describe the retention time for the samples (ensuring alignment with the ICF).
* Indicate the types of analyses that may be studied for each sample.
* Define the PK parameters to be calculated and the calculation methods.

<Enter Pharmacokinetics>

* 1. Biomarkers

No text is intended here (header only). Include any specific instructions for the collection of samples and interpretation of biomarkers in the sub-sections below as applicable. Safety biomarkers should be included in Section 8.4 and immunogenicity markers in Section 8.7.

* + 1. Genetics and Pharmacogenomics

Include any specific instructions for the collection and assay of samples for genetic and/or pharmacogenomic analysis.

* Describe the biological samples that will be collected (for example, tissue, serum, plasma, etc.), handling of samples, and the assay method.
  + Specific sample collection and processing instructions can be described in an appendix or a separate document and cross-referenced.
* Describe the retention time for the samples (ensuring alignment with the ICF).
* Indicate the types of analyses that may be studied for each sample.

<Enter Genetics and Pharmacogenomics>

* + 1. Pharmacodynamic Biomarkers

Include any specific instructions for the collection of samples and assessment of pharmacodynamic biomarkers.

* Describe the biological samples that will be collected (for example, tissue, serum, plasma, etc.).
  + Specific sample collection and processing instructions can be described in an appendix or a separate document and cross-referenced.
* Describe the retention time for the samples (ensuring alignment with the ICF).
* Indicate the types of biomarkers that will be studied for each sample.
* Specify whether each sample is optional or required. Required samples must be based on a protocol objective.

<Enter Pharmacodynamic Biomarkers>

* + 1. {Other Biomarkers}

Include any specific instructions for the collection of samples and assessment of other biomarkers.

* Describe the biological samples that will be collected (for example, tissue, serum, plasma, etc.).
  + Specific sample collection and processing instructions can be described in an appendix or a separate document and cross-referenced.
* Describe the retention time for the samples (ensuring alignment with the ICF).
* Indicate the types of biomarkers that will be studied for each sample.
* Specify whether each sample is optional or required. Required samples must be based on a protocol objective.

{<Enter Other Biomarkers>}

* 1. Immunogenicity Assessments

Include any specific instructions for the collection of samples and interpretation of immunogenicity. If immunogenicity assessments are included within Efficacy Assessments or Safety Assessments, cross-reference to that section.

* Describe the biological samples that will be collected (for example, tissue, serum, plasma, etc.).
  + Specific sample collection and processing instructions can be described in an appendix or a separate document and cross-referenced.
* Describe the retention time for the samples (ensuring alignment with the ICF).
* Indicate the types of biomarkers that will be studied for each sample.
* Specify whether each sample is optional or required. Required samples must be based on a protocol objective.

<Enter Immunogenicity Assessments>

* 1. Medical Resource Utilisation and Health Economics

This section does not apply to COAs. Include this section only for any value evidence and outcomes assessments not included in either the efficacy or safety sections.

Describe the health outcome measures, collection method (for example, diary, physician interview), and participant burden.

<Enter Medical Resource Utilisation and Health Economics>

1. Adverse Events, Serious Adverse Events, Product Complaints, Pregnancy and Postpartum Information
   1. Definitions

No text is intended here (header only).

* + 1. Definitions of Adverse Events

Specify the AE definitions, including:

* Any relevant regional AE requirements.
* Any events that meet and do not meet the AE definition.
* Any trial-specific AE clarifications.
* If applicable, any clarifications on the AE and SAE definitions for efficacy trials (for example, lack of efficacy or failure of pharmacological actions reporting).

<Enter AE definition>

* + 1. Definitions of Serious Adverse Events

Specify the SAE definitions, including:

* Any relevant regional SAE requirements.
* Any events that meet and do not meet the SAE definition.
* Any trial-specific SAE clarifications.

<Enter SAE definition>

* + 1. {Definition of Medical Device Product Complaints}

{<Enter Definition of Medical Device Product Complaints>}

* 1. Timing and Procedures for Collection and Reporting

Optional table of AE timing and procedures

This table describes the timing, deadlines, and mechanism for collecting events.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **<Event Type>** | **<Situational Scope>** | **<Reportable Period Start>** | **<Reportable Period End>** | **<Timing for Reporting to Sponsor or Designee>** | **<Method for Reporting>** | **<Back-up Method for Reporting>** |
| <Event Type> | <Situational Scope> | <Reportable Period Start> | <Reportable Period End> | <Timing for reporting to Sponsor or Designee> | <Method for Reporting> | <Backup Method for Reporting> |

* + 1. Timing

Specify timing for collection and reporting of AEs, SAEs, product complaints and pregnancy and postpartum information, including:

* Start and end dates for collection and reporting
* Frequency of collection and reporting

<Enter Timing for collection and reporting of AEs, SAEs, product complaints, and pregnancy and postpartum information >

* + 1. Identification and Assessment

Specify the Investigator’s actions for identification, recording and follow-up of AEs and SAEs, including severity, causality, and the final outcome.

<Enter Identification, Recording and Follow-Up of AEs, SAEs, product complaints, and pregnancy and postpartum information>

**Identification**

Specify how AEs, SAEs, product complaints and pregnancy and postpartum information will be identified (for example, spontaneous reporting, solicited questions).

<Enter Identification>

**Severity**

Specify the intensity rating categories/scale.

<Enter Severity>

**Causality**

Specify:

* The causality categories/scale.
* Procedures for assessing causality.

<Enter Causality>

* + 1. Follow-up

Specify the procedures for follow-up of AEs, SAEs, pregnancy and product complaints. Include the assessment tools that will be used to monitor the events and the duration of follow-up after appearance of the events.

<Enter Follow-up of AEs and SAEs>

* 1. Reporting

Specify the SAE reporting method (for example, an electronic data collection tool or a paper CRF) and reporting timeline to the Sponsor.

<Enter Reporting of SAEs>

* + 1. Regulatory Reporting Requirements

Specify:

* The investigators’ responsibilities for reporting SAEs and Medical Device Product Complaints to the Sponsor (and to Ethics Committees, where required), specifying timing of reporting to allow the Sponsor to meet their responsibilities
* The Sponsor’s legal/regulatory responsibilities to report SAEs to regulatory authorities, ethics committees, and investigators
* Serious and unexpected adverse reaction reporting

<Enter Regulatory Reporting Requirements for SAEs>

* + 1. Adverse Events of Special Interest

Specify any Adverse Events of Special Interest (AESI):

* Other events that merit reporting to the Sponsor, trial leadership, IRB, and regulatory agencies (for example, secondary malignancies in oncology trials).
* Other reportable events not already included in the previous sections, such as cardiovascular events, medical device incidents (including malfunctions), laboratory test abnormalities, and trial intervention overdose.

Include the following for each AESI:

* The definition of the event.
* If it is a measurable quantity, specify how will the measurement be done.
* If it is a clinical event, specify how will it be confirmed.

<Enter Adverse Events of Special Interest or state Not Applicable>

* + 1. Disease-related Events or Outcomes Not Qualifying as AEs or SAEs

Specify any Disease-Related Events (DREs), disease-related outcomes (DROs), or both that will **not** be reported as AEs or SAEs (for example, seizures in anticonvulsant trials) or state not applicable.

<Enter Disease-related Events or Outcomes not Qualifying as AEs or SAEs>

* 1. Pregnancy and Postpartum Information

No text is intended here (header only).

While pregnancy itself is not considered to be an AE or SAE, if negative or consequential outcome occurs in the participant or child/foetus, it will be reported as an AE or SAE. Refer to Sections 9.2 and 9.3 for AE and SAE related procedures as applicable. If the negative event meets the seriousness criteria, then this is considered an SAE (for example, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy, or pre-eclampsia) and reported per Section 9.3.

* + 1. {Participants Who Become Pregnant During the Trial}

Specify

* the assessments to be performed,
* type and duration of monitoring,
* whether participants who become pregnant during the trial must be discontinued from trial intervention (refer to Section 7 as applicable), and
* what information will be collected about a participant who becomes pregnant during the trial (for example, recording and reporting to the Sponsor, postpartum follow-up, trial intervention discontinuation or continuation, or trial withdrawal).

For postpartum follow-up, include the time period (for example, initial child development) with the justification.

If exposure to trial intervention during breastfeeding is applicable, specify

* the assessments to be performed,
* type and duration of monitoring, and
* what information will be collected for both the participant and child.

{<Enter Participants Who Become Pregnant During the Trial>}

* + 1. {Participants Whose Partners Become Pregnant}

Specify:

* If the investigator will attempt to collect pregnancy information about a participant’s partner, who becomes pregnant during the specified period in the trial,
* Whether the participant whose partner becomes pregnant should be discontinued from trial intervention (refer to Section 7 as applicable), and
* The assessments to be performed, type and duration of monitoring, and what information will be collected.

{<Enter Participants Whose Partners Become Pregnant>}

* 1. Special Safety Situations

Specify special safety situations associated with the trial intervention(s) that do not qualify as an AE or SAE, but require regulatory reporting. Examples include:

* Misuse or abuse
* Off-label use (if applicable)
* Medication error (prescription or dispensing error)
* Occupational exposure
* Use outside of what is foreseen in the protocol
* Exposure of embryo, fetus, or child via material exposure (pregnancy or breastfeeding) or via paternal exposure (semen)
* Lack of therapeutic efficacy. This is not applicable for studies that measure efficacy as a study endpoint
* Suspected transmission of an infectious agent. This is only applicable for injected or biologic medicinal products; otherwise, omit.
* Product complaint, including falsified or counterfeit products
* Suspected drug-food or drug-drug interaction

1. Statistical Considerations

Ensure that the data analysis complies with ICH E9 Guideline and ICH E9(R1) Guideline.

In general, all relevant data collected in the trial should be considered in this section.

No text is intended here (header only).

* 1. General Considerations

Provide statements relevant to statistical considerations in general. For example, this might include statements indicating whether there is a separate statistical analysis plan, which general summary statistics will be provided, and when the analyses will be conducted (e.g., “The analysis will be conducted on all participant data at the time the trial ends.”).

<Enter General Considerations>

* 1. Analysis Sets

Describe analysis sets to be considered at the trial level, i.e., the set of participants whose data are to be included in the analyses. For each analysis described in Section 10, it should be clear which analysis set should be used.

<Enter Analysis Sets>

* 1. Analyses of Demographics and Other Baseline Variables

Describe the summary statistics that will be used to describe the distribution of demographic and other relevant variables at baseline. Specify the timing of the measurement of the variables (e.g., at inclusion in the trial; before , or at randomization). Relevant variables include, but are not limited to: stratification variables specified in Section 6.8, covariates for the statistical models specified in Section 10.4, other suspected predictive or prognostic variables, and variables used for planned subgroup analyses.

<Enter Analyses of Demographics and Other Baseline Variables>

* 1. Analyses Associated with the Primary Objective(s)
     1. Statistical Method of Analysis

Describe the statistical analysis methods that will be used to evaluate the primary objective(s) and associated estimand(s) in Section 3.1. Ensure that the statistical hypothesis/model/analysis (and corresponding assumptions) is aligned with the primary estimand(s). If there is more than one primary objective, present each objective as a level 3 heading and present each subsequent heading in Section 10.4 as a level 4 heading.

For each objective, state the null and alternative hypotheses, including the pre-planned type 1 error rate, or alternative criteria for evaluating whether the objective has been met, and relevant operating characteristics if appropriate. Describe the statistical model used and the factors that will be included (covariates and interactions) and any rules for handling these factors (for example, pooling of centres).

If modelling and simulation methods are to be used, please describe the model (inputs and outputs), the underlying assumptions, and the method of model fitting.

<Enter Statistical Method of Analysis>

* + 1. Handling of Data in Relation to Primary Estimand(s)

For each intercurrent event of the primary estimand(s) (Section 3.1, Estimand(s) for the Primary Objective(s)), explain how data will be handled for the statistical analysis in line with the primary estimand. The handling of intercurrent events in statistical analysis should be aligned with the specific estimand strategies being used.

This section should describe with more detail the rationale and handling of the data rather than repeating the guidance from the preceding sections.

<Enter Handling of Data in Relation to Primary Estimand(s)>

* + 1. Handling of Missing Data in Relation to Primary Estimand(s)

Describe how missing data will be addressed (e.g., imputation method and model), state the underlying assumptions, and provide a rationale for the approach.

<Enter Handling of Missing Data in Relation to Primary Estimand(s)>

* + 1. {Sensitivity Analysis}

Describe sensitivity analyses. Sensitivity analyses are a series of analyses conducted with the intent to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data.

{<Enter Sensitivity Analysis>}

* + 1. {Supplementary Analysis}

Describe any supplementary analysis if applicable. Supplementary analyses are conducted in addition to the main and sensitivity analysis with the intent to provide additional insights into the understanding of the treatment effect.

{<Enter Supplementary Analysis>}

* 1. Analysis Associated with the Secondary Objective(s)

Describe the statistical analysis methods in alignment with the secondary objectives and associated estimands in Section 3.2. Use the same section structure as the Analyses Associated with the Primary Objective(s) section.

{Not Applicable}

or use the following subheadings:

* + 1. {Statistical Method of Analysis}

Clearly specify any secondary hypotheses that will be tested for confirmatory purposes.

{<Enter Statistical Method of Analysis>}

* + 1. {Handling of Data in Relation to Secondary Estimand(s)}

{<Enter Handling of Data in Relation to Secondary Estimand(s)>}

* + 1. {Handling of Missing Data in Relation to Secondary Estimand(s)}

{<Enter Handling of Missing Data in Relation to Secondary Estimand(s)>}

* + 1. {Sensitivity Analyses}

{<Enter Sensitivity Analyses>}

* + 1. {Supplementary Analyses}

{<Enter Supplementary Analyses>}

* 1. Analysis Associated with the Exploratory Objective(s)

Describe any exploratory analyses, if applicable. Additional subsections could be created to describe the analyses, as needed.

<Enter Analyses Associated with the Exploratory Objective(s)>

* 1. Safety Analyses

If safety is a primary and/or secondary objective, describe the corresponding safety analyses in the appropriate section above (Section 10.4 or Section 10.5). In this section, describe statistical methods that will be used to analyze relevant safety outcomes, including any adverse events of special interest. This should typically include specification of a measure to estimate risk within treatment arms, a measure to compare risk across treatment arms, and a measure of statistical uncertainty around the comparison such as a confidence interval.

<Enter Safety Analyses>

* 1. Other Analyses

Describe other analyses not included in Sections 10.3-10.8, such as subgroup analyses.

<Enter Other Analyses>

* 1. Interim Analyses

Describe any interim analysis and criteria for stopping or adapting the trial. Ensure alignment with Section 4.3.

The description should include, but is not limited to, the following:

* Any planned interim analysis, even if it is only to be performed at the request of an oversight body (for example, DMC).
* The purpose of the interim analysis, including whether the interim analysis may be used for stopping and/or for other trial adaptations such as sample size re-estimation, alteration to the proportion of participants allocated to each trial group, or changes to eligibility criteria.
* The applied statistical method, for example, group sequential test and spending function (for example, O’Brien-Fleming), as applicable.
* The party(ies) responsible for performing and reviewing the results of the analyses (e.g., adaptation committee, DMC, independent statistician).
* When the analyses will be conducted (timing and/or triggers).
* The decision criteria—statistical or other—that will be adopted to judge the interim results as part of a guideline for early stopping or other adaptations.
* Who will see the outcome data while the trial is ongoing.
* Whether these individuals will remain blinded to trial groups.
* How the integrity of the trial implementation will be protected (for example, maintaining blinding) when decisions are made after interim analyses (e.g., a decision to continue the trial or implement a specific adaptation).
* Who has the ultimate authority to stop or modify the trial, for example, investigator, principal investigator, DMC, or sponsor.

<Enter Interim Analyses>

* 1. Multiplicity Adjustments

Multiple testing procedures may be needed to limit the probability of false positive findings in a trial. Reasons for carrying out multiple statistical tests include - but are not restricted to - multiple endpoints, multiple treatment groups, multiple hypotheses, subgroups, different statistical methods, etc.

Describe any approaches to multiplicity control for the trial. This description might go beyond the analysis of primary objectives.

Specify the statistical approach to control the overall type I error rate as well as the (adjusted) significance levels to test specific hypotheses, as applicable. Clarify whether the tests/confidence intervals are one- or two-sided.

State the circumstances under which a study will be considered to have met its primary objective(s). For example, in a study with two primary efficacy endpoints, this section should state whether the study would be expected to provide evidence on at least one or on both of the endpoints in order to confirm the efficacy of the treatment.

For some statistical approaches it might be helpful to include a graphical depiction, as visualization will be helpful for understanding, coupled with the clinical translation of the mathematical choices.

Details regarding Interim Analyses should be provided in section 10.9.

<Enter Multiplicity Adjustments>

* 1. Sample Size Determination

This section should detail the methods used for the determination of the sample size.

The sample size calculation should be aligned with the primary estimand and the primary analysis, otherwise a justification is needed. Details of sample size calculation should include all relevant information to enable reproduction of the sample size, for example:

* referencing of any prior studies on which assumptions were based,
* significance level (including information on the choice of one- or two-sided level),
* power,
* assumed treatment effect and variability,
* impact of dropout rate and intercurrent events on sample size calculation,
* precision of estimator/length of confidence interval

Any assumptions made should be stated and justified. Further analysis of how deviations from the assumptions will affect the sample size should be included.

If complex simulations were used to calculate the sample size, consider including details in a separate simulation report as an appendix to the protocol.

If the planned sample size is not derived statistically, then this should be explicitly stated along with a rationale for the intended sample size (for example, exploratory nature of pilot trials; pragmatic considerations for trials in rare diseases).

<Enter Sample Size Determination>

1. Trial Oversight and Other General Considerations

No text is intended here (header only).

* 1. Regulatory and Ethical Considerations

Concisely summarize the prevailing ethical, legal, and regulatory guidelines that will be applied throughout the trial.

This trial will be conducted in accordance with the protocol and with the following:

* World Medical Association Declaration of Helsinki ethical principles for medical research involving human subjects
* Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
* ICH Good Clinical Practice (GCP) Guidelines
* Applicable laws and regulations

<Enter Regulatory and Ethical Considerations>

* 1. Trial Oversight

Concisely summarize the trial oversight listing the investigator and sponsor responsibilities not covered in other sections of the protocol which are essential for the operations of the trial, specifying the ones related to quality assurance.

* + 1. Investigator Responsibilities

<Enter Investigator Responsibilities>

* + 1. Sponsor Responsibilities

Describe the sponsor duties to be delegated to a third party that may impact the investigators sites, if applicable.

<Enter Sponsor Responsibilities>

* 1. Informed Consent Process

Specify the key elements of the informed consent process, including any special needs and how these are addressed (for example, assent, capacity, legally acceptable representative, adolescents who may reach age of majority during the trial, pregnant participants and pregnant partners of participants).

<Enter Description of Informed Consent Process>

<Enter Description of Assent Process>

If enrollment in the trial may occur during an emergency in which the participant or their legally acceptable representative is not able or available to give consent, describe the consent process.

<Enter Description of Emergency Consent Process>

* + 1. Informed Consent for Rescreening

If participants can be rescreened, add the text to state whether the participant needs to complete a new consent. Screen failure and rescreening should be clearly defined in the protocol, with cross-reference to those definitions.

<Enter Consent Requirements for Rescreening>

* + 1. Informed Consent for Use of Remaining Samples in Exploratory Research

If participants will be asked to consent to optional exploratory research using the remainder of mandatory samples, include text that addresses the use of remaining samples for optional exploratory research.

If any exploratory research is planned and additional written consent regarding the use of remaining samples for exploratory research will be obtained, describe the consent process.

<Enter Additional ICF text for Use of Remaining Samples in Exploratory Research>

* 1. Committees

Briefly describe the administrative structure of committees that will be reviewing data while the trial is ongoing, and the type of committee (for example, Dose Escalation Committee, Data Monitoring Committee or Data Safety Monitoring Board). Note that specific details may be required depending on local law or regulation. If applicable, Committee Charters may be cross-referenced. If no committees are applicable, state “Not Applicable.”

<Enter Committees>

* 1. Insurance and Indemnity

Concisely summarize the arrangements for participants insurance and indemnity if not addressed in a separate agreement, if required by the applicable regulatory requirements.

<Enter Insurance and Indemnity>

* 1. Risk Management

Describe how the critical to quality factors will be mitigated or refer to separate document where this is described.

<Enter Risk Management>

* 1. Data Governance

Describe the key processes for critical trial integrity, traceability and security enabling accurate collection, reporting, monitoring, transfer, retention, access and publication if not addressed in separate agreement(s).

Describe the measures to protect the privacy and confidentiality of personal information of trial participants in accordance with applicable regulatory requirements on personal data protection and any measures that should be taken in case of a data security breach.

<Enter Data Governance>

* 1. Source Data

Establish the importance of source data and expectation for traceability of transcribed information back to source. Delineate expectations for investigators (for example, maintain source data at the site, ensure availability of current records) and trial monitors (for example, verify CRF data relative to source, safety of participants is being protected, conduct is in accordance with GCP). Define what constitutes source data and its origin or provide a reference to the location of these definitions, if contained in a separate document, such as a monitoring guideline or source data acknowledgement).

Describe the provision for direct access to source data and documents enabling clinical trial-related monitoring, audits and regulatory inspections, if not included in separate agreement(s).

<Enter Source Data Introduction>

<Enter Investigator Expectations for Source Data>

<Enter Trial Monitor Expectations for Source Data>

<Enter Definition of Source Data>

* 1. Protocol Deviations

Plans for detecting, reviewing, and reporting any deviations from the protocol should be described or a reference to separate document included.

<Protocol Deviations Plans>

* 1. Early Site Closure

List the sponsor’s rights to close a site. Likewise, list the investigator’s rights to initiate early site closure.

<Enter Decision Rights for Site Closure >

List the criteria for early closure of a site by the sponsor or investigator.

<Enter Criteria for Early Closure>

List the responsibilities of the sponsor and investigator following early site closure, such as informing the ethics committee(s), and prompt notification of the participant and transition to appropriate therapy and/or follow-up.

<Enter Responsibilities Following Early Site Closure>

1. Appendix: Supporting Details

No text is intended here (header only).

* 1. Clinical Laboratory Tests

Specify which laboratory parameters should be included in each clinical laboratory assessment panel (for example, for haematology, chemistry, urinalysis). A tabular presentation for such information is common. If applicable, include equations and references for locally calculated laboratory results. If not applicable, retain header and enter “Not Applicable.”

<Enter Clinical Laboratory Tests>

* 1. Country/Region-Specific Differences

Although global clinical trial practices are increasingly harmonised, some country/ region-specific differences in requirements do exist (for example, document retention periods, contraception requirements). Where differences in requirements cannot be reconciled, sponsors should explain how they will document and communicate country/region-specific differences (for example, by country/region-specific amendments or addenda).

An alternative to country/region-specific amendments is to list the specific differences by country or countries in this section, including a reference to the relevant section of the protocol where the differing requirement applies.

If not applicable, retain the heading and enter “Not Applicable.”

<Not Applicable>

or

[Country/Region Identifier]

<Enter Country/Region Specific Requirements>

<Enter Country/Region Specific Protocol Clarifications>

* 1. Prior Protocol Amendment(s)

Choose the applicable statement below. For an original protocol that has not been amended, retain the first sentence below and delete the remainder of this entire section.

{Not applicable. This protocol has not been amended.}

Or

{Not applicable. This is the first protocol amendment.}

Or include the below as applicable.

{This protocol has been amended previously. The Protocol Amendment Summary of Changes for the current amendment is located directly before the Table of Contents. Prior amendment(s) to this protocol are listed in the table below, beginning with the most recent.}

Do not include the current amendment in the table below, as the table is focused on previous amendments. Previous amendments should appear in reverse chronological order with the most recent at the top (for example, Amendment 3, 2, 1). Delete lines not needed, add lines as needed. Inclusion of regional-, country-, and site-specific amendments in the table is optional. If included, ensure that the scope is clearly distinguishable from global amendments.

If including the column with enrollment numbers, follow the instructions below.

* For global amendments to international clinical trials or amendments to a single-country trial, list approximate global enrollment total or percentage at the time of the amendment and select “globally”.
* For global amendments consolidating only country/region-specific requirements, list approximate local enrollment total or percentage at the time of the amendment and select “locally”. If consolidating a series of local amendments, the status of all the relevant locations can be listed.
* For country/region amendments to international clinical trials, list the approximate local enrollment total or percentage at the time of the amendment and select “locally”.
* For studies in which enrollment status by cohort is more meaningful, such as for single-site or early-phase studies, listing approximate enrollment by cohort is an option. If multiple cohorts are ongoing at the time of the amendment, the status of all the ongoing cohorts can be listed.

|  |  |  |
| --- | --- | --- |
| **Document** | **Sponsor Approval Date (dd/mmm/yyyy)** | **Approximate Enrollment when Sponsor Approved Amendment** |
| <Enter Amendment Number> | <Enter Amendment Date> | <Enter # or % enrolled globally/locally/per cohort> |
| Original Protocol | <Enter Original Protocol Date> | 0 |

The Overview of Changes from each prior protocol amendment is {provided below} or <specify alternative location>}.

Move the Overview of Changes table from the previous amendments to this section in reverse chronological order (most recent first).

**Overview of Changes in Amendment** <enter amendment number> (<enter date>)

| Description of Change | Brief Rationale for Change | Section # and Name |
| --- | --- | --- |
| <Enter Description of Amendment Change> | <Enter Rationale for Amendment Change> | <Enter Section of Amendment Change> |
| <Enter Description of Amendment Change> | <Enter Rationale for Amendment Change> | <Enter Section of Amendment Change> |

(Add lines as needed)

Add additional Overview of Changes tables as protocol amendments accrue.

**Overview of Changes in Amendment** <enter amendment number> (<enter date>)

| Description of Change | Brief Rationale for Change | Section # and Name |
| --- | --- | --- |
| <Enter Description of Amendment Change> | <Enter Rationale for Amendment Change> | <Enter Section of Amendment Change> |
| <Enter Description of Amendment Change> | <Enter Rationale for Amendment Change> | <Enter Section of Amendment Change> |

1. Appendix: Glossary of Terms and Abbreviations

Define abbreviations and other terms used in the protocol. A tabular presentation is common and may serve as the definition at first use.

<Enter Glossary of Terms and Abbreviations>

1. Appendix: References

References should be listed in a common format that includes all relevant information to identify the source and date published. If not published, this should be clearly indicated.

<Enter References>