M11 Clinical Electronic Structured Harmonized Protocol (CeSHarP)

Guidance for Industry

M11 Template

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2026
ICH-Multidisciplinary

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U.S. Department of Health and Human Services
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ICH-Multidisciplinary

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

Final version

Adopted on 19 November 2025

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

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 27 September 2022)	27 September 2022
M11	Updated *Step 2* Draft provided as reference only for second round of public consultation of the M11 Technical Specification (document dated 03 Feb 2025)	03 February 2025
M11	Adoption by the Regulatory Members of the ICH Assembly under *Step 4*.	19 November 2025

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 trial protocols and 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 trials. 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 during the development of this template. Where guidelines are cited, 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 text consistent with the sponsor's preferred typeface 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 with pre-defined valid values (i.e., a pick list) in the electronic manifestation of the protocol
Text insertion point	<Chevrons> in the prevailing typeface with grey shading When complete, remove chevrons and restyle text to match other text in the final document	Chevrons are used to indicate where to insert text Any text within chevrons is intended to be replaced by applicable content
Instructional text	Red Calibri font	Instructional text that is to be removed prior to finalisation of the protocol

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 headings Retain heading and indicate "Not applicable"	**Do not add** L1 headings
1.1	Level 2 (L2)	14 point **Times New Roman Bold Black**	**Do not delete or modify** L2 headings Retain heading and indicate "Not applicable"	Add L2 headings, if needed, at the end of the higher-level section to preserve the established L1 and L2 headings 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 unless otherwise specified 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 trial	Add L3 headings, if needed, at the end of the higher-level section to preserve the established L1, L2 and L3 headings structure
1.1.1.1	Level 4 (L4)	12 point **Times New Roman Bold Black**	**Do not delete or modify** L4 headings that appear in black text unless otherwise specified Retain heading and indicate "Not applicable" L4 headings that appear in blue text are optional and may be retained, deleted or	Add L4 headings, if needed, at the end of the higher-level section to preserve the established L1, L2, L3 and L4 headings structure

Example Heading	Heading Level	Typeface in this Template	Modification or Deletion	Addition
			modified as applicable to the trial	
Additional Non-Numbered Heading	Non-numbered heading	12 point **Times New Roman Bold Black**	**Do not delete or modify** non-numbered headings that appear in black text unless otherwise specified Retain heading and indicate "Not applicable" Non-numbered headings that appear in blue text are optional and may be retained, deleted or modified as applicable to the trial	Insert where needed

Table and Figure Numbering

Tables and figures should be numbered sequentially and should 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 to participate in the clinical trial (including consent by participant's legally acceptable representative when relevant). *Patient* or *individual* is used to distinguish the population represented by the trial participants, when necessary.
- *Trial intervention* is used to refer to any pre-specified therapeutic, prophylactic, or diagnostic agent including pharmaceuticals, biologics, vaccines, cell or gene therapy products, and drug-device combination products when registered as a drug, intended for

the participants during the trial. Procedures conducted to manage participants or to collect data are excluded from the usage of this term. Refer to Section 6 for additional details.

- While *blinding* is the more commonly used term, *masking* is an alternative term that 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 not applicable optional level 3 or lower headings and ensure remaining level 3 or 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
- remove brackets after making appropriate selections

0.4 Abbreviations Used in This Template

Abbreviation or Acronym	Definition
AE	Adverse event
AESI	Adverse event of special interest
AxMP	Auxiliary medicinal product
CIOMS	Council for International Organisations of Medical Sciences
COA	Clinical outcome assessment
CRF	Case report form
DMC	Data monitoring committee
DRE	Disease-related event
DRO	Disease-related outcome
ECG	Electrocardiogram
EU	European Union
GCP	Good Clinical Practice
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational medicinal product
IND	Investigational new drug
INN	International nonproprietary name
IP	Investigational product
IRB	Institutional review board
IRT	Interactive Response Technology
jRCT	Japan Registry of Clinical Trials
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	Noninvestigational medicinal product *or* Auxiliary medicinal product
PK	Pharmacokinetic(s)
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. 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.
Original Protocol:	[Original Protocol Indicator]
Version Number:	<Enter Version Number> For use by the sponsor at their discretion.
Version Date:	<Enter Version Date> 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, delete this row or enter "Not applicable".

{**Amendment Scope:**}	{[Amendment Scope]} {[Country Identifier] or [Region Identifier] or <Enter Site Identifier>} If this is the original instance of the protocol, delete this row or enter "Not applicable". For an amendment that applies to all sites in the trial, enter “Global” and delete the Country, Region and Site Identifier fields. If amending a single-country trial, enter “Global”. For an amendment that does not apply to all sites in the trial, select “Not Global” and utilise one of the identifiers based on amendment scope.
Sponsor’s Investigational Product Code(s):	<Enter Sponsor’s Investigational Product Code(s)> Enter the sponsor’s unique identifier for investigational product(s) in the trial. Add fields as needed.
Investigational Product Name(s):	<Enter Nonproprietary Name(s)> <Enter Proprietary Name(s)> Omit nonproprietary name field if a nonproprietary name has not yet been assigned. Omit proprietary name field if not yet established.
Trial Phase:	[Trial Phase] 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 should be 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 consent forms (ICFs) and ethics committee submissions.

Sponsor Name and Address:	<Enter Sponsor Name> <Enter Sponsor Legal Address> Co-Sponsor Name and Address: <Enter Co-Sponsor Name> <Enter Co-Sponsor Legal Address> Provide the legal name and address 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 the Sponsor Name and Sponsor Legal Address fields. If co-sponsor is applicable, enter co-sponsor name and legal address. Add additional fields if more than one co-sponsor is applicable. Local Sponsor Name and Address: <Enter Local Sponsor Name> <Enter Local Sponsor Legal Address> In some countries, the clinical trial sponsor may be the local affiliate company (or designee). In such cases, indicate this in the Local Sponsor Name and Local Sponsor Legal Address Fields.
Device Manufacturer Name and Address:	<Enter Device Manufacturer Name> <Enter Device Manufacturer Legal Address> Manufacturer name and address information is required only for drug/device combination 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 or if there are multiple manufacturers for a single device. Delete this line if not applicable.

Regulatory or Clinical Trial Identifier(s):	<EU CT Number> <FDA IND Number> <IDE Number> <jRCT Number> <NCT Number> <NMPA IND Number> <WHO/UTN Number> <Other Regulatory or Clinical Trial Identifier> Include all identifiers that are applicable for the trial and available at the time of protocol or amendment finalisation. Delete prompts for identifiers not available at the time of document finalisation. Delete unused fields. Add fields for "other" if more than one is needed.
Sponsor Approval:	{<Enter Sponsor Approval Date> or <State location where sponsor approval information can be found>} All versions should be uniquely identifiable.

Sponsor Signatory: {<Enter sponsor signatory (e.g., name, title, signature and date)> or <State location where sponsor signatory information can be found (e.g., electronic signature)>}

Medical Expert Contact: {<Enter Medical Expert contact information (as designated by sponsor)> or <State location where Medical Expert contact information can be found>}

Amendment Details

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

{This protocol has not been amended.}

Or

{This is the first protocol amendment.}

Or include the below

{This protocol has been amended previously. Details of prior amendments are presented in Section 12.3 Prior Protocol Amendment(s).}

{Current Amendment}

{The table below describes the current amendment.}

Approximate <#/%> Enrolled at Time of Sponsor Approval:	Approximately <#/%> enrolled <enter Amendment Scope Enrollment Definition> 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 percentage 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 the sponsor approved the amendment. • For global amendments providing (or 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, list the status of all the relevant locations. 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]} *	Secondary: {[Secondary Reason for Amendment]} *

{Amendment Summary:}	{<Amendment Summary>} Briefly describe key changes. Changes that 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 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 new Overview of Changes 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 (e.g., change to 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 itemised in this table.
- The changes listed 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 Change>	<Enter Brief Rationale for Change>	<Enter Section # and Name>

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1 PROTOCOL SUMMARY

No text is intended here (heading only).

1.1 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 (heading only).

1.1.1 Primary and Secondary Objectives and Estimands

Summarise the primary and secondary objectives and any associated estimands in natural, nontechnical (layperson) language.

For trials intended to estimate a treatment effect or test a hypothesis related to a treatment effect, include the primary and secondary objectives and any associated estimands using a nontechnical summary describing the objective and treatment effect of interest (estimand).

For other types of trials not intended to estimate a treatment effect or test a hypothesis related to a treatment effect, define trial objectives and describe additional information relevant to the clinical question(s) of interest (e.g., the endpoint(s) associated with each objective).

For trials with numerous objectives in which the description of objectives will exceed half a page, consider including the most important objectives and estimands in the synopsis and refer to Section 3 Trial Objectives and Associated Estimands, which covers the objectives and estimands in technical detail. For considerations on estimands, refer to ICH E9(R1).

<Enter Primary and Secondary Objectives and Estimands>

1.1.2 Overall Design

Key aspects of the trial design are summarised below.

Intervention:	{<Enter Sponsor's Investigational Product Code(s)> And/or <Enter Nonproprietary Name(s)>}	**Population Type:**	[Population Type]
Intervention Model:	[Intervention Model]	**Population Diagnosis or Condition:**	[Population Diagnosis or Condition]

Control Type:	[Control Type]	**Population Age:**	Minimum: <Enter Minimum Age> [Units of Age] Maximum: <Enter Maximum Age> [Units of Age]
Control Description:	{[Nonproprietary Name] or [INN] or <Enter "Not applicable">}	**Site Distribution and Geographic Scope:**	[Site Distribution] [Site Geographic Scope]
Intervention Assignment Method: **Stratification**	[Intervention Assignment Method] If Intervention Assignment Method is "Randomisation" then enter {<Randomisation Type>} If Intervention Assignment Method is "Other" then enter {<Other Intervention Assignment Method>} [Stratification Indicator]	**Master Protocol:**	[Master Protocol Indicator]
Drug/Device Combination Product Indicator:	[Drug/Device Combination Product Indicator]	**Adaptive Trial Design:**	[Adaptive Trial Design Indicator]

Further clarification:

- Control Description: if active comparator or low dose, pick nonproprietary name or International Nonproprietary Name; indicate "Not applicable" if not applicable.
- Intervention Assignment Method: If applicable, describe the type of randomisation to be used (e.g., simple randomisation, block randomisation). If applicable,, describe the other intervention assignment method.

- Population Diagnosis or Condition: MedDRA Preferred Term(s) or indicate "other" and describe.
- Population Age: for trials in which multiple age ranges may be eligible (e.g., 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**]**

Select 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. Additional details can be provided in Section 6.7.3 Measures to Maintain Blinding.

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 a trial intervention. When duration will vary, provide a short explanation (e.g., "event-driven" or "adaptive design").

Total planned duration of trial intervention for each participant:

{<Enter total planned duration of trial intervention> [total planned duration of trial intervention unit of time]}

Or, if duration will vary

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

Total planned duration of trial participation for each participant:

{<Enter total planned duration of trial participation> [total planned duration of trial participation unit of time]}

Or, if duration will vary

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

If necessary, include any clarifications or cross references to details 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 Committees.

Independent Committees: <Enter Independent Committees>

Other Committees: <Enter 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 participant through the progression of trial period(s)/epochs (such as screening, washout/run-in, intervention, and key milestones [e.g., 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>

1.3 Schedule of Activities

The schedule of activities must capture the procedures that will be accomplished at each trial visit, and all contact with participants (e.g., 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 (e.g., serial PK sampling), a separate table may be added.

<Enter Schedule of Activities>

2 INTRODUCTION

No text is intended here (heading only).

2.1 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; rather, cross reference to the IB as applicable to the description.

<Enter Purpose of Trial>

2.2 Assessment of Risks and Benefits

Include an assessment of known and potential risks and benefits, if any, as a result of participating in the trial from the perspective of an individual participant, including the basis of the risk (e.g., nonclinical trials or prior clinical trials). This section may be structured under one single heading 2.2 Assessment of Risks and Benefits, or if applicable under 3 subheadings as 2.2.1 Risk Summary and Mitigation Strategy, 2.2.2 Benefit Summary and 2.2.3 Overall Risk-Benefit Assessment

2.2.1 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 – Describe risks associated with the design (e.g., placebo arm) and procedures specific to this trial (e.g., 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.

<Enter Trial-specific Procedure Risks and Mitigations>

Other – Consider risks associated with other items (e.g., 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>

2.2.2 Benefit Summary

The benefit summary should describe any physical, psychological, social, or 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 or trials in healthy participants, 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>

2.2.3 Overall Risk-Benefit Assessment

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 Risk-Benefit Assessment>

3 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, refer to ICH E9(R1). Ensure alignment with every other section of the protocol.

Include additional level 3 headings (e.g., add a new level 3 heading for each secondary objective as needed). If there is more than one objective in a category (e.g., more than one secondary objective), number each objective consecutively as the level 3 heading (e.g., Secondary Objective 1, Secondary Objective 2, etc.).

No text is intended here (heading only).

3.1 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, nontechnical language for clear understanding by 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 population targeted by the clinical question, the treatment condition(s), the endpoint (or variable), and the population-level summary. Precise specifications of treatment, population, and variable are likely to address many of the intercurrent events. Other intercurrent events not already addressed in the clinical question of interest by the aforementioned attributes should be described with their associated strategies. 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 (at a minimum, present the endpoint(s) associated with each objective).

No text is intended here (heading only).

3.1.1 Primary Objective <#>

<Enter Primary Objective>

Enter information in table of estimand characteristics below including endpoint at a minimum.

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 treatment 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>}
{Other Intercurrent Event}	**{Strategy}**
{<Enter Description of Intercurrent Event>}	Description of the strategy to address the intercurrent event (e.g., a treatment policy strategy); cross reference the justification in Section 4 Trial Design. If there is >1 intercurrent event for an objective, add additional intercurrent event rows. {<Enter Intercurrent Event Strategy>}

3.2 Secondary Objective(s) and Associated Estimand(s)

Describe the secondary objective(s) and associated estimand(s) as outlined in Section 3.1 Primary Objective(s) and Associated Estimand(s). Use the same approach as above and include table for a precise estimand description.

No text is intended here (heading only) unless there is no secondary objective, in which case indicate “Not applicable”.

3.2.1 {Secondary Objective <#>}

{<Enter Secondary Objective>}

If a Secondary Objective has been entered, enter information in table of estimand characteristics below including endpoint at a minimum:

{<Enter Table of Estimand Characteristics >}

3.3 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. Use the same approach as above and include table for a precise estimand description.

No text is intended here (heading only) unless there is no exploratory objective, in which case indicate “Not applicable”.

3.3.1 {Exploratory Objective <#>}

{<Enter Exploratory Objective>}

If an Exploratory Objective has been entered, enter information in table of estimand characteristics below including endpoint at a minimum:

{<Enter Table of Estimand Characteristics >}

4 TRIAL DESIGN

In the subsections 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 Trial Objectives and Associated Estimands.

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.

No text is intended here (heading only).

4.1 Description of Trial Design

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

If applicable, indicate other design characteristics (e.g., superiority, noninferiority, dose escalation, or equivalence).

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

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

<Enter Overall Description of Trial Design and 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 (e.g., 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 and the level and method of blinding that will be used, with cross reference to Section 6.7 Investigational Trial Intervention Assignment, Randomisation and Blinding.

<Enter Description of Method of Assignment to Trial Intervention>

<Enter Description of Level and Method of Blinding>

Describe any other important aspects of the design, e.g.:

- geographic scope of trial (e.g., single-centre, multicentre, or multicentre and multinational)
- use of decentralised elements 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; if so, refer to details in Section 10.9 Interim Analyses
- any planned extension trial, long-term follow-up/registry, future use of samples or data, or post-trial sample analysis or other data-related activities

<Enter Additional Description of Trial Design>

4.1.1 Stakeholder Input into Design

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

<Enter Stakeholder Input into Design>

4.2 Rationale for Trial Design

{<Enter Overall Rationale for Trial Design>} if not using below optional subheadings.

OR

4.2.1 Rationale for Estimand(s)

When estimands are associated with the Primary and Secondary Objectives described in Section 3 Trial Objectives and Associated Estimands, provide a rationale for the estimand(s) not described elsewhere in the document. 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(s). It should also include a rationale for the selected strategies for handling intercurrent events.

<Enter Rationale for Estimand(s)>

4.2.2 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 6.2 Rationale for Investigational Trial Intervention Dose and Regimen. Rationale for choice of comparator, if applicable, should be described separately in Section 4.2.3 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>

4.2.3 Rationale for Control Type

If applicable, provide a rationale for the type and choice of control selected for the trial (e.g., placebo, active drug, combination, external). 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 and/or dose

regimen is explained in Section 6.2 Rationale for Investigational Trial Intervention Dose and Regimen.

<Enter Rationale for Control Type>

4.2.4 Rationale for Trial 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 Trial Duration>

4.2.5 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 Trial Design>

4.2.6 Rationale for Interim Analysis

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

<Enter Rationale for Interim Analysis>

4.2.7 Rationale for Other Trial Design Aspects

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

<Enter Rationale for Other Trial Design Aspects>

4.3 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-specific stopping rules are aligned with the specifications that are described in Section 10.9 Interim Analyses.

<Enter Trial Stopping Rules>

4.4 Start of Trial and End of Trial

Define key timepoints in the trial, including trial start and end definitions (e.g., a key timepoint definition for start of trial might be when the ICF 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). Consider local regulatory requirements for these and other definitions (e.g., the first act of recruitment).

If appropriate, provide a cross reference to Section 11.11 Early Site Closure.

<Enter Start of Trial>

<Enter End of Trial>

4.5 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 in Section 4.1 Description of Trial Design, do not need to be repeated in this section.

<Enter Access to Trial Intervention After End of Trial>

5 TRIAL POPULATION

In the subsections 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 Trial Objectives and Associated Estimands.

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 and any documentation needed to demonstrate the criterion is met (e.g., laboratory tests or imaging). 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 (heading only).

5.1 Description of Trial Population and Rationale

Describe the population selected (e.g., healthy participants, adult participants, paediatric participants, pregnant participants, or breastfeeding participants) and how the enrollment criteria reflect the populations that are likely to use the drug if approved. Specify the population age range (e.g., ≤ 3 months, ≥ 18 to ≤ 80 years old) including the timepoint at which qualification for age criteria is determined (e.g., at time of screening vs randomisation for paediatric trials). Specify any key diagnostic criteria for the population (e.g., “acute lung injury”, or a specific biomarker profile). If applicable, describe similar conditions or diseases and their differential diagnosis.

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 reflect the population of interest.

If a clinical question targets a subset of the entire trial population, such as one defined by a baseline characteristic (e.g., a specific biomarker), the rationale for selecting this subset should be provided in this section.

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 (e.g., 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.

5.2 Inclusion Criteria

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

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

<#> <Enter Inclusion Criterion>

Add criteria as needed. Consider numbering the criteria sequentially.

5.3 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:

<#> <Enter Exclusion Criterion>

Add criteria as needed. Consider numbering the criteria sequentially.

5.4 Contraception

No text is intended here (heading only).

5.4.1 Definitions Related to Childbearing Potential

Specify the definitions of:

- participant of childbearing potential
- participant of nonchildbearing potential

<Enter Definitions Related to Childbearing Potential >

5.4.2 Contraception Requirements

Specify the:

- contraceptive methods required
- duration of use

<Enter Contraception Requirements.>

5.5 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>}

5.5.1 Meals and Dietary Restrictions

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

<Enter Meals and Dietary Restrictions>

5.5.2 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>

5.5.3 Physical Activity Restrictions

If applicable, describe any restrictions on physical activity (e.g., participants may be required to remain in bed for 4 to 6 hours after dosing).

<Enter Physical Activity Restrictions>

5.5.4 Other Activity Restrictions

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

<Enter Other Activity Restrictions>

5.6 Screen Failure and Rescreening

Describe screen failure and indicate how screen failure will be handled in the trial, including conditions and criteria under 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>

6 TRIAL INTERVENTION AND CONCOMITANT THERAPY

Trial interventions are all pre-specified investigational and noninvestigational medicinal products, medical devices or other interventions intended for the participants during the trial. The investigational trial intervention is the product(s) used in the trial as part of trial objectives,

including control(s) (e.g., active comparator, placebo). Description of the investigational trial intervention is provided in Section 6.1 Description of Investigational Trial Intervention. Other trial interventions that are not part of trial objectives or do not have an investigational role in this trial are described in Section 6.9 Description of Noninvestigational Trial Intervention.

Any regional requirements should be noted in the appropriate subsections.

Provide an overview of investigational and noninvestigational trial interventions. Designate the trial intervention as IMP or NIMP/AxMP based on trial design and regional requirements. Consider the optional table below.

<Enter description of the overview of trial interventions or a heading for the optional table>

Arm Name	Arm Type	Intervention Name	Intervention Type	Pharmaceutical Dose Form	Dosage Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP/NIMP	Sourcing
<Enter Arm Name>	[Select Arm Type]	<Enter Intervention Name>	[Select Intervention Type]	[Select Pharmaceutical Dose Form]	<Enter Dosage Strength(s)>	<Enter Dosage Level(s)>	[Select Route of Administration]	<Enter Regimen/Treatment Period/Vaccination Regimen>	[Select Use]	[Select IMP or NIMP]	[Select Sourcing]

IMP=Investigational Medicinal Product; NIMP=NonInvestigational/Auxiliary Medicinal Product.

6.1 Description of Investigational Trial Intervention

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 investigational 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>

6.2 Rationale for Investigational Trial Intervention Dose and Regimen

Provide a rationale for the selection of the dose(s) or dose range, pharmaceutical dose form, route of administration, and dosing regimen of the investigational trial interventions, as applicable. This rationale should include relevant results from nonclinical studies and clinical trials that support selection of the dose and regimen. Discuss impact of differences in trial population characteristics (e.g., age, sex, race) that could lead to differences in pharmacokinetics and pharmacodynamics in this trial as compared to previous trials. 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 trial intervention.

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

<Enter Rationale for Investigational Trial Intervention Dose and Regimen>

6.3 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 (e.g., time of day, interval), the duration (e.g., the length of time participants will be administered the investigational trial intervention), and the timing of dosing relative to meals.

Include any specific instructions on who, when or how to prepare and take the dose(s) and how to handle any delayed or missed doses.

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>

6.4 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 described in Section 7 Participant Discontinuation of Trial Intervention and Discontinuation or Withdrawal from Trial.

<Enter Investigational Trial Intervention Dose Modification>

6.5 Management of Investigational Trial Intervention Overdose

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

<Enter Management of Investigational Trial Intervention Overdose>

6.6 Preparation, Storage, Handling and Accountability of Investigational Trial Intervention

No text is intended here (heading only).

6.6.1 Preparation of Investigational Trial Intervention

Describe any preparation of the investigational trial intervention, and when necessary, who should prepare it. 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 separate documents provided to the site (e.g., a pharmacy manual) and reference the separate documents.

<Enter Preparation of Investigational Trial Intervention >

6.6.2 Storage and Handling of Investigational Trial Intervention

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

Explain how the investigational trial intervention will be provided to the investigator. If applicable, include details about 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 separate documents provided to the site (e.g., a pharmacy manual) and reference the separate documents.

<Enter Storage and Handling of Investigational Trial Intervention>

6.6.3 Accountability of Investigational Trial Intervention

Describe the accountability method, including:

- how the investigational trial intervention will be distributed
- who will distribute the investigational trial intervention
- participation of a drug storage repository or pharmacy, if applicable
- plans for disposal or return of unused product
- plans for reconciliation of investigational trial intervention, if applicable

<Enter Accountability of Investigational Trial Intervention>

6.7 Investigational Trial Intervention Assignment, Randomisation and Blinding

No text is intended here (heading only).

6.7.1 Participant Assignment to Investigational Trial Intervention

State that at enrollment, participant identification codes should be assigned. 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 will occur relative to screening.

If permuted block randomisation is employed, do not state the block size in the protocol. 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>

6.7.2 {Randomisation}

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

{<Enter Randomisation>}

6.7.3 {Measures to Maintain Blinding}

Describe measures that will be used to maintain blinding:

- The investigational trial interventions are as indistinguishable as possible
- Plans for the maintenance of randomisation codes and appropriate blinding for the trial
- Procedures for planned (e.g., interim analysis) and unintentional (e.g., breach of procedure) breaking of randomisation codes

For unplanned but intentional actions (e.g., safety events), refer to Section 6.7.4 Emergency Unblinding at the Site.

If the trial allows for some investigators or other designated staff to remain unblinded (e.g., 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 Measures to Maintain Blinding>}

6.7.4 {Emergency Unblinding at the Site}

Describe the criteria for breaking the trial blind or participant code. Describe the circumstances that would require breaking the blind, either for an individual participant or for all participants, and specify who will be responsible for this decision. Include the procedure for emergency unblinding as well as documentation of unblinding. Indicate to whom the intentional and unplanned unblinding should be reported.

{<Enter Emergency Unblinding at the Site>}

6.8 Investigational Trial Intervention Adherence

Describe the measures to monitor and document participants' adherence to investigational trial intervention (e.g., trial intervention accountability records, paper or electronic diaries, or investigational trial intervention concentration measurements).

List what documents are mandatory to complete (e.g., participant drug log) and identify which records will be used as the source records for documenting investigational trial intervention adherence.

<Enter Investigational Trial Intervention Adherence>

6.9 Description of Noninvestigational Trial Intervention

As stated in Section 6 Trial Intervention and Concomitant Therapy, noninvestigational interventions are pre-specified products used in the trial but are not part of trial objectives and hence, are not investigational trial interventions.

<Enter Description of Noninvestigational Trial Intervention>

6.9.1 {Background Trial Intervention}

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

{<Enter Background Trial Intervention>}

6.9.2 {Rescue Therapy}

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

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

{<Enter Rescue Therapy>}

6.9.3 {Other Noninvestigational Trial Intervention}

If applicable, describe the use of any other noninvestigational trial intervention (e.g., challenge agents or diagnostics).

{<Enter Other Noninvestigational Trial Intervention>}

6.10 Concomitant Therapy

Specify the concomitant medications, supplements, complementary and alternative therapies, treatments, and/or procedures that are prohibited or permitted during the trial and include details about when the information will be collected (e.g., during screening, at each visit).

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

<Enter Concomitant Therapy>

6.10.1 {Prohibited Concomitant Therapy}

If applicable, describe any prohibited concomitant therapy.

{<Enter Prohibited Concomitant Therapy>}

6.10.2 {Permitted Concomitant Therapy}

If applicable, describe any permitted concomitant therapy.

{<Enter Permitted Concomitant Therapy>}

7 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 Associated Estimands, and with the investigational trial intervention described in Section 6 Trial Intervention and Concomitant Therapy.

No text is intended here (heading only).

7.1 Discontinuation of Trial Intervention for Individual Participants

No text is intended here (heading only).

7.1.1 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

- how participants who discontinue trial intervention will be followed after discontinuation. Depending on the chosen intercurrent event handling strategy, it will be important to continue to follow and ascertain outcomes in participants who discontinue trial intervention through the end of the trial to prevent missing data in important analyses. Refer to Section 1.3 Schedule of Activities for assessments to be performed at the time of and following discontinuation of trial intervention
- the process for collecting and recording the detailed reasons for discontinuing trial intervention if not described elsewhere

<Enter Permanent Discontinuation of Trial Intervention>

7.1.2 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 has to temporarily discontinue or interrupt trial intervention
- which assessments will be performed for the stated duration of the trial

Details of any rechallenge or restart after temporary discontinuation of trial intervention due to a safety-related event should be included in Section 7.1.3 Rechallenge.

<Enter Temporary Discontinuation of Trial Intervention>

7.1.3 Rechallenge

Describe the criteria for rechallenge/restarting trial intervention, how and when to perform rechallenge, the 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>

7.2 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 of data to be collected for the final assessments with reference to the schedule of activities for the participant's 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 trial intervention, should remain in the trial and continue to be followed to prevent missing data in important analyses. Refer to Section 10 Statistical Considerations for the data that must be collected for the trial estimands.

<Enter Participant Discontinuation or Withdrawal from Trial>

7.3 Management of Loss 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 to contact them. Also describe approaches that will be used to minimise 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 Management of Loss to Follow-Up>

8 TRIAL ASSESSMENTS AND PROCEDURES

In this section:

- 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 Objectives and Associated Estimands
    - trial intervention and therapies outlined in Section 6 Trial Intervention and Concomitant Therapy
    - discontinuation and withdrawal procedures in Section 7 Participant Discontinuation of Trial Intervention and Discontinuation or Withdrawal From Trial
    - the statistical analysis that is defined in Section 10 Statistical Considerations
- 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.
- Include minimums and limits for procedures (e.g., number of imaging procedures/biopsies, radiation exposure, etc.) if appropriate to the trial.

No text is intended here (heading only).

8.1 Trial Assessments and Procedures Considerations

Describe general considerations applicable across trial assessments and procedures.

<Enter Trial Assessments and Procedures Considerations>

8.2 Screening/Baseline Assessments and Procedures

Describe any assessments and procedures that are unique to screening/baseline (e.g., 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 when screening and baseline are different or performed at different visits.

<Enter Screening Assessments and Procedures>

{<Enter Baseline Assessments and Procedures>}

8.3 Efficacy Assessments and Procedures

Describe efficacy assessments and procedures in this section. Cross reference Section 8.7 Immunogenicity Assessments if immunogenicity assessments are used in efficacy determination.

<Enter Efficacy Assessments and Procedures>

8.4 Safety Assessments and Procedures

Describe safety assessments and procedures utilising the following subsections as applicable. Add level 3 headings as needed.

- Identify any noninvestigator party involved in the evaluation of laboratory or other safety assessments (e.g., sponsor or external Independent Data Monitoring Committee; cross reference Section 11.4 Committees for details as applicable).
- Include guidelines for the medical management of relevant laboratory or other safety assessment abnormalities.

<Enter Safety Assessments and Procedures>

8.4.1 {Physical Examination}

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

{<Enter Physical Examination>}

8.4.2 {Vital Signs}

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

{<Enter Vital Signs>}

8.4.3 {Electrocardiograms}

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

{<Enter Electrocardiograms>}

8.4.4 {Clinical Laboratory Assessments}

Describe any specific instructions for the collection and interpretation of clinical laboratory assessments, including:

- 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 (e.g., a pandemic or natural disaster)
- treatment algorithms for results out of normal range
- cross reference Section 12.1 Clinical Laboratory Tests for laboratory assessment panels

{<Enter Clinical Laboratory Assessments>}

8.4.5 {Pregnancy Testing}

Include any specific instructions for the collection and interpretation of pregnancy testing.

{<Enter Pregnancy Testing>}

8.4.6 {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 should also be provided in Section 9.2.4 Adverse Events of Special Interest.

{<Enter Suicidal Ideation and Behaviour Risk Monitoring>}

8.5 Pharmacokinetics

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

- Describe the biological samples 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 for each sample.
- Define the PK parameters to be calculated and the calculation methods.

<Enter Pharmacokinetics>

8.6 Biomarkers

Include any specific instructions for the collection of samples and interpretation of biomarkers in the subsections below as applicable. Safety biomarkers should be included in Section 8.4 Safety Assessments and Procedures, and immunogenicity biomarkers should be included in Section 8.7 Immunogenicity Assessments.

No text is intended here (heading only).

8.6.1 Genetics, Genomics, Pharmacogenetics, and Pharmacogenomics

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

- Describe the biological samples that will be collected (e.g., tissue, serum, plasma), 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, Genomics, Pharmacogenetics and Pharmacogenomics>

8.6.2 Pharmacodynamic Biomarkers

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

- Describe the biological samples that will be collected (e.g., tissue, serum, plasma).
    - 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>

8.6.3 {Other Biomarkers}

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

- Describe the biological samples that will be collected (e.g., tissue, serum, plasma).
    - 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>}

8.7 Immunogenicity Assessments

Include any specific instructions for the collection of samples and interpretation of immunogenicity. If immunogenicity assessments are included within Section 8.3 Efficacy Assessments and Procedures or Section 8.4 Safety Assessments and Procedures, cross reference that section.

- Describe the biological samples that will be collected (e.g., tissue, serum, plasma).
    - 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>

8.8 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 (e.g., diary, physician interview), and participant burden.

<Enter Medical Resource Utilisation and Health Economics>

9 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, PRODUCT COMPLAINTS, PREGNANCY AND POSTPARTUM INFORMATION, AND SPECIAL SAFETY SITUATIONS

9.1 Definitions

No text is intended here (heading only).

9.1.1 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 (e.g., lack of efficacy or failure of pharmacological actions)

<Enter Definitions of Adverse Events>

9.1.2 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 Definitions of Serious Adverse Events>

9.1.3 Definitions of Product Complaints

Specify the definitions of product complaints in the context of the trial.

<Enter Definitions of Product Complaints>

9.1.3.1 {Definitions of Medical Device Product Complaints}

{<Enter Definitions of Medical Device Product Complaints>}

9.2 Timing and Procedures for Collection and Reporting

Specify timing and procedures for collection and reporting of AEs, SAEs, product complaints (including medical device product complaints if applicable) and pregnancy and postpartum information in the sections below. This information may be summarised in a tabular format as shown in the example table below.

This table describes the timing and procedures for collecting and reporting 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>

9.2.1 Timing

Specify timing for collection and reporting, including:

- start and end dates for collection and reporting
- frequency of collection and reporting
- cross reference to the Schedule of Assessments as appropriate

<Enter Event Collection and Reporting Timing>

9.2.2 Collection Procedures

Specify procedures for collection and recording of AEs, SAEs, product complaints (including medical device product complaints if applicable) and pregnancy and postpartum information in the sections below.

Identification

Specify how information will be identified (e.g., self-reported, 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>

Recording

Specify procedures for recording.

<Enter Recording>

Follow-up

Specify the procedures for follow-up. 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>

9.2.3 Reporting

Specify the reporting method (e.g., an electronic data collection tool or a paper CRF), backup reporting method, if applicable, and reporting timeline to the sponsor.

<Enter Reporting>

9.2.3.1 Regulatory Reporting Requirements

Specify:

- the investigator's responsibilities for reporting 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 for reporting to regulatory authorities, ethics committees, and investigators
- suspected unexpected serious adverse reaction reporting

<Enter Regulatory Reporting Requirements>

9.2.4 Adverse Events of Special Interest

Specify any AESI, including:

- any event (serious or nonserious) of scientific and medical concern relative to the trial intervention, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate
- other events that merit reporting to the sponsor, trial leadership, IRB, and regulatory agencies

Include the following for each AESI:

- the definition
- the approach for ascertaining information
- if applicable, any approach to confirm or adjudicate the event

{<Enter Adverse Events of Special Interest >}

Or

{<Enter Not Applicable >}

9.2.5 Disease-Related Events or Outcomes Not Qualifying as AEs or SAEs

Specify any DREs, DROs, or both that will **not** be reported as AEs or SAEs (e.g., seizures in anticonvulsant trials) or state "Not applicable."

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

9.3 Pregnancy and Postpartum Information

Whenever possible, pregnancy (direct or via partner) should be documented and followed up to collect relevant pregnancy outcomes. Any negative or consequential outcome(s) in the pregnant participant/partner or foetus, neonate or infant should be reported as an AE or SAE. Refer to Section 9.2 Timing and Procedures for Collection and Reporting for AE and SAE related procedures as applicable. If the negative event meets the seriousness criteria, then this is considered an SAE (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy, or pre-eclampsia) and reported per Section 9.2.3 Reporting.

No text is intended here (heading only).

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 may continue with trial intervention or must be discontinued from trial intervention (refer to Section 7 Participant Discontinuation of Trial Intervention and Discontinuation or Withdrawal from Trial as applicable)
- any trial modifications that need to be made for participants who become pregnant
- what information will be collected about a participant who becomes pregnant during the trial (e.g., 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 (e.g., initial child development) with justification.

If exposure to trial intervention during breastfeeding is applicable, specify:

- the assessments to be performed
- type and duration of monitoring
- information to be collected for both the participant and child

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

9.3.2 {Participants Whose Partners Become Pregnant During the Trial}

Specify:

- whether 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 Participant Discontinuation of Trial Intervention and Discontinuation or Withdrawal from Trial as applicable)
- the assessments to be performed, type and duration of monitoring, and the information to be collected

{<Enter Participants Whose Partners Become Pregnant During the Trial>}

9.4 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
- unintended exposure of embryo, foetus, or child via maternal 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
- product complaint, including falsified or counterfeit products
- suspected drug-food or drug-drug interaction

<Enter Special Safety Situations>

10 STATISTICAL CONSIDERATIONS

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

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

No text is intended here (heading only).

10.1 General Considerations

Provide general statements related to statistical considerations, such as whether a separate statistical analysis plan exists, which summary statistics will be provided, and the timing of analyses (e.g., "The analysis will include all participant data at trial completion").

<Enter General Considerations>

10.2 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, aligned with estimands. Clearly specify the analysis set to be used for each analysis described in Section 10 Statistical Considerations.

<Enter Analysis Sets>

10.3 Analyses of Demographics and Other Baseline Variables

Describe the summary statistics that will be used to characterise the distribution of demographic and other relevant variables at baseline. Specify when the variables will be measured (e.g., at trial inclusion, prior to randomisation, or at the time of randomisation). Relevant variables include but are not limited to: stratification variables specified in Section 6.7 Investigational Trial Intervention Assignment, Randomisation and Blinding, covariates for the statistical models specified in Section 10.4 Analyses Associated with the Primary Objective(s), other suspected predictive or prognostic variables, and variables used for planned subgroup analyses.

<Enter Analyses of Demographics and Other Baseline Variables>

10.4 Analyses Associated with the Primary Objective(s)

Include additional level 3 headings for each primary objective as needed. If there is more than one primary objective, number each objective consecutively as the level 3 heading (e.g., Primary Objective 1, Primary Objective 2, etc.).

No text is intended here (heading only).

10.4.1 Primary Objective <#>

No text is intended here (heading only).

10.4.1.1 Statistical Analysis Method

Describe the statistical analysis methods that will be used to evaluate the primary objective(s) and associated estimand(s) in Section 3.1 Primary Objective(s) and Associated Estimand(s). Ensure that the statistical hypothesis/model/analysis (and corresponding assumptions) is aligned with the primary estimand(s).

For each objective, when applicable, 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 (e.g., covariates and interactions) and any rules for handling these factors (e.g., pooling of centres).

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

<Enter Statistical Analysis Method>

10.4.1.2 Handling of Data in Relation to Primary Estimand(s)

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

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

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

10.4.1.3 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)>

10.4.1.4 {Sensitivity Analysis}

Describe any sensitivity analyses and how their assumptions changed from the assumptions of the main statistical 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.

{<Enter Sensitivity Analysis>}

10.4.1.5 {Supplementary Analysis}

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

{<Enter Supplementary Analysis>}

10.5 Analyses Associated with the Secondary Objective(s)

Describe the statistical analysis methods that will be used to evaluate the secondary objective(s) and associated estimand(s) in Section 3.2 Secondary Objective(s) and Associated Estimand(s). Use the same section structure as Section 10.4 Analyses Associated with the Primary Objective(s). Include additional level 3 headings for each secondary objective as needed. If there is more than one secondary objective, number each objective consecutively as the level 3 heading (e.g., Secondary Objective 1, Secondary Objective 2, etc.).

No text is intended here (heading only) unless there is no secondary objective, in which case indicate “Not applicable.”

10.5.1 {Secondary Objective <#>}

No text is intended here (heading only).

10.5.1.1 {Statistical Analysis Method}

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

{<Enter Statistical Analysis Method>}

10.5.1.2 {Handling of Data in Relation to Secondary Estimand(s)}

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

10.5.1.3 {Handling of Missing Data in Relation to Secondary Estimand(s)}

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

10.5.1.4 {Sensitivity Analysis}

{<Enter Sensitivity Analysis>}

10.5.1.5 {Supplementary Analysis}

{<Enter Supplementary Analysis>}

10.6 Analyses Associated with the Exploratory Objective(s)

Describe any exploratory analyses, if applicable. Additional subsections may be created to describe the analyses for each exploratory objective, as needed. If there is no exploratory objective, indicate “Not applicable”.

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

10.7 Safety Analyses

If safety is a primary and/or secondary objective, describe the corresponding safety analyses in the appropriate section above (Section 10.4 Analyses Associated with the Primary Objective[s] or Section 10.5 Analyses Associated with the Secondary Objective[s]). In this section, describe statistical methods that will be used to analyse relevant safety outcomes, including any AESI. This should typically include specification of a measure to estimate risk within treatment arms, a measure to compare risks across treatment arms, and a measure of statistical uncertainty around the comparison (e.g., a confidence interval).

<Enter Safety Analyses>

10.8 Other Analyses

Describe other analyses not included in Sections 10.3-10.7, such as subgroup analyses.

<Enter Other Analyses>

10.9 Interim Analyses

Describe any interim analyses and criteria for stopping or adapting the trial. Ensure alignment with Section 4.3 Trial Stopping Rules.

The description should include, but is not limited to, the following. Under circumstances where interim analysis details could impede the integrity of the trial, some of the information can be added in other documents outside of the protocol.

- 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 other trial adaptations (e.g., sample size re-estimation, alteration to the proportion of participants allocated to each trial group, or changes to eligibility criteria)
- the applied statistical method (e.g., group sequential test) and spending function (e.g., O'Brien-Fleming), as applicable
- the parties responsible for performing and reviewing the results of the analyses (e.g., 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 will be protected (e.g., maintaining blinding) when decisions are made after interim analyses (e.g., a decision to continue the trial or implement a specific adaptation)

<Enter Interim Analyses>

10.10 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, and multiple timepoints.

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 trial 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 statistical 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 visualisation 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 Interim Analyses.

<Enter Multiplicity Adjustments>

10.11 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(s) 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, e.g.,:

- references to 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
- how dropout rate and intercurrent events have been incorporated into 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 (e.g., exploratory nature of pilot trials; pragmatic considerations for trials in rare diseases).

<Enter Sample Size Determination>

11 TRIAL OVERSIGHT AND OTHER GENERAL CONSIDERATIONS

No text is intended here (heading only).

11.1 Regulatory and Ethical Considerations

Provide a high-level statement on 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:

- Ethical principles that have their origin in the Declaration of Helsinki 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>

11.2 Trial Oversight

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

{<Enter Trial Oversight >} if not using below optional subheadings.

OR

11.2.1 Investigator Responsibilities

Describe the investigator responsibilities, including the oversight of trial-related activities delegated to a third party that may impact the trial conduct at sites, if applicable and if not addressed elsewhere.

<Enter Investigator Responsibilities>

11.2.2 Sponsor Responsibilities

Describe the sponsor responsibilities, including activities to be transferred to a third party that may impact the investigator sites, if applicable.

<Enter Sponsor Responsibilities>

11.3 Informed Consent Process

Specify the key elements of the informed consent process, including any special needs and how these are addressed (e.g., 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>

11.3.1 {Informed Consent for Rescreening}

If participants can be rescreened as described in Section 5.6 Screen Failure and Rescreening, state whether the participant needs to complete a new ICF. Screen failure and rescreening should be clearly defined in the protocol, with a cross reference to those definitions.

{<Enter Informed Consent for Rescreening>}

11.3.2 {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, describe 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 Informed Consent for Use of Remaining Samples in Exploratory Research>}

11.4 Committees

Briefly describe the administrative structure of committees that will be reviewing data while the trial is ongoing, and the type of committee (e.g., 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 involved, state "Not applicable."

<Enter Committees>

11.5 Insurance and Indemnity

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

<Enter Insurance and Indemnity>

11.6 Risk-Based Quality Management

Describe the identified critical to quality factors, associated risks and risk mitigation strategies for the trial or refer to the location where this information is described and updated during the trial based on emerging data.

<Enter Risk-Based Quality Management>

11.7 Data Governance

Describe the key systems and processes for critical trial integrity, traceability and security including a summary of the approaches enabling accurate data collection, reporting, monitoring, transfer, retention, and access if not addressed in separate agreement(s).

<Enter Data Governance>

11.8 Data Protection

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 Protection>

11.9 Source Records

State the importance of source records and expectation for traceability. Delineate expectations for investigators (e.g., maintain and ensure availability of essential records) and trial monitors (e.g., ensure participant protections, ensure that the trial is conducted according to GCP). Identify what constitutes source records and its origin or provide a reference to the location of this information, if contained in a separate document.

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

<Enter Source Records Introduction>

<Enter Investigator Expectations for Source Records>

<Enter Trial Monitor Expectations for Source Records>

<Enter Identification of Source Records>

11.10 Protocol Deviations

Describe plans for detecting, reviewing, and reporting any deviations from the protocol or include reference to a separate document.

<Enter Protocol Deviations>

11.11 Early Site Closure

List the sponsor's rights to close a site early. 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 (e.g., informing the ethics committee[s], and prompt notification of the participant and their transition to appropriate therapy and/or follow-up).

<Enter Responsibilities Following Early Site Closure>

11.12 Data Dissemination

Describe whether the clinical trial will be registered in public databases, including reporting of results, if applicable.

<Enter Data Dissemination>

12 APPENDIX: SUPPORTING DETAILS

No text is intended here (heading only).

Additional supporting detail appendices may be added at the end of the existing level 2 headings as needed.

12.1 Clinical Laboratory Tests

Specify which laboratory parameters should be included in each clinical laboratory assessment panel (e.g., 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 heading and enter "Not applicable."

<Enter Clinical Laboratory Tests>

12.2 Country/Region-Specific Differences

Although global clinical trial practices are increasingly harmonised, some country/region-specific differences in requirements do exist (e.g., document retention periods, contraception requirements). Where differences in requirements cannot be reconciled, the sponsor should explain how country/region-specific differences will be documented and communicated (e.g., 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 each 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>

12.3 Prior Protocol Amendment(s)

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

{This protocol has not been amended}.

Or

{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}.

Previous amendments should appear in reverse chronological order with the most recent at the top (e.g., Amendment 3, 2, 1). Delete or add lines as needed. Inclusion of region-, 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 the 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, list the status of all the relevant locations.
- For country/region-specific amendments to international clinical trials, list the approximate local enrollment total or percentage at the time of the amendment and select "locally".
- For trials in which enrollment status by cohort is more meaningful, such as for single-site or early-phase studies, listing the approximate enrollment by cohort is an option. If multiple cohorts are ongoing at the time of the amendment, list the status of all the ongoing cohorts.
- Enter the approximate number or percentage of participants enrolled as a percentage of the expected total.

Document	**Sponsor Approval Date**	**Approximate Enrollment when Sponsor Approved Amendment**
<Enter Amendment Identifier>	<Enter Sponsor Approval Date>	Approximately <#/%> enrolled <Enter Amendment Scope Enrollment Description>
Original Protocol	<Enter Sponsor Approval 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 Identifier> (<enter Sponsor Approval Date>)}

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

(Add rows as needed)

Add additional Overview of Changes tables as protocol amendments accrue.

12.X {Additional Appendices}

{<Enter Additional Appendices>}

13 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>

14 APPENDIX: REFERENCES

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

<Enter References>