M11 TEMPLATE:

CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL

(CeSHarP)

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page. The draft guidance has been left in the original International Council for Harmonisation format. The final guidance will be reformatted and edited to conform with FDA's good guidance practice regulation and style.

For questions regarding this draft document, contact (CDER) Veronica Pei, 240-402-7091, Veronica.Pei@fda.hhs.gov.

FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

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 27 September 2022

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 4 September 2022).	27 September 2022

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 of drugs, vaccines, and drug/device combinations intended to be registered as drugs. The template is suitable for all phases of clinical research and all therapeutic areas. Existing ICH Guidelines and ISO 14155 were considered in its development. 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.

0.3 Template Conventions and General Instructions

This template uses the typefaces described in the table below to distinguish between their intended use and applicability. Use of consistent font sizes (12 point) 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 that should appear in all protocols
Instructional text	Red Calibri font (Delete for final document)	Text that provides instructions, but which should not appear in a final protocol
Suggested text	Blue Century font Restyle to Black Times New Roman for final document	Text that is suitable for many trials, but which may need to be modified, deleted, or replaced according to the specific aspects of the trial
Variable text	{braces} in the prevailing typeface Select from choices by eliminating unwanted options; remove braces and restyle remaining text to match other text in the final document	Where a choice is suggested between options in a passage of text, braces are used to separate them
Fields	[Square brackets] in the prevailing typeface with grey shading	Brackets with grey shading are used to indicate variable text modelled as a field in the electronic manifestation of the protocols

Type of Text (Applicability)	Typeface Details	Description (Intended Use)
	Populate field from available choices, or with free text if indicated; remove brackets and restyle text to match other text in the final document	

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 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 Level 3 safety subheadings (Section 8.4)** **Other Level 3 headings may be deleted or modified as needed**	

Example Heading	Heading Level	Typeface in this Template	Modification or Deletion	Addition
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.

Terminology

The following terminology has been selected for use within this template and is 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 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 include the agent being tested or used as a control (for example, placebo or active comparator). 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 Publishing a Paper or .pdf 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 and Level 2 headings are visible in the navigation pane or bookmark view). Visible Level 3 bookmarks are also recommended.
- Delete unneeded or non-applicable Level 3 or lower headings and ensure remaining Level 3 and lower headings are numbered appropriately
- Delete any unused variable text and related prompts
- Restyle any "suggested", "example", or "variable" text to match the regular text
- Remove all instructional text, and
- Remove brackets that denote variable or field text after making appropriate selections.

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

0.4 Abbreviations Used in this Template

Abbreviation or Acronym	Definition
AE	Adverse Event
AESI	Adverse Events of Special Interest
AxMP	Auxiliary Medicinal Product
CDISC	Clinical Data Interchange Standards Consortium
COAs	Clinical Outcome Assessment(s)
CRF	Case Report Form
DREs	Disease-Related Events
ECG	Electrocardiogram
EU	European Union
EUDAMED	European Databank on Medical Devices
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

Abbreviation or Acronym	Definition
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
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
PD	Pharmacodynamics
PK	Pharmacokinetics
SAE	Serious Adverse Event
SoA	Schedule of Activities
TOC	Table of Contents
WHO	World Health Organization

63

Protocol Full Title:	[Protocol 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.
Sponsor Confidentiality Statement:	[Sponsor Confidentiality Statement] Insert the Sponsor's confidentiality statement, if applicable, otherwise delete.
Protocol Number:	[Protocol Number] 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.
Version:	[Version] An optional field for use by the Sponsor at their discretion.
Amendment Number:	[Amendment Number] Enter the amendment number. If this is the original instance of the protocol, indicate Not Applicable.
Amendment Scope:	[Amendment Scope] [Country/Region Identifier] Acceptable entries for amendment scope are: "global" or "Country-specific/Regional" Use the ISO-3166 region or country identifier (for example, DE or EU). For global trials delete the Country/Region Identifier field.
Compound Number(s):	[Compound Number] Enter the Sponsor's unique identifier for investigational compound(s) in the trial. Add or delete additional fields as needed.
Compound Name(s):	[Nonproprietary Name], [Proprietary Name], [Additional Proprietary Name] Delete this line from the table if a nonproprietary name has not yet been assigned. Omit proprietary name fields if not yet established.
Trial Phase:	[Trial Phase] [Description of Trial Phase Other] Acceptable entries are: "Early Phase 1", "Phase 1", "Phase 1/Phase 2", "Phase 2", "Phase 2/Phase 3", "Phase 3", "Phase 4",

	or "Other". For trials combining investigational drugs or vaccines with devices, classify according to the phase of drug development.
Acronym:	[Protocol Acronym] Acronym or abbreviation used publicly to identify the clinical trial, if any. The acronym may include numerals, such as -1, -2, or I, II, III, or IV. Delete this line from the table if not applicable.
Short Title:	[Protocol 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:	[Sponsor Name] [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: [Sponsor Local Name] [Sponsor Local 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:	[Device Manufacturer Name] [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 from the table if not applicable.

Regulatory Agency Identifier Number(s):	[EUDAMED: [EUDAMED Number]] [EudraCT Number: [EudraCT Number]] [EU Trial Number: EU Trial Number]] [IDE: [IDE Number]] [IND: [IND]] [jRCT: [jRCT Number]] [NCT: [NCT Number]]: [NMPA IND: [NMPA IND]] [WHO: [WHO Number]]: [Other: [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 Date:	[Approval Date] or [The approval date is included with the electronic signature, located {describe location}.] 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:

[Name] [Sponsor Signature Date]

[Title of Sponsor Signatory]

or

[This protocol was approved via {describe method} as described on the approval page appended to the document]

Where allowed, an electronic/digital signature may be used for approval rather than a wet signature. In such cases, replace the signature block with appropriate description of the electronic/digital approval and the location of relevant information for traceability.

Medical Monitor Name and Contact Information: [Medical Monitor Institution Name], [Medical Monitor Institution Address] or [is provided separately/can be found in {describe location}].

Report Serious Adverse Events within 24 hours {via E-mail/fax provided in the site manual. /per the options below:}

E-mail: [Rapid Alert E-mail Address]

Fax: [Rapid Alert Fax Number]

Amendment Details

Delete this entire section for an original protocol.

History of Amendments

{#/A total of #} prior {global} amendments have occurred, as shown in the table below:

Document	**Sponsor Approval Date (dd/mmm/yyyy)**	**Approximate {(#/%)} Enrolled**
[Amendment x]	[Amendment x Date]	{(#/%)} {globally/locally}}
[Amendment x]	[Amendment x Date]	{(#/%)} {globally/locally}
[Amendment x]	[Amendment x Date]	{(#/%)} {globally/locally}
Original Protocol	[Original Protocol Date]	0

Do not include the current amendment in the table above, as final approval dates are often difficult to predict during document preparation. 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, list approximate global enrollment total or percentage at the time of the amendment and select "globally".
- For country/region amendments, list the approximate local enrollment total or percentage at the time of the amendment and select "locally".

Current Amendment

The table below provides an overview of the current amendment.

Amendment Number:	[Amendment Number]
Approximate {%/#} Enrolled:	[Estimated % or # Enrolled] enrolled [Globally/Locally] 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 amendment, provide the estimated global enrollment at the time of the Sponsor approved the amendment. 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] * Select from the following (multiple selections allowed): • Regulatory agency request to amend • New regulatory guidance • IRB/IEC feedback • New safety information available • Manufacturing change • Adaptive clinical trial IMP addition • Change in strategy • Change in standard of care • New data available (other than safety data) • Investigator/site feedback • Recruitment difficulty • Inconsistency and/or error in the protocol • Protocol design error • Other: [Describe]	Other: [Other Reason for Amendment] * Select from the following (multiple selections allowed): • Regulatory agency request to amend • New regulatory guidance • IRB/IEC feedback • New safety information available • Manufacturing change • Adaptive clinical trial IMP addition • Change in strategy • Change in standard of care • New data available (other than safety data) • Investigator/site feedback • Recruitment difficulty • Inconsistency and/or error in the protocol • Protocol design error • Other: [Describe] • Not applicable
Summary of the Amendment:	[Summary of Amendment] Specify on the primary reason for the amendment with details specific to the trial. If more than one key change prompted the amendment, discuss briefly. Incidental 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 • safety or rights of the participants, or	[Yes/No] Indicate whether the current amendment is likely to have a significant impact on either of the criteria listed.	

• on the reliability and robustness of the data generated in the clinical trial?	

* 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 key measures or endpoints 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.

Summary of Changes in the Current Amendment:

Section # and Name	Description of Change	Brief Rationale for Change
[Location of Change]	[Description of Change]	[Rationale for Amendment Change]
[Location of Change]	[Description of Change]	[Rationale for Amendment Change]
[Location of Change]	[Description of Change]	[Rationale for Amendment Change]

(Add lines as needed)

Follow the steps below to prepare the summary of changes.

- If a Summary of Changes already exists from a prior amendment, move it to Section 13.4, History of Previous Amendments, and populate a clean summary table for the present amendment.
- List the changes that apply to the current amendment. Provide a brief description of the change(s) and a brief scientific rationale for specific changes (for example, change to individual inclusion/exclusion criteria).

Tabular presentation is common but not required. The page can be changed to landscape orientation if necessary.

Table of Contents

1 PROTOCOL SUMMARY

No text is intended here (header only).

1.1 Protocol Synopsis

The protocol synopsis is a short summary of the key points of the trial.

No text is intended here (header only).

Primary and Secondary Objectives and Endpoints

Include a copy of the Objectives/Endpoints Table including primary and secondary endpoints only from Section 3 of the protocol and follow all the same instructions. Not all trials will have a complete estimand. Do not include exploratory endpoints in the synopsis.

[Primary and Secondary Objectives and Endpoints]

Overall Design

Several key aspects of the trial design are summarised below.

Intervention Model:	[intervention model]	**Population Type:**	[population type]
Control:	[control]	**Population Diagnosis or Condition:**	[diagnosis or condition]
Active Comparator:	[comparator]	**Population Age:**	Minimum: [minimum age] – Maximum: [maximum age]
Trial Intervention Assignment Method:	[intervention assignment method]	**Site Distribution:**	[geographic scope]

Briefly state the following:

- Intervention model (for example, single group, parallel group, cross-over, factorial, sequential).
- Control (for example, placebo, active comparator, low dose, historical, standard of care, sham procedure, or none [uncontrolled]).
- Active comparator, if applicable; indicate N/A if not applicable.
- Trial intervention assignment method (for example, randomisation, stratification, or both). Do NOT state block size. If assignment to intervention is by randomisation, describe when randomisation occurs relative to screening.

- Trial population type (for example, healthy volunteers, adult patients, paediatric patients).
- Population Diagnosis or Condition (for example, "acute lung injury," or a specific biomarker profile); indicate "N/A – Healthy" for trials in healthy volunteers.
- Population age range (for example ≤3 mos, ≥18 to ≤80 years old). List N/A if a maximum or minimum age limit does not apply. 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.
- Site distribution (select from: single-site, multi-site, or multi-site and multi-regional). If none of these applies, indicate *other* and describe.

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 period with the greatest number of arms.

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

Select from the following blinded roles:

- Participant
- Care Provider
- Investigator
- Outcomes Assessor: the individual who evaluates the outcome(s) of interest
- Not applicable (No blinding).

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 greatest blinding occurs. More details can be provided in Section 6.6 of the protocol. Note that this list does not include Sponsor staff or their designees who may be unblinded to complete ongoing safety oversight and surveillance reporting.

"Not Applicable (No blinding)" indicates an open-label trial.

Number of Participants:

Number {randomly assigned to trial intervention/ enrolled}: {x} participants [{Target/ Maximum}]

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.

Arms and Duration

Total duration of trial intervention for each participant:

[Approximately] [x] Year(s)/[x] Month(s)/[x] Day(s)

or

Duration will vary [Reason duration of trial intervention will vary]

Total duration of trial participation for each participant:

[Approximately] [x] Year(s)/[x] Month(s)/[x] Day(s)

or

Duration will vary [Reason duration of trial participation will vary]

Select the text that applies to the trial. Note that total duration of participation should include any washout and any follow-up periods in which the participant is not receiving trial intervention. Where the total durations can be provided, indicate whether the duration is approximate, and delete terms that are not applicable (for example, for a trial of only a few days, delete the years and months terms). When duration cannot be approximated, provide a short explanation (for example, "event-driven" or "adaptive design").

[Arms and Duration Description]

Briefly state:

- Total duration of participation for each participant with sequence and duration of trial periods (for example, screening, run-in, fixed dose/titration, follow-up/washout periods)
- Dose regimens in each trial period and stage (if applicable) including frequency (for example, twice daily) and route of administration and criteria for individualised dosing (for example, participant weight or plasma concentrations), if applicable
- Rules/procedures for any dose changes/adjustments including flexible dosing; dose reductions, dose interruptions, or tapering; discontinuation; and any circumstances for resuming trial intervention, as applicable

If sufficiently detailed, a cross-reference to the trial schema is appropriate in lieu of text description.

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 at the

Sponsor's discretion in the separate space provided. Committees listed here should be fully described in Section 10.3, Committees Structure.

Independent Committees: [Independent Committees]

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

Other Committees: [Other Committees]

Delete "Other Committees" if not applicable.

1.2 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]). For complex trials, additional schemas may be added to describe activities or trial periods in greater detail.

[Schema]

1.3 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.

[Schedule of Activities]

2 INTRODUCTION

No text is intended here (header only).

2.1 Purpose of Trial

Explain why the trial is needed, why the research questions being asked are important. Do not restate the IB.

[Purpose]

Refer to the Section 1.2, Trial Schema, and Section 1.3, Schedule of Activities, for more information about the trial design.

2.2 Summary of Benefits and Risks

Include an assessment of known benefits and potential risks, including the basis of the risk (for example, preclinical studies or prior clinical trials).

Benefit Summary

The benefit summary should be written from the perspective of an individual participant, and should describe any physical, psychological, social, legal, 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 discussed separately.

[Benefit Summary]

Risk Summary and Mitigation Strategy

Trial Intervention – Discuss risks related to trial-specific treatments and interventions. For the protocol, focus discussion only 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.

[Trial-specific Discussion of 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 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.

[Trial-specific Discussion of Procedure Risks and Mitigations]

Other – Consider risks associated with other items (for example, comparators, challenge agents, imaging agents, medical devices). Insert a line for each, as needed.

[Trial-specific Discussion of Other Risks and Mitigations]

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. Risks need to be assessed against the benefits for the individual participant at least once a year.

[Overall Benefit:Risk Conclusion]

3 TRIAL OBJECTIVES, ENDPOINTS AND ESTIMANDS

In this section, precisely define each clinical question of interest by stating each trial objective and specifying the endpoint(s) and estimand(s) that correspond to each objective. Ensure alignment with every other section of the protocol.

Include additional level 2 headers under Section 3 Trial Objectives, Endpoints, and Estimands as needed.

No text is intended here (header only).

3.1 {Primary/Secondary/Exploratory} Objective + Associated Endpoint {and Estimand}

{Primary/Secondary/Exploratory} Objective	**{Primary/Secondary/Exploratory} Endpoint**
[Objective]	[Endpoint]

{Primary/Secondary/Exploratory} Estimand

Describe the attributes that construct the estimand: the treatment condition of interest, the population of participants targeted by the clinical question of interest, other intercurrent events (if applicable), a population level summary, and the endpoint (or variable) specified in the table above.

[Estimand Description]

4 TRIAL DESIGN

In this section, 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 across Section 1.1, Protocol Synopsis and Section 1.2, Trial Schema.

No text is intended here (header only).

4.1 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 applicable, indicate the type of trial (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.

[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 10.2, Committees Structure.

[Description of Trial Duration]

Describe the method of assignment to trial intervention (for example, stratified randomisation). If assignment to trial intervention is by randomisation, describe when randomisation occurs relative to screening.

Describe the level and method of blinding; for example, single-blind, double-blind, [including Sponsor unblinded], matching placebo, double-dummy, or open-label). Include mention of measures taken to minimise bias on the part of participants, investigators, and analysts.

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.

[Method of Assignment to Trial Intervention]

Discuss any other important aspects of the design, including but not limited to the following, where applicable:

- 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 10.2, Committees, for details,
- Whether an interim analysis is planned and, if so, refer to details in Section 9.7, Interim Analysis, and/or
- Any planned extension trial, long-term follow-up/registry, or post-trial sample analysis or other data-related activities.

[Additional Description of Design]

4.1.1 Participant Input into Design

If applicable, describe any participant involvement in the design of the trial and any participant suggestions implemented.

[Participant Input]

4.2 Rationale for Trial Design

Provide a rationale for the trial intervention model selected in Section 4.1, Description of Trial Design. A rationale for the choice of comparator, if applicable, should be described separately in Section 4.2.1, Rationale for Comparator.

[Rationale for Intervention Model]

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

[Rationale for Duration]

Provide a rationale that the trial endpoint(s) described in Section 3, Trial Objectives, Endpoints, and Estimands, are clinically relevant and provide a reliable and valid measurement of the intended intervention effect.

[Rationale for Endpoints]

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.

[Interim Analysis]

4.2.1 Rationale for Comparator

If applicable, provide a rationale for the type of control selected for the trial (for example, placebo, active drug, combination, historical). Discuss 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. Describe prior trials that support the dose and/or dose regimen.

[Rationale for Comparator]

4.2.2 Rationale for Adaptive or Novel Trial Design

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

[Rationale for Adaptive or Novel Design]

4.2.3 Other Trial Design Considerations

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

[Other Design Considerations]

4.3 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.

[Access to Trial Intervention after End of Trial]

4.4 Start of Trial and End of Trial

Define key timepoints in the trial, such as the start date, first act of recruitment, and site closure. These definitions should consider local regulatory requirements. Delineate sponsor and investigator decision rights to close a site or end the trial, including criteria for early closure of a site. List responsibilities of the sponsor and investigator following termination or suspension of the trial. Provide a cross-reference to Section 10.5, Early Site Closure or Trial Termination for criteria and responsibilities related to early site closure or trial termination.

[Trial Start and End]

5 TRIAL POPULATION

In this section, describe the trial population. Use the following guidance when developing participant eligibility criteria to be listed in Section 5.3, Inclusion Criteria, and Section 5.4, 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.
- 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.

No text is intended here (header only).

5.1 Selection of Trial Population

Describe the population selected (for example, healthy volunteers, 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) and 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.

[Selection of Trial Population]

5.2 Rationale for Trial Population

Provide a rationale for the trial population ensuring that the population selected is well defined and clinically recognisable. Justify whether the trial intervention is to be evaluated in children, 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).

[Rationale for Trial Population]

Individuals who do not meet criteria for trial eligibility must not be enrolled via protocol waivers or exemptions.

5.3 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]
[Inclusion Criterion]

Add criteria as needed. Number sequentially.

5.4 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]
[Exclusion Criterion]

Add criteria as needed.

5.5 Lifestyle Considerations

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.

[Lifestyle Considerations]

5.5.1 Meals and Dietary Restrictions

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

[Meals and Dietary Restrictions]

5.5.2 Caffeine, Alcohol, Tobacco, and Other Habits

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

[Caffeine, Alcohol, Tobacco, and Other Habits]

5.5.3 Physical Activity

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).

[Physical Activity]

5.5.4 Other Activity

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

[Other Activity]

5.6 Screen Failures

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.

[Screen Failure]

6 TRIAL INTERVENTION AND CONCOMITANT THERAPY

In this section, describe the trial intervention being tested and any control product being used. If multiple trial interventions are to be evaluated, Section 6.1, Description of Trial Intervention, Section 6.3, Dosing and Administration, and Section 6.5, Preparation, Handling, Storage, and Accountability should differentiate between each product.

No text is intended here (header only).

6.1 Description of Trial Intervention

Describe the 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, packaging, labelling, and storage conditions. Include information for all trial interventions (experimental, placebo, active comparator, sham comparator).

The trial intervention should be designated as an investigational medicinal product (IMP) or non-investigational medicinal product (NIMP)/auxiliary medicinal product (AxMP).

It is suggested that the trial intervention(s) be described concisely in a table.

[Table of Trial Interventions]

Indicate whether an additional product will be provided as part of the trial and its intended use (background intervention, challenge agent, rescue medication, diagnostic, or other). If use of an additional product is planned, include dosing information. Refer to approved regional labelling or describe any differences.

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.

[Additional Text, if Needed]

6.2 Rationale for Trial Intervention

Provide a rationale for the selection of the dose(s) or dose range, the route of administration, and dosing regimen (including starting dose, dose titration, dose interval) of the trial intervention and any control product. This rationale should include relevant results from previous preclinical studies and clinical trials that support selection of the dose and regimen. Include any information about age or sex-based pharmacokinetic or pharmacodynamic differences known from previous trials. If applicable, justify any differences in specifications, dose regimen, or therapeutic use relative to approved labelling.

Include a rationale for prospective dose adjustments incorporated in the trial, if any; for example, as a result of interim analysis.

[Rationale for Dose and Regimen]

6.3 Dosing and Administration

Describe the detailed procedures for administration of each participant's dose of trial intervention and control product. 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 trial intervention), the planned route of administration (for example, oral, nasal, intramuscular), 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.

For an individual participant, describe dose modifications allowed. 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.

Discussion of dose escalation or cohort expansion as part of the overall design should be covered in Section 4.2 (Rationale for Trial Design).

[Dosing and Administration]

6.3.1 Trial Intervention Dose Modification

If applicable, the protocol should state the conditions under which a dose modification will be made for an individual participant, particularly regarding failure to respond or to toxic or untoward changes in stipulated indicators. This section can also include discussion of dose titration. Do not include information on stopping trial intervention for individual participants due to safety/other reasons as this is detailed in Section 7, Discontinuation of Trial Intervention and Participant Discontinuation/Withdrawal from the Trial.

[Dose Modification]

6.4 Treatment of Overdose

Specify what is meant by trial intervention overdose and any known antidote or therapies. Although clinical experience with overdose is often limited in early phases of development, provide any available project-specific guidance and information; however, ensure consistency with and avoid unnecessary duplication with any overdose information in the Investigator's Brochure /package insert. Cross-reference these documents if appropriate. Refer to the approved product label of the comparator (as applicable) for advice on overdose.

[Treatment of Overdose]

6.5 Preparation, Handling, Storage and Accountability

No text is intended here (header only).

6.5.1 Preparation of Trial Intervention

Describe any preparation of the trial intervention and control product and by whom. Discuss the maximum hold time once thawed/mixed, if appropriate, before administration. Include thawing, diluting, mixing, and reconstitution/preparation instructions in this section, as

applicable. For drug/device combination products, include any relevant assembly or use instructions.

If the instructions are lengthy or complicated, it is acceptable to reference the label (if applicable) or include them as a separate document(s) provided to the site (for example, a pharmacy manual). If instructions are provided to the site as a separate document(s), this should be noted in here.

[Trial Intervention Preparation]

6.5.2 Handling and Storage of Trial Intervention

Describe storage and handling requirements (for example, protection from light, temperature, humidity) for the trial intervention and control product. 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).

[Trial Intervention Storage and Handling]

State how the trial intervention and control product will be provided to the Investigator. If applicable, describe the kits, packaging, or other material of the trial intervention for blinding purposes.

6.5.3 Accountability of Trial Intervention

Describe the method by which the accountability will be achieved, including trial intervention will be distributed and related details, including:

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

[Accountability]

6.6 Participant Assignment, Randomisation and Blinding

No text is intended here (header only).

6.6.1 Participant Assignment

Describe the method of assigning participants to trial intervention without being so specific that blinding or randomisation might be compromised. If assignment to trial intervention is by randomisation, describe when randomisation occurs relative to screening. If participants will be assigned to intervention sequences as in a cross-over trial, then describe these sequences.

If adaptive randomisation or other methods of covariate balancing/minimisation are employed, include a cross-reference to the methods of analysis in Section 9, Statistical Considerations. As applicable, details regarding the implementation of procedures to minimise bias should be described.

[Participant Assignment]

6.6.2 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 or not IVRS/IWRS will be used. To maintain the integrity of the blinding, do not include the block size. Describe the use and validation of any computer systems or programmes in randomisation, stratification, and unblinding.

[Randomisation]

6.6.3 Blinding and Unblinding

Describe efforts to ensure that the trial intervention and control products are as indistinguishable as possible. Plans for the maintenance of randomisation codes and appropriate blinding for the trial should be discussed. Procedures for planned and unplanned breaking of randomisation codes should be provided.

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

[Blinding and Unblinding]

Emergency Unblinding

Describe the criteria for breaking the trial blind or participant code. Discuss the circumstances in which the blinding would be broken for an individual or for all participants (for example, for SAEs) and who has responsibility. Include the procedure for emergency unblinding such as via IVRS/IWRS or code envelopes as well as documentation of unblinding. Indicate to whom the intentional and unintentional unblinding should be reported.

[Emergency Unblinding]

6.7 Trial Intervention Compliance

Describe measures employed to ensure and document dosing information and trial intervention compliance (for example, accountability records, diary cards, or concentration measurements). Include a discussion of what documents are mandatory to complete (for example, participant drug log) and what source data/records will be used to document trial intervention compliance.

[Additional Trial Intervention Compliance]

6.8 Concomitant Therapy

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed. Describe the concomitant medications, supplements, complementary and alternative therapies, treatments, and/or procedures which are allowed or prohibited

during the trial, and include details about when the information will be collected (for example, screening, all visits).

[Concomitant Therapy]

6.8.1 Prohibited Concomitant Therapy

If applicable, describe any prohibited concomitant therapy.

[Prohibited Concomitant Therapy]

6.8.2 Permitted Concomitant Therapy

If applicable, describe any permitted concomitant therapy.

[Permitted Concomitant Therapy]

6.8.3 Rescue Therapy

List all medications, treatments, and/or procedures which may be provided during the trial for rescue therapy and provide relevant instructions about the administration of rescue medications. Describe the circumstances under which use of rescue therapy is permitted.

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, Discontinuation of Trial Intervention and Participant Discontinuation/Withdrawal from the Trial.

[Rescue Therapy]

6.8.4 Other Therapy

If applicable, describe the use of other non-investigational or auxiliary therapy, for example, challenge agents.

[Other Therapy]

7 DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT WITHDRAWAL FROM TRIAL

This section must align with the intercurrent events introduced in Section 3, Trial Objectives, Endpoints, and Estimands, and the treatment described in Section 6 Trial Intervention and Concomitant Therapy.

No text is intended here (header only).

7.1 Discontinuation of Trial Intervention

Discontinuation of trial intervention for a participant occurs when trial intervention is stopped earlier than the protocol planned duration.

7.1.1 Criteria for Permanent Discontinuation of Trial Intervention

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

Specify whether participants who discontinue trial intervention can or cannot continue the trial (continue trial visits). Refer to the SoA for assessments to be performed at the time of and following discontinuation of trial intervention.

[Criteria for Permanent Discontinuation of Trial Intervention]

7.1.2 Temporary Discontinuation or Interruption 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.

[Temporary Discontinuation/Interruption of Trial Intervention]

7.1.3 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.

[Rechallenge]

7.2 Participant Withdrawal from the Trial

Describe the criteria for participant withdrawal from the trial.

[Participant Withdrawal from Trial]

7.3 Lost to Follow-Up

Describe how the trial will define and address participants who are lost to follow-up to help limit the amount and impact of missing data. Describe the nature and duration of follow-up, as appropriate.

[Lost to Follow-Up]

7.4 Trial Stopping Rules

If applicable, describe any trial-specific stopping rules, including guidance on when the trial should be stopped for safety reasons, when a cohort or dose escalation should be terminated, and/or when a given treatment arm should be terminated.

[Trial Stopping Rules]

8 TRIAL ASSESSMENTS AND PROCEDURES

- Describe the assessments and procedures required during each phase of the trial that are relevant to the stated endpoints. Provide details that are not already presented in the SoA, taking care not to duplicate information.
- Describe methods, training, tools, instruments/questionnaires, calibration methods, etc. that will be used to record and assess data and ensure consistency across centres and participants. Include instructions on timing/conditions of assessments and if a specifically qualified person should be performing these assessments. Describe whether centralised readings and measurements will be utilised. Describe procedures to be used to maintain the blind.
- Reference the literature for the validation of scales/instruments/questionnaires/assays.
- Instructions or protocols for specialised tests 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 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, volume of blood draws, number of imaging procedures/biopsies, radiation exposure, etc.) if appropriate to the trial.

8.1 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.

[Screening/Baseline Assessments and Procedures]

8.2 Efficacy Assessments and Procedures

Describe efficacy assessments and procedures in this section.

[Efficacy Assessments and Procedures]

8.3 Safety Assessments and Procedures

Describe safety assessments and procedures in this section. Level 3 headings can be added 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).

- Include guidelines for the management of relevant laboratory or other safety assessment abnormalities.

[Safety Assessments and Procedures]

8.3.1 Physical Examination

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

[Physical Examination]

8.3.2 Vital Signs

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

[Vital Signs]

8.3.3 Electrocardiograms

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

[Electrocardiograms]

8.3.4 Clinical Laboratory Assessments

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

- Specify if and when the use of local laboratories is allowed.
- Specify which laboratory parameters should be included in each panel (for example, for haematology, chemistry, urinalysis).

[Clinical Safety Laboratory Assessments]

8.3.5 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 any specific instructions for the collection and interpretation of the assessment

[Suicidal Ideation and Behaviour Risk Monitoring]

8.4 Adverse Events and Serious Adverse Events

No text is intended here (header only).

8.4.1 Definitions of AE and SAE

Specify the AE and SAE definitions.

[AE definition]

[SAE definition]

Additional details and clarifications for AEs and SAEs are in Appendices 12.1 and 12.2.

8.4.2 Time Period and Frequency for Collecting AE and SAE Information

Specify the starting and ending time periods for collecting AEs and SAEs.

[Time period and/or frequency for collecting AEs and SAEs]

8.4.3 Identifying AEs and SAEs

Specify how AEs and SAEs will be identified (for example, spontaneous reporting, solicited questions).

[Identifying AEs and SAEs]

8.4.4 Recording of AEs and SAEs

Specify the Investigator's actions for recording AEs and SAEs, including severity, causality, and the final outcome.

[Recording of AEs and SAEs]

Further details on assessing severity and causality of AEs and SAEs are in Appendices 12.3 and 12.4.

8.4.5 Follow-up of AEs and SAEs

Specify the procedures for follow-up of AEs and SAEs until they are resolved or considered stable. Include the assessment tools that will be used to monitor the events and the duration of follow-up after appearance of the events. Specify any procedures to be used for trials in which death is not an endpoint.

[Follow-up of AEs and SAEs]

8.4.6 Reporting of SAEs

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

[Reporting of SAEs]

8.4.7 Regulatory Reporting Requirements for SAEs

Specify:

- The Sponsor's legal/regulatory responsibilities to report SAEs to regulatory authorities, ethics committees, and investigators.
- The investigators' responsibilities for promptly reporting SAEs to the Sponsor (and to Ethics Committees, where required) to allow the Sponsor to meet their responsibilities.

8.4.8 Serious and Unexpected Adverse Reaction Reporting

Include this section, if applicable.

[Serious and Unexpected Adverse Reaction Reporting]

8.4.9 Adverse Events of Special Interest

Include this section, if applicable.

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 and death events, medical device incidents (including malfunctions), laboratory test abnormalities, and trial intervention overdose.

Include the following for each AESI:

- The definition of the event. Specify the MedDRA preferred terms to use to report the AESI.
- 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.

[Adverse Events of Special Interest]

8.4.10 Disease-related Events or Outcomes Not Qualifying as AEs or SAEs

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

[Disease-related Events or Outcomes not Qualifying as AEs or SAEs]

8.5 Pregnancy and Postpartum Information

No text is intended here (header only).

8.5.1 Participants Who Become Pregnant During the Trial

Specify

- the assessments to be performed,
- type and duration of monitoring, and
- what information will be collected for 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.

Specify that pregnancy is not an AE, unless a negative or consequential outcome occurs in the participant or child/foetus. 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 8.4.5, Reporting of SAEs.

[Participants Who Become Pregnant During the Trial]

8.5.2 Participants Whose Partners Become Pregnant

Specify:

- If the investigator will attempt to collect pregnancy information for a participant's partner, who becomes pregnant while the participant is in the trial.
- The assessments to be performed, type and duration of monitoring, and what information will be collected.

[Participants Whose Partners Become Pregnant]

8.6 Medical Device Product Complaints for Drug/Device Combination Products

Optional section to include for drug/device combination products.

8.6.1 Definition of Medical Device Product Complaints

[Definition of Medical Device Product Complaints]

8.6.2 Recording of Medical Device Product Complaints

Optional section to specify the investigator's actions for recording product complaints, including the final complaint outcome.

[Recording of Medical Device Product Complaints]

8.6.3 Time Period and Frequency for Collecting Medical Device Product Complaints

Optional section to specify the start and ending time periods for collecting Medical Device Product Complaints (for example, from when the medical device use begins to end of trial participation).

[Time Period and Frequency for Collecting Medical Device Product Complaints]

8.6.4 Follow-Up of Medical Device Product Complaints

[Follow-up of Medical Device Product Complaints]

8.6.5 Regulatory Reporting Requirements for Medical Device Product Complaints

Optional section to specify the investigators' responsibilities for reporting Medical Device Product Complaints (for example, within 24 hours) to the Sponsor.

[Reporting of Medical Device Product Complaints]

8.7 Pharmacokinetics

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

- Specific sample collection and processing instructions can be described in an appendix or a separate document and cross-referenced.
- Describe the biological sample(s) collected, the handling of samples, and the assay method.

[Pharmacokinetics]

8.8 Genetics

Include any specific instructions for the collection of samples for genetic analysis.

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

[Genetics]

8.9 Biomarkers

Include any specific instructions for the collection of samples and interpretation of biomarkers, including pharmacodynamics.

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

[Biomarkers]

8.10 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.

[Immunogenicity Assessments]

8.11 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.

[Medical Resource Utilisation and Health Economics]

9 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 statistical considerations section.

Provide a statement with regard to when the primary analyses will be conducted. For example: The analysis will be conducted on all participant data at the time the trial ends.

[Statistical Considerations]

9.1 Analysis Sets

Analysis sets to support each analysis will be specified here and described in the Statistical Analysis Plan.

[Analysis Datasets]

9.2 Analyses Supporting Primary Objective(s)

This section introduces the Statistical Analysis Plan, with the detail to be provided in the subsequent subsections. This includes describing the methods of estimation (analytic approach) in alignment with how the estimands are defined. Sensitivity analyses should be aligned with how the estimands and estimators are defined.

[Analysis Supporting Primary Objectives]

9.2.1 Statistical Model, Hypothesis, and Method of Analysis

Ensure that the statistical hypothesis/model (and corresponding assumptions)/analysis is aligned with the primary estimand(s).

For all applicable objectives (for example, primary, secondary), under the appropriate header, state the null and alternative hypotheses, including the pre-planned type 1 error, or alternative criteria to define trial success 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 applicable, state and discuss any adjustments to account for multiplicity.

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.

[Statistical Model, Hypothesis, and Method of Analysis]

9.2.2 Handling of Intercurrent Events of 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.

[Handling of Intercurrent Events of Primary Estimand]

9.2.3 Handling of Missing Data

This section should describe how missing data will be dealt with. Refer to the E9(R1) addendum when estimand framework is used.

The protocol should describe how missing data will be handled (for example, type of imputation technique, if any, and provide justification)

In cases where the Primary Objective is related to safety, this section should also be completed. It may also be helpful to include additional statements regarding handling of missing data in general for other important efficacy or safety endpoints or this information can be included in the analysis of secondary endpoint section below.

[Handling of Missing Data]

9.2.4 Sensitivity Analysis

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.

[Sensitivity Analysis]

9.2.5 Supplementary Analysis

Describe any supplementary analysis if applicable.

[Supplementary Analysis]

9.3 Analysis Supporting Secondary Objective(s)

This section should focus on estimands for Secondary Objectives.

In this section describe the statistical analysis, handling of intercurrent events, handling of missing data, and if applicable, sensitivity analysis corresponding to each secondary estimand.

[Analyses Supporting Secondary Objectives]

9.4 Analysis of Exploratory Objective(s)

[Analyses Supporting Tertiary/Exploratory Objective(s)]

9.5 Safety Analyses

If safety is a primary and/or secondary objective, describe the corresponding safety analyses in the appropriate section above (Section 9.2 or Section 9.3).

[Safety Analyses]

9.6 Other Analyses

Describe Other Analyses such as Subgroup analyses, Adjusted analysis if needed.

[Other Analyses]

9.7 Interim Analyses

Describe any interim analysis and criteria for stopping or adapting the trial.

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

- Any interim analysis plan, even if it is only to be performed at the request of an oversight body (for example, DMC).
- Describe (briefly and concisely) and reference the applied statistical method, for example, group sequential test and spending function (for example, O'Brien-Fleming), as applicable.
- Who will perform the analyses.
- When they 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 any adaptations to the trial are made.
- Who has the ultimate authority to stop or modify the trial, for example, investigator, principal investigator, Data Monitoring Committee, or sponsor.
- The stopping guidelines.
- If pre-specified interim analyses are to be used for other trial adaptations such as sample size re-estimation, alteration to the proportion of participants allocated to each trial group, and changes to eligibility criteria.

[Interim Analyses]

9.8 Sample Size Determination

This section should detail the methods used for the determination of the sample size and a reference to tables or statistical software used to carry out the calculation. Sufficient information should be provided so that the sample size calculation can be reproduced or described.

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).

[Sample Size Determination]

9.9 Protocol Deviations

Plans for detecting, reviewing, and reporting any deviations from the protocol should be described.

[Protocol Deviations Plans]

10 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

No text is intended here (header only).

10.1 Regulatory and Ethical Considerations

List 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:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
- ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

List the investigators' and sponsor's responsibilities in this regard.

Investigator Responsibilities

[Investigator Responsibilities]

Sponsor Responsibilities

[Sponsor Responsibilities]

10.2 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.

[Committees Structure]

10.3 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).

[Informed Consent Process]

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

[Emergency Consent Process]

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.

[Consent Requirements for Rescreening]

[Additional ICF text for Use of Remaining Samples in Optional Exploratory Research]

10.4 Data Protection

Describe how personal data will be protected and any measures that should be taken in case of a data security breach.

[Data Protection]

10.5 Early Site Closure or Trial Termination

List the decision rights of sponsor or designee to close a site or terminate the trial. Likewise, list the investigator's right to initiate site closure.

[Decision Rights for Site Closure and Trial Termination]

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

[Criteria for Early Closure]

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

[Responsibilities following Termination or Suspension]

11 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

No text is intended here (header only).

11.1 Quality Tolerance Limits

Indicate where Quality Tolerance Limits will be predefined, how they will be monitored during the trial, and expected discussion in the clinical trial report.

[QTL]

11.2 Data Quality Assurance

Delineate the responsibilities of the Sponsor with respect to data quality assurance.

[Sponsor or Designee Responsibilities for Data Quality Assurance]

[Investigator Responsibilities for Data Quality Assurance]

11.3 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).

[Source Data Introduction]

[Investigator Expectations for Source Data]

[Trial Monitor Expectations for Source Data]

[Definition of Source Data]

12 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY

No text is intended here (header only).

12.1 Further Details and Clarifications on the AE Definition

Specify:

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

12.2 Further Details and Clarifications on the SAE Definition

Specify:

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

12.3 Severity

Specify the severity rating categories/scale.

[Severity]

12.4 Causality

Specify:

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

[Causality]

13 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

No text is intended here (header only).

13.1 Contraception and Pregnancy Testing

No text is intended here (header only).

13.1.1 Definitions Related to Childbearing Potential

Optional section to specify the definitions of:

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

[Definitions Related to Childbearing Potential]

13.1.2 Contraception

Optional section to specify the:

- Contraceptive methods required
- Duration of use

[Contraception]

13.1.3 Pregnancy Testing

Optional section to specify pregnancy testing requirements.

[Pregnancy Testing]

13.2 Clinical Laboratory Tests

Provide additional information, if needed, about clinical laboratory tests, such as

- whether they will be performed by a central or local laboratory (if important to distinguish)
- specific analytes or parameters included in a panel
- equations and references for locally calculated labs
- 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.

A tabular presentation for such information is common.

[Clinical Laboratory Tests]

13.3 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.

[Country/Region-specific Differences]

13.4 Prior Protocol Amendments

Choose the appropriate text.

{This protocol has not been amended.}

or

{The Protocol Amendment Summary of Changes for the current amendment is located directly before the Table of Contents. Details of prior amendments are presented below, beginning with the most recent}.

See the instructions in the Protocol Amendment Summary of Changes located before the Table of Contents. Move all Protocol Amendment Summaries of Changes for previous amendments to this section in reverse chronological order (most recent first).

Amendment {amendment number}: ({date})

{Amendment details from this amendment}

Add additional amendments/details as protocol amendments accrue.

Amendment {amendment number}: ({date})

{Amendment details from this amendment}

14 APPENDIX: GLOSSARY OF TERMS

Define abbreviations and other terms used in the protocol. Abbreviations do not need to be defined at first mention within the protocol, and definition of abbreviations in common usage is not necessary (for example, *DNA*). A tabular presentation is common.

Ensure the following terms are clearly defined within the protocol unless not applicable to the trial:

- Pre-screening
- Screening
- Enrollment
- Product Complaint

[Abbreviations and Definitions]

15 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.

[References]