



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

ICH HARMONISED GUIDELINE

**CLINICAL ELECTRONIC STRUCTURED HARMONISED  
PROTOCOL  
(CESHARP)**

**M11 TEMPLATE**

Draft version

Endorsed on 27 September 2022

*Currently under public consultation*

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

**M11 Template  
Document History**

<b>Code</b>	<b>History</b>	<b>Date</b>
M11	Endorsement by the Members of the ICH Assembly under <i>Step 2</i> and release for public consultation (document dated 4 September 2022).	27 September 2022

***Legal notice:*** This document is protected by copyright and may, with the exception of the ICH logo, be used, reproduced, incorporated into other works, adapted, modified, translated or distributed under a public license provided that ICH's copyright in the document is acknowledged at all times. In case of any adaption, modification or translation of the document, reasonable steps must be taken to clearly label, demarcate or otherwise identify that changes were made to or based on the original document. Any impression that the adaption, modification or translation of the original document is endorsed or sponsored by the ICH must be avoided.

The document is provided "as is" without warranty of any kind. In no event shall the ICH or the authors of the original document be liable for any claim, damages or other liability arising from the use of the document.

The above-mentioned permissions do not apply to content supplied by third parties. Therefore, for documents where the copyright vests in a third party, permission for reproduction must be obtained from this copyright holder.

1 **Interventional Clinical Trial Protocol Template**

2 **0 Foreword**

3 **0.1 Template Revision History**

Date	Description of Revision
(To be determined)	Initial template

4 **0.2 Intended Use of Template**

5 This template is intended for interventional clinical trials of drugs, vaccines, and drug/device  
6 combinations intended to be registered as drugs. The template is suitable for all phases of  
7 clinical research and all therapeutic areas. Existing ICH Guidelines and ISO 14155 were  
8 considered in its development. The template is designed to enable modification suitable for the  
9 particular trial. Refer to the sections below for additional details and conventions related to  
10 flexibility.

11 **0.3 Template Conventions and General Instructions**

12 This template uses the typefaces described in the table below to distinguish between their  
13 intended use and applicability. Use of consistent font sizes (12 point) throughout the document  
14 is recommended, but not required.

<b>Type of Text (Applicability)</b>	<b>Typeface Details</b>	<b>Description (Intended Use)</b>
Universal text	Black Times New Roman font	Text that should appear in all protocols
Instructional text	Red Calibri font (Delete for final document)	Text that provides instructions, but which should not appear in a final protocol
Suggested text	Blue Century font  Restyle to Black Times New Roman for final document	Text that is suitable for many trials, but which may need to be modified, deleted, or replaced according to the specific aspects of the trial
Variable text	{braces} in the prevailing typeface  Select from choices by eliminating unwanted options; remove braces and restyle remaining text to match other text in the final document	Where a choice is suggested between options in a passage of text, braces are used to separate them
Fields	[Square brackets] in the prevailing typeface with grey shading	Brackets with grey shading are used to indicate variable text modelled as a field in the electronic manifestation of the protocols

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

15

16 **Heading Structure and Flexibility**

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

Example Heading	Heading Level	Typeface in this Template	Modification or Deletion	Addition
<b>1</b>	<b>LEVEL 1 (L1)</b>	14 point Times New Roman Bold Black ALL CAPS	Do not delete or modify L1 or L2 headings Retain heading and indicate "Not Applicable"	Do not add L1 Headings
<b>1.1</b>	Level 2 (L2)	14 point Times New Roman Bold Black		Add L2 headings, if needed, at the end of the higher-level section to preserve the established L1 and L2 heading structure
<b>1.1.1</b>	Level 3 (L3)	12 point Times New Roman Bold Black	Do not delete or modify Level 3 safety subheadings (Section 8.4) Other Level 3 headings may be deleted or modified as needed	

Example Heading	Heading Level	Typeface in this Template	Modification or Deletion	Addition
1.1.1.1	Level 4 (L4)			
<b>Additional Non-Numbered Heading</b>	Non-numbered heading		Delete heading or modify as needed	Insert where needed

22

23 **Table and Figure Numbering**

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

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

28 **Terminology**

29 The following terminology has been selected for use within this template and is considered to  
 30 be appropriate for all phases, trial populations, and therapeutic areas:

- 31 • Because the scope of this protocol template is focused on interventional clinical trials,  
 32 the term *clinical trials* is used rather than clinical studies when referring to  
 33 interventional clinical trials.
- 34 • *Participant* is used rather than subject, healthy volunteer, or patient when referring to  
 35 an individual who has consented to participate in the clinical trial. Patient or individual is  
 36 used to distinguish the population represented by the trial participants, when  
 37 necessary.
- 38 • *Trial intervention* refers to any therapeutic, prophylactic, or diagnostic agent including  
 39 pharmaceuticals, biologics, vaccines, cell or gene therapy products (when applicable),  
 40 and drug-device combination products when registered as a drug. Trial interventions  
 41 include the agent being tested or used as a control (for example, placebo or active  
 42 comparator). Procedures conducted to manage participants or to collect data are  
 43 excluded from the usage of this term.
- 44 • While *blinding* is the more commonly used term, masking is an alternative term which  
 45 may be used in certain situations.

46 **Suggestions for Publishing a Paper or .pdf Document:**

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

## ICH M11 Template

- 50 • Delete Section 0 and all its contents
- 51 • Update the Table of Contents (TOC).
- 52 • Confirm that the Level 1 and Level 2 headings are visible in the navigation pane or  
53 bookmark view). Visible Level 3 bookmarks are also recommended.
- 54 • Delete unneeded or non-applicable Level 3 or lower headings and ensure remaining  
55 Level 3 and lower headings are numbered appropriately
- 56 • Delete any unused variable text and related prompts
- 57 • Restyle any “suggested”, “example”, or “variable” text to match the regular text
- 58 • Remove all instructional text, and
- 59 • Remove brackets that denote variable or field text after making appropriate selections.

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

### 62 **0.4 Abbreviations Used in this Template**

<b>Abbreviation or Acronym</b>	<b>Definition</b>
AE	Adverse Event
AESI	Adverse Events of Special Interest
AxMP	Auxiliary Medicinal Product
CDISC	Clinical Data Interchange Standards Consortium
COAs	Clinical Outcome Assessment(s)
CRF	Case Report Form
DREs	Disease-Related Events
ECG	Electrocardiogram
EU	European Union
EUDAMED	European Databank on Medical Devices
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
IB	Investigator’s Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug

ICH M11 Template

<b>Abbreviation or Acronym</b>	<b>Definition</b>
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
jRCT	Japan Registry of Clinical Trials
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NCT	National Clinical Trial
NIMP	Non-Investigational Medicinal Product
PD	Pharmacodynamics
PK	Pharmacokinetics
SAE	Serious Adverse Event
SoA	Schedule of Activities
TOC	Table of Contents
WHO	World Health Organization

ICH M11 Template

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



## ICH M11 Template

	<p>or “Other”. For trials combining investigational drugs or vaccines with devices, classify according to the phase of drug development.</p>
<b>Acronym:</b>	<p>[Protocol Acronym]</p> <p>Acronym or abbreviation used publicly to identify the clinical trial, if any. The acronym may include numerals, such as -1, -2, or I, II, III, or IV. Delete this line from the table if not applicable.</p>
<b>Short Title:</b>	<p>[Protocol Short Title]</p> <p>Short title should convey <u>in plain language</u> what the trial is about and is suitable for use as “Brief Title” or “Title in Plain Language” in global clinical trial registries. It can also be suitable for use with informed consents and ethics committee submissions.</p>
<b>Sponsor Name and Address:</b>	<p>[Sponsor Name] [Sponsor Legal Address]</p> <p>Provide the legal name of the individual or pharmaceutical or medical device company, governmental agency, academic institution, private organisation, or other organisation who takes primary responsibility for and initiates a clinical investigation. If more than one Sponsor, list the Primary Sponsor in this field.</p> <p>Local Sponsor Name and Address: [Sponsor Local Name] [Sponsor Local Address]</p> <p>In some countries, the clinical trial Sponsor may be the local affiliate company (or designee). In such cases, indicate in the Sponsor Local Name and Address Field.</p>
<b>Manufacturer Name and Address:</b>	<p>[Device Manufacturer Name] [Device Manufacturer Address]</p> <p>Manufacturer name and address information is required only for protocols that include investigational device(s) and <u>should not</u> be included for other protocols. Include the manufacturer address only if the manufacturer is different than the Sponsor listed above.</p> <p>Add additional fields as needed if multiple investigational devices will be used in the trial. Delete this line from the table if not applicable.</p>

<p><b>Regulatory Agency Identifier Number(s):</b></p>	<p>[EUDAMED: [EUDAMED Number]]  [EudraCT Number: [EudraCT Number]]  [EU Trial Number: EU Trial Number]]  [IDE: [IDE Number]]  [IND: [IND]]  [jRCT: [jRCT Number]]  [NCT: [NCT Number]]:  [NMPA IND: [NMPA IND]]  [WHO: [WHO Number]]:  [Other: [Other Regulatory Agency Identifier Number]]</p> <p style="color: red;">Include all numbers that are applicable for the trial and available at the time of protocol or amendment finalisation. Delete prompts for numbers not available at the time of document finalisation. Delete unused fields. Add fields for “other” if more than one is needed.</p>
<p><b>Sponsor Approval Date:</b></p>	<p>[Approval Date] or [The approval date is included with the electronic signature, located {describe location}.]</p> <p style="color: red;">All versions should be uniquely identifiable. Use the CDISC date format (dd/mmm/yyyy, for example 07/JUN/2015) to indicate the date the protocol (or amendment) was approved by the Sponsor.</p>

64  
65  
66  
67

**Sponsor Signatory:**

[Name]

[Sponsor Signature Date]

[Title of Sponsor Signatory]

68 or

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

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

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

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

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

80 Fax: [Rapid Alert Fax Number]

81 **Amendment Details**

82 Delete this entire section for an original protocol.

83 History of Amendments

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

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

85 Do not include the current amendment in the table above, as final approval dates are often  
 86 difficult to predict during document preparation. Previous amendments should appear in  
 87 reverse chronological order with the most recent at the top (for example, Amendment 3, 2, 1).  
 88 Delete lines not needed, add lines as needed. Inclusion of regional-, country-, and site-specific  
 89 amendments in the table is optional. If included, ensure that the scope is clearly  
 90 distinguishable from global amendments.

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

- 92 • For global amendments, list approximate global enrollment total or percentage at the  
 93 time of the amendment and select “globally”.
- 94 • For country/region amendments, list the approximate local enrollment total or  
 95 percentage at the time of the amendment and select “locally”.

96 Current Amendment

97 The table below provides an overview of the current amendment.

<b>Amendment Number:</b>	[Amendment Number]
<b>Approximate {%/#} Enrolled:</b>	[Estimated % or # Enrolled] enrolled [Globally/Locally]  Enter the approximate number or percentage of participants enrolled as a percentage of the expected total. If the number of expected participants is changing as a result of the current amendment, use the updated number of expected participants to

ICH M11 Template

	<p>estimate the current percent of enrollment. Estimates are adequate, as precise enrollment figures will likely be changing while an amendment is being prepared. <u>For a global amendment</u>, provide the estimated global enrollment at the time of the Sponsor approved the amendment. <u>For a country/regional amendment</u>, provide the estimated local or regional enrollment at the time the Sponsor approved the amendment.</p>	
<p><b>Reason(s) for Amendment:</b></p>	<p><b>Primary:</b> <u>[Primary Reason for Amendment]</u> *</p> <p>Select from the following (multiple selections allowed):</p> <ul style="list-style-type: none"> <li>• Regulatory agency request to amend</li> <li>• New regulatory guidance</li> <li>• IRB/IEC feedback</li> <li>• New safety information available</li> <li>• Manufacturing change</li> <li>• Adaptive clinical trial IMP addition</li> <li>• Change in strategy</li> <li>• Change in standard of care</li> <li>• New data available (other than safety data)</li> <li>• Investigator/site feedback</li> <li>• Recruitment difficulty</li> <li>• Inconsistency and/or error in the protocol</li> <li>• Protocol design error</li> <li>• Other: [Describe]</li> </ul>	<p><b>Other:</b> <u>[Other Reason for Amendment]</u> *</p> <p>Select from the following (multiple selections allowed):</p> <ul style="list-style-type: none"> <li>• Regulatory agency request to amend</li> <li>• New regulatory guidance</li> <li>• IRB/IEC feedback</li> <li>• New safety information available</li> <li>• Manufacturing change</li> <li>• Adaptive clinical trial IMP addition</li> <li>• Change in strategy</li> <li>• Change in standard of care</li> <li>• New data available (other than safety data)</li> <li>• Investigator/site feedback</li> <li>• Recruitment difficulty</li> <li>• Inconsistency and/or error in the protocol</li> <li>• Protocol design error</li> <li>• Other: [Describe]</li> <li>• Not applicable</li> </ul>
<p><b>Summary of the Amendment:</b></p>	<p><u>[Summary of Amendment]</u></p> <p>Specify on the primary reason for the amendment with details specific to the trial. If more than one key change prompted the amendment, discuss briefly. Incidental changes which are included in the amendment but unrelated to the key changes do not need to be described here.</p>	
<p>Is this amendment likely to have a substantial impact on</p> <ul style="list-style-type: none"> <li>• safety or rights of the participants, or</li> </ul>	<p><u>[Yes/No]</u></p> <p>Indicate whether the current amendment is likely to have a significant impact on either of the criteria listed.</p>	

<ul style="list-style-type: none"> <li>on the reliability and robustness of the data generated in the clinical trial?</li> </ul>	
--	--

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

103 **Summary of Changes in the Current Amendment:**

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

104 (Add lines as needed)

105 Follow the steps below to prepare the summary of changes.

- 106
- 107 • If a Summary of Changes already exists from a prior amendment, move it to Section  
 108 13.4, History of Previous Amendments, and populate a clean summary table for the  
 present amendment.
  - 109 • List the changes that apply to the current amendment. Provide a brief description of  
 110 the change(s) and a brief scientific rationale for specific changes (for example, change to  
 111 individual inclusion/exclusion criteria).

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

114 **Table of Contents**

115

116 1 PROTOCOL SUMMARY ..... 19

117 1.1 Protocol Synopsis ..... 19

118 1.2 Trial Schema ..... 22

119 1.3 Schedule of Activities ..... 22

120 2 INTRODUCTION ..... 23

121 2.1 Purpose of Trial ..... 23

122 2.2 Summary of Benefits and Risks ..... 23

123 3 TRIAL OBJECTIVES, ENDPOINTS AND ESTIMANDS ..... 25

124 3.1 {Primary/Secondary/Exploratory} Objective + Associated Endpoint {and Estimand} 25

125 4 TRIAL DESIGN ..... 26

126 4.1 Description of Trial Design ..... 26

127 4.1.1 Participant Input into Design ..... 27

128 4.2 Rationale for Trial Design ..... 27

129 4.2.1 Rationale for Comparator ..... 27

130 4.2.2 Rationale for Adaptive or Novel Trial Design ..... 28

131 4.2.3 Other Trial Design Considerations ..... 28

132 4.3 Access to Trial Intervention After End of Trial ..... 28

133 4.4 Start of Trial and End of Trial ..... 28

134 5 TRIAL POPULATION ..... 29

135 5.1 Selection of Trial Population ..... 29

136 5.2 Rationale for Trial Population ..... 29

137 5.3 Inclusion Criteria ..... 29

138 5.4 Exclusion Criteria ..... 30

139 5.5 Lifestyle Considerations ..... 30

140 5.5.1 Meals and Dietary Restrictions ..... 30

141 5.5.2 Caffeine, Alcohol, Tobacco, and Other Habits ..... 30

142 5.5.3 Physical Activity ..... 30

143 5.5.4 Other Activity ..... 30

144 5.6 Screen Failures ..... 30

145 6 TRIAL INTERVENTION AND CONCOMITANT THERAPY ..... 31

146 6.1 Description of Trial Intervention ..... 31

## ICH M11 Template

147	6.2	Rationale for Trial Intervention.....	31
148	6.3	Dosing and Administration .....	32
149	6.3.1	Trial Intervention Dose Modification .....	32
150	6.4	Treatment of Overdose.....	32
151	6.5	Preparation, Handling, Storage and Accountability.....	32
152	6.5.1	Preparation of Trial Intervention .....	32
153	6.5.2	Handling and Storage of Trial Intervention .....	33
154	6.5.3	Accountability of Trial Intervention .....	33
155	6.6	Participant Assignment, Randomisation and Blinding .....	33
156	6.6.1	Participant Assignment .....	33
157	6.6.2	Randomisation .....	34
158	6.6.3	Blinding and Unblinding.....	34
159	6.7	Trial Intervention Compliance .....	34
160	6.8	Concomitant Therapy .....	34
161	6.8.1	Prohibited Concomitant Therapy.....	35
162	6.8.2	Permitted Concomitant Therapy.....	35
163	6.8.3	Rescue Therapy.....	35
164	6.8.4	Other Therapy .....	35
165	7	DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT	
166		WITHDRAWAL FROM TRIAL .....	36
167	7.1	Discontinuation of Trial Intervention.....	36
168	7.1.1	Criteria for Permanent Discontinuation of Trial Intervention .....	36
169	7.1.2	Temporary Discontinuation or Interruption of Trial Intervention .....	36
170	7.1.3	Rechallenge.....	36
171	7.2	Participant Withdrawal from the Trial .....	37
172	7.3	Lost to Follow-Up .....	37
173	7.4	Trial Stopping Rules.....	37
174	8	TRIAL ASSESSMENTS AND PROCEDURES .....	38
175	8.1	Screening/Baseline Assessments and Procedures .....	38
176	8.2	Efficacy Assessments and Procedures .....	38
177	8.3	Safety Assessments and Procedures.....	38
178	8.3.1	Physical Examination.....	39
179	8.3.2	Vital Signs.....	39

## ICH M11 Template

180	8.3.3	Electrocardiograms .....	39
181	8.3.4	Clinical Laboratory Assessments.....	39
182	8.3.5	Suicidal Ideation and Behaviour Risk Monitoring .....	39
183	8.4	Adverse Events and Serious Adverse Events.....	39
184	8.4.1	Definitions of AE and SAE.....	39
185	8.4.2	Time Period and Frequency for Collecting AE and SAE Information .....	40
186	8.4.3	Identifying AEs and SAEs.....	40
187	8.4.4	Recording of AEs and SAEs.....	40
188	8.4.5	Follow-up of AEs and SAEs.....	40
189	8.4.6	Reporting of SAEs .....	40
190	8.4.7	Regulatory Reporting Requirements for SAEs.....	40
191	8.4.8	Serious and Unexpected Adverse Reaction Reporting .....	40
192	8.4.9	Adverse Events of Special Interest .....	41
193	8.4.10	Disease-related Events or Outcomes Not Qualifying as AEs or SAEs .....	41
194	8.5	Pregnancy and Postpartum Information.....	41
195	8.5.1	Participants Who Become Pregnant During the Trial.....	41
196	8.5.2	Participants Whose Partners Become Pregnant .....	42
197	8.6	Medical Device Product Complaints for Drug/Device Combination Products .....	42
198	8.6.1	Definition of Medical Device Product Complaints .....	42
199	8.6.2	Recording of Medical Device Product Complaints .....	42
200	8.6.3	Time Period and Frequency for Collecting Medical Device Product Complaints .	42
201	8.6.4	Follow-Up of Medical Device Product Complaints .....	42
202	8.6.5	Regulatory Reporting Requirements for Medical Device Product Complaints.....	42
203	8.7	Pharmacokinetics .....	43
204	8.8	Genetics.....	43
205	8.9	Biomarkers .....	43
206	8.10	Immunogenicity Assessments .....	43
207	8.11	Medical Resource Utilisation and Health Economics.....	44
208	9	STATISTICAL CONSIDERATIONS.....	45
209	9.1	Analysis Sets .....	45
210	9.2	Analyses Supporting Primary Objective(s).....	45
211	9.2.1	Statistical Model, Hypothesis, and Method of Analysis.....	45



## ICH M11 Template

212	9.2.2	Handling of Intercurrent Events of Primary Estimand(s).....	45
213	9.2.3	Handling of Missing Data.....	46
214	9.2.4	Sensitivity Analysis .....	46
215	9.2.5	Supplementary Analysis .....	46
216	9.3	Analysis Supporting Secondary Objective(s) .....	46
217	9.4	Analysis of Exploratory Objective(s).....	46
218	9.5	Safety Analyses .....	46
219	9.6	Other Analyses .....	47
220	9.7	Interim Analyses .....	47
221	9.8	Sample Size Determination.....	47
222	9.9	Protocol Deviations .....	48
223	10	GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL	
224		OVERSIGHT .....	48
225	10.1	Regulatory and Ethical Considerations .....	48
226	10.2	Committees.....	48
227	10.3	Informed Consent Process.....	48
228	10.4	Data Protection.....	49
229	10.5	Early Site Closure or Trial Termination.....	49
230	11	GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY	
231		ASSURANCE.....	50
232	11.1	Quality Tolerance Limits .....	50
233	11.2	Data Quality Assurance.....	50
234	11.3	Source Data .....	50
235	12	APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS –	
236		DEFINITIONS, SEVERITY, AND CAUSALITY .....	51
237	12.1	Further Details and Clarifications on the AE Definition.....	51
238	12.2	Further Details and Clarifications on the SAE Definition .....	51
239	12.3	Severity.....	51
240	12.4	Causality.....	51
241	13	APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS.....	52
242	13.1	Contraception and Pregnancy Testing.....	52
243	13.1.1	Definitions Related to Childbearing Potential .....	52
244	13.1.2	Contraception.....	52

ICH M11 Template

245	13.1.3	Pregnancy Testing.....	52
246	13.2	Clinical Laboratory Tests .....	52
247	13.3	Country/Region-Specific Differences .....	53
248	13.4	Prior Protocol Amendments .....	53
249	14	APPENDIX: GLOSSARY OF TERMS .....	54
250	15	APPENDIX: REFERENCES.....	54
251			
252			

253 **1 PROTOCOL SUMMARY**

254 No text is intended here (header only).

255 **1.1 Protocol Synopsis**

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

257 No text is intended here (header only).

258 **Primary and Secondary Objectives and Endpoints**

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

262 [\[Primary and Secondary Objectives and Endpoints\]](#)

263 **Overall Design**

264 Several key aspects of the trial design are summarised below.

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

265 Briefly state the following:

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

- 274 • Trial population type (for example, healthy volunteers, adult patients, paediatric  
275 patients).
- 276 • Population Diagnosis or Condition (for example, “acute lung injury,” or a specific  
277 biomarker profile); indicate “N/A – Healthy” for trials in healthy volunteers.
- 278 • Population age range (for example  $\leq 3$  mos,  $\geq 18$  to  $\leq 80$  years old). List N/A if a maximum  
279 or minimum age limit does not apply. For trials in which multiple age ranges may be  
280 eligible (for example, a younger cohort and an older cohort), indicate the minimum and  
281 maximum ages for the trial overall, with an additional comment for any excluded age  
282 ranges.
- 283 • Site distribution (select from: single-site, multi-site, or multi-site and multi-regional). If  
284 none of these applies, indicate *other* and describe.

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

286 Enter the numeric value for the number of arms in the trial. For trials with a different number  
287 of arms in different periods, populate this field based on the period with the greatest number  
288 of arms.

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

291 Select from the following blinded roles:

- 292 • Participant
- 293 • Care Provider
- 294 • Investigator
- 295 • Outcomes Assessor: the individual who evaluates the outcome(s) of interest
- 296 • Not applicable (No blinding).

297 For designs in which these details may differ in one or more trial periods, answer according to  
298 the portion of the trial in which the greatest blinding occurs. More details can be provided in  
299 Section 6.6 of the protocol. Note that this list does not include Sponsor staff or their designees  
300 who may be unblinded to complete ongoing safety oversight and surveillance reporting.

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

302 **Number of Participants:**

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

305 State the expected number of participants to be assigned to trial intervention/enrolled.

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

308 **Arms and Duration**

309 Total duration of trial intervention for each participant:

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

311 or

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

313 Total duration of trial participation for each participant:

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

315 or

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

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

323 [Arms and Duration Description]

324 Briefly state:

- 325
- 326 • Total duration of participation for each participant with sequence and duration of trial periods (for example, screening, run-in, fixed dose/titration, follow-up/washout periods)
  - 327 • Dose regimens in each trial period and stage (if applicable) including frequency (for example, twice daily) and route of administration and criteria for individualised dosing (for example, participant weight or plasma concentrations), if applicable
  - 328 • Rules/procedures for any dose changes/adjustments including flexible dosing; dose reductions, dose interruptions, or tapering; discontinuation; and any circumstances for resuming trial intervention, as applicable
- 329
- 330
- 331
- 332

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

335

336 **Committees:**

337 Indicate whether any committee(s) will be reviewing data while the trial is ongoing, and the  
338 type of committee. Common examples include Data Monitoring Committee, Dose Escalation  
339 Committee, or Endpoint Adjudication Committee; describe others, if applicable. List  
340 independent committees in the space indicated. Other committees may be included at the

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

343 Independent Committees: [Independent Committees]

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

345 Other Committees: [Other Committees]

346 Delete "Other Committees" if not applicable.

## 347 **1.2 Trial Schema**

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

354 [Schema]

## 355 **1.3 Schedule of Activities**

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

360 [Schedule of Activities]

361

362 **2 INTRODUCTION**

363 No text is intended here (header only).

364 **2.1 Purpose of Trial**

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

367 [Purpose]

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

370 **2.2 Summary of Benefits and Risks**

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

373 **Benefit Summary**

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

381 Benefits to society in general may also be included but should be discussed separately.

382 [Benefit Summary]

383 **Risk Summary and Mitigation Strategy**

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

388 [Trial-specific Discussion of Intervention Risks and Mitigations]

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

396 [Trial-specific Discussion of Procedure Risks and Mitigations]

ICH M11 Template

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

399 [Trial-specific Discussion of Other Risks and Mitigations]

400 **Overall Benefit:Risk Conclusion**

401 Provide a succinct, concluding statement on the perceived balance between risks that have  
402 been identified from cumulative safety data, protocol procedures, and anticipated  
403 efficacy/benefits within the context of the proposed trial. Risks need to be assessed against the  
404 benefits for the individual participant at least once a year.

405 [Overall Benefit:Risk Conclusion]

406



407 **3 TRIAL OBJECTIVES, ENDPOINTS AND ESTIMANDS**

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

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

413 No text is intended here (header only).

414 **3.1 {Primary/Secondary/Exploratory} Objective + Associated Endpoint**  
 415 **{and Estimand}**

<b>{Primary/Secondary/Exploratory} Objective</b>	<b>{Primary/Secondary/Exploratory} Endpoint</b>
[Objective]	[Endpoint]

416 **{Primary/Secondary/Exploratory} Estimand**

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

421 [Estimand Description]

422

## 423 **4 TRIAL DESIGN**

424 In this section, describe the trial design with specific mention, as applicable, of the components  
425 of an adequate and well-controlled trial and reflect the principles of Quality by Design. The  
426 description of the design should be concise and consistent across Section 1.1, Protocol Synopsis  
427 and Section 1.2, Trial Schema.

428 No text is intended here (header only).

### 429 **4.1 Description of Trial Design**

430 Describe the trial intervention model (for example, single group, parallel group, cross-over,  
431 factorial, sequential), the expected number of participants, and the control method (for  
432 example, placebo, active comparator, low dose, historical, standard of care, sham procedure, or  
433 none [uncontrolled]).

434 If applicable, indicate the type of trial (for example, superiority, non-inferiority, dose escalation,  
435 or equivalence).

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

#### 438 [Description of Intervention Model]

439 Describe the trial duration with reference to Section 1.2, Trial Schema. Explain what the overall  
440 duration for an individual participant is anticipated to be and why, including the sequence and  
441 duration of trial periods (for example, screening, run-in, randomisation, treatment [fixed  
442 dose/titration], follow-up/washout periods). Where applicable, include discussion of sentinel  
443 dosing (or lack thereof), dose escalation, and cohort expansion. If dose modification decisions  
444 are dependent upon review by a committee, include details in Section 10.2, Committees  
445 Structure.

#### 446 [Description of Trial Duration]

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

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

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

#### 455 [Method of Assignment to Trial Intervention]

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

- 458 • Geographic scope of trial (for example, single-centre, multi-centre, or multi-centre and  
459 multi-national)
- 460 • Use of decentralised processes, tools, or features in the trial
- 461 • Planned use of a Data Monitoring Committee, or similar review group and cross-  
462 reference Section 10.2, Committees, for details,
- 463 • Whether an interim analysis is planned and, if so, refer to details in Section 9.7, Interim  
464 Analysis, and/or
- 465 • Any planned extension trial, long-term follow-up/registry, or post-trial sample analysis  
466 or other data-related activities.

#### 467 [Additional Description of Design]

##### 468 4.1.1 Participant Input into Design

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

#### 471 [Participant Input]

##### 472 4.2 Rationale for Trial Design

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

#### 476 [Rationale for Intervention Model]

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

#### 479 [Rationale for Duration]

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

#### 483 [Rationale for Endpoints]

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

#### 486 [Interim Analysis]

##### 487 4.2.1 Rationale for Comparator

488 If applicable, provide a rationale for the type of control selected for the trial (for example,  
489 placebo, active drug, combination, historical). Discuss any known or potential problems  
490 associated with the control group selected in light of the specific disease and intervention(s)  
491 being studied. If comparators will differ by region, describe. Describe prior trials that support  
492 the dose and/or dose regimen.

493 [\[Rationale for Comparator\]](#)

494 **4.2.2 Rationale for Adaptive or Novel Trial Design**

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

496 [\[Rationale for Adaptive or Novel Design\]](#)

497 **4.2.3 Other Trial Design Considerations**

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

499 [\[Other Design Considerations\]](#)

500 **4.3 Access to Trial Intervention After End of Trial**

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

504 [\[Access to Trial Intervention after End of Trial\]](#)

505 **4.4 Start of Trial and End of Trial**

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

512 [\[Trial Start and End\]](#)

513

514 **5 TRIAL POPULATION**

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

- 518 • List the criteria necessary for participation in the trial. Ensure that each criterion can be  
 519 easily assessed definitively and answered with yes/no responses.
- 520 • If participants require screening, distinguish between screening vs enrolling participants.  
 521 Identify specific laboratory tests or clinical characteristics that will be used as criteria for  
 522 inclusion or exclusion. If permitting existing medical diagnosis, imaging, genetic tests, or  
 523 laboratory results, state any required window or acceptable test type.
- 524 • If measures to enrich the trial population for pre-specified subgroups of interest are  
 525 used, these should be described.

526 No text is intended here (header only).

527 **5.1 Selection of Trial Population**

528 Describe the population selected (for example, healthy volunteers, adult participants,  
 529 paediatric participants) and how the enrollment criteria reflect the populations that are likely to  
 530 use the drug if approved. Specify the population age range (for example, ≤3 months, ≥18 to ≤80  
 531 years old) and any key diagnostic criteria for the population (for example, “acute lung injury”,  
 532 or a specific biomarker profile). If applicable, describe similar conditions or diseases and their  
 533 differential diagnosis.

534 [\[Selection of Trial Population\]](#)

535 **5.2 Rationale for Trial Population**

536 Provide a rationale for the trial population ensuring that the population selected is well defined  
 537 and clinically recognisable. Justify whether the trial intervention is to be evaluated in children,  
 538 in adults unable to consent for themselves, other vulnerable participant populations, or those  
 539 that may respond to the trial intervention differently (for example, elderly, hepatic or renally  
 540 impaired, or immunocompromised participants).

541 [\[Rationale for Trial Population\]](#)

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

544 **5.3 Inclusion Criteria**

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

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

- 548 # [Inclusion Criterion]
- 549 # [Inclusion Criterion]
- 550 # [Inclusion Criterion]

551 Add criteria as needed. Number sequentially.

## 552 **5.4 Exclusion Criteria**

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

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

556 # [Exclusion Criterion]

557 # [Exclusion Criterion]

558 # [Exclusion Criterion]

559 Add criteria as needed.

## 560 **5.5 Lifestyle Considerations**

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

564 [Lifestyle Considerations]

### 565 **5.5.1 Meals and Dietary Restrictions**

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

568 [Meals and Dietary Restrictions]

### 569 **5.5.2 Caffeine, Alcohol, Tobacco, and Other Habits**

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

572 [Caffeine, Alcohol, Tobacco, and Other Habits]

### 573 **5.5.3 Physical Activity**

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

576 [Physical Activity]

### 577 **5.5.4 Other Activity**

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

580 [Other Activity]

## 581 **5.6 Screen Failures**

582 Indicate how screen failure will be handled in the trial, including conditions and criteria upon  
583 which rescreening is acceptable. If applicable, indicate the circumstances and time window

584 under which a repeat procedure is allowed for screen failure relating to specific  
585 inclusion/exclusion criteria for the trial.

586 [Screen Failure]

## 587 **6 TRIAL INTERVENTION AND CONCOMITANT THERAPY**

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

592 No text is intended here (header only).

### 593 **6.1 Description of Trial Intervention**

594 Describe the intervention to be administered in each arm of the trial and for each period of the  
595 trial including route and mode of administration, dose, dosage regimen, duration of  
596 intervention, packaging, labelling, and storage conditions. Include information for all trial  
597 interventions (experimental, placebo, active comparator, sham comparator).

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

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

601 [Table of Trial Interventions]

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

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

608 [Additional Text, if Needed]

### 609 **6.2 Rationale for Trial Intervention**

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

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

619 [Rationale for Dose and Regimen]

## 620 **6.3 Dosing and Administration**

621 Describe the detailed procedures for administration of each participant's dose of trial  
622 intervention and control product. This may include the timing of dosing (for example, time of  
623 day, interval), the duration (for example, the length of time participants will be administered  
624 the trial intervention), the planned route of administration (for example, oral, nasal,  
625 intramuscular), and the timing of dosing relative to meals.

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

628 For an individual participant, describe dose modifications allowed. State any minimum period  
629 required before a participant's dose might be raised to the next higher dose or dose range.  
630 Include whether it is permissible to start and stop treatment and how dose reductions (if  
631 permitted) are to be managed.

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

634 [\[Dosing and Administration\]](#)

### 635 **6.3.1 Trial Intervention Dose Modification**

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

642 [\[Dose Modification\]](#)

## 643 **6.4 Treatment of Overdose**

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

650 [\[Treatment of Overdose\]](#)

## 651 **6.5 Preparation, Handling, Storage and Accountability**

652 No text is intended here (header only).

### 653 **6.5.1 Preparation of Trial Intervention**

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



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

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

663 [Trial Intervention Preparation]

#### 664 **6.5.2 Handling and Storage of Trial Intervention**

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

669 [Trial Intervention Storage and Handling]

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

#### 673 **6.5.3 Accountability of Trial Intervention**

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

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

680 [Accountability]

### 681 **6.6 Participant Assignment, Randomisation and Blinding**

682 No text is intended here (header only).

#### 683 **6.6.1 Participant Assignment**

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

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

## 6.6.1 Participant Assignment

### 6.6.2 Randomisation

Describe the randomisation procedures (for example, central randomisation procedures), the method used to generate the randomisation schedule (for example, computer generated), the source of the randomisation schedule (for example, sponsor, investigator, or other), and whether or not IVRS/IWRS will be used. To maintain the integrity of the blinding, do not include the block size. Describe the use and validation of any computer systems or programmes in randomisation, stratification, and unblinding.

## 6.6.3 Randomisation

### 6.6.3 Blinding and Unblinding

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

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

## 6.6.3 Blinding and Unblinding

### Emergency Unblinding

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

## 6.6.3 Emergency Unblinding

### 6.7 Trial Intervention Compliance

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

## 6.7 Trial Intervention Compliance

### 6.8 Concomitant Therapy

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

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

731 [Concomitant Therapy]

732 **6.8.1 Prohibited Concomitant Therapy**

733 If applicable, describe any prohibited concomitant therapy.

734 [Prohibited Concomitant Therapy]

735 **6.8.2 Permitted Concomitant Therapy**

736 If applicable, describe any permitted concomitant therapy.

737 [Permitted Concomitant Therapy]

738 **6.8.3 Rescue Therapy**

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

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

745 [Rescue Therapy]

746 **6.8.4 Other Therapy**

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

749 [Other Therapy]

750

751 **7 DISCONTINUATION OF TRIAL INTERVENTION AND**  
752 **PARTICIPANT WITHDRAWAL FROM TRIAL**

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

756 No text is intended here (header only).

757 **7.1 Discontinuation of Trial Intervention**

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

760 **7.1.1 Criteria for Permanent Discontinuation of Trial Intervention**

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

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

766 [\[Criteria for Permanent Discontinuation of Trial Intervention\]](#)

767 **7.1.2 Temporary Discontinuation or Interruption of Trial Intervention**

768 Describe

- 769
- 770 • the criteria for temporary discontinuation or interruption of trial intervention for an individual participant
  - 771 • what to do and which restrictions still apply if the participant needs to temporarily discontinue or interrupt trial intervention
  - 772
  - 773 • whether they will continue in the trial, and
  - 774 • whether all, or specify which, assessments will be performed for the stated duration of the trial.
  - 775

776 Details of any rechallenge or restart after a safety-related event should be included in Section  
777 7.1.3, Rechallenge.

778 [\[Temporary Discontinuation/Interruption of Trial Intervention\]](#)

779 **7.1.3 Rechallenge**

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

783 If rechallenge is not allowed, state this.

784 [\[Rechallenge\]](#)

785 **7.2 Participant Withdrawal from the Trial**

786 Describe the criteria for participant withdrawal from the trial.

787 [\[Participant Withdrawal from Trial\]](#)

788 **7.3 Lost to Follow-Up**

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

792 [\[Lost to Follow-Up\]](#)

793 **7.4 Trial Stopping Rules**

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

797 [\[Trial Stopping Rules\]](#)

798

799 **8 TRIAL ASSESSMENTS AND PROCEDURES**

- 800 • Describe the assessments and procedures required during each phase of the trial that  
 801 are relevant to the stated endpoints. Provide details that are not already presented in  
 802 the SoA, taking care not to duplicate information.
- 803 • Describe methods, training, tools, instruments/questionnaires, calibration methods, etc.  
 804 that will be used to record and assess data and ensure consistency across centres and  
 805 participants. Include instructions on timing/conditions of assessments and if a  
 806 specifically qualified person should be performing these assessments. Describe whether  
 807 centralised readings and measurements will be utilised. Describe procedures to be used  
 808 to maintain the blind.
- 809 • Reference the literature for the validation of scales/instruments/questionnaires/assays.
- 810 • Instructions or protocols for specialised tests may be presented in an appendix or a  
 811 separate document and cross-referenced.
- 812 • If the trial includes qualitative interviews, describe these evaluations.
- 813 • If COA measures are utilised, include instructions for the investigators per local  
 814 guidance. All COA parameters should be fully integrated into the appropriate sections of  
 815 the protocol; separate COA sections should not be created in the protocol.
- 816 • Include minimums and limits for procedures (for example, volume of blood draws,  
 817 number of imaging procedures/biopsies, radiation exposure, etc.) if appropriate to the  
 818 trial.

819 **8.1 Screening/Baseline Assessments and Procedures**

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

823 [Screening/Baseline Assessments and Procedures]

824 **8.2 Efficacy Assessments and Procedures**

825 Describe efficacy assessments and procedures in this section.

826 [Efficacy Assessments and Procedures]

827 **8.3 Safety Assessments and Procedures**

828 Describe safety assessments and procedures in this section. Level 3 headings can be added as  
 829 needed.

- 830 • Identify any non-investigator party responsible for evaluation of laboratory or other  
 831 safety assessments (for example, Sponsor or external Independent Data Monitoring  
 832 Committee).

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

835 [Safety Assessments and Procedures]

### 836 **8.3.1 Physical Examination**

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

838 [Physical Examination]

### 839 **8.3.2 Vital Signs**

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

841 [Vital Signs]

### 842 **8.3.3 Electrocardiograms**

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

844 [Electrocardiograms]

### 845 **8.3.4 Clinical Laboratory Assessments**

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

- 848       • Specify if and when the use of local laboratories is allowed.

- 849       • Specify which laboratory parameters should be included in each panel (for example, for  
850       haematology, chemistry, urinalysis).

851 [Clinical Safety Laboratory Assessments]

### 852 **8.3.5 Suicidal Ideation and Behaviour Risk Monitoring**

853 If the trial meets any of the criteria requiring suicidal ideation and behaviour risk monitoring by  
854 the guidance/guideline in each region, include any specific instructions for the collection and  
855 interpretation of the assessment

856 [Suicidal Ideation and Behaviour Risk Monitoring]

## 857 **8.4 Adverse Events and Serious Adverse Events**

858 No text is intended here (header only).

### 859 **8.4.1 Definitions of AE and SAE**

860 Specify the AE and SAE definitions.

861 [AE definition]

862 [SAE definition]

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

864

865 **8.4.2 Time Period and Frequency for Collecting AE and SAE Information**

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

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

868 **8.4.3 Identifying AEs and SAEs**

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

871 [Identifying AEs and SAEs]

872 **8.4.4 Recording of AEs and SAEs**

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

875 [Recording of AEs and SAEs]

876 Further details on assessing severity and causality of AEs and SAEs are in Appendices 12.3 and  
877 12.4.

878 **8.4.5 Follow-up of AEs and SAEs**

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

883 [Follow-up of AEs and SAEs]

884 **8.4.6 Reporting of SAEs**

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

887 [Reporting of SAEs]

888 **8.4.7 Regulatory Reporting Requirements for SAEs**

889 Specify:

- 890
- The Sponsor's legal/regulatory responsibilities to report SAEs to regulatory authorities,  
891 ethics committees, and investigators.
  - The investigators' responsibilities for promptly reporting SAEs to the Sponsor (and to  
892 Ethics Committees, where required) to allow the Sponsor to meet their responsibilities.
- 893

894 **8.4.8 Serious and Unexpected Adverse Reaction Reporting**

895 Include this section, if applicable.

896 [Serious and Unexpected Adverse Reaction Reporting]



897 **8.4.9 Adverse Events of Special Interest**

898 Include this section, if applicable.

899 Specify any Adverse Events of Special Interest (AESI):

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

905 Include the following for each AESI:

- 906 • The definition of the event. Specify the MedDRA preferred terms to use to report the
- 907 AESI.
- 908 • If it is a measurable quantity, specify how will the measurement be done.
- 909 • If it is a clinical event, specify how will it be confirmed.

910 [Adverse Events of Special Interest]

911 **8.4.10 Disease-related Events or Outcomes Not Qualifying as AEs or SAEs**

912 Specify any Disease-Related Events (DREs), disease-related outcomes, or both that will **not** be

913 reported as AEs or SAEs (for example, seizures in anticonvulsant trials).

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

915 **8.5 Pregnancy and Postpartum Information**

916 No text is intended here (header only).

917 **8.5.1 Participants Who Become Pregnant During the Trial**

918 Specify

- 919 • the assessments to be performed,
- 920 • type and duration of monitoring, and
- 921 • what information will be collected for a participant who becomes pregnant during the
- 922 trial (for example, recording and reporting to the Sponsor, postpartum follow-up, trial
- 923 intervention discontinuation or continuation, or trial withdrawal).

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

925 the justification.

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

- 927 • the assessments to be performed,
- 928 • type and duration of monitoring, and

- 929       • what information will be collected for both the participant and child.

930 Specify that pregnancy is not an AE, unless a negative or consequential outcome occurs in the  
931 participant or child/foetus. If the negative event meets the seriousness criteria, then this is  
932 considered an SAE (for example, spontaneous abortion, foetal death, stillbirth, congenital  
933 anomalies, ectopic pregnancy, or pre-eclampsia) and reported per Section 8.4.5, Reporting of  
934 SAEs.

935 [Participants Who Become Pregnant During the Trial]

### 936 **8.5.2 Participants Whose Partners Become Pregnant**

937 Specify:

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

942 [Participants Whose Partners Become Pregnant]

## 943 **8.6 Medical Device Product Complaints for Drug/Device Combination** 944 **Products**

945 Optional section to include for drug/device combination products.

### 946 **8.6.1 Definition of Medical Device Product Complaints**

947 [Definition of Medical Device Product Complaints]

### 948 **8.6.2 Recording of Medical Device Product Complaints**

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

951 [Recording of Medical Device Product Complaints]

### 952 **8.6.3 Time Period and Frequency for Collecting Medical Device Product Complaints**

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

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

### 957 **8.6.4 Follow-Up of Medical Device Product Complaints**

958 [Follow-up of Medical Device Product Complaints]

### 959 **8.6.5 Regulatory Reporting Requirements for Medical Device Product Complaints**

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

962 [Reporting of Medical Device Product Complaints]

## 963 **8.7 Pharmacokinetics**

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

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

970 [Pharmacokinetics]

## 971 **8.8 Genetics**

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

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

978 [Genetics]

## 979 **8.9 Biomarkers**

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

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

989 [Biomarkers]

## 990 **8.10 Immunogenicity Assessments**

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

994 [Immunogenicity Assessments]

995 **8.11 Medical Resource Utilisation and Health Economics**

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

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

1000 [\[Medical Resource Utilisation and Health Economics\]](#)

1001

## 1002 **9 STATISTICAL CONSIDERATIONS**

1003 Ensure that the data analysis complies with ICH E9 Guideline and ICH E9(R1) Guideline.

1004 In general, all relevant data collected in the trial should be considered in this statistical  
1005 considerations section.

1006 Provide a statement with regard to when the primary analyses will be conducted. For example:  
1007 The analysis will be conducted on all participant data at the time the trial ends.

1008 [\[Statistical Considerations\]](#)

### 1009 **9.1 Analysis Sets**

1010 Analysis sets to support each analysis will be specified here and described in the Statistical  
1011 Analysis Plan.

1012 [\[Analysis Datasets\]](#)

### 1013 **9.2 Analyses Supporting Primary Objective(s)**

1014 This section introduces the Statistical Analysis Plan, with the detail to be provided in the  
1015 subsequent subsections. This includes describing the methods of estimation (analytic approach)  
1016 in alignment with how the estimands are defined. Sensitivity analyses should be aligned with  
1017 how the estimands and estimators are defined.

1018 [\[Analysis Supporting Primary Objectives\]](#)

#### 1019 **9.2.1 Statistical Model, Hypothesis, and Method of Analysis**

1020 Ensure that the statistical hypothesis/model (and corresponding assumptions)/analysis is  
1021 aligned with the primary estimand(s).

1022 For all applicable objectives (for example, primary, secondary), under the appropriate header,  
1023 state the null and alternative hypotheses, including the pre-planned type 1 error, or alternative  
1024 criteria to define trial success and relevant operating characteristics if appropriate. Describe the  
1025 statistical model used and the factors that will be included (covariates and interactions) and any  
1026 rules for handling these factors (for example, pooling of centres). If applicable, state and discuss  
1027 any adjustments to account for multiplicity.

1028 If modelling and simulation methods are to be used, please describe the model (inputs and  
1029 outputs), the underlying assumptions, and the method of model fitting.

1030 [\[Statistical Model, Hypothesis, and Method of Analysis\]](#)

#### 1031 **9.2.2 Handling of Intercurrent Events of Primary Estimand(s)**

1032 For each intercurrent event of the primary estimand(s) (Section 3.1, Estimand[s] for the Primary  
1033 Objective[s]), explain how data will be handled for the statistical analysis in line with the  
1034 primary estimand. The handling of intercurrent events in statistical analysis should be aligned  
1035 with the specific estimand strategies being used.

1036 This section should describe with more detail the rationale and handling of the data rather than  
1037 repeating the guidance from the preceding sections.

1038 [\[Handling of Intercurrent Events of Primary Estimand\]](#)

### 1039 **9.2.3 Handling of Missing Data**

1040 This section should describe how missing data will be dealt with. Refer to the E9(R1) addendum  
1041 when estimand framework is used.

1042 The protocol should describe how missing data will be handled (for example, type of imputation  
1043 technique, if any, and provide justification)

1044 In cases where the Primary Objective is related to safety, this section should also be completed.  
1045 It may also be helpful to include additional statements regarding handling of missing data in  
1046 general for other important efficacy or safety endpoints or this information can be included in  
1047 the analysis of secondary endpoint section below.

1048 [\[Handling of Missing Data\]](#)

### 1049 **9.2.4 Sensitivity Analysis**

1050 Sensitivity analyses are a series of analyses conducted with the intent to explore the robustness  
1051 of inferences from the main estimator to deviations from its underlying modelling assumptions  
1052 and limitations in the data.

1053 [\[Sensitivity Analysis\]](#)

### 1054 **9.2.5 Supplementary Analysis**

1055 Describe any supplementary analysis if applicable.

1056 [\[Supplementary Analysis\]](#)

## 1057 **9.3 Analysis Supporting Secondary Objective(s)**

1058 This section should focus on estimands for Secondary Objectives.

1059 In this section describe the statistical analysis, handling of intercurrent events, handling of  
1060 missing data, and if applicable, sensitivity analysis corresponding to each secondary estimand.

1061 [\[Analyses Supporting Secondary Objectives\]](#)

## 1062 **9.4 Analysis of Exploratory Objective(s)**

1063 [\[Analyses Supporting Tertiary/Exploratory Objective\(s\)\]](#)

## 1064 **9.5 Safety Analyses**

1065 If safety is a primary and/or secondary objective, describe the corresponding safety analyses in  
1066 the appropriate section above (Section 9.2 or Section 9.3).

1067 [\[Safety Analyses\]](#)

1068 **9.6 Other Analyses**

1069 Describe Other Analyses such as Subgroup analyses, Adjusted analysis if needed.

1070 [\[Other Analyses\]](#)

1071 **9.7 Interim Analyses**

1072 Describe any interim analysis and criteria for stopping or adapting the trial.

1073 The description should include, but is not limited to, the following:

- 1074 • Any interim analysis plan, even if it is only to be performed at the request of an
- 1075 oversight body (for example, DMC).
- 1076 • Describe (briefly and concisely) and reference the applied statistical method, for
- 1077 example, group sequential test and spending function (for example, O’Brien-Fleming), as
- 1078 applicable.
- 1079 • Who will perform the analyses.
- 1080 • When they will be conducted (timing and/or triggers).
- 1081 • The decision criteria—statistical or other—that will be adopted to judge the interim
- 1082 results as part of a guideline for early stopping or other adaptations.
- 1083 • Who will see the outcome data while the trial is ongoing.
- 1084 • Whether these individuals will remain blinded to trial groups.
- 1085 • How the integrity of the trial implementation will be protected (for example,
- 1086 maintaining blinding) when any adaptations to the trial are made.
- 1087 • Who has the ultimate authority to stop or modify the trial, for example, investigator,
- 1088 principal investigator, Data Monitoring Committee, or sponsor.
- 1089 • The stopping guidelines.
- 1090 • If pre-specified interim analyses are to be used for other trial adaptations such as
- 1091 sample size re-estimation, alteration to the proportion of participants allocated to each
- 1092 trial group, and changes to eligibility criteria.

1093 [\[Interim Analyses\]](#)

1094 **9.8 Sample Size Determination**

1095 This section should detail the methods used for the determination of the sample size and a

1096 reference to tables or statistical software used to carry out the calculation. Sufficient information

1097 should be provided so that the sample size calculation can be reproduced or described.

1098 If the planned sample size is not derived statistically, then this should be explicitly stated along

1099 with a rationale for the intended sample size (for example, exploratory nature of pilot trials;

1100 pragmatic considerations for trials in rare diseases).

1101 [\[Sample Size Determination\]](#)

1102

1103 **9.9 Protocol Deviations**

1104 Plans for detecting, reviewing, and reporting any deviations from the protocol should be  
1105 described.

1106 [Protocol Deviations Plans]

1107 **10 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND**  
1108 **TRIAL OVERSIGHT**

1109 No text is intended here (header only).

1110 **10.1 Regulatory and Ethical Considerations**

1111 List the prevailing ethical, legal, and regulatory guidelines that will be applied throughout the  
1112 trial.

1113 This trial will be conducted in accordance with the protocol and with the following:

- 1114 • Consensus ethical principles derived from international guidelines including the  
1115 Declaration of Helsinki and Council for International Organisations of Medical  
1116 Sciences (CIOMS) International Ethical Guidelines
- 1117 • ICH Good Clinical Practice (GCP) Guidelines
- 1118 • Applicable laws and regulations

1119 List the investigators' and sponsor's responsibilities in this regard.

1120 **Investigator Responsibilities**

1121 [Investigator Responsibilities]

1122 **Sponsor Responsibilities**

1123 [Sponsor Responsibilities]

1124 **10.2 Committees**

1125 Briefly describe the administrative structure of committees that will be reviewing data while  
1126 the trial is ongoing, and the type of committee (for example, Dose Escalation Committee, Data  
1127 Monitoring Committee or Data Safety Monitoring Board). Note that specific details may be  
1128 required depending on local law or regulation. If applicable, Committee Charters may be cross-  
1129 referenced.

1130 [Committees Structure]

1131 **10.3 Informed Consent Process**

1132 Specify the key elements of the informed consent process, including any special needs and how  
1133 these are addressed (for example, assent, capacity, legally acceptable representative).

1134 [Informed Consent Process]

1135 If enrollment in the trial may occur during an emergency in which the participant or their legally  
1136 authorised representative is not able or available to give consent, describe the consent process.



1137 [Emergency Consent Process]

1138 **Rescreening**

1139 If participants can be rescreened, add the text to state whether the participant needs to  
1140 complete a new consent. Screen failure and rescreening should be clearly defined in the  
1141 protocol, with cross-reference to those definitions.

1142 [Consent Requirements for Rescreening]

1143 [Additional ICF text for Use of Remaining Samples in Optional Exploratory  
1144 Research]

1145 **10.4 Data Protection**

1146 Describe how personal data will be protected and any measures that should be taken in case of  
1147 a data security breach.

1148 [Data Protection]

1149 **10.5 Early Site Closure or Trial Termination**

1150 List the decision rights of sponsor or designee to close a site or terminate the trial. Likewise, list  
1151 the investigator's right to initiate site closure.

1152 [Decision Rights for Site Closure and Trial Termination]

1153 List the criteria for early closure of a site by the sponsor or investigator.

1154 [Criteria for Early Closure]

1155 List the responsibilities of the sponsor and investigator following termination or suspension,  
1156 such as informing the ethics committee(s), and prompt notification of the participant and  
1157 transition to appropriate therapy and/or follow-up.

1158 [Responsibilities following Termination or Suspension]

1159

1160

1161 **11 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND**  
1162 **QUALITY ASSURANCE**

1163 No text is intended here (header only).

1164 **11.1 Quality Tolerance Limits**

1165 Indicate where Quality Tolerance Limits will be predefined, how they will be monitored during  
1166 the trial, and expected discussion in the clinical trial report.

1167 [QTL]

1168 **11.2 Data Quality Assurance**

1169 Delineate the responsibilities of the Sponsor with respect to data quality assurance.

1170 [Sponsor or Designee Responsibilities for Data Quality Assurance]

1171 [Investigator Responsibilities for Data Quality Assurance]

1172 **11.3 Source Data**

1173 Establish the importance of source data and expectation for traceability of transcribed  
1174 information back to source. Delineate expectations for investigators (for example, maintain  
1175 source data at the site, ensure availability of current records) and trial monitors (for example,  
1176 verify CRF data relative to source, safety of participants is being protected, conduct is in  
1177 accordance with GCP). Define what constitutes source data and its origin or provide a  
1178 reference to the location of these definitions, if contained in a separate document, such as a  
1179 monitoring guideline or source data acknowledgement).

1180 [Source Data Introduction]

1181 [Investigator Expectations for Source Data]

1182 [Trial Monitor Expectations for Source Data]

1183 [Definition of Source Data]

1184 **12 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE**  
1185 **EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY**

1186 No text is intended here (header only).

1187 **12.1 Further Details and Clarifications on the AE Definition**

1188 Specify:

- 1189 • Any relevant regional AE requirements.
- 1190 • Any events that meet and do **not** meet the AE definition.
- 1191 • Any trial-specific AE clarifications.
- 1192 • The trial-specific definition for an overdose.
- 1193 • If applicable, any clarifications on the AE and SAE definitions for efficacy trials (for example,  
1194 lack of efficacy or failure of pharmacological actions reporting).

1195 **12.2 Further Details and Clarifications on the SAE Definition**

1196 Specify:

- 1197 • Any relevant regional SAE requirements.
- 1198 • Any events that meet and do **not** meet the SAE definition.
- 1199 • Any trial-specific SAE clarifications.

1200 **12.3 Severity**

1201 Specify the severity rating categories/scale.

1202 [Severity]

1203 **12.4 Causality**

1204 Specify:

- 1205 • The causality categories/scale.
- 1206 • Procedures for assessing causality.

1207 [Causality]

1208

1209 **13 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL**  
1210 **DETAILS**

1211 No text is intended here (header only).

1212 **13.1 Contraception and Pregnancy Testing**

1213 No text is intended here (header only).

1214 **13.1.1 Definitions Related to Childbearing Potential**

1215 Optional section to specify the definitions of:

- 1216 • Participant of childbearing potential
- 1217 • Participant of non-childbearing potential

1218 [\[Definitions Related to Childbearing Potential\]](#)

1219 **13.1.2 Contraception**

1220 Optional section to specify the:

- 1221 • Contraceptive methods required
- 1222 • Duration of use

1223 [\[Contraception\]](#)

1224 **13.1.3 Pregnancy Testing**

1225 Optional section to specify pregnancy testing requirements.

1226 [\[Pregnancy Testing\]](#)

1227 **13.2 Clinical Laboratory Tests**

1228 Provide additional information, if needed, about clinical laboratory tests, such as

- 1229 • whether they will be performed by a central or local laboratory (if important to  
1230 distinguish)
- 1231 • specific analytes or parameters included in a panel
- 1232 • equations and references for locally calculated labs
- 1233 • acceptability of additional tests deemed necessary by the investigator or local  
1234 regulations
- 1235 • instructions for situations in which central laboratory results are not available in time for  
1236 trial intervention and/or response evaluation, or in the event of a severe disruption (for  
1237 example, a pandemic or natural disaster)
- 1238 • treatment algorithms for results out of normal range.

1239 A tabular presentation for such information is common.

1240 [\[Clinical Laboratory Tests\]](#)

1241

### 1242 **13.3 Country/Region-Specific Differences**

1243 Although global clinical trial practices are increasingly harmonised, some country/ region-  
 1244 specific differences in requirements do exist (for example, document retention periods,  
 1245 contraception requirements). Where differences in requirements cannot be reconciled,  
 1246 sponsors should explain how they will document and communicate country/region-specific  
 1247 differences (for example, by country/region-specific amendments or addenda).

1248 An alternative to country/region-specific amendments is to list the specific differences by  
 1249 country or countries in this section, including a reference to the relevant section of the protocol  
 1250 where the differing requirement applies.

1251 [\[Country/Region-specific Differences\]](#)

### 1252 **13.4 Prior Protocol Amendments**

1253 Choose the appropriate text.

1254 {This protocol has not been amended.}

1255 or

1256 {The Protocol Amendment Summary of Changes for the current amendment is located directly  
 1257 before the Table of Contents. Details of prior amendments are presented below, beginning with  
 1258 the most recent}.

1259 See the instructions in the Protocol Amendment Summary of Changes located before the Table  
 1260 of Contents. Move all Protocol Amendment Summaries of Changes for previous amendments to  
 1261 this section in reverse chronological order (most recent first).

1262 [Amendment {amendment number}: \({date}\)](#)

1263 [{Amendment details from this amendment}](#)

1264 Add additional amendments/details as protocol amendments accrue.

1265 [Amendment {amendment number}: \({date}\)](#)

1266 [{Amendment details from this amendment}](#)

1267

1268 **14 APPENDIX: GLOSSARY OF TERMS**

1269 Define abbreviations and other terms used in the protocol. Abbreviations do not need to be  
1270 defined at first mention within the protocol, and definition of abbreviations in common usage is  
1271 not necessary (for example, *DNA*). A tabular presentation is common.

1272 Ensure the following terms are clearly defined within the protocol unless not applicable to the  
1273 trial:

- 1274 • Pre-screening
- 1275 • Screening
- 1276 • Enrollment
- 1277 • Product Complaint

1278 [\[Abbreviations and Definitions\]](#)

1279 **15 APPENDIX: REFERENCES**

1280 References should be listed in a common format that includes all relevant information to  
1281 identify the source and date published. If not published, this should be clearly indicated.

1282 [\[References\]](#)