

# **E6(R3) GOOD CLINICAL PRACTICE (GCP)**

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## FOREWORD

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

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



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

**ICH HARMONISED GUIDELINE**  
**GOOD CLINICAL PRACTICE (GCP)**  
**E6(R3)**

Draft version

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**ICH HARMONISED GUIDELINE**  
**GOOD CLINICAL PRACTICE (GCP)**  
**E6(R3)**

**ICH Consensus Guideline**

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1 **I. INTRODUCTION**

2 Good Clinical Practice (GCP) is an international, ethical, scientific and quality standard for the  
3 conduct of trials that involve human participants. Clinical trials conducted in accordance with  
4 this standard will help to assure that the rights, safety and well-being of trial participants are  
5 protected; that the conduct is consistent with the principles that have their origin in the  
6 Declaration of Helsinki; and that the clinical trial results are reliable. The term “trial conduct”  
7 in this document includes processes from planning to reporting, including planning, initiating,  
8 performing, recording, oversight, evaluation, analysis and reporting activities as appropriate.

9 The objective of this ICH GCP Guideline is to provide a unified standard to facilitate the mutual  
10 acceptance of clinical trial data for ICH member countries and regions by applicable regulatory  
11 authorities.

12 This guideline builds on key concepts outlined in ICH E8(R1) General Considerations for  
13 Clinical Studies. This includes fostering a quality culture and proactively designing quality into  
14 clinical trials and drug development planning, identifying factors critical to trial quality, and  
15 engaging stakeholders, as appropriate, using a proportionate risk-based approach.

16 Clinical trials vary widely in scale, complexity and cost. Careful evaluation of the priorities  
17 involved in each trial and the risks associated with the priorities will help ensure efficiency by  
18 focusing on activities critical to achieving the trial objectives.

19 **Guideline Scope**

20 This guideline applies to interventional clinical trials of investigational products<sup>1</sup> that are  
21 intended to be submitted to regulatory authorities. This guideline may also be applicable to  
22 other interventional clinical trials of investigational products that are not intended to support  
23 marketing authorisation applications in accordance with local requirements.

24 **Guideline Structure**

25 This ICH GCP Guideline is composed of principles and annexes that expand on the principles,  
26 with specific details for different types of clinical trials. The principles are intended to apply  
27 across clinical trial types and settings and to remain relevant as technological and  
28 methodological advances occur. The principles outlined in this guideline may be satisfied using  
29 differing approaches and should be applied to fit the intended purpose of the clinical trial.

30 Annex-1 is intended to provide information on how the principles can be appropriately applied  
31 to clinical trials. Additional annexes may be developed to respond to stakeholder needs and to  
32 address emerging innovations in trial design and conduct. This guideline should be read in  
33 conjunction with other ICH guidelines relevant to the design and conduct of clinical trials,  
34 including multiregional trials.

---

<sup>1</sup> For the purpose of this guideline, the term “investigational products” should be considered synonymous with drugs, medicines, medicinal products, vaccines and biological products.

**35 II. PRINCIPLES OF ICH GCP**

36 Clinical trials are a fundamental part of clinical research that support the development of new  
37 medicines or uses of existing medicines. Well-designed and conducted clinical trials help  
38 answer key questions in healthcare and drug development. Their results are essential for  
39 evidence-based healthcare decisions. Trials with inadequate design and/or poorly conducted  
40 trials may place participant safety at risk and yield inadequate or unreliable evidence and are  
41 unethical. They waste resources and the efforts and time of investigators and participants.

42 The principles of GCP are designed to be flexible and applicable to a broad range of clinical  
43 trials. This guideline, along with ICH E8(R1), encourages thoughtful consideration and  
44 planning to address specific and potentially unique aspects of an individual clinical trial. This  
45 includes evaluation of trial characteristics, such as the design elements, the investigational  
46 product being evaluated, the medical condition being addressed, the characteristics of the  
47 participants, the setting in which the clinical trial is being conducted, and the type of data being  
48 collected. Careful consideration of factors relevant to ensuring trial quality is needed for each  
49 clinical trial.

50 The principles are intended to support efficient approaches to trial design and conduct. For  
51 example, innovative digital health technologies, such as wearables and sensors, may expand  
52 the possible approaches to trial conduct. Such technologies can be incorporated into existing  
53 healthcare infrastructures and enable the use of a variety of relevant data sources in clinical  
54 trials. This will aid in keeping clinical trial conduct in line with advancing science and  
55 technological developments. The use of technology in the conduct of clinical trials should be  
56 adapted to fit the participant characteristics and the particular trial design. This guideline is  
57 intended to be media neutral to enable the use of different technologies for the purposes of  
58 documentation.

59 The use of innovative clinical trial designs and technologies may help include diverse patient  
60 populations, as appropriate, and enable wider participation. The design of the trial, to ensure  
61 appropriate quality and meaningful trial outcomes, may be supported by the perspectives of  
62 stakeholders; for example, patients and/or healthcare providers. Their input can increase the  
63 likelihood of meaningful trial outcomes, which are relevant to both trial participants and future  
64 patients. This input will also guide decisions on the feasibility of data collection and assure that  
65 participation in the trial does not become unduly burdensome for those involved.

66 Clinical trials should be designed to protect the rights, safety and well-being of participants and  
67 assure the reliability of results. Quality by design should be implemented to identify the factors  
68 (i.e., data and processes) that are critical to ensuring trial quality and the risks that threaten the  
69 integrity of those factors and ultimately the reliability of the trial results. Clinical trial processes  
70 and risk mitigation strategies implemented to support the conduct of the trial should be  
71 proportionate to the importance of the data being collected and the risks to trial participant  
72 safety and data reliability. Trial designs should be operationally feasible and avoid unnecessary  
73 complexities.

74 The overarching principles provide a flexible framework for clinical trial conduct. They are  
75 structured to provide guidance throughout the life cycle of the clinical trial. These principles  
76 are applicable to trials involving human participants. The principles are interdependent and  
77 should be considered in their totality to assure ethical trial conduct and reliable results.

78 **1. Clinical trials should be conducted in accordance with the ethical principles that**  
 79 **have their origin in the Declaration of Helsinki and that are consistent with GCP**  
 80 **and applicable regulatory requirement(s). Clinical trials should be designed and**  
 81 **conducted in ways that ensure the rights, safety and well-being of participants.**  
 82

83 1.1 The rights, safety and well-being of the participants are the most important  
 84 considerations and should prevail over interests of science and society.

85 1.2 The safety of the participants should be reviewed periodically as new safety  
 86 information becomes available, which could have an impact on the participant  
 87 or the conduct of the trial.

88 1.3 Foreseeable risks and inconveniences should be weighed against the anticipated  
 89 benefits for the individual participants and society. A trial should be initiated  
 90 and continued only if the anticipated benefits justify the known and anticipated  
 91 risks.

92 1.4 When designing a clinical trial, the scientific goal and purpose should be  
 93 carefully considered so as not to unnecessarily exclude particular participant  
 94 populations. The participant selection process should be representative of the  
 95 anticipated population who is likely to use the medicinal product in future  
 96 clinical practice to allow for generalising the results across the broader  
 97 population. Certain trials (e.g., early phase, proof of concept trials,  
 98 bioequivalence studies) may not require a heterogeneous population.

99 1.5 A qualified physician or, when appropriate, a qualified dentist (or other  
 100 qualified healthcare professionals in accordance with local regulatory  
 101 requirements) should have the overall responsibility for the trial-related medical  
 102 care given to, and medical decisions made on behalf of, participants; however,  
 103 the practical interactions and the delivery of medical care and decisions can be  
 104 carried out by appropriately qualified healthcare professionals in accordance  
 105 with applicable regulatory requirements.

106 1.6 The confidentiality of information that could identify participants should be  
 107 protected in accordance with applicable privacy and data protection  
 108 requirements.  
 109

110 **2. Informed consent is an integral feature of the ethical conduct of a trial. Clinical**  
 111 **trial participation should be voluntary and based on a consent process that**  
 112 **ensures participants (or their legally acceptable representatives, where**  
 113 **applicable) are well-informed.**  
 114

115 2.1 Freely given informed consent should be obtained and documented from every  
 116 participant prior to clinical trial participation. For potential participants unable  
 117 to provide informed consent, their legally acceptable representative should  
 118 provide consent prior to clinical trial participation.

119 2.2 The process and information provided should be designed to achieve the  
 120 primary objective of enabling potential trial participants to evaluate the benefits  
 121 and risks of participating in the trial and to make an informed decision on  
 122 whether or not to participate in the trial. The information provided during the

123 informed consent process should be clear and concise so as to be understandable  
124 by potential participants or legally acceptable representatives.

125 2.3 The informed consent process should take into consideration relevant aspects of  
126 the trial, such as the characteristics of the participants, the trial design, the  
127 anticipated benefit and risk of medical intervention(s), the setting and context  
128 in which the trial will be conducted (e.g., trials in emergency situations), and  
129 the potential use of technology to inform participants (or their legally acceptable  
130 representatives) and obtain informed consent.

131

132 **3. Clinical trials should be subject to an independent review by an institutional**  
133 **review board/independent ethics committee (IRB/IEC).**

134

135 3.1 A trial should always be conducted in compliance with the protocol that  
136 receives prior IRB/IEC approval/favourable opinion.

137 3.2 Periodic review of the trial by the IRB/IEC should also be conducted in  
138 accordance with applicable regulatory requirements.

139

140 **4. Clinical trials should be scientifically sound for their intended purpose and based**  
141 **on robust and current scientific knowledge and approaches.**

142

143 4.1 The available nonclinical and clinical information on an investigational  
144 product(s) should be adequate to support the proposed clinical trial.

145 4.2 Clinical trials should be scientifically sound and reflect the state of knowledge  
146 and experience with the investigational product(s), including, if applicable, the  
147 condition to be treated, diagnosed or prevented; the current understanding of  
148 the underlying biological mechanism (of both the condition and the treatment);  
149 and the population for which the investigational product is intended.

150 4.3 There should be periodic review of current scientific knowledge and approaches  
151 to determine whether modifications to the trial are needed, since new or  
152 unanticipated information may arise once the trial has begun.

153

154 **5. Clinical trials should be designed and conducted by qualified individuals.**

155

156 5.1 Individuals with different expertise and training may be needed across all  
157 phases of a clinical trial, such as physicians, scientists, ethicists, technology  
158 experts, trial coordinators, monitors, auditors and statisticians. Individuals  
159 involved in a trial should be qualified by education, training and experience to  
160 perform their respective task(s).

161

162 **6. Quality should be built into the scientific and operational design and conduct of**  
163 **clinical trials.**

164

165 6.1 Quality of a clinical trial is considered in this guideline as fit for purpose. The  
166 quality and amount of the information generated during a clinical trial should  
167 support good decision making.

168 6.2 Factors critical to the quality of the trial should be identified. These factors are  
169 attributes of a trial that are fundamental to the protection of participants, the  
170 reliability and interpretability of the trial results and the decisions made based  
171 on those trial results. Quality by design involves focusing on the design of all  
172 components of the trial in order to maximise the likelihood of trial success (i.e.,  
173 that the trial will answer the research question).

174 6.3 Strategies should be implemented to avoid, detect and address serious non-  
175 compliance with GCP, the trial protocol and applicable regulatory requirements  
176 to prevent recurrence.

177  
178 **7. Clinical trial processes, measures and approaches should be implemented in a**  
179 **way that is proportionate to the risks to participants and to the importance of**  
180 **the data collected.**

181  
182 7.1 Trial processes should be proportionate to the risks inherent in the trial and the  
183 importance of the information collected. Risks in this context include risks to  
184 the rights, safety and well-being of trial participants as well as risks to the  
185 reliability of the trial results.

186 7.2 The focus should be on the risks to participants beyond those associated with  
187 standard medical care. The risks relating to investigational products that have a  
188 marketing authorisation when used in the clinical trial context may differ from  
189 the routine care of patients and should be taken into consideration.

190 7.3 Risks to critical to quality factors should be managed prospectively and  
191 adjusted when new or unanticipated issues arise once the trial has begun.

192  
193 **8. Clinical trials should be described in a clear, concise and operationally feasible**  
194 **protocol.**

195  
196 8.1 A well-designed trial protocol is fundamental to the protection of participants  
197 and for the generation of reliable results.

198 8.2 The scientific objectives of any trial should be clear and explicitly stated in the  
199 protocol.

200 8.3 The clinical trial protocol as well as the plans or documents for the protocol  
201 execution (e.g., statistical analysis plan, data management plan, monitoring  
202 plan) should be clear, concise and operationally feasible.

203  
204 **9. Clinical trials should generate reliable results.**

205  
206 9.1 The quality and amount of the information generated in a clinical trial should  
207 be sufficient to provide confidence in the trial's results and support good  
208 decision making.

209 9.2 Systems and processes that aid in data capture, management and analyses, as  
210 well as those that help ensure the quality of the information generated from the  
211 trial, should be fit for purpose, should capture the data required by the protocol  
212 and should be implemented in a way that is proportionate to the risks to  
213 participants and the importance of acquired data.

- 214 9.3 Trial processes should be operationally feasible and avoid unnecessary  
215 complexity, procedures and data collection. Trial processes should support the  
216 key trial objectives.
- 217 9.4 Computerised systems used in clinical trials should be fit for purpose, and  
218 factors critical to their quality should be addressed in their design or adaptation  
219 for clinical trial purposes.
- 220 9.5 Clinical trials should incorporate efficient and well-controlled processes for  
221 managing records through appropriate management of data integrity,  
222 traceability and protection of personal information, thereby allowing the  
223 accurate reporting, interpretation and verification of the clinical trial-related  
224 information.
- 225 9.6 Clinical trial-related records should be retained securely by sponsors and  
226 investigators for the required period of time and should be available to  
227 regulatory authorities upon request to enable reconstruction of the trial conduct  
228 and results in order to ensure the reliability of trial results.
- 229 9.7 The transparency of clinical trials in drug development includes registration on  
230 publicly accessible and recognised databases and the public posting of clinical  
231 trial results.

232  
233 **10. Roles and responsibilities in clinical trials should be clear and documented**  
234 **appropriately.**

- 235  
236 10.1 The sponsor may transfer or the investigator may delegate some or all their  
237 tasks, duties or functions (hereafter referred to as activities), but they retain  
238 overall responsibility for their respective activities.
- 239 10.2 Agreements should clearly define the roles, activities and responsibilities for  
240 the clinical trial and be documented appropriately. Where activities have been  
241 transferred or delegated to service providers, the responsibility for the conduct  
242 of the trial, including quality and integrity of the trial data, resides with the  
243 sponsor or investigator, respectively.
- 244 10.3 The sponsor or investigator should maintain appropriate oversight or  
245 supervision of the aforementioned activities, respectively.

246  
247 **11. Investigational products used in a clinical trial should be manufactured in**  
248 **accordance with applicable Good Manufacturing Practice (GMP) standards and**  
249 **be stored, shipped, handled and disposed of in accordance with the product**  
250 **specifications and the trial protocol.**

- 251  
252 11.1 Investigational products used in a clinical trial should be manufactured in  
253 accordance with applicable GMP standards.
- 254 11.2 Measures should be in place to ensure that the investigational product provided  
255 to trial participants retains its quality.
- 256 11.3 Investigational products should be used in accordance with the protocol and  
257 relevant trial documents.

- 258 11.4 Manufacturing, handling and labelling of investigational products should be  
259 undertaken in a manner that aligns with treatment assignment and maintains  
260 blinding, where applicable.
- 261 11.5 Investigational product labelling should follow applicable regulatory  
262 requirements.
- 263 11.6 Adequate measures to ensure that the investigational product is handled and  
264 shipped appropriately should be implemented.

265  
266 **III. ANNEX 1**

267 **1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE**  
268 **(IRB/IEC)**

269 The IRB/IEC is responsible for the ethical review of the trial. The requirements for  
270 the IRB/IEC in this guideline should be read in conjunction with local regulatory  
271 requirements.

272 **1.1 Responsibilities**

273 1.1.1 The purpose of an IRB/IEC is to safeguard the rights, safety and well-being of all trial  
274 participants.

275  
276 1.1.2 The IRB/IEC should review the following information, where applicable:

- 277
- 278 (a) protocol and any amendments;
  - 279
  - 280 (b) informed consent material(s), assent form(s), where applicable, and any  
281 updates, including the description of the process for how informed consent is  
282 to be obtained;
  - 283
  - 284 (c) Investigator's Brochure or current scientific information, such as a basic  
285 product information brochure (e.g., Summary of Product Characteristics  
286 (SmPC), package leaflet or labelling), as appropriate, including their updates;
  - 287
  - 288 (d) any other information to be provided to the trial participant(s), including a  
289 description of the media through which such information will be provided;
  - 290
  - 291 (e) advertisement for participant recruitment (if used) and information on the  
292 recruitment process;
  - 293
  - 294 (f) plans to compensate participants (if any);
  - 295
  - 296 (g) ongoing updates to safety information (dependent on requirements of the  
297 IRB/IEC);
  - 298
  - 299 (h) investigator's current curriculum vitae and/or other documentation evidencing  
300 qualifications;
  - 301

- 302 (i) any other documents that the IRB/IEC may need to fulfil its responsibilities.  
303
- 304 1.1.3 The IRB/IEC should review a proposed clinical trial within a reasonable time and  
305 document its reviews clearly identifying the trial, the documents reviewed and the  
306 dates for the following:  
307
- 308 (a) approval/favourable opinion;  
309
- 310 (b) modifications required prior to its approval/favourable opinion;  
311
- 312 (c) disapproval/negative opinion;  
313
- 314 (d) termination/suspension of any prior approval/favourable opinion.  
315
- 316 1.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals  
317 appropriate to the degree of risk to participants.  
318
- 319 1.1.5 The IRB/IEC may request more information than is outlined in section 2.8.11 be given  
320 to participants when, in the judgement of the IRB/IEC, the additional information  
321 would add meaningfully to the protection of the rights, safety and/or well-being of the  
322 participants.  
323
- 324 1.1.6 Where the protocol indicates that prior consent of the trial participant or the  
325 participant's legally acceptable representative is not possible (see section 2.8.9), the  
326 IRB/IEC should determine that the proposed protocol and/or other document(s)  
327 adequately address relevant ethical concerns and meet applicable regulatory  
328 requirements for such trials (e.g., in emergency situations).  
329
- 330 1.1.7 If minors are to be included in a trial, the IRB/IEC should review the assent  
331 information considering the age, maturity and psychological state of the minor, as well  
332 as applicable regulatory requirements.  
333
- 334 1.1.8 If the trial participants are compensated for their participation in the trial, the IRB/IEC  
335 should review both the amount and method of payment to participants to assure that  
336 neither presents problems of coercion or undue influence on the trial participants.  
337 Payments to a participant should be prorated and not wholly contingent on completion  
338 of the trial by the participant. Reasonable reimbursement of participants for travel and  
339 lodging is not typically coercive.  
340
- 341 1.1.9 The IRB/IEC should ensure that information regarding payment to participants,  
342 including the methods, amounts and schedule of payment to trial participants, is set  
343 forth in the informed consent material and any other information to be provided to  
344 participants.



345 **1.2 Composition, Functions and Operations**

346 1.2.1 The IRB/IEC should consist of a reasonable number of members who collectively  
347 have the qualifications and experience to review and evaluate the science, medical  
348 aspects and ethics of the proposed trial. It is recommended that the IRB/IEC should  
349 include:

- 350
- 351 (a) at least five members;
  - 352
  - 353 (b) at least one member whose primary area of interest is not in medical sciences;
  - 354
  - 355 (c) at least one member who is independent of the institution/investigator site.
- 356

357 Only those IRB/IEC members who are independent of the investigator and the sponsor  
358 of the trial should vote/provide an opinion. A list of IRB/IEC members and their  
359 qualifications should be maintained.

360

361 1.2.2 The IRB/IEC should perform its functions according to documented operating  
362 procedures, should maintain records of its activities and minutes of its meetings, and  
363 should comply with GCP and with the applicable regulatory requirement(s).

364

365 1.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a  
366 quorum, as stipulated in its documented operating procedures, is present.

367

368 1.2.4 Only members who participate in the IRB/IEC review and discussion should  
369 vote/provide their opinion and/or advise.

370

371 1.2.5 The investigator, investigator site staff and/or sponsor, where appropriate, may  
372 provide information on any aspect of the trial but should not participate in the decision  
373 making of the IRB/IEC or in the vote/opinion of the IRB/IEC.

374

375 1.2.6 An IRB/IEC may invite non-members with expertise in special areas for assistance.

376 **1.3 Procedures**

377 The IRB/IEC should establish, document in writing or electronically, and follow its procedures,  
378 which should include:

379 1.3.1 Determining its composition (names and qualifications of the members) and the  
380 authority under which it is established;

381

382 1.3.2 Scheduling, notifying its members of and conducting its meetings;

383

384 1.3.3 Conducting initial and continuing review of trials;

385

386 1.3.4 Determining the frequency of continuing review, as appropriate;

387

- 388 1.3.5 Providing, according to the applicable regulatory requirements, expedited review and  
 389 approval/favourable opinion of minor change(s) in ongoing trials that have the  
 390 approval/favourable opinion of the IRB/IEC;  
 391
- 392 1.3.6 Specifying that no participant should be admitted to a trial before the IRB/IEC issues  
 393 its documented approval/favourable opinion of the trial;  
 394
- 395 1.3.7 Specifying that no deviations from the protocol should be initiated without prior  
 396 documented IRB/IEC approval/favourable opinion, except when necessary to  
 397 eliminate immediate hazards to the participants;  
 398
- 399 1.3.8 Specifying that the investigator/institution should promptly report to the IRB/IEC (see  
 400 section 1.5):  
 401
- 402 (a) deviations from the protocol to eliminate immediate hazards to the trial  
 403 participants (see sections 1.3.7, 2.5.3 and 2.5.4);  
 404
  - 405 (b) changes increasing the risk to participants and/or significantly affecting the  
 406 conduct of the trial (see section 2.4.6);  
 407
  - 408 (c) all suspected unexpected serious adverse reactions (SUSARs) in line with  
 409 applicable regulatory requirements;  
 410
  - 411 (d) new information that may affect adversely the safety of the participants or the  
 412 conduct of the trial.  
 413
- 414 1.3.9 Ensuring that the IRB/IEC (see section 1.5) promptly notifies in writing or  
 415 electronically the investigator/institution or sponsor concerning:  
 416
- 417 (a) its trial-related decisions/opinions;  
 418
  - 419 (b) the reasons for its decisions/opinions;  
 420
  - 421 (c) procedures for appeal of its decisions/opinions.  
 422
- 422 **1.4 Records**
- 423 1.4.1 The IRB/IEC should retain all relevant records (e.g., documented procedures,  
 424 membership lists, lists of occupations/affiliations of members, submitted documents,  
 425 minutes of meetings and correspondence) in accordance with applicable regulatory  
 426 requirements and make them available upon request from the regulatory  
 427 authority(ies).  
 428
- 429 1.4.2 The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to  
 430 provide its documented procedures and membership lists.

431 **1.5 Submission and Communication**

432 For the submission to or communication with the IRB/IEC, it is recognised that in most regions,  
 433 there is also a requirement to make a submission to the relevant regulatory authority, and these  
 434 may be combined, in line with applicable regulatory requirements, in a single submission in  
 435 some regions. In addition, applicable regulatory requirements may require that submissions to  
 436 the IRB/IEC are made in some regions by the investigator/institution and in others by the  
 437 sponsor.

438

439 **2. INVESTIGATOR**

440 **2.1 Qualifications and Training**

441 2.1.1 The investigator(s) should be qualified by education, training and experience to  
 442 assume responsibility for the proper conduct of the trial and should provide evidence  
 443 of such qualifications.

444

445 2.1.2 The investigator should be familiar with the appropriate use of the investigational  
 446 product(s) as described in the protocol, in the current Investigator’s Brochure, in the  
 447 product information and/or in other information sources provided by the sponsor.

448 **2.2 Resources**

449 2.2.1 The investigator should be able to demonstrate (e.g., based on retrospective or  
 450 currently available data) a potential for recruiting the proposed number of eligible  
 451 participants within the recruitment period as agreed with the sponsor.

452

453 2.2.2 The investigator should have sufficient time, an adequate number of available and  
 454 qualified staff, and adequate facilities for the foreseen duration of the trial to conduct  
 455 the trial properly and safely.

456 **2.3 Responsibilities**

457 2.3.1 The investigator may delegate trial-specific activities to other persons or parties.

458 The investigator may be supported by the sponsor to identify a suitable service  
 459 provider(s); however, the investigator retains the final decision on whether the service  
 460 provider intended to support the investigator is appropriate based on information  
 461 provided by the sponsor (see section 3.6.6).

462 The investigator retains the ultimate responsibility and maintains appropriate  
 463 supervision of the persons or parties undertaking the activities delegated to ensure the  
 464 rights, safety and well-being of the trial participants and data reliability.

465

466 2.3.2 The investigator should ensure that persons or parties to whom the investigator has  
 467 delegated trial-specific activities are appropriately qualified and supervised and are  
 468 adequately informed about the protocol, the investigational product(s) and their  
 469 assigned trial activities (including activities conducted by staff provided by other  
 470 parties, for example, home nurses arranged by the sponsor). Trial-related training to

471 persons assisting in the trial should correspond to what is necessary to enable them to  
472 fulfil their delegated trial activities that go beyond their usual training and experience.  
473

474 2.3.3 The investigator should ensure a record is maintained of the persons and parties to  
475 whom the investigator has delegated significant trial-related activities. In situations  
476 where the clinical trial activities are performed in accordance with routine clinical  
477 care, delegation documentation may not be required.  
478

479 2.3.4 Agreements made by the investigator/institution with service providers for trial-  
480 related activities should be documented.  
481

482 2.3.5 The investigator/institution should permit monitoring and auditing by the sponsor and  
483 inspection by the appropriate regulatory authority(ies).

## 484 **2.4 Communication with IRB/IEC**

485 2.4.1 Submission to the IRB/IEC may be made by the investigator/institution or sponsor in  
486 accordance with applicable regulatory requirements (see section 1.5).  
487

488 2.4.2 Before initiating a trial, the investigator/institution should have a documented and  
489 dated approval/favourable opinion from the IRB/IEC for the trial protocol, informed  
490 consent material, participant recruitment procedures (e.g., advertisements) and any  
491 other information to be provided to participants.  
492

493 2.4.3 As part of the investigator's/institution's or sponsor's (in accordance with applicable  
494 regulatory requirements) submission to the IRB/IEC, a current copy of the  
495 Investigator's Brochure or basic product information brochure should be provided  
496 (see section A.1.1 of Appendix A. Investigator's Brochure). If the Investigator's  
497 Brochure is updated during the trial, the IRB/IEC should receive the current version  
498 in accordance with applicable regulatory requirements.  
499

500 2.4.4 As the trial progresses, the investigator/institution or sponsor should provide any  
501 updates to the participant information according to applicable regulatory  
502 requirements.  
503

504 2.4.5 The investigator or the sponsor should submit documented summaries of the trial  
505 status to the IRB/IEC in accordance with local regulatory requirements or upon  
506 request.  
507

508 2.4.6 The investigator or the sponsor should promptly communicate to the IRB/IEC (see  
509 section 1.3.8) and, where applicable, the institution about any changes significantly  
510 affecting the conduct of the trial and/or increasing the risk to participants.

## 511 **2.5 Compliance with Protocol**

512 2.5.1 The investigator should comply with the protocol and GCP and applicable regulatory  
513 requirements. The investigator/institution should sign the protocol or an alternative  
514 contract to confirm agreement with the sponsor.

515 2.5.2 The investigator should document all protocol deviations and review deviations  
 516 communicated to them by the sponsor. For important deviations, the investigator  
 517 should explain the deviation and implement appropriate measures to prevent a  
 518 recurrence, where applicable, see section 3.9.3.

519  
 520 2.5.3 The investigator should follow the protocol and deviate only where necessary to  
 521 eliminate an immediate hazard(s) to trial participants. In case of deviations undertaken  
 522 to eliminate immediate hazard to trial participants, the investigator should inform the  
 523 sponsor, IRB/IEC and/or regulatory authorities promptly.

524  
 525 2.5.4 The investigator should report information on the immediate hazard, the implemented  
 526 change and the subsequent proposed protocol amendment to the IRB/IEC and/or  
 527 regulatory authorities.

528 **2.6 Premature Termination or Suspension of a Trial**

529 2.6.1 If the trial is prematurely terminated or suspended for any reason, the  
 530 investigator/institution should promptly inform the trial participants and should assure  
 531 appropriate therapy and follow-up for the participants.

532  
 533 2.6.2 Where the investigator terminates or suspends their involvement in a trial without  
 534 prior agreement by the sponsor, the investigator should promptly inform the sponsor,  
 535 the IRB/IEC and the regulatory authorities in accordance with applicable regulatory  
 536 requirements and should provide a detailed explanation of the reasons.

537  
 538 2.6.3 If the sponsor terminates or suspends a trial, the investigator/institution, or the  
 539 sponsor, in accordance with applicable regulatory requirement(s), should promptly  
 540 inform the IRB/IEC and the regulatory authorities. See section 3.17.1.

541  
 542 2.6.4 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see  
 543 sections 1.1.3 and 1.3.9), the investigator should inform the institution, where  
 544 applicable, and the investigator/institution should promptly notify the sponsor.

545 **2.7 Participant Medical Care and Safety Reporting**

546 *2.7.1 Medical Care of Trial Participants*

547 (a) A qualified physician or, where appropriate, a qualified dentist (or other  
 548 qualified healthcare professionals in accordance with local regulatory  
 549 requirements) who is an investigator or a sub-investigator for the trial should  
 550 have the overall responsibility for trial-related medical care and decisions.

551  
 552 (b) Other appropriately qualified healthcare professionals may be involved in the  
 553 medical care of trial participants, in line with their normal activities and in  
 554 accordance with local regulatory requirements.

555  
 556 (c) During and following participation in a trial, the investigator/institution should  
 557 ensure that adequate medical care is provided to a participant for any adverse  
 558 events, including clinically significant laboratory values, related to the trial.

559 The investigator/institution should inform a participant when medical care is  
560 needed for intercurrent illness(es) of which the investigator becomes aware.

561  
562 (d) The investigator should inform the participant's primary physician about the  
563 participant's involvement in the trial if the participant has a primary physician  
564 and agrees to the primary physician being informed.

#### 565 2.7.2 *Safety Reporting*

566 (a) Adverse events and/or laboratory abnormalities required for safety evaluations  
567 (as outlined in the protocol) should be reported to the sponsor according to the  
568 reporting requirements and within the time periods specified in the protocol.

569  
570 (b) All serious adverse events (SAEs) should be reported immediately (after the  
571 investigator reasonably becomes aware of the event) to the sponsor. In  
572 accordance with applicable regulatory requirements, the protocol may identify  
573 SAEs not requiring immediate reporting, for example, deaths or other events  
574 that are endpoints. Subsequent information should be submitted as a follow-  
575 up report, as necessary.

576  
577 (c) For reported deaths, the investigator should supply the sponsor, the IRB/IEC  
578 and, where applicable, the regulatory authority with any additional requested  
579 information (e.g., autopsy reports and terminal medical reports) when they  
580 become available.

581  
582 (d) The investigator may delegate activities for safety reporting to qualified  
583 investigator site staff but retains the overall responsibility for safety of  
584 participants under their responsibility and compliance with the reporting  
585 requirements.

### 586 **2.8 Informed Consent of Trial Participants**

587 2.8.1 In obtaining and documenting informed consent (paper or electronic format), the  
588 investigator should comply with the applicable regulatory requirement(s) and should  
589 adhere to GCP and to the ethical principles that have their origin in the Declaration of  
590 Helsinki. See the glossary term "informed consent." The informed consent process  
591 should include the following:

592  
593 (a) Prior to consenting and enrolling participants, the investigator should have the  
594 IRB/IEC's documented approval/favourable opinion of the informed consent  
595 materials and process;

596  
597 (b) The information should be as clear and concise as possible, use simple  
598 language and avoid unnecessary volume and complexity. This is to ensure that  
599 the trial participants or their legally acceptable representatives have an  
600 adequate understanding of the objectives of the trial, alternative treatments,  
601 the potential benefits and risks, burdens and their rights and obligations to be  
602 able to make an informed decision as to their participation in the trial;

603 (c) Varied approaches (e.g., text, images, videos and other interactive methods) may  
604 be used in the informed consent process including for providing information  
605 to the participant. Obtaining consent remotely may be considered where  
606 appropriate.  
607

608 2.8.2 The participant or the participant's legally acceptable representative should be  
609 informed in a timely manner if new information becomes available that may be  
610 relevant to the participant's willingness to continue trial participation. The  
611 communication of this information and confirmation of the willingness to continue  
612 trial participation should be documented.  
613

614 New information that could impact a participant's willingness to continue  
615 participation should be assessed to determine if re-consent is needed (e.g., depending  
616 on the stage of the trial, consideration should be given to whether the new information  
617 is relevant only to new participants or to existing participants). If re-consent is needed  
618 (e.g., information on emerging safety concerns), new information should be clearly  
619 identified in the revised informed consent materials. Revised informed consent  
620 materials should receive the IRB/IEC's approval/favourable opinion in advance of  
621 use.  
622

623 2.8.3 Neither the investigator nor the investigator site staff should coerce or unduly  
624 influence a participant to participate or to continue their participation in the trial.  
625

626 2.8.4 None of the information provided to the participant during the informed consent  
627 process should contain any language that causes the participant or the participant's  
628 legally acceptable representative to waive or to appear to waive any legal rights, or  
629 that releases or appears to release the investigator, the institution, the sponsor or their  
630 service providers from liability for negligence.  
631

632 2.8.5 The informed consent process should be conducted by the investigator or other  
633 investigator site staff delegated by the investigator, in accordance with applicable  
634 regulatory requirements. If the participant is unable to provide consent themselves,  
635 the participant's legally acceptable representative should provide their consent on  
636 behalf of the participant.  
637

638 2.8.6 The information provided during the informed consent process and translations should  
639 be relevant, clear, simple, concise and understandable to the participant or the  
640 participant's legally acceptable representative and the impartial witness, where  
641 applicable.  
642

643 2.8.7 Before informed consent may be obtained, the investigator or investigator site staff  
644 delegated by the investigator, in accordance with the protocol and conditions of  
645 IRB/IEC favourable opinions/approvals, should provide the participant or the  
646 participant's legally acceptable representative ample time unless justified (e.g., in an  
647 emergency situation) and opportunity to enquire about trial details and to decide  
648 whether or not to participate in the trial. Questions about the trial should be answered

649 to the satisfaction of the participant or the participant's legally acceptable  
 650 representative.

651  
 652 2.8.8 Prior to trial participation, the informed consent form should be signed and dated by  
 653 the participant or by the participant's legally acceptable representative and, where  
 654 appropriate, impartial witness and by the investigator or delegated investigator site  
 655 staff who conducted the informed consent discussion. The informed consent process  
 656 may involve a physical signature or an electronic signature.

657  
 658 2.8.9 In emergency situations, when prior consent of the participant is not possible, the  
 659 consent of the participant's legally acceptable representative, if present, should be  
 660 requested. When prior consent of the participant is not possible and the participant's  
 661 legally acceptable representative is not available, enrolment of the participant should  
 662 require measures described in the protocol and/or elsewhere, with documented  
 663 approval/favourable opinion by the IRB/IEC, to protect the participant's rights, safety  
 664 and well-being and to ensure compliance with applicable regulatory requirements.  
 665 The participant or the participant's legally acceptable representative should be  
 666 informed about the trial as soon as possible, and consent as appropriate (see section  
 667 2.8.10) should be requested.

668  
 669 2.8.10 If a participant or the legally acceptable representative is unable to read, an impartial  
 670 witness should be present (remotely or in-person) during the entire informed consent  
 671 discussion. After the informed consent form and any other information is read and  
 672 explained to the participant or the participant's legally acceptable representative and  
 673 they have orally consented to the participant's trial participation and, if capable of  
 674 doing so, have signed and personally dated the informed consent form, the witness  
 675 should contemporaneously sign and personally date the consent form. By signing the  
 676 consent form, the witness attests that the consent information was accurately  
 677 explained to and apparently understood by the participant or the participant's legally  
 678 acceptable representative and that informed consent was freely given by the  
 679 participant or the participant's legally acceptable representative.

680  
 681 2.8.11 The informed consent discussion and the informed consent materials to be provided  
 682 to participants should explain the following as applicable:

- 683  
 684 (a) the purpose of the trial;  
 685  
 686 (b) that the trial involves research and summary of the experimental aspects of the  
 687 trial;  
 688  
 689 (c) the trial's investigational product(s) and the probability for random  
 690 assignment to the investigational product, if applicable;  
 691  
 692 (d) the trial procedures to be followed including all invasive procedures;  
 693  
 694 (e) the participant's obligations;



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- 695 (f) the reasonably foreseeable risks or inconveniences to the participant and, when  
696 applicable, the participant's partner, to an embryo, foetus or nursing infant;  
697
- 698 (g) the reasonably expected benefits. When there is no intended clinical benefit to  
699 the participant, the participant should be made aware of this;  
700
- 701 (h) the alternative procedure(s) or course(s) of treatment that may be available to  
702 the participant and their important potential benefits and risks;  
703
- 704 (i) the compensation and/or treatment available to the participant in the event of  
705 trial-related injury;  
706
- 707 (j) any anticipated prorated compensation to the participant for trial participation;  
708
- 709 (k) any anticipated expenses to the participant for trial participation;  
710
- 711 (l) that the participant's trial participation is voluntary, and the participant may  
712 refuse to participate or may withdraw, at any time, without penalty or loss of  
713 benefits to which the participant is otherwise entitled;  
714
- 715 (m) the process by which the participant's data will be handled, including in the  
716 event of the withdrawal of participation in accordance with regulatory  
717 requirements;  
718
- 719 (n) that by agreeing to participate in the trial, the participant or their legally  
720 acceptable representative allows direct access to original medical records, per  
721 applicable regulatory requirements, while safeguarding the confidentiality of  
722 the participant. This access is limited for the purpose of reviewing trial  
723 activities and/or reviewing or verifying data and records by the IRB/IEC(s),  
724 regulatory authority(ies) and the sponsor's representatives, for example,  
725 monitor(s) or auditor(s);  
726
- 727 (o) that records identifying the participant will be kept confidential and, to the  
728 extent permitted by the applicable regulatory requirements, will not be made  
729 publicly available. If the trial results are published, the participant's identity  
730 will remain confidential. The trial may be registered on publicly accessible  
731 and recognised databases, per applicable regulatory requirements;  
732
- 733 (p) that the participant or the participant's legally acceptable representative will  
734 be informed in a timely manner if information becomes available that may be  
735 relevant to the participant's willingness to continue trial participation;  
736
- 737 (q) the person(s) to contact for further trial information and the trial participant's  
738 rights, and whom to contact in the event of suspected trial-related injury;  
739

- 740 (r) the foreseeable circumstances and/or reasons under which the participant's  
 741 trial participation may be terminated;  
 742  
 743 (s) the expected duration of the participant's trial participation;  
 744  
 745 (t) the approximate number of participants involved in the trial;  
 746  
 747 (u) that trial results and information on the participant's actual treatment, if  
 748 appropriate, will be made available to them should they desire it.  
 749

750 2.8.12 Prior to participation, the participant or the participant's legally acceptable  
 751 representative should receive a copy (paper or electronic) of the signed informed  
 752 consent form and any other informed consent materials provided to the participants,  
 753 or in accordance with applicable regulatory requirements. During trial participation,  
 754 the participant or the participant's legally acceptable representative should receive a  
 755 copy of the consent form updates and any other updated informed consent materials  
 756 provided to participants.  
 757

758 2.8.13 Where a minor is to be included as a participant, age-appropriate assent information  
 759 should be provided and discussed with the minor as part of the consent process, and  
 760 assent from the minor to enrol in the trial should be obtained as appropriate. A process  
 761 for re-consent should be considered if, during the course of the trial, the minor reaches  
 762 the age of legal consent, in accordance with applicable regulatory requirements.  
 763

764 2.8.14 When a clinical trial includes participants who may only be enrolled in the trial with  
 765 the consent of the participant's legally acceptable representative (e.g., minors, patients  
 766 with severe impaired decision-making capacity), the participant should be informed  
 767 about the trial to the extent compatible with the participant's understanding and, if  
 768 capable, the participant should sign and personally date the informed consent form or  
 769 assent form as appropriate.  
 770

771 2.8.15 In exceptional circumstances (e.g., public health emergencies), when the usual  
 772 methods to obtain and document informed consent are not possible, the use of  
 773 alternative measures and technologies in accordance with local IRBs/IECs and  
 774 applicable regulatory requirements should be considered.

## 775 **2.9 End of Participation in a Clinical Trial**

776 2.9.1 When a participant decides to stop treatment with the investigational product, stop  
 777 trial visits or completely withdraw from a trial; is discontinued from the trial; or  
 778 reaches routine end of trial, the investigator should follow the protocol and other  
 779 sponsor instructions to determine appropriate follow-up measures. This may include  
 780 instructions to avoid unnecessary loss of already collected critical data in accordance  
 781 with applicable regulatory requirements.  
 782

783 2.9.2 Although a participant is not obliged to provide a reason(s) for withdrawing  
 784 prematurely from a trial, the investigator should make a reasonable effort to ascertain

785 the reason(s), while fully respecting the participant's rights. The investigator should  
786 consider discussing with the participant or the participant's legally acceptable  
787 representative the reasons for withdrawal to determine if there are ways to address the  
788 concerns. The investigator site staff should make an effort to explain to the participant  
789 the value and importance of continuing their participation to minimise trial  
790 participants withdrawal.

791  
792 2.9.3 Where relevant, the investigator should inform the participant about the trial results  
793 and treatment received when this information is available from the sponsor after  
794 unblinding, with due respect to the participant's preference to be informed.

## 795 **2.10 Investigational Product Management**

796 2.10.1 Responsibility for investigational product(s) accountability rests with the  
797 investigator/institution. The sponsor may facilitate this process.

798  
799 2.10.2 When the investigator/institution assigns some or all of their activities for  
800 investigational product(s) accountability to a pharmacist or another individual, they  
801 should be under the supervision of the investigator/institution.

802  
803 2.10.3 The investigator/institution and/or a pharmacist or other appropriate individual should  
804 maintain records of the product's delivery, the inventory, the use by each participant  
805 (including documenting that the participants were provided the doses specified by the  
806 protocol) and the return to the sponsor and destruction or alternative disposition of  
807 unused product(s). These records should include dates, quantities, batch/serial  
808 numbers, expiration dates (if applicable) and the unique code numbers assigned to the  
809 investigational product(s) and trial participants. For authorised medicinal products,  
810 alternative approaches to the aforementioned may be considered, in accordance with  
811 local regulatory requirements.

812  
813 2.10.4 The investigational product(s) should be stored as specified by the sponsor and in  
814 accordance with applicable regulatory requirement(s).

815  
816 2.10.5 The investigator should ensure that the investigational product(s) are used only in  
817 accordance with the approved protocol.

818  
819 2.10.6 Where applicable, the investigator or a person designated by the  
820 investigator/institution should explain the correct use of the investigational product(s)  
821 to each participant and should check, at intervals appropriate for the trial, that each  
822 participant is following the instructions properly.

## 823 **2.11 Randomisation Procedures and Unblinding**

824 The investigator should follow the trial's randomisation procedures, if any, and, in the case of  
825 an investigator-blinded trial, should ensure that the identification code is broken only in  
826 accordance with the protocol. In the case of an emergency, to protect patient safety, the  
827 investigator should be prepared and capable from the start of the trial to perform unblinding  
828 without undue delay and hinderance. The investigator should promptly document and explain

829 to the sponsor any premature unblinding (e.g., accidental unblinding, emergency unblinding to  
830 protect trial participant, unblinding due to an SAE) of the investigational product(s).

## 831 **2.12 Records**

832 2.12.1 In generating, recording and reporting trial data, the investigator should ensure the  
833 integrity of data under their responsibility, irrespective of the media used.

834  
835 2.12.2 The investigator/institution should maintain adequate source records that include  
836 pertinent observations on each of the trial participants under their responsibility.  
837 Source records should be attributable, legible, contemporaneous, original, accurate  
838 and complete. Changes to source records should be traceable, should not obscure the  
839 original entry and should be explained if necessary (via an audit trail). The  
840 investigator should define what is considered to be a source record(s), the methods of  
841 data capture and their location prior to starting the trial and should update this  
842 definition when needed. Unnecessary transcription steps in between the source record  
843 and the data acquisition tool should be avoided.

844  
845 2.12.3 The investigator should have timely access to and be responsible for the timely review  
846 of data, including relevant data from external sources (e.g., central laboratory data,  
847 centrally read imaging data, other institution's records and, if appropriate, electronic  
848 patient-reported outcome (ePRO) data) which can have an impact on, for example,  
849 participant eligibility, treatment or safety. The protocol may provide exceptions for  
850 access, for instance, to protect blinding.

851  
852 2.12.4 The investigator should ensure that data acquisition tools and other systems deployed  
853 by the sponsor for clinical trial purposes are used as specified in the protocol or trial-  
854 related instructions.

855  
856 2.12.5 The investigator should ensure the accuracy, completeness, legibility and timeliness  
857 of the data reported to the sponsor in the data acquisition tools completed by the  
858 investigator site (e.g., case report form (CRF)) and in all required reports. The  
859 investigator should review and endorse the reported data at milestones agreed upon  
860 with the sponsor (e.g., interim analysis).

861  
862 2.12.6 Data reported to the sponsor should be consistent with the source records or the  
863 discrepancies explained. Changes or corrections in the reported data should be  
864 traceable, should be explained (if necessary) and should not obscure the original entry.

865  
866 2.12.7 The investigator/institution should implement appropriate measures to protect the  
867 privacy and confidentiality of personal information of trial participants in accordance  
868 with applicable regulatory requirements on personal data protection. Data reported to  
869 the sponsor should be identified by an unambiguous participant code that can be traced  
870 back to the identity of the participant by the investigator/institution.

871  
872 2.12.8 For systems deployed by the investigator/institution that maintain and retain trial  
873 data/information, the investigator/institution should ensure that such data are

874 protected from unauthorised access, disclosure, dissemination or alteration and from  
875 inappropriate destruction or accidental loss.

876  
877 2.12.9 When using computerised systems in a clinical trial, the investigator/institution should  
878 do the following:

879  
880 (a) for systems deployed by the investigator/institution, ensure that appropriate  
881 individuals have secure and attributable access;

882  
883 (b) for systems deployed by the investigator/institution specifically for the  
884 purposes of clinical trials, ensure that the requirements for computerised  
885 systems in section 4 are addressed;

886  
887 (c) where equipment for data acquisition is provided to trial participants by the  
888 investigator, ensure that traceability is maintained and participants are  
889 provided with appropriate training;

890  
891 (d) ensure that incidents in the use and operation of computerised systems, which  
892 in their judgement may have a significant and/or persistent impact on the trial  
893 data, are reported to the sponsor and, where applicable, to the IRB/IEC.

894  
895 2.12.10 The investigator/institution should maintain the trial records as specified in Appendix  
896 C. Essential Records for the Conduct of a Clinical Trial and as required by the  
897 applicable regulatory requirement(s). The investigator/institution should have control  
898 of all essential records generated by the investigator/institution before, during and  
899 after the trial. The investigator/institution should take measures to prevent accidental  
900 or premature destruction of these records. If the investigator closes a site or leaves a  
901 site during or after the end of the clinical trial, the sponsor should be notified of the  
902 appropriate individual responsible for retention of the site's essential records.

903  
904 2.12.11 The investigator/institution should retain the essential records for the required  
905 retention period in accordance with applicable regulatory requirements or until the  
906 sponsor informs the investigator/institution that these records are no longer needed,  
907 whichever is the longer (see Appendix C).

908  
909 2.12.12 Upon request of the monitor, auditor, IRB/IEC or regulatory authority, the  
910 investigator/institution should make available for direct access all requested trial-  
911 related records.

## 912 **2.13 Clinical Trial/Study Reports**

913 2.13.1 Upon completion of the trial, the investigator, where applicable, should inform the  
914 institution. The investigator/institution should provide the IRB/IEC with a summary  
915 of the trial's outcome and, if applicable, the regulatory authority(ies) with any required  
916 reports.

917

918 2.13.2 Where a coordinating investigator is involved in a trial, consideration should be given  
919 to them being a signatory on the clinical trial report; see ICH E3 Structure and Content  
920 of Clinical Study Reports.

921

### 922 3. SPONSOR

923 The responsibility of the sponsor entails the implementation of risk-proportionate processes to  
924 ensure the safety of the trial participants and the reliability of the trial results throughout the  
925 clinical trial life cycle.

#### 926 3.1 Trial Design

927 3.1.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy  
928 data from nonclinical studies and/or clinical trials and/or real-world data are available  
929 to support human exposure by the route, at the dosages, for the duration and in the  
930 trial population to be studied.

931

932 3.1.2 Sponsors should incorporate quality into the design of the clinical trial by identifying  
933 factors that are critical to the quality of the trial and by managing risks to those factors.

934

935 3.1.3 Sponsors should consider inputs from a wide variety of stakeholders, for example,  
936 healthcare professionals and patients, to support the development plan and clinical  
937 trial protocols as described in ICH E8(R1) and when developing the informed consent  
938 material and any other participant-facing information.

939

940 3.1.4 The sponsor should ensure that all aspects of the trial are operationally feasible and  
941 should avoid unnecessary complexity, procedures and data collection. Protocols, data  
942 acquisition tools and other operational documents should be fit for purpose, clear,  
943 concise and consistent, when applicable.

#### 944 3.2 Resources

945 The sponsor should ensure that sufficient resources are available to appropriately conduct the  
946 trial.

#### 947 3.3 Allocation of Activities

948 Prior to initiating clinical trial activities, the sponsor should determine the roles and allocate  
949 trial-related activities accordingly.

#### 950 3.4 Qualification and Training

951 The sponsor should utilise appropriately qualified individuals for the activities to which they  
952 are assigned (e.g., biostatisticians, clinical pharmacologists, physicians, data scientists/data  
953 managers, auditors and monitors) throughout the trial process.

##### 954 3.4.1 *Medical Expertise*

955 The sponsor should have medical personnel readily available who will be able to  
956 advise on specific trial-related medical questions or problems.

957 **3.5 Financing**

958 The financial aspects of the trial should be documented in an agreement between the sponsor  
959 and the investigator/institution.

960 **3.6 Agreements**

961 3.6.1 Agreements made by the sponsor with the investigator/institution, service providers  
962 and any other parties (e.g., independent data monitoring committee (IDMC),  
963 adjudication committee) involved with the clinical trial should be documented prior  
964 to initiating the activities.

965  
966 3.6.2 Agreements should be updated when necessary to reflect significant changes in the  
967 activities delegated.

968  
969 3.6.3 The sponsor should obtain the investigator's/institution's and, where applicable,  
970 service provider's agreement:

971  
972 (a) to conduct the trial in accordance with the approved protocol and in  
973 compliance with GCP and applicable regulatory requirement(s);

974  
975 (b) to comply with procedures for data recording/reporting;

976  
977 (c) to retain the trial-related essential records for the required retention period in  
978 accordance with applicable regulatory requirements or until the sponsor  
979 informs the investigator/institution or, where applicable, the service provider,  
980 that these documents are no longer needed, whichever is longer;

981  
982 (d) to permit monitoring, auditing and inspections by sponsors, IRB/IECs and  
983 regulatory authorities (domestic and foreign) including providing direct access  
984 to source records and facilities, including to those of service providers.

985  
986 3.6.4 The responsibilities of coordinating investigator(s) and the other participating  
987 investigators should be documented prior to the start of the trial.

988  
989 3.6.5 Any of the sponsor's trial-related activities that are transferred to and assumed by a  
990 service provider should be documented in an agreement. The sponsor's trial-related  
991 activities that are not specifically transferred to and assumed by a service provider are  
992 retained by the sponsor.

993  
994 3.6.6 The sponsor should provide information to the investigator on any service provider  
995 identified by the sponsor to undertake any activities under the responsibility of the  
996 investigator. The responsibility for such activities remains with the investigator.

997  
998 3.6.7 A sponsor may transfer any or all of the sponsor's trial-related activities to a service  
999 provider; however, the ultimate responsibility for the sponsor's trial-related activities,  
1000 including protection of participants' rights, safety and well-being and reliability of the  
1001 trial data, resides with the sponsor. Any service provider used for clinical trial

1002 activities should implement appropriate quality management and report to the sponsor  
 1003 any incidents that might have an impact on the safety of trial participants or/and trial  
 1004 results.

1005  
 1006 3.6.8 The sponsor is responsible for assessing the suitability of and selecting the service  
 1007 provider to ensure that they can adequately undertake the activities transferred to  
 1008 them. The sponsor should provide the service providers with the protocol where  
 1009 necessary as well as any other documents required for them to perform their activities.

1010  
 1011 3.6.9 The sponsor should have access to relevant information (e.g., SOPs and performance  
 1012 metrics) for selection and oversight of service providers.

1013  
 1014 3.6.10 The sponsor should ensure appropriate oversight of important trial-related activities  
 1015 that are transferred to service providers and further subcontracted.

1016  
 1017 3.6.11 Trial-related activities performed by service providers should be conducted in  
 1018 accordance with relevant GCP requirements, which may be fulfilled by a service  
 1019 provider's existing processes.

1020  
 1021 3.6.12 A clinical trial may have one or several sponsors where permitted under applicable  
 1022 regulatory requirements. In trials with more than one sponsor, the sponsors should  
 1023 have a documented agreement that sets out their respective responsibilities, in  
 1024 accordance with local regulatory requirements and/or practice. Where the documented  
 1025 agreement does not specify to which sponsor a given responsibility is attributed, that  
 1026 responsibility lies with all sponsors.

1027 **3.7 Investigator Selection**

1028 3.7.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each  
 1029 investigator should be qualified by education, training and experience and should  
 1030 demonstrate they have adequate resources and facilities to properly conduct the trial.  
 1031 If organisation of a coordinating committee and/or selection of coordinating  
 1032 investigator(s) are to be utilised in multicentre trials, their organisation and/or  
 1033 selection are the sponsor's responsibility, and their roles should be documented prior  
 1034 to their involvement in the trial.

1035  
 1036 3.7.2 The sponsor should provide the investigator(s)/institution(s) with the protocol and an  
 1037 up-to-date Investigator's Brochure as well as sufficient time for the review of the  
 1038 protocol and the information provided.

1039 **3.8 Communication with IRB/IEC and Regulatory Authority(ies)**

1040 *3.8.1 Notification/Submission to Regulatory Authority(ies)*

1041 In accordance with applicable regulatory requirement(s), before initiating the clinical  
 1042 trial(s), the sponsor (or the sponsor and the investigator) should submit any required  
 1043 application(s) to the appropriate regulatory authority(ies) for review, acceptance  
 1044 and/or permission to begin the trial(s). Any notification/submission should be dated  
 1045 and contain sufficient information to identify the protocol.



1046 3.8.2 *Confirmation of Review by IRB/IEC*

1047 (a) Where reference is made to a submission to the IRB/IEC, this can be made by  
1048 the investigator/institution or sponsor in accordance with applicable regulatory  
1049 requirements (see section 1.5).

1050  
1051 (b) The sponsor should ensure that the following is obtained:

1052  
1053 (i) The name and address of the relevant IRB/IEC along with:

1054  
1055 (aa) a statement that it is organised and operates according to GCP  
1056 and the applicable regulatory requirements;

1057  
1058 (bb) documented initial and subsequent IRB/IEC  
1059 approval/favourable opinion as well as any termination of the  
1060 trial or the suspension of approval/favourable opinion.

1061 **3.9 Sponsor Oversight**

1062 3.9.1 The sponsor should ensure that the trial design and trial conduct, the processes  
1063 undertaken, and the information and data generated are of sufficient quality to ensure  
1064 reliable trial results, trial participant's safety and appropriate decision making.

1065  
1066 3.9.2 The sponsor should ensure that trial processes are conducted in compliance with the  
1067 trial protocol and related documents as well as with applicable regulatory  
1068 requirements and ethical standards.

1069  
1070 3.9.3 The sponsor should determine necessary trial-specific criteria for classifying protocol  
1071 deviations as important (i.e., those that impact the rights, safety and well-being of trial  
1072 participants and the reliability of results).

1073  
1074 3.9.4 Decisions related to the trial should be appropriately assessed for their impact on  
1075 participant's rights, safety and well-being and the reliability of trial results. Risks  
1076 related to such decisions should be suitably managed throughout the planning, conduct  
1077 and reporting of the trial.

1078  
1079 3.9.5 The range and extent of oversight measures should be fit for purpose and tailored to  
1080 the complexity of and risks associated with the trial. The selection and oversight of  
1081 investigators and service providers are fundamental features of the oversight process.  
1082 Oversight by the sponsor includes quality assurance and quality control processes  
1083 relating to the trial-related activities of investigators and service providers.

1084  
1085 3.9.6 The sponsor should ensure appropriate and timely escalation and follow-up of issues  
1086 to allow the implementation of appropriate actions in a timely manner.

1087  
1088 3.9.7 The sponsor may consider establishing an IDMC to assess the progress of a clinical  
1089 trial including the safety data and the efficacy endpoints at intervals and to recommend  
1090 to the sponsor whether to continue, modify or stop a trial.

1091 3.9.8 Where appropriate, sponsors may also establish an endpoint assessment/adjudication  
 1092 committee in certain trials to review important endpoints reported by investigators to  
 1093 determine whether the endpoints meet protocol-specified criteria. Such committees  
 1094 should typically be blinded to the assigned treatments when performing their  
 1095 assessments, regardless of whether the trial itself is conducted in a blinded manner, to  
 1096 ensure that the data reviewed by committee are as free of bias as possible.

1097  
 1098 3.9.9 Committees established for purposes that could impact participant safety or the  
 1099 reliability of trial results should include members with relevant expertise and with  
 1100 managed conflicts of interest, have written operating procedures (e.g., charters) and  
 1101 document their decisions.

### 1102 **3.10 Quality Management**

1103 The sponsor should implement an appropriate system to manage quality throughout all stages  
 1104 of the trial process. Quality management includes the design and implementation of efficient  
 1105 clinical trial protocols including tools and procedures for trial conduct (including for data  
 1106 collection and management) in order to support participant's rights, safety and well-being and  
 1107 the reliability of trial results. The sponsor should adopt a proportionate and risk-based approach  
 1108 to quality management, which involves incorporating quality into the design of the clinical trial  
 1109 (i.e., quality by design) and identifying those factors that are likely to have a meaningful impact  
 1110 on participant's rights, safety and well-being and the reliability of the results (i.e., critical to  
 1111 quality factors as described in ICH E8(R1)). The sponsor should describe the quality  
 1112 management approach implemented in the trial in the clinical trial report (see ICH E3).

#### 1113 *3.10.1 Risk Management*

1114 A proportionate approach to the identification and management of risk is described below:

##### 1115 *3.10.1.1 Risk Identification*

1116 The sponsor should identify risks that may have a meaningful impact on critical to  
 1117 quality factors. Risks should be considered across the processes used in the clinical  
 1118 trial (e.g., patient selection, informed consent process, randomisation and  
 1119 investigational product administration, data handling, and service provider activities).

##### 1120 *3.10.1.2 Risk Evaluation*

1121 The sponsor should evaluate potential risks by considering:

- 1122 (a) the likelihood of harm/hazard occurring;
- 1123
- 1124 (b) the extent to which such harm/hazard would be detectable;
- 1125
- 1126 (c) the impact of such harm/hazard on trial participant protection and the
- 1127 reliability of trial results.

##### 1128 *3.10.1.3 Risk Control*

- 1129 (a) Risk control should be proportionate to the importance of the risk to
- 1130 participants' rights, safety and well-being and the reliability of trial results.

1131 Risk mitigation activities may be incorporated in protocol design and  
1132 implementation, monitoring plans, agreements between parties defining roles  
1133 and responsibilities, systematic safeguards to ensure adherence to SOPs, and  
1134 training in processes and procedures.

1135  
1136 (b) The sponsor should set acceptable ranges to support this process within which  
1137 variation can be accepted. Where deviation beyond these ranges is detected,  
1138 an evaluation should be performed to determine if there is a possible systemic  
1139 issue and if action is needed.

#### 1140 3.10.1.4 Risk Communication

1141 The sponsor should communicate the identified risks and mitigating activities, if  
1142 applicable, to those who are involved in taking action or are affected by such activities.  
1143 Communication also facilitates risk review and continual improvement during clinical  
1144 trial conduct.

#### 1145 3.10.1.5 Risk Review

1146 The sponsor should periodically review risk control measures to ascertain whether the  
1147 implemented quality management activities remain effective and relevant, taking into  
1148 account emerging knowledge and experience.

#### 1149 3.10.1.6 Risk Reporting

1150 The sponsor should summarise and report the risks and the remedial actions taken in  
1151 relation to important deviations from the acceptable ranges as detailed in section  
1152 3.10.1.3(b) and document them in the clinical trial report (ICH E3).

### 1153 3.11 Quality Assurance and Quality Control

1154 The sponsor is responsible for establishing, implementing and maintaining  
1155 appropriate quality assurance and quality control processes and documented  
1156 procedures to ensure that trials are conducted and data are generated, recorded and  
1157 reported in compliance with the protocol, GCP and the applicable regulatory  
1158 requirement(s).

#### 1159 3.11.1 Quality Assurance

1160 Quality assurance should be applied throughout the clinical trial and includes  
1161 implementing strategies to identify potential or actual causes of serious non-  
1162 compliance with the protocol, GCP and/or applicable regulatory requirements to  
1163 enable their corrective and/or preventive actions.

#### 1164 3.11.2 Audit

1165 When performed, audits should be conducted in a manner that is proportionate to the  
1166 risks associated with the conduct of the trial.

1167 The purpose of a sponsor's audit, which is independent of and separate from routine  
1168 monitoring or quality control functions, is to evaluate whether the processes put in  
1169 place to manage and conduct the trial are effective and compliant.

1170 *3.11.2.1 Selection and Qualification of Auditors*

1171 (a) The sponsor should appoint individuals who are independent of the clinical  
1172 trial being audited.

1173  
1174 (b) The sponsor should ensure that the auditors are qualified by training and  
1175 experience to conduct audits properly.

1176 *3.11.2.2 Auditing Procedures*

1177 (a) The sponsor should ensure that the auditing of clinical trials/processes is  
1178 conducted in accordance with the sponsor's documented procedures on what  
1179 to audit, how to audit (i.e., on-site or remote), the frequency of audits and the  
1180 form and content of audit reports.

1181  
1182 (b) The sponsor's audit plan, program and procedures for a trial audit should be  
1183 guided by the importance of the trial to submissions to regulatory authorities,  
1184 the number of participants in the trial, the type and complexity of the trial, the  
1185 level of risks to the trial participants and any identified problem(s).

1186  
1187 (c) The observations and findings of the auditor(s) should be documented.

1188  
1189 (d) To preserve the independence and value of the audit function, the regulatory  
1190 authority(ies) should not routinely request the audit reports. Regulatory  
1191 authority(ies) may seek access to an audit report on a case-by-case basis when  
1192 evidence of serious GCP non-compliance exists or in the course of legal  
1193 proceedings.

1194  
1195 (e) When required by applicable regulatory requirements, the sponsor should  
1196 provide an audit certificate.

1197 *3.11.3 Quality Control*

1198 Quality control should be applied to each stage of the data handling to ensure that data  
1199 are reliable and have been processed correctly. Within clinical trials, monitoring and  
1200 data management processes are the main quality control activities.

1201  
1202 The quality control of sites (other than investigator sites, such as centralised imaging  
1203 reading facilities), including on site and/or centralised activities, may be undertaken  
1204 and reported using a risk-based approach.

1205 *3.11.4 Monitoring*

1206 The aim of monitoring is to ensure the participants' rights, safety and well-being and  
1207 the reliability of trial results as the trial progresses. Monitoring is one of the principal  
1208 quality control activities.

1209 Monitoring involves a broad range of activities including, but not limited to,  
1210 communication with investigator sites, verification of the investigator and investigator  
1211 site staff qualifications and site resources, training and review of trial documents and

1212 information using a range of approaches including source data review, source data  
 1213 verification, data analytics and visits to institutional facilities undertaking trial-related  
 1214 activities. Some of these monitoring activities may be conducted by different methods  
 1215 and persons with different roles. However, monitoring should be performed by  
 1216 persons not involved in the clinical conduct of the trial being monitored. The  
 1217 monitoring approach should consider the activities and services involved, including  
 1218 decentralised settings, and be included in the monitoring plan. Monitors and other trial  
 1219 staff should adhere to data protection and confidentiality requirements in accordance  
 1220 with applicable regulatory requirements, institution policy and established data  
 1221 security standards.

1222 Monitoring activities may include site monitoring (performed on-site or remotely) and  
 1223 centralised monitoring, depending on the monitoring strategy and the design of the  
 1224 clinical trial.

1225 The sponsor should determine the appropriate extent and nature of monitoring, based  
 1226 on identified risks. Factors such as the objective, purpose, design, complexity,  
 1227 blinding, number of trial participants, investigational product, current knowledge of  
 1228 the safety profile and endpoints of the trial should be considered.

#### 1229 *3.11.4.1 Investigator Site Monitoring*

1230 (a) Monitoring may be performed in relation to the clinical trial activities at the  
 1231 investigator sites (e.g., including their pharmacies and local laboratories, as  
 1232 appropriate). The frequency of monitoring activities should also be determined  
 1233 based on identified risks. Monitoring activities and their frequency should be  
 1234 modified as appropriate using knowledge gained.

1236 (b) This monitoring activity may be performed on-site or remotely depending on  
 1237 the nature of the activity and its objectives.

1239 (c) Monitoring may include secure, remote, direct read-only access to source  
 1240 records, other data acquisition tools and essential record retention systems.

#### 1241 *3.11.4.2 Centralised Monitoring*

1242 (a) Centralised monitoring is an evaluation of accumulated data, performed in a  
 1243 timely manner, by the sponsor's qualified and trained persons (e.g., medical  
 1244 monitor, data scientist/data manager, biostatistician).

1246 (b) Centralised monitoring processes provide additional monitoring capabilities  
 1247 that can complement and reduce the extent and/or frequency of site monitoring  
 1248 or be used on its own. Use of centralised data analytics can help identify  
 1249 systemic or site-specific issues, including protocol non-compliance and  
 1250 potentially unreliable data.

1252 (c) Centralised monitoring may support the selection of sites and/or processes for  
 1253 targeted site monitoring.

1254 3.11.4.3 *Monitoring Plan*

1255 The sponsor should develop a monitoring plan that is tailored to the identified  
1256 potential safety risks, the risks to data quality and/or other risks to the reliability of the  
1257 trial results. Particular attention should be given to procedures relevant to participant  
1258 safety and to trial endpoints. The plan should describe the monitoring strategy, the  
1259 monitoring activities of all the parties involved, the various monitoring methods and  
1260 tools to be used, and the rationale for their use. The monitoring strategy should ensure  
1261 appropriate oversight of trial conduct and consider site capabilities and the potential  
1262 burden. The plan should focus on aspects that are critical to quality. The monitoring  
1263 plan should reference the sponsor's applicable policies and procedures.

1264 Monitoring of key data and processes (e.g., those related to primary endpoints and key  
1265 secondary endpoints and processes intended to assure patient safety) performed  
1266 outside the investigator site (e.g., central reading facilities, central laboratories) should  
1267 be addressed in the monitoring plan.

1268 3.11.4.4 *Monitoring Procedures*

1269 Persons performing monitoring should follow the sponsor's monitoring plan and  
1270 applicable monitoring procedures.

1271 3.11.4.5 *Monitoring Activities*

1272 Monitoring in accordance with the sponsor's requirements and monitoring plan  
1273 should generally include the following activities across the clinical trial life cycle, as  
1274 applicable.

1275 3.11.4.5.1 *Communication with Parties Conducting the Trial*

1276 (a) Establishing and maintaining a line of communication between the  
1277 sponsor and the investigator and other parties and individuals involved  
1278 in the trial conduct (e.g., centrally performed activities). In general, each  
1279 site should have an assigned monitor as their contact point.

1280  
1281 (b) Informing the investigator or other parties and individuals involved in  
1282 the trial conduct of identified deviations from the protocol, GCP and the  
1283 applicable regulatory requirements and taking appropriate action  
1284 designed to prevent recurrence of the detected deviations. Important  
1285 deviations should be highlighted and should be the focus of remediation  
1286 efforts as appropriate.

1287  
1288 (c) Informing the investigator or other parties and individuals involved in  
1289 the trial conduct of source record(s) or entry errors or omissions in data  
1290 acquisition tools and ensuring that corrections, additions or deletions are  
1291 made as appropriate, dated, explained (if necessary) and that approval  
1292 of the change is properly documented.

1293  
1294 (d) Actions taken in relation to the deviations, errors or omissions should be  
1295 proportionate to their importance.

- 1296            3.11.4.5.2    *Investigator Site Selection, Initiation, Management and Close-out*
- 1297            (a)    Selecting the site and confirming that the investigator and individuals or  
1298            parties involved in the trial conduct have adequate qualifications,  
1299            resources (see sections 3.1, 3.2, and 4.7) and facilities, including  
1300            laboratories, equipment and investigator site staff, to safely and properly  
1301            conduct the trial.
- 1302
- 1303            (b)    Confirming that the investigator, investigator site staff and other parties,  
1304            and individuals involved in the trial conduct are adequately informed  
1305            about the trial and follow the current approved protocol and other  
1306            protocol-related documents, such as the current Investigator’s Brochure  
1307            and relevant information related to the investigational product and  
1308            instructions related to their delegated activities.
- 1309
- 1310            (c)    Confirming that the investigator is maintaining the essential records (see  
1311            Appendix C).
- 1312
- 1313            (d)    Confirming that informed consent was obtained before participation in  
1314            the trial (see section 2.8) for all enrolled participants at the site.
- 1315
- 1316            (e)    Determining whether adverse events are appropriately reported within  
1317            the time periods required by the protocol, GCP and the applicable  
1318            regulatory requirement(s).
- 1319
- 1320            (f)    Clarifying the sponsor’s protocol requirements for source records and  
1321            the site’s location of such data.
- 1322
- 1323            (g)    Verifying that the blinding is maintained, where applicable.
- 1324
- 1325            (h)    Reviewing and reporting the participant recruitment and retention rates.
- 1326
- 1327            (i)    Confirming that the investigator provides the required reports,  
1328            notifications or other information in accordance with the protocol and  
1329            trial procedures.
- 1330
- 1331            (j)    Confirming the arrangement for the retention of the essential records and  
1332            the final accountability of the investigational product (e.g., return and  
1333            destruction or alternative disposition, if appropriate) during site close-  
1334            out activity.
- 1335            3.11.4.5.3    *Monitoring of Investigational Product Management*
- 1336            (a)    Confirming, for the investigational product(s):
- 1337
- 1338            (i)    that storage conditions are acceptable and in accordance with the  
1339            storage requirement specified in the protocol;
- 1340

- 1341 (ii) that supplies are sufficient throughout the trial and are used  
1342 within their shelf-life;  
1343
- 1344 (iii) that the correct investigational product(s) are supplied only to  
1345 participants who are eligible to receive it at the protocol-  
1346 specified dose(s) and, where appropriate, in accordance with the  
1347 randomisation procedures;  
1348
- 1349 (iv) that the participants, investigator, investigator site staff and other  
1350 relevant parties and individuals involved in the trial conduct are  
1351 provided with necessary instruction on properly using, handling,  
1352 storing, returning and destroying, or alternative disposition of the  
1353 investigational product(s);  
1354
- 1355 (v) that the receipt, use, return and destruction, or alternative  
1356 disposition of the investigational product(s) are controlled and  
1357 documented adequately;  
1358
- 1359 (vi) that the disposition of unused investigational product(s)  
1360 complies with applicable regulatory requirement(s) and is in  
1361 accordance with the sponsor requirements;  
1362
- 1363 (vii) where product available on the market is dispensed and used in  
1364 accordance with applicable regulatory requirements, some of the  
1365 previously outlined considerations may not be applicable.

1366 3.11.4.5.4 *Monitoring of Clinical Trial Data*

- 1367 (a) Verifying that the investigator is enrolling only eligible trial participants.  
1368
- 1369 (b) Checking the accuracy, completeness and consistency of the reported  
1370 trial data against the source records and other trial-related records and  
1371 whether these were reported in a timely manner. This can be done on the  
1372 basis of using samples and supported by data analytics, as appropriate.  
1373 The sample size may need adjustment based on previous monitoring  
1374 results or other indications of insufficient data quality. Monitoring  
1375 should:  
1376
- 1377 (i) verify that the data required by the protocol and identified as  
1378 critical in the monitoring plan are consistent with the source;  
1379
- 1380 (ii) identify missing data, inconsistent data, data outliers, unexpected  
1381 lack of variability and protocol deviations;  
1382
- 1383 (iii) examine data trends, such as the range, consistency and  
1384 variability of data within and across sites;  
1385



1386 (c) Identifying significant errors in data collection and reporting at a site or  
1387 across sites, potential data manipulation and data integrity problems.

1388 *3.11.4.6 Monitoring Report*

1389 (a) Reports of monitoring activities should include a summary of what was  
1390 reviewed, a description of significant findings, conclusions and actions  
1391 required to resolve them and follow-up on their resolution including those not  
1392 resolved in previous reports. The requirements of monitoring reports  
1393 (including their content and frequency) should be described in the sponsor's  
1394 procedures.

1396 (b) Reports of investigator site and/or centralised monitoring should be provided  
1397 to the appropriate sponsor staff as described in the sponsor's procedures in a  
1398 timely manner for review and follow-up.

1400 (c) When needed, the report should describe findings requiring escalation for  
1401 action and resolution. The sponsor should decide on the appropriate action to  
1402 be taken, and these decisions and the resolution of the actions involved, where  
1403 needed, should be recorded.

1404 **3.12 Noncompliance**

1405 3.12.1 Noncompliance with the protocol, SOPs, GCP and/or applicable regulatory  
1406 requirement(s) by an investigator/institution or by member(s) of the sponsor's staff  
1407 should lead to appropriate and proportionate action by the sponsor to secure  
1408 compliance.

1410 3.12.2 If noncompliance that significantly affects or has the potential to significantly affect  
1411 trial participant's rights, safety or well-being or the reliability of trial results is  
1412 discovered, the sponsor should perform a root cause analysis, implement appropriate  
1413 corrective and preventive actions and confirm their adequacy unless otherwise  
1414 justified. Where the sponsor identifies issues that could significantly impact  
1415 participant's rights, safety and well-being or the reliability of trial results, the sponsor  
1416 should notify the regulatory authority and/or IRB/IEC in line with applicable  
1417 regulatory requirements.

1418  
1419 3.12.3 If the monitoring and/or auditing identifies serious noncompliance on the part of an  
1420 investigator/institution that persists despite efforts at remediation, the sponsor should  
1421 terminate the investigator's/institution's participation in the trial. When an  
1422 investigator's/institution's participation is terminated because of noncompliance, the  
1423 sponsor should promptly notify the regulatory authority(ies) and IRB/IEC as  
1424 appropriate.

1425 **3.13 Safety Assessment and Reporting**

1426 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

1427 The Investigator’s Brochure or, where applicable, the current scientific information such as a  
 1428 basic product information brochure, forms the basis of safety assessment and reporting for the  
 1429 clinical trial. For further information, see Appendix A.

1430 *3.13.1 Sponsor Review of Safety Information*

1431 The sponsor should aggregate, as appropriate, and periodically review relevant safety  
 1432 information. This may result in the update of the protocol, Investigator’s Brochure,  
 1433 informed consent materials and related documents.

1434 The sponsor should review the available emerging safety information to assess  
 1435 whether there is any new data that may affect the participant’s willingness to continue  
 1436 in the trial, impact the conduct of the trial, or alter the approval/favourable opinion of  
 1437 the IRB/IEC and/or regulatory authority(ies), as applicable. Any information of this  
 1438 nature should be communicated to the participants, investigator, IRB/IEC and  
 1439 regulatory authorities, as applicable, in a timely manner.

1440 *3.13.2 Safety Reporting*

1441 (a) The sponsor should submit to the regulatory authority(ies) safety updates and  
 1442 periodic reports, including changes to the Investigator’s Brochure, as required  
 1443 by applicable regulatory requirements.  
 1444

1445 (b) The sponsor should, in accordance with the applicable regulatory  
 1446 requirement(s) and with ICH E2A Clinical Safety Data Management:  
 1447 Definitions and Standards for Expedited Reporting, expedite the reporting to  
 1448 the regulatory authority(ies) of all adverse drug reactions (ADRs) that meet  
 1449 three criteria: suspected, unexpected and serious (i.e., SUSARs).  
 1450

1451 (c) Safety reporting to regulatory authorities should be undertaken by assessing  
 1452 the expectedness of the reaction in relation to the applicable product  
 1453 information (e.g., the reference safety information (RSI) contained within the  
 1454 Investigator’s Brochure or alternative documents) in accordance with  
 1455 applicable regulatory requirements. Refer to ICH E2F Development Safety  
 1456 Update Report for more information about RSI.  
 1457

1458 (d) The reporting of SUSARs to investigator(s)/institutions(s) and to the  
 1459 IRB(s)/IEC(s) should be undertaken in a manner that reflects the urgency of  
 1460 action required and should take into consideration the evolving knowledge of  
 1461 the safety profile of the product. Reporting of SUSARs to the  
 1462 investigators/institutions should be made in accordance with regulatory  
 1463 requirements. In some regions, periodic reporting of line listings with an  
 1464 overall safety assessment may be appropriate.  
 1465

1466 (e) Urgent safety issues requiring immediate attention or action should be  
 1467 reported to the IRB/IEC and/or regulatory authority(ies) and investigators  
 1468 without undue delay and as specified in regulatory requirements.  
 1469

1470 (f) Alternative arrangements for safety reporting to regulatory authorities,  
 1471 IRBs/IECs, and investigators and for reporting by investigators to the sponsor  
 1472 should be prospectively agreed upon with the regulatory authority(ies) and the  
 1473 IRB/IEC if applicable, and described in the clinical trial protocol, (e.g., SAEs  
 1474 considered efficacy or safety endpoints, which would not be subject to  
 1475 unblinding and expedited reporting; see ICH E2A). See ICH E19.

1476 **3.13.3 *Managing an Immediate Hazard***

1477 The sponsor should take prompt action to address immediate hazards to participants.  
 1478 The sponsor should determine the causes of the hazard and based on this, take  
 1479 appropriate remedial actions.

1480 The sponsor should consider whether the protocol requires amendment in response to  
 1481 an immediate hazard. The information on the immediate hazard, if required, and any  
 1482 subsequent protocol amendment should be submitted to the IRB/IEC and/or  
 1483 regulatory authorities by the investigator/institution or sponsor (in accordance with  
 1484 applicable regulatory requirements).

1485 **3.14 Insurance/Indemnification/Compensation to Participants and Investigators**

1486 3.14.1 If required by the applicable regulatory requirement(s), the sponsor should provide  
 1487 insurance or should indemnify (legal and financial coverage) the investigator/the  
 1488 institution against claims arising from the trial except for claims that arise from  
 1489 malpractice and/or negligence.

1491 3.14.2 The sponsor's policies and procedures should address the costs of treatment of trial  
 1492 participants in the event of trial-related injuries in accordance with the applicable  
 1493 regulatory requirement(s).

1495 3.14.3 The approach to compensating trial participants should comply with applicable  
 1496 regulatory requirement(s).

1497 **3.15 Investigational Product(s)**

1498 **3.15.1 *Information on Investigational Product(s)***

1499  
 1500 The sponsor should ensure that an Investigator's Brochure is developed and updated  
 1501 as significant new information on the investigational product becomes available.  
 1502 Alternatively, for authorised medicinal products, the sponsor should identify the basic  
 1503 product information to be used in the trial (see Appendix A).

1504 **3.15.2 *Manufacturing, Packaging, Labelling and Coding Investigational Product(s)***

1505 (a) The sponsor should ensure that the investigational product(s) (including active  
 1506 control(s) and placebo, if applicable) is characterised as appropriate to the  
 1507 stage of development of the product(s), is manufactured in accordance with  
 1508 any applicable GMP and is coded and labelled in a manner that protects the  
 1509 blinding, if applicable. In addition, the labelling should comply with  
 1510 applicable regulatory requirement(s).

1511

- 1512 (b) The sponsor should determine acceptable storage temperatures and other  
 1513 storage conditions (e.g., protection from light) for the investigational  
 1514 product(s), appropriate reconstitution fluids and procedures, and devices for  
 1515 product infusion, if any. The sponsor should inform all involved parties (e.g.,  
 1516 monitors, investigators, pharmacists, storage managers) of these  
 1517 determinations.  
 1518
- 1519 (c) The investigational product(s) should be packaged to prevent contamination  
 1520 and unacceptable deterioration during transport and storage.  
 1521
- 1522 (d) In blinded trials, the sponsor should implement:  
 1523
- 1524 (i) a process to blind the sponsor staff, trial participant and/or investigator  
 1525 as appropriate to the investigational product identity and assignment to  
 1526 prevent and detect inappropriate unblinding;  
 1527
- 1528 (ii) a procedure and mechanism that permits the investigator to rapidly  
 1529 identify the product(s) in case of a medical emergency where  
 1530 unblinding is considered necessary, while protecting the identity of the  
 1531 treatment assignment of the other trial participants;  
 1532
- 1533 (iii) a mechanism that protects the blinding of the trial where a participant's  
 1534 treatment assignment is unblinded for the purpose of safety reporting  
 1535 to regulatory authorities and/or IRB/IEC, where appropriate.  
 1536
- 1537 (e) If significant formulation changes are made in the investigational product(s)  
 1538 (including active control(s) and placebo, if applicable) during the course of  
 1539 clinical development, the results of any additional studies of the formulated  
 1540 product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess  
 1541 whether these changes would significantly alter the pharmacokinetic profile  
 1542 of the product should be available prior to the use of the new formulation in  
 1543 clinical trials.

1544 *3.15.3 Supplying and Handling Investigational Product(s)*

- 1545 (a) The sponsor is responsible for supplying the investigator(s)/institution(s) with  
 1546 the investigational product(s) or, where appropriate, supplying trial  
 1547 participants in accordance with applicable regulatory requirements and after  
 1548 obtaining the required approval/favourable opinion from the IRB/IEC and the  
 1549 regulatory authority(ies) for the trial.  
 1550
- 1551 (b) The sponsor should ensure that instructions are available for the  
 1552 investigator/institution or trial participants on the handling and storage of  
 1553 investigational product(s). The procedures should consider adequate and safe  
 1554 receipt, handling, storage, dispensing, retrieval of unused product from  
 1555 participants and return of unused investigational product(s) to the sponsor (or

1556 alternative disposition if authorised by the sponsor and in compliance with the  
 1557 applicable regulatory requirement(s).

1558  
 1559 (c) The sponsor should:

1560  
 1561 (i) ensure timely delivery of investigational product(s) to the  
 1562 investigator(s) or, where appropriate, to trial participants in accordance  
 1563 with applicable regulatory requirements to avoid any interruption to  
 1564 the trial as well as for the continuation of treatment for participants.

1565  
 1566 (ii) maintain records that document the identity, shipment, receipt, return  
 1567 and destruction, or alternative disposition of the investigational  
 1568 product(s) (see Appendix C);

1569  
 1570 (iii) maintain a system for retrieving investigational products and  
 1571 documenting this retrieval (e.g., for deficient product recall, return and  
 1572 destruction, or alternative disposition after trial completion, or expired  
 1573 product reclaim);

1574  
 1575 (iv) maintain a system for the disposition of unused investigational  
 1576 product(s) and for the documentation of this disposition;

1577  
 1578 (v) take steps to ensure that the investigational product(s) are stable over  
 1579 the period of use and only used within the current shelf-life;

1580  
 1581 (vi) maintain sufficient quantities of the investigational product(s) used in  
 1582 the trials to reconfirm specifications should this become necessary and  
 1583 maintain records of batch sample analyses and characteristics. The  
 1584 samples should be retained either until the analyses of the trial data are  
 1585 complete or as required by the applicable regulatory requirement(s),  
 1586 whichever represents the longer retention period. The samples do not  
 1587 need to be kept by the sponsor in trials where an authorised medicinal  
 1588 product is used as an investigational product unmodified from its  
 1589 authorised state, since samples are kept by the manufacturer.

1590 **3.16 Data and Records**

1591 *3.16.1 Data Handling*

1592 (a) The sponsor should ensure the integrity and confidentiality of data generated  
 1593 and managed.

1594  
 1595 (b) The sponsor should apply quality control to the relevant stages of data  
 1596 handling to ensure that the data are of sufficient quality to generate reliable  
 1597 results. The sponsor should focus their quality assurance and quality control  
 1598 activities and data review on critical data, including its relevant metadata.  
 1599

- 1600 (c) The sponsor should pre-specify data to be collected and the method of its  
1601 collection in the protocol (see Appendix B. Clinical Trial Protocol and  
1602 Protocol Amendment(s)). Where necessary, additional details, including a data  
1603 flow diagram, should be contained in a protocol-related document (e.g., a data  
1604 management plan).  
1605
- 1606 (d) The sponsor should ensure that data acquisition tools are fit for purpose and  
1607 designed to capture the information required by the protocol. They should be  
1608 validated and ready for use prior to their required use in the trial.  
1609
- 1610 (e) The sponsor should ensure that documented processes are implemented to  
1611 ensure the data integrity for the full data life cycle.  
1612
- 1613 (f) The sponsor should implement measures to ensure the safeguarding of the  
1614 blinding, if any (e.g., maintain the blinding during data entry and processing).  
1615
- 1616 (g) The sponsor should provide guidance to investigators/institutions, service  
1617 providers and trial participants, where relevant, on the expectations for data  
1618 capture, data changes, data retention and data disposal.  
1619
- 1620 (h) The sponsor should not make changes to data entered by the investigator or  
1621 trial participants unless justified and documented by the sponsor and agreed  
1622 upon by the investigator.  
1623
- 1624 (i) The sponsor should allow correction of errors to data, including data entered  
1625 by participants, where requested by the investigators/participants. Such data  
1626 corrections should be justified and supported by source records around the  
1627 time of original entry.  
1628
- 1629 (j) The sponsor should ensure that the investigator has access to data collected in  
1630 accordance with the protocol during the course of the trial including relevant  
1631 data from external sources, for example, central laboratory data, centrally read  
1632 imaging data and, if appropriate, ePRO data that are necessary to enable the  
1633 investigators to make decisions (e.g., on eligibility, treatment, continuing  
1634 participation in the trial and care for the safety of the individual trial  
1635 participants). The sponsor should pay special attention to data that may  
1636 unblind the investigator and include the appropriate provisions in the protocol.  
1637
- 1638 (k) The sponsor should not have exclusive control of data captured in data  
1639 acquisition tools.  
1640
- 1641 (l) The sponsor should ensure that the investigator has access to the required data  
1642 for retention purposes.  
1643

- 1644 (m) The sponsor should ensure that the investigator receives instructions on how  
 1645 to navigate systems, data and relevant metadata for the trial participants under  
 1646 their responsibility.  
 1647
- 1648 (n) The sponsor should seek investigator endorsement of their data at  
 1649 predetermined milestones.  
 1650
- 1651 (o) The sponsor should document the data management steps to be undertaken  
 1652 prior to data analysis. These steps may vary depending on the purpose of the  
 1653 analysis to be conducted (e.g., data for IDMC, for interim analysis or the final  
 1654 analysis).  
 1655
- 1656 (p) Prior to provision of the data for analysis, edit access to the data acquisition  
 1657 tools should be restricted as appropriate to the purpose of the analysis; for  
 1658 example, for interim analysis, the restriction may only be temporary or  
 1659 managed differently compared to the final analysis.  
 1660
- 1661 (q) Deviations from the planned statistical analysis or changes made to the data  
 1662 analysis set after the trial has been unblinded (where applicable) should be  
 1663 clearly documented and justified and should only occur in exceptional  
 1664 circumstances (e.g., data discrepancies that must be resolved for the reliability  
 1665 of the trial results). Data changes should be authorised by the investigator and  
 1666 reflected in an audit trail. Post-unblinding data changes and deviations from  
 1667 the planned statistical analyses should be reported in the clinical trial report.  
 1668
- 1669 (r) The sponsor should use an unambiguous trial participant identification code  
 1670 (see glossary term) that allows identification of all the data reported for each  
 1671 participant.  
 1672
- 1673 (s) The sponsor should implement appropriate measures to protect the privacy and  
 1674 confidentiality of personal information of trial participants, in accordance with  
 1675 applicable regulatory requirements on personal data protection.  
 1676
- 1677 (t) In accordance with applicable regulatory requirements, the sponsor should  
 1678 document what happens to data when a participant withdraws or discontinues  
 1679 from the trial.  
 1680
- 1681 (u) The sponsor should ensure that trial data are protected from unauthorised  
 1682 access, disclosure, dissemination or alteration and from inappropriate  
 1683 destruction or accidental loss.  
 1684
- 1685 (v) The sponsor should have processes and procedures in place for reporting  
 1686 incidents (including security breaches) that have a significant impact on the  
 1687 trial data to relevant parties, including regulatory authorities, where relevant.  
 1688  
 1689

- 1690 (w) When using computerised systems in a clinical trial, the sponsor should:  
1691  
1692 (i) have a record of the computerised systems used in a clinical trial. This  
1693 should include the use, functionality, interfaces and validation status  
1694 of each computerised system, and who is responsible for its  
1695 management should be described. The record should also include a  
1696 description of implemented access controls and internal and external  
1697 security measures;  
1698  
1699 (ii) ensure that the requirements for computerised systems deployed by the  
1700 sponsor (e.g., requirements for validation, audit trails, user  
1701 management, backup, disaster recovery and IT security) are addressed  
1702 and implemented and that documented procedures and adequate  
1703 training are in place to ensure the correct development, maintenance  
1704 and use of computerised systems in clinical trials (see section 4). These  
1705 requirements should be proportionate to the importance of the  
1706 computerised system and the data or activities they are expected to  
1707 process;  
1708  
1709 (iii) maintain a record of the individual users who are authorised to access  
1710 the system, their roles and their access privileges;  
1711  
1712 (iv) ensure that access rights granted to investigator site staff are in  
1713 accordance with delegations by the investigator and visible to the  
1714 investigator;  
1715  
1716 (v) for systems deployed by the investigator/institution, assess whether  
1717 such systems, if identified as containing source records in the trial,  
1718 (e.g., electronic health records and other record keeping systems for  
1719 source data collection and investigator site files) are fit for purpose or  
1720 whether the known issue(s) can be appropriately mitigated. This  
1721 assessment should occur during the process of selecting clinical trial  
1722 sites and should be documented;  
1723  
1724 (vi) ensure that there is a process in place for service providers and  
1725 investigators to inform the sponsor of system defects identified or  
1726 incidents that could potentially constitute a serious non-compliance  
1727 with the clinical trial protocol, trial procedures or GCP in accordance  
1728 with section 3.13.



1729 3.16.2 *Statistical Programming and Data Analysis*

1730 This section concerning documentation of operational aspects of clinical trial  
 1731 statistical activities should be read in conjunction with ICH E9 Statistical Principles  
 1732 for Clinical Trials, which provides detailed guidance on statistical principles for  
 1733 clinical development, trial design, conduct, analysis and reporting.

1734 (a) The sponsor should ensure that appropriate and documented quality control of  
 1735 statistical programming and data analysis is implemented (e.g., for sample size  
 1736 calculations, results for IDMC, outputs for clinical trial report, statistical or  
 1737 centralised monitoring).

1738  
 1739 (b) The sponsor should ensure the traceability of data transformations and  
 1740 derivations during data processing and analysis.

1741  
 1742 (c) The sponsor should ensure that the allocation to or exclusion of each trial  
 1743 participant from any analysis set is predefined (e.g., in the protocol or the  
 1744 statistical analysis plan). The rationale for inclusion or exclusion for any  
 1745 participant (or particular data point) should be clearly described and  
 1746 documented.

1747  
 1748 (d) Procedures should be in place to describe unblinding; these descriptions  
 1749 should include:

1750  
 1751 (i) who was unblinded, at what timepoint and for what purpose they were  
 1752 unblinded;

1753  
 1754 (ii) who should remain blinded;

1755  
 1756 (iii) the safeguards in place to preserve the blinding.

1757  
 1758 (e) The sponsor should retain the statistical programming records that relate to the  
 1759 output contained or used in reports of the trial results, including quality  
 1760 control/validation activities performed. Outputs should be traceable to the  
 1761 statistical software programs, and they should be dated and time stamped and  
 1762 protected against any changes.

1763 3.16.3 *Record Keeping and Retention*

1764 (a) The sponsor (or subsequent owners of the data) should retain all of the  
 1765 sponsor-specific essential records pertaining to the trial in conformance with  
 1766 the applicable regulatory requirement(s).

1767  
 1768 (b) The sponsor should inform the investigator(s)/institution(s) and service  
 1769 providers, when appropriate, in writing of the need for essential records  
 1770 retention and should notify the investigator(s)/institution(s) and service  
 1771 providers, when appropriate, in writing when the trial-related records are no  
 1772 longer needed.

1773 (c) The sponsor should report any transfer of ownership of the essential records  
 1774 to the appropriate authority(ies) as required by the applicable regulatory  
 1775 requirement(s).

1776 **3.16.4 Record Access**

1777 (a) The sponsor should ensure that it is specified in the protocol or other  
 1778 documented agreement that the investigator(s)/institution(s) provide direct  
 1779 access to source records for trial-related monitoring, audits, IRB/IEC review  
 1780 and regulatory inspection.

1781  
 1782 (b) The sponsor should ensure that trial participants have consented to direct  
 1783 access to their original medical records and other participant-related trial  
 1784 documents for trial-related monitoring, audit, IRB/IEC review and regulatory  
 1785 inspection as part of the informed consent.

1786 **3.17 Reports**

1787 **3.17.1 Premature Termination or Suspension of a Trial**

1788 If a trial is prematurely terminated or suspended, the sponsor should promptly inform  
 1789 the investigators/institutions and the regulatory authority(ies) of the termination or  
 1790 suspension and the reason(s) for the termination or suspension. The IRB/IEC should  
 1791 also be informed promptly and provided with the reason(s) for the termination or  
 1792 suspension by the sponsor or by the investigator/institution, in accordance with  
 1793 applicable regulatory requirement(s).

1794 **3.17.2 Clinical Trial/Study Reports**

1795 (a) Whether the trial is completed or prematurely terminated or an interim analysis  
 1796 is undertaken for regulatory submission, the sponsor should ensure that the  
 1797 clinical trial reports, including interim reports, are prepared and provided to  
 1798 the regulatory agency(ies) as required by the applicable regulatory  
 1799 requirement(s). The sponsor should also ensure that the clinical trial reports in  
 1800 marketing applications meet the standards of ICH E3 or are otherwise in  
 1801 accordance with applicable regulatory requirements. (Note: ICH E3 specifies  
 1802 that abbreviated study reports may be acceptable in certain cases.)  
 1803

1804 (b) Investigators should be provided with a summary of the trial results.  
 1805

1806 (c) Consideration should be given to providing the investigator with information  
 1807 about the final treatment taken by their participants for blinded trials and a  
 1808 brief summary of the overall outcome of the trial. Where this information is  
 1809 provided to participants, the language should be non-technical, understandable  
 1810 to a layperson and non-promotional. The sponsor should only supply this  
 1811 information after the trial has been unblinded and all relevant  
 1812 analyses/conclusions have been completed and finalised.

1813 **4. DATA GOVERNANCE – INVESTIGATOR AND SPONSOR**

1814 This section provides guidance to investigators and sponsors (i.e., the responsible parties) on  
 1815 appropriate management of data integrity, traceability and security, thereby allowing the  
 1816 accurate reporting, verification and interpretation of the clinical trial-related information. This  
 1817 section should be read in conjunction with corresponding responsibilities for the investigator  
 1818 and the sponsor as defined in sections 2 and 3, along with ICH E8(R1) and ICH E9.

1819 The quality and amount of the information generated in a clinical trial should be sufficient to  
 1820 address trial objectives, provide confidence in the trial’s results and support good decision  
 1821 making.

1822 The systems and processes that help ensure this quality should be designed and implemented  
 1823 in a way that is proportionate to the risks to participants and the reliability of trial results.

1824 The following key processes should address the full data life cycle with a focus on the criticality  
 1825 of the data and should be implemented proportionately and documented appropriately:

- 1826 (a) processes to ensure data protection of trial participants’ confidential data;  
 1827
- 1828 (b) processes for managing computerised systems to ensure that they are fit for  
 1829 purpose and used appropriately;  
 1830
- 1831 (c) processes to safeguard essential elements of the clinical trial, such as  
 1832 randomisation, dose escalation and blinding;  
 1833
- 1834 (d) processes to support key decision making, such as data finalisation prior to  
 1835 analysis, unblinding, allocation to analysis data sets, changes in clinical trial  
 1836 design and, where applicable, the activities of, for example, an IDMC.

1837 **4.1 Safeguard Blinding in Data Governance**

1838 4.1.1 Maintaining the integrity of the blinding is important in particular in the design of  
 1839 systems, management of users’ account, delegation of responsibilities with respect to  
 1840 data handling and provision of data access at sites, data transfers, database review  
 1841 prior to planned unblinding and statistical analysis across all appropriate stages of the  
 1842 trial.  
 1843

1844 4.1.2 Roles, responsibilities and procedures for access to unblinded information should be  
 1845 defined and documented by all relevant parties according to the protocol; this  
 1846 information may also be included in the data management plans and statistical analysis  
 1847 plans. For example, in blinded trials, sponsor staff or designated third parties who are  
 1848 involved in operation of the trial and directly or indirectly interact with site  
 1849 investigator staff should not have access to unblinding information.  
 1850

1851 4.1.3 The potential for unblinding should be part of the risk assessment of a blinded trial.  
 1852 Any planned or unplanned unblinding, including accidental or emergency unblinding,  
 1853 should be documented and assessed for impact to trial results.

1854 **4.2 Data Life Cycle Elements**

1855 Procedures should be in place to cover the full data life cycle.

1856 *4.2.1 Data Capture*

1857 (a) The requirements for and extent of data verification, when data captured on  
 1858 paper or in an electronic health record are manually transcribed into a  
 1859 computerised system, should take the criticality of the data into account. Refer  
 1860 to section 4.2.3 for data entered directly in data acquisition tools.

1861 (b) Acquired data from any source should be accompanied by relevant metadata.  
 1862 At the point of data capture, automated data validation checks should be  
 1863 considered as required based upon risk, and their implementation should be  
 1864 controlled and documented.  
 1865

1866 *4.2.2 Relevant Metadata, Including Audit Trails*

1867 The approach used by the responsible party for implementing, evaluating, accessing,  
 1868 managing and reviewing relevant metadata associated with critical data should entail:  
 1869

1870 (a) Evaluating the system for the types and content of metadata available to ensure  
 1871 that:

1872 (i) computerised systems maintain logs of user account creation, changes  
 1873 to user roles and permissions and user access;

1874  
 1875 (ii) systems are designed to permit data changes in such a way that the  
 1876 initial data entry and any subsequent changes or deletions are  
 1877 documented, including, where appropriate, using a risk-based  
 1878 evaluation, the reason for the change if it is not implicit;  
 1879

1880 (iii) systems record and maintain workflow actions in addition to direct data  
 1881 entry/changes into the system.

1882 (b) Ensuring that audit trails, reports and logs are not disabled or modified except  
 1883 in rare circumstances and only if a log of such action and justification is  
 1884 maintained;

1885  
 1886 (c) Ensuring that audit trails and logs are decipherable and can facilitate analysis;  
 1887

1888 (d) Ensuring that the automatic capture of date and time of data entries or transfer  
 1889 using data acquisition tools are unambiguous (e.g., coordinated universal time  
 1890 (UTC));

1891  
 1892 (e) Determining which of the identified metadata require review and retention.

1893 4.2.3 *Review of Data and Metadata*

1894 Procedures for review of trial-specific data, audit trails and other relevant metadata  
 1895 should be in place. It should be a planned activity, and the extent and nature should  
 1896 be adapted to the individual trial and adjusted based on experience during the trial.

1897 4.2.4 *Data Corrections*

1898 There should be processes to correct data errors that could impact the reliability of the  
 1899 trial results. Corrections should be attributed to the entity making the correction,  
 1900 justified and supported by source records around the time of original entry, and  
 1901 performed in a timely manner.

1902 4.2.5 *Data Transfer, Exchange and Migration*

1903 Validated processes or other appropriate processes such as reconciliation should be in  
 1904 place to ensure that electronic data transferred between computerised systems retains  
 1905 its integrity and preserves its confidentiality. The transfer process should be  
 1906 documented to ensure traceability, and data reconciliation should be implemented as  
 1907 appropriate.

1908 4.2.6 *Finalisation of Data Sets Prior to Analysis*

1909 (a) Data of sufficient quality for interim and final analysis are achieved by  
 1910 implementing timely and reliable processes for data capture, verification,  
 1911 validation, review and rectification of errors and omissions that have a  
 1912 meaningful impact on the safety of trial participants and/or the reliability of  
 1913 the trial results.

1914  
 1915 (b) Activities undertaken to finalise the data sets prior to analysis should be  
 1916 confirmed and documented in accordance with pre-specified procedures.  
 1917 These activities may include reconciliation of entered data and data sets or  
 1918 reconciliation of relevant databases, correction of data errors and omissions,  
 1919 medical coding, compilation and addressing the impact of non-compliance  
 1920 including protocol deviations.

1921  
 1922 (c) Data extraction and determination of data analysis sets should take place in  
 1923 accordance with the planned statistical analysis and should be documented.

1924 **4.3 Computerised Systems**

1925 As described in sections 2 and 3, the responsibilities of the sponsor, investigator and  
 1926 the activities of other parties with respect to a computerised system used in clinical  
 1927 trials should be clear and documented. In summary, the sponsor is responsible for  
 1928 ensuring that for computerised systems which they put in place, the expectations for  
 1929 computerised systems as described in this section are addressed in a risk proportionate  
 1930 manner. The sponsor should review whether the systems used by the  
 1931 investigator/institution (e.g., electronic health records and other record keeping  
 1932 systems for source data collection) are fit for purpose in the context of the trial. In the  
 1933 event that the investigator/institution deploys systems specifically for the purposes of

|      |            |  |
|------|------------|--|
| 1934 |            | conducting clinical trials, the investigator/institution should ensure that the              |
| 1935 |            | expectations are proportionately addressed and implemented.                                  |
| 1936 |            | The responsible party should ensure that those developing computerised systems for           |
| 1937 |            | clinical trials are aware of the intended purpose and the regulatory requirements that       |
| 1938 |            | apply to them.   |
| 1939 |            | It is recommended that representatives of intended participant populations and               |
| 1940 |            | healthcare professionals are involved in the design of the system, where relevant, to        |
| 1941 |            | ensure that computerised systems are suitable for use by the intended user population.       |
| 1942 | 4.3.1      | <i>Procedures for the Use of Computerised Systems</i>  |
| 1943 |            | Documented procedures should be in place to ensure the appropriate use of                    |
| 1944 |            | computerised systems in clinical trials for essential activities related to data collection, |
| 1945 |            | handling and management.   |
| 1946 | 4.3.2      | <i>Training</i>  |
| 1947 |            | The responsible party should ensure that those using computerised systems are                |
| 1948 |            | appropriately trained in their use.  |
| 1949 | <b>4.4</b> | <b>Security of Computerised Systems</b>  |
| 1950 | 4.4.1      | The security of the trial data and records should be managed throughout the data life        |
| 1951 |            | cycle.   |
| 1952 |            |  |
| 1953 | 4.4.2      | The responsible party should ensure that security controls are maintained for                |
| 1954 |            | computerised systems. These controls should include user management and ongoing              |
| 1955 |            | measures to prevent, detect and/or mitigate security breaches. Aspects such as user          |
| 1956 |            | authentication requirements and password management, firewall settings, antivirus            |
| 1957 |            | software, security patching, system monitoring and penetration testing should be             |
| 1958 |            | considered.  |
| 1959 |            |  |
| 1960 | 4.4.3      | The responsible party should maintain adequate backup of the data.                           |
| 1961 |            |  |
| 1962 | 4.4.4      | Procedures should cover the following: system security measures, data backup and             |
| 1963 |            | disaster recovery.   |
| 1964 | <b>4.5</b> | <b>Validation of Computerised Systems</b>  |
| 1965 | 4.5.1      | The responsible party is responsible for the validation status of the system throughout      |
| 1966 |            | its life cycle. The approach to validation of computerised systems should be based on        |
| 1967 |            | a risk assessment that considers the intended use of the system; the purpose and             |
| 1968 |            | importance of the data/record that is collected/generated, maintained and retained in        |
| 1969 |            | the system; and the potential of the system to affect the well-being, rights and safety      |
| 1970 |            | of trial participants and the reliability of trial results.                                  |
| 1971 |            |  |
| 1972 | 4.5.2      | Validation should demonstrate that the system conforms to the established                    |
| 1973 |            | requirements for completeness, accuracy, and reliability and is consistent with              |
| 1974 |            | intended performance.  |

- 1975 4.5.3 Systems should be appropriately validated prior to use with adequate change control  
 1976 procedures implemented.  
 1977
- 1978 4.5.4 Validation of changes should be based on risk and consider both previously collected  
 1979 and new data.  
 1980
- 1981 4.5.5 Both basic system functionality and protocol specific configurations and  
 1982 customisations, including automated data entry checks and calculations, should be  
 1983 validated. Interfaces between systems should also be defined and validated. Different  
 1984 degrees of qualification/validation may be needed for bespoke systems, systems  
 1985 designed to be configured or systems where no alterations are needed.  
 1986
- 1987 4.5.6 Where relevant, procedures should cover the following: system design, validation,  
 1988 and functionality testing; release; setup; installation and change control until  
 1989 decommissioning.  
 1990
- 1991 4.5.7 The responsible party should ensure that the computerised systems used in clinical  
 1992 trial processes are qualified and validated, including those developed by other parties.  
 1993 They should ensure that qualification and validation documentation is maintained and  
 1994 retained.  
 1995
- 1996 4.5.8 Validation should generally include defining the requirements and specifications for  
 1997 the system and their testing, along with the associated documentation, to ensure the  
 1998 system is fit for purpose, especially for critical functionality, such as randomisation,  
 1999 dosing and dose titrations and reductions, and collection of endpoint data.  
 2000
- 2001 4.5.9 Unresolved issues, if any, should be justified and, where relevant, addressed by  
 2002 mitigations prior to and/or during the continued use of the system.  
 2003
- 2004 4.5.10 The trial-specific systems (including updates resulting from protocol amendments)  
 2005 should only be implemented to enable the conduct of the trial by the investigator after  
 2006 all necessary approvals for the clinical trial have been received.
- 2007 **4.6 System Failure**
- 2008 Contingency procedures should be in place to prevent loss or lack of accessibility to data  
 2009 essential to participant safety, trial decisions or trial outcomes.
- 2010 **4.7 Technical Support**
- 2011 4.7.1 Where appropriate, there should be mechanisms (e.g., help desk support) in place to  
 2012 document, evaluate and manage issues with the computerised systems (e.g., raised by  
 2013 users), and there should be periodic review of these cumulative issues to identify those  
 2014 that are repeated and/or systemic.  
 2015
- 2016 4.7.2 Defects and issues should be resolved according to their criticality. Issues with high  
 2017 criticality should be resolved in a timely manner.

2018 **4.8 User Management**

2019 4.8.1 Access controls are integral to computerised systems used in clinical trials to limit  
2020 system access to authorised users and to ensure attributability to an individual. The  
2021 security measures should be selected in such a way that they achieve the intended  
2022 security and do not unduly impact user-friendliness.

2023 4.8.2 Procedures should be in place to ensure that user access rights are appropriately  
2024 assigned based on a user's duties and functions, blinding arrangements and the  
2025 organisation to which users belong. Access rights should be revoked when they are  
2026 no longer needed.

2027 4.8.3 Authorised users and access privileges should be clearly documented, maintained and  
2028 retained. These records should include any updates to a user's roles, access rights and  
2029 permissions, and time of access privileges given (e.g., time stamp).



2030 **GLOSSARY**

2031 **Adverse Events and Adverse Reaction-related definitions:**

2032 **Adverse Event (AE):** Any unfavourable medical occurrence in a trial participant. The  
2033 adverse event does not necessarily have a causal relationship with the treatment.

2034 **Adverse Drug Reaction (ADR):**

2035 • in the pre-approval clinical experience with a new investigational product or its new  
2036 usages (particularly as the therapeutic dose(s) may not be established):  
2037 unfavourable and unintended responses, such as a sign (e.g., laboratory results),  
2038 symptoms or disease related to any dose of a medicinal product where a causal  
2039 relationship between a medicinal product and an adverse event is a reasonable  
2040 possibility. The level of certainty about the relatedness of the adverse drug reaction  
2041 to an investigational product will vary. If the ADR is suspected to be medicinal  
2042 product-related with a high level of certainty, it should be included in the reference  
2043 safety information (RSI) and/or the Investigator's Brochure (IB).

2044  
2045 • for marketed medicinal products: a response to a drug that is noxious and  
2046 unintended and that occurs at doses normally used in humans for prophylaxis,  
2047 diagnosis or therapy of diseases or for modification of physiological function.  
2048 (See ICH E2A Clinical Safety Data Management: Definitions and Standards for  
2049 Expedited Reporting).

2050 **Serious Adverse Event (SAE):** Any unfavourable medical occurrence that is considered  
2051 serious at any dose if it:

- 2052 • results in death
- 2053 • is life-threatening
- 2054 • requires inpatient hospitalisation or prolongation of existing hospitalisation
- 2055 • results in persistent or significant disability/incapacity
- 2056 • is a congenital anomaly/birth defect (see ICH E2A)

2057 **Suspected Unexpected Serious Adverse Reaction (SUSAR):** an adverse reaction that  
2058 meets three criteria: suspected, unexpected and serious.

2059 • Suspected: There is a reasonable possibility that the drug caused the adverse drug  
2060 reaction.

2061  
2062 • Unexpected: An adverse reaction, the nature or severity of which is not consistent  
2063 with the applicable product information (e.g., the RSI, see glossary term contained  
2064 within the Investigator's Brochure or alternative documents according to applicable  
2065 regulatory requirements. Refer to ICH E2F Development Safety Update Report for  
2066 more information about RSI.

2067  
2068 • Serious: See above for **SAE**.

2069

2070 **Agreement**

2071 A document or set of documents describing the details of any arrangements on delegation or  
 2072 transfer, distribution and/or sharing of activities and, if appropriate, on financial matters  
 2073 between two or more parties. This could be in the form of a contract. The protocol may serve  
 2074 as the basis of an agreement.

2075 **Applicable Regulatory Requirement(s)**

2076 Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational  
 2077 products.

2078 **Assent**

2079 Affirmative agreement of a minor to participate in clinical trial. The absence of expression of  
 2080 agreement or disagreement should not be interpreted as assent.

2081 **Audit**

2082 A systematic and independent examination of trial-related activities and records performed by  
 2083 the sponsor, service provider (including contract research organisation (CRO)) or institution to  
 2084 determine whether the evaluated trial-related activities were conducted and the data were  
 2085 recorded, analysed and accurately reported according to the protocol, applicable standard  
 2086 operating procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory  
 2087 requirement(s).

2088 **Audit Certificate**

2089 A declaration of confirmation by the auditor that an audit has taken place.

2090 **Audit Report**

2091 A record describing the conduct and outcome of the audit.

2092 **Audit Trail**

2093 Metadata records that allow reconstruction of the course of events by capturing details on  
 2094 actions (manual or automated) performed relating to information and data collection and, where  
 2095 applicable, to activities in computerised systems. The audit trail should show activities, initial  
 2096 entry, and changes to data fields or records, by whom, when and, where applicable, why. In  
 2097 computerised systems, the audit trail should be secure, computer generated and timestamped.

2098 **Blinding/Masking**

2099 A procedure in which one or more parties to the trial are kept unaware of the treatment  
 2100 assignment(s). Single-blinding usually refers to the participant(s) being unaware, and double-  
 2101 blinding usually refers to the participant(s), investigator(s) or other trial staff, as appropriate,  
 2102 being unaware of the treatment assignment(s).

2103 **Case Report Form (CRF)**

2104 A tool designed to record protocol-required information to be reported by the investigator to  
 2105 the sponsor on each trial participant (see **Data Acquisition Tool**).

2106

2107 **Certified Copy**

2108 A copy (irrespective of the type of media used) of the original record that has been verified  
2109 (i.e., by a dated signature or by generation through a validated process) to have the same  
2110 information as the original, including relevant metadata, where applicable.

2111 **Clinical Trial**

2112 Any interventional investigation in human participants intended to discover or verify the  
2113 clinical, pharmacological and/or other pharmacodynamic effects of an investigational  
2114 product(s); and/or to identify any adverse reactions to an investigational product(s); and/or to  
2115 study absorption, distribution, metabolism and excretion of an investigational product(s) with  
2116 the object of ascertaining its safety and/or efficacy.

2117 **Clinical Trial/Study Report (CSR)**

2118 A documented description of a trial of any investigational product conducted in human  
2119 participants, in which the clinical and statistical description, presentations and analyses are  
2120 fully integrated into a single report (see ICH E3 Structure and Content of Clinical Study  
2121 Reports).

2122 **Comparator**

2123 An investigational or authorised medicinal product (i.e., active control), placebo or standard of  
2124 care used as a reference in a clinical trial.

2125 **Compliance (in relation to trials)**

2126 Adherence to the trial-related requirements, GCP requirements and the applicable regulatory  
2127 requirements.

2128 **Confidentiality**

2129 Prevention of disclosure to other than authorised individuals of a sponsor's proprietary  
2130 information or of a participant's identity or their confidential information.

2131 **Coordinating Investigator**

2132 An investigator assigned the responsibility for the coordination of investigators at different  
2133 investigator sites participating in a multicentre trial (if appropriate).

2134 **Computerised Systems Validation**

2135 A process of establishing and documenting that the specified requirements of a computerised  
2136 system can be consistently fulfilled from design until decommissioning of the system or  
2137 transition to a new system. The approach to validation should be based on a risk assessment  
2138 that takes into consideration the intended use of the system and the potential of the system to  
2139 affect trial participant protection and the reliability of trial results.

2140 **Contract Research Organisation (CRO)**

2141 See **Service Provider**.

2142

2143 **Data Acquisition Tool (DAT)**

2144 A paper or electronic tool designed to collect data and associated metadata from a data  
2145 originator in a clinical trial according to the protocol and to report the data to the sponsor.

2146 The data originator may be a human (e.g., the participant or trial staff), a machine (e.g.,  
2147 wearables and sensors) or an electronic transfer of data from one system to another (e.g.,  
2148 extraction of data from an electronic health record or laboratory system).

2149 Examples of DATs include but are not limited to CRFs, interactive response technologies  
2150 (IRTs), patient-reported outcomes (PROs), clinical outcome assessments (COAs) and wearable  
2151 devices, irrespective of the media used.

2152 **Direct Access**

2153 Permission to examine, analyse and verify records that are important to the evaluation of a  
2154 clinical trial and may be performed in person or remotely. Any party (e.g., domestic and foreign  
2155 regulatory authorities, sponsor's monitors and auditors) with direct access should take  
2156 reasonable precautions within the constraints of the applicable regulatory requirement(s) to  
2157 maintain the confidentiality of participants' identities and their data and sponsor's proprietary  
2158 information.

2159 **Essential Records**

2160 Essential records are the documents and data (and relevant metadata), in any format, associated  
2161 with a clinical trial that facilitate the ongoing management of the trial and collectively allow  
2162 the evaluation of the methods used, the factors affecting a trial and the actions taken during the  
2163 trial conduct to determine the reliability of the trial results produced and the verification that  
2164 the trial was conducted in accordance with GCP and applicable regulatory requirements (see  
2165 Appendix C. Essential Records for the Conduct of a Clinical Trial).

2166 **Good Clinical Practice (GCP)**

2167 A standard for the planning, initiating, performing, recording, oversight, evaluation, analysis  
2168 and reporting of clinical trials that provides assurance that the data and reported results are  
2169 reliable and that the rights, safety and well-being of trial participants are protected.

2170 **Impartial Witness**

2171 A person who is independent of the trial who cannot be unfairly influenced by people involved  
2172 with the trial, who attends the informed consent process if the participant or the participant's  
2173 legally acceptable representative cannot read, and who reads the informed consent form and  
2174 any other documented information supplied or read to the participant and/or their legally  
2175 acceptable representative.

2176 **Independent Data Monitoring Committee (IDMC)**

2177 An independent data monitoring committee (e.g., data safety monitoring board) that may be  
2178 established by the sponsor to assess at intervals the progress of a clinical trial, the safety data  
2179 and the critical efficacy endpoints, and to recommend to the sponsor whether to continue,  
2180 modify or stop a trial.

2181

**2182 Informed Consent**

2183 A process by which a participant or their legally accepted representative voluntarily confirms  
2184 their willingness to participate in a trial after having been informed and been provided with the  
2185 opportunity to discuss all aspects of the trial that are relevant to the participant's decision to  
2186 participate. Varied approaches to the provision of information and the discussion about the trial  
2187 can be used. This can include, for example, providing text in different formats, images and  
2188 videos and using telephone or video conferencing with investigator site staff. Informed consent  
2189 is documented by means of a written or electronic, signed and dated informed consent form.  
2190 Obtaining consent remotely may be considered when appropriate.

**2191 Inspection**

2192 The act by a regulatory authority(ies) of conducting an official review of documents, facilities,  
2193 records and any other resources that are deemed by the authority(ies) to be related to the clinical  
2194 trial and that may be accessed at the investigator site, at the sponsor's and/or service provider's  
2195 (including CRO's) facilities, or at other establishments deemed appropriate by the regulatory  
2196 authority(ies). Some aspects of the inspection may be conducted remotely.

**2197 Institution**

2198 Any public or private entity or agency or medical or dental organisation in whose remit clinical  
2199 trials are conducted.

**2200 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

2201 An independent body (a review board or a committee, institutional, regional, national or  
2202 supranational) constituted of medical professionals and non-medical members whose  
2203 responsibility it is to ensure the protection of the rights, safety and well-being of human  
2204 participants involved in a trial and to provide public assurance of that protection by, among  
2205 other things, reviewing and approving/providing favourable opinion on the trial protocol, the  
2206 suitability of the investigator(s), the facilities, and the methods and material to be used in  
2207 obtaining and documenting informed consent of the trial participants. The legal status,  
2208 composition, function, operations and regulatory requirements pertaining to IRBs/IECs may  
2209 differ among countries but should allow the IRB/IEC to act in agreement with GCP as described  
2210 in this guideline.

**2211 Interim Clinical Trial/Study Report**

2212 A report of intermediate results and their evaluation based on analyses performed during the  
2213 course of a trial.

**2214 Investigational Product**

2215 A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in  
2216 a clinical trial, including a product with a marketing authorisation when used or assembled  
2217 (formulated or packaged) in a way different from the approved form, or when used for an  
2218 unapproved indication, or when used to gain further information about an approved use.

2219

2220

2221 **Investigator**

2222 A person responsible for the conduct of the clinical trial, including the trial participants for  
 2223 whom that person has responsibility during the conduct of the trial. If a trial is conducted by a  
 2224 team of individuals, the investigator is the responsible leader of the team and may be called the  
 2225 principal investigator. Where an investigator/institution is referenced in this guideline, it  
 2226 describes expectations that may be applicable to the investigator and/or the institution in some  
 2227 regions. Where required by the applicable regulatory requirements, the “investigator” should  
 2228 be read as “investigator and/or the institution.”

2229 **Investigator’s Brochure (IB)**

2230 A compilation of the clinical and nonclinical data on the investigational product(s) that is  
 2231 relevant to the study of the investigational product(s) in human participants (see Appendix A.  
 2232 Investigator’s Brochure).

2233 **Investigator Site**

2234 The location(s) at or from where trial-related activities are conducted under the  
 2235 investigator’s/institution’s supervision.

2236 **Legally Acceptable Representative**

2237 An individual or juridical or other body authorised under applicable law to consent, on behalf  
 2238 of a prospective participant, to the participant’s participation in the clinical trial.

2239 **Metadata**

2240 The contextual information required to understand a given data element. Metadata is structured  
 2241 information that describes, explains or otherwise makes it easier to retrieve, use or manage  
 2242 data. For the purpose of this guideline, relevant metadata are those needed to reconstruct the  
 2243 trial conduct.

2244 **Monitoring**

2245 The act of overseeing the progress of a clinical trial and of ensuring that the clinical trial is  
 2246 conducted, recorded and reported in accordance with the protocol, SOPs, GCP and the  
 2247 applicable regulatory requirement(s).

2248 **Monitoring Plan**

2249 A document that describes the strategy, methods, responsibilities and requirements for  
 2250 monitoring the trial.

2251 **Monitoring Report**

2252 A documented report following site and/or centralised monitoring activities.

2253 **Multicentre Trial**

2254 A clinical trial conducted according to a single protocol but at more than one investigator site.

2255 **Nonclinical Study**

2256 Biomedical studies not performed on human participants.

2257 **Original Medical Record**

2258 See **Source Records**.

2259 **Protocol**

2260 A document that describes the objective(s), design, methodology, statistical considerations and  
2261 organisation of a trial. The protocol usually also gives the background and rationale for the  
2262 trial, but these could be provided in other protocol referenced documents. Throughout the ICH  
2263 GCP Guideline, the term protocol refers to protocol and protocol amendments.

2264 **Protocol Amendment**

2265 A documented description of a change(s) to a protocol.

2266 **Quality Assurance (QA)**

2267 All those planned and systematic actions that are established to ensure that the trial is performed  
2268 and the data are generated, documented (recorded) and reported in compliance with GCP and  
2269 the applicable regulatory requirement(s).

2270 **Quality Control (QC)**

2271 The operational techniques and activities undertaken to verify that the requirements for quality  
2272 of the trial-related activities have been fulfilled.

2273 **Randomisation**

2274 The process of deliberately including an element of chance when assigning participants to  
2275 groups that receive different treatments in order to reduce bias.

2276 **Reference Safety Information (RSI)**

2277 Contains a cumulative list of ADRs that are expected for the investigational product being  
2278 administered to participants in a clinical trial. The RSI is included in the Investigator's  
2279 Brochure.

2280 **Regulatory Authorities**

2281 Bodies having the power to regulate, including those that review submitted protocols and  
2282 clinical data and those that conduct inspections. These bodies are sometimes referred to as  
2283 competent authorities.

2284 **Service Provider**

2285 A person or organisation (commercial, academic or other) providing a service used during the  
2286 conduct of a clinical trial to either the sponsor or the investigator to fulfil one or more of their  
2287 trial-related activities.

2288 **Signature**

2289 A unique mark, symbol or entry in line with applicable regulatory requirements and/or practice  
2290 to show expression of will and allow authentication of the signatory.

2291

2292 **Source Records**

2293 Original documents or data (which includes relevant metadata) or certified copies of the  
 2294 original documents or data, irrespective of the media used. This may include trial participants’  
 2295 medical/health records/notes/charts; data provided/entered by trial participants (e.g., electronic  
 2296 patient-reported outcome (ePROs)); healthcare providers’ records from pharmacies,  
 2297 laboratories and other facilities involved in the clinical trial; and data from automated  
 2298 instruments, such as wearables and sensors.

2299 **Sponsor**

2300 An individual, company, institution, or organisation that takes responsibility for the initiation,  
 2301 management and arrangement of the financing of a clinical trial. A clinical trial may have one  
 2302 or several sponsors where permitted under regulatory requirements. All sponsors have the  
 2303 responsibilities of a sponsor set out in this guideline. In accordance with regulatory  
 2304 requirements, sponsors may decide in a documented agreement setting out their respective  
 2305 responsibilities. Where the agreement does not specify to which sponsor a given responsibility  
 2306 is attributed, that responsibility lies with all sponsors.

2307 **Sponsor-Investigator**

2308 An individual who both initiates and conducts, alone or with others, a clinical trial, and under  
 2309 whose immediate direction the investigational product is administered to, dispensed to or used  
 2310 by a participant. The term does not include any person other than an individual (e.g., the term  
 2311 does not include a corporation or an agency). The obligations of a sponsor-investigator include  
 2312 both those of a sponsor and those of an investigator.

2313 **Standard Operating Procedures (SOPs)**

2314 Detailed, documented instructions to achieve uniformity of the performance of a specific  
 2315 activity.

2316 **Sub-investigator**

2317 Any individual member of the clinical trial team designated and supervised by the investigator  
 2318 to perform critical trial-related procedures and/or to make important trial-related decisions  
 2319 (e.g., associates, residents, research fellows).

2320 **Trial Participant**

2321 An individual who participates in a clinical trial, either as a recipient of the investigational  
 2322 product(s) or as a control.

2323 **Trial Participant Identification Code**

2324 A unique identifier assigned to each trial participant to protect the participant’s identity and  
 2325 used in lieu of the participant’s name when the investigator reports adverse events and/or other  
 2326 trial-related data.

2327 **Vulnerable Participants**

2328 Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the  
 2329 expectation, whether justified or not, of benefits associated with participation or of a retaliatory



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2330 response from senior members of a hierarchy in case of refusal to participate. Examples are  
2331 members of a group with a hierarchical structure, such as medical, pharmacy, dental and  
2332 nursing students; subordinate hospital and laboratory personnel; employees of the  
2333 pharmaceutical industry; members of the armed forces and persons kept in detention. Other  
2334 vulnerable participants may include persons in nursing homes, unemployed or impoverished  
2335 persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads,  
2336 refugees, minors and those incapable of giving consent.

2337 **APPENDICES**2338 **Appendix A. INVESTIGATOR'S BROCHURE**2339 **A.1 Introduction**

2340 The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the  
2341 investigational product(s)<sup>1</sup> that are relevant to the study of the product(s) in human participants.  
2342 Its purpose is to provide the investigators and others involved in the trial with the information  
2343 to facilitate their understanding of the rationale for and their compliance with many key features  
2344 of the protocol, such as the dose, dose frequency/interval, methods of administration and safety  
2345 monitoring procedures.

2347 *A.1.1 Development of the Investigator's Brochure*

2348 Generally, the sponsor is responsible for ensuring that an up-to-date IB is developed.  
2349 In the case of an investigator-initiated trial, the sponsor-investigator should determine  
2350 whether a brochure is available from the product license/marketing authorisation  
2351 holder. If the investigational product is provided by the sponsor-investigator, then they  
2352 should provide the necessary information to the investigator site staff. Where  
2353 permitted by regulatory authorities, the current scientific information such as a basic  
2354 product information brochure (e.g., summary of product characteristics package  
2355 leaflet, or labelling) may be an appropriate alternative, provided that it includes  
2356 current, comprehensive and detailed information on all aspects of the investigational  
2357 product that might be of importance to the investigator. If an authorised medicinal  
2358 product is being studied for a new use (i.e., a new indication), an IB specific to that  
2359 new use should be prepared unless there is a rationale for only one IB. The IB should  
2360 be reviewed at least annually and revised as necessary in compliance with a sponsor's  
2361 documented procedures. More frequent revision may be appropriate depending on the  
2362 stage of development and the generation of relevant new information. Relevant new  
2363 information may be so important that it needs to be communicated to the investigators  
2364 and possibly to the IRBs/IECs and/or regulatory authorities before it is included in a  
2365 revised IB.

2367 *A.1.2 Reference Safety Information and Risk-Benefit Assessment*

2368 The reference safety information (RSI) contained in the IB provides an important  
2369 reference point for expedited reporting of suspected unexpected serious adverse  
2370 reactions (SUSARs) in the clinical trial. The IB also provides insight to support the  
2371 clinical management of the participants during the course of the clinical trial. The  
2372 information should be presented in a concise, simple, objective, balanced and non-  
2373 promotional form that enables a clinician or potential investigator to understand it and  
2374 make their own unbiased risk-benefit assessment of the appropriateness of the  
2375 proposed trial. For this reason, a medically qualified person should be involved in the  
2376 generation of an IB, but the contents of the IB should be approved by the disciplines  
2377 that generated the described data.

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<sup>1</sup> For the purpose of this guideline, the term "investigational products" should be considered synonymous with drugs, medicines, medicinal products, vaccines and biological products.

**2378 A.2 General Considerations**

2379 These considerations delineate the minimum information that should be included in an IB. It is  
2380 expected that the type and extent of information available will vary with the stage of  
2381 development of the investigational product.

2382 The IB should include;

**2383 A.2.1 Title Page**

2384 This should provide the sponsor's name, the identity of each investigational product  
2385 (i.e., research number, chemical or approved generic name and trade name(s) where  
2386 legally permissible and desired by the sponsor) and the release date. It is also  
2387 suggested that an edition number and a reference to the number and date of the edition  
2388 it supersedes be provided along with the cut-off date for data inclusion in the version.  
2389 Where appropriate, a signature page may be included.

**2390 A.2.2 Confidentiality Statement**

2391 The sponsor may wish to include a statement instructing the investigator and other  
2392 recipients to treat the IB as a confidential document for the sole information and use  
2393 of the investigator/institution, investigator site staff, regulatory authorities and the  
2394 institutional review board/independent ethics committee (IRB/IEC).

**2395 A.3 Contents of the Investigator's Brochure**

2396 The IB should contain the following sections, each with literature references (publications or  
2397 reports) included at the end of each chapter, where appropriate;

**2398 A.3.1 Table of Contents****2399 A.3.2 Summary**

2400 A brief summary (preferably not exceeding two pages) should be given, highlighting  
2401 the significant physical, chemical, pharmaceutical, pharmacological, toxicological,  
2402 pharmacokinetic, metabolic and clinical information available that is relevant to the  
2403 stage of clinical development of the investigational product.

**2404 A.3.3 Introduction**

2405 A brief introductory statement should be provided that contains the chemical name  
2406 (and generic and trade name(s) when approved) of the investigational product(s); all  
2407 active ingredients; the pharmacological class of the investigational product(s) and its  
2408 expected position within this class (e.g., advantages); the rationale for performing  
2409 research with the investigational product(s); and the anticipated prophylactic,  
2410 therapeutic or diagnostic indication(s). Finally, the introductory statement should  
2411 provide the general approach to be followed in evaluating the investigational product.

**2412 A.3.4 Physical, Chemical and Pharmaceutical Properties and Formulation**

2413 A description should be provided of the investigational product substance(s)  
2414 (including the chemical and/or structural formula(e)), and a brief summary should be  
2415 given of the relevant physical, chemical and pharmaceutical properties.

2416 To permit appropriate safety measures to be taken in the course of the trial, a  
 2417 description of the formulation(s) to be used, including excipients, should be provided  
 2418 and justified if clinically relevant. Instructions for the storage and handling of the  
 2419 dosage form(s) should also be given.

2420 Any structural similarities to other known compounds should be mentioned.

2421 *A.3.5 Nonclinical Studies*

2422 *Introduction*

2423 The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic and  
 2424 investigational product metabolism studies should be provided in summary form. This  
 2425 summary should address the methodology used, the results and a discussion of the  
 2426 relevance of the findings to the investigated therapeutic and the possible unfavourable  
 2427 and unintended effects in humans.

2428 The information provided may include the following, as appropriate, if  
 2429 known/available:

- 2430 • species tested
- 2431 • number and sex of animals in each group
- 2432 • unit dose (e.g., milligram/kilogram (mg/kg))
- 2433 • dose interval
- 2434 • route of administration
- 2435 • duration of dosing
- 2436 • information on systemic distribution
- 2437 • duration of post-exposure follow-up
- 2438 • results, including the following aspects:
  - 2439 – nature and frequency of pharmacological or toxic effects
  - 2440 – severity or intensity of pharmacological or toxic effects
  - 2441 – time to onset of effects
  - 2442 – reversibility of effects
  - 2443 – duration of effects
  - 2444 – dose response

2445 Tabular format/listings should be used whenever possible to enhance the clarity of the  
 2446 presentation.

2447 The following sections should discuss the most important findings from the studies,  
 2448 including the dose response of observed effects, the relevance to humans and any  
 2449 aspects to be studied in humans. If applicable, the effective and nontoxic dose findings  
 2450 in the same animal species should be compared (i.e., the therapeutic index should be  
 2451 discussed). The relevance of this information to the proposed human dosing should  
 2452 be addressed. Whenever possible, comparisons should be made in terms of  
 2453 blood/tissue levels rather than on a mg/kg basis.

2454 *(a) Nonclinical Pharmacology*

2455 A summary of the pharmacological aspects of the investigational product and, where  
 2456 appropriate, its significant metabolites studied in animals should be included. Such a

2457 summary should incorporate studies that assess potential therapeutic activity (e.g.,  
 2458 efficacy models, receptor binding and specificity) as well as those that assess safety  
 2459 (e.g., special studies to assess pharmacological actions other than the intended  
 2460 therapeutic effect(s)).

2461 *(b) Pharmacokinetics and Product Metabolism in Animals*

2462 A summary of the pharmacokinetics and biological transformation and disposition of  
 2463 the investigational product in all species studied should be given. The discussion of  
 2464 the findings should address the absorption and the local and systemic bioavailability  
 2465 of the investigational product and its metabolites and their relationship to the  
 2466 pharmacological and toxicological findings in animal species.

2467 *(c) Toxicology*

2468 A summary of the toxicological effects found in relevant studies conducted in  
 2469 different animal species should be described under the following headings where  
 2470 appropriate:

- 2471 • single dose
- 2472 • repeated dose
- 2473 • carcinogenicity
- 2474 • special studies (e.g., irritancy and sensitisation)
- 2475 • reproductive toxicity
- 2476 • genotoxicity (mutagenicity)

2477 *A.3.6 Effects in Humans*

2478 *Introduction*

2479 A thorough discussion of the known effects of the investigational product(s) in  
 2480 humans should be provided, including information on pharmacokinetics, metabolism,  
 2481 pharmacodynamics, dose response, safety, efficacy and other pharmacological  
 2482 activities. Where possible, a summary of each completed clinical trial and ongoing  
 2483 trials where interim results are available that may inform the safety evaluation should  
 2484 be provided. Information should also be provided regarding results of any use of the  
 2485 investigational product(s) other than from in clinical trials, such as from experience  
 2486 during marketing.

2487 *(a) Pharmacokinetics and Product Metabolism in Humans*

2488 A summary of information on the pharmacokinetics of the investigational product(s)  
 2489 should be presented, including the following, if available:

- 2490 • pharmacokinetics (including metabolism, as appropriate, and absorption,  
 2491 plasma protein binding, distribution and elimination)
- 2492 • bioavailability of the investigational product (absolute, where possible, and/or  
 2493 relative) using a reference dosage form
- 2494 • population subgroups (e.g., sex, age and impaired organ function)
- 2495 • interactions (e.g., product-product interactions and effects of food)

- 2496                   •     other pharmacokinetic data (e.g., results of population studies performed within  
2497                                    clinical trial(s))

2498  
2499                   **(b) Safety and Efficacy**

2500                   A summary of information should be provided about the investigational  
2501                   product's/products' (including metabolites, where appropriate) safety,

2502                   pharmacodynamics, efficacy and dose response that was obtained from preceding  
2503                   trials in humans (healthy volunteers and/or patients). The implications of this  
2504                   information should be discussed. In cases where a number of clinical trials have been  
2505                   completed, the use of summaries of safety and efficacy across multiple trials by  
2506                   indications in subgroups may provide a clear presentation of the data. Tabular  
2507                   summaries of adverse drug reactions for all the clinical trials (including those for all  
2508                   the studied indications) would be useful. Important differences in adverse drug  
2509                   reaction patterns/incidences across indications or subgroups should be discussed.

2510                   The IB should provide a description of the possible risks and adverse drug reactions  
2511                   to be anticipated on the basis of prior experiences with the product under investigation  
2512                   and with related products. There should be a list of adverse reactions, clearly identified  
2513                   as the reference safety information section, including information on their frequency  
2514                   and nature. This list should be used for determining the expectedness of a suspected  
2515                   serious adverse reaction and subsequently whether it needs to be expedited in  
2516                   accordance with regulatory requirements. A description should also be provided of  
2517                   the precautions or special monitoring to be done as part of the investigational use of  
2518                   the product(s).

2519                   **(c) Marketing Experience**

2520                   The IB should identify countries where the investigational product has been marketed  
2521                   or approved. Any significant information arising from the marketed use should be  
2522                   summarised (e.g., formulations, dosages, routes of administration, adverse drug  
2523                   reactions). The IB should also identify all the countries where the investigational  
2524                   product did not receive approval/registration for marketing or was withdrawn from  
2525                   marketing/registration.

2526                   **A.3.7 Summary of Data and Guidance for the Investigator**

2527                   This section should provide an overall discussion of the nonclinical and clinical data  
2528                   and should summarise the information from various sources on different aspects of  
2529                   the investigational product(s), wherever possible. In this way, the investigator can be  
2530                   provided with the most informative interpretation of the available data and with an  
2531                   assessment of the implications of the information for future clinical trials.

2532                   Where appropriate, the published reports on related products should be discussed.  
2533                   This could help the investigator to anticipate adverse drug reactions or other problems  
2534                   in clinical trials.

2535                   The overall aim of this section is to provide the investigator with a clear understanding of the  
2536                   possible risks and adverse reactions and of the specific tests, observations and precautions that  
2537                   may be needed for a clinical trial. This understanding should be based on the available physical,

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2538 chemical, pharmaceutical, pharmacological, toxicological and clinical information on the  
2539 investigational product(s). Guidance should also be provided to the clinical investigator on the  
2540 recognition and treatment of possible overdose and adverse drug reactions that is based on  
2541 previous human experience and on the pharmacology of the investigational product.

2542 **Appendix B. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)**

2543 Clinical trials should be described in a clear, concise and operationally feasible protocol. The  
 2544 protocol should be designed in such a way as to minimise unnecessary complexity and to  
 2545 mitigate or eliminate important risks to the rights, safety, and wellbeing of trial participants  
 2546 and the reliability of data. Protocol development processes should incorporate input from  
 2547 relevant stakeholders, where appropriate. Building adaptability into the protocol, for example,  
 2548 by including acceptable ranges for specific protocol provisions, can reduce the number of  
 2549 deviations or in some instances the requirement for a protocol amendment. Such adaptability  
 2550 should not adversely affect participant safety or the scientific validity of the trial. For additional  
 2551 information, refer to ICH E8(R1) General Considerations for Clinical Studies and ICH E9  
 2552 Statistical Principles for Clinical Trials.

2553 The contents of a trial protocol should generally include the following topics, which may vary  
 2554 depending on the trial design. Investigator site-specific information may be provided on  
 2555 separate protocol page(s) or addressed in a separate agreement, and some of the information  
 2556 listed below may be contained in other protocol referenced documents, such as an  
 2557 Investigator's Brochure.

2558 **B.1 General Information**

2559 B.1.1 Protocol title, unique protocol identifying number, and date. Any amendment(s)  
 2560 should also bear the amendment number(s) and date(s).

2561 B.1.2 Name and address of the sponsor.

2562 B.1.3 Name and title of the person(s) authorised to sign the protocol and the protocol  
 2563 amendment(s) for the sponsor.

2564 **B.2 Background Information**

2565 B.2.1 Name and description of the investigational product(s).

2566 B.2.2 A summary of findings from nonclinical studies that potentially have clinical  
 2567 significance and from clinical trials that are relevant to the trial.

2568 B.2.3 Summary of the known and potential risks and benefits, if any, to human participants.

2569 B.2.4 Description of and justification for the route of administration, dosage, dosage  
 2570 regimen and treatment period(s).

2571 B.2.5 A statement that the trial will be conducted in compliance with the protocol, Good  
 2572 Clinical Practice (GCP) and the applicable regulatory requirement(s).

2573 B.2.6 Description of the population to be studied.

2574 B.2.7 References to literature and data that are relevant to the trial and that provide  
 2575 background for the trial.

2576 **B.3 Trial Objectives and Purpose**

2577 A clear description of the scientific objectives and the purpose of the trial. Information on  
 2578 estimands, where appropriate, if not included in any other trial-related document, see ICH



2579 E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline  
 2580 on Statistical Principles for Clinical Trials.

2581 **B.4 Trial Design**

2582 The scientific integrity of the trial and the reliability of the results from the trial depend  
 2583 substantially on the trial design. A description of the trial design should include:

2584 B.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to  
 2585 be measured during the trial.

2586 B.4.2 A description of the type and design of trial to be conducted (e.g., double-blind,  
 2587 placebo-controlled, parallel design, adaptive design, platform/umbrella/basket, trials  
 2588 with decentralised elements) and a schematic diagram of trial design, procedures and  
 2589 stages.

2590 B.4.3 A description of the measures taken to minimise/avoid bias, including:

2591 (a) Randomisation

2592 (b) Blinding

2593 B.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the  
 2594 investigational product(s), including a description of the dosage form, packaging and  
 2595 labelling.

2596 B.4.5 The expected duration of the participant’s involvement in the trial and a description  
 2597 of the sequence and duration of all trial periods, including follow-up, if any.

2598 B.4.6 A description of the “stopping rules” or “discontinuation criteria” and “dose  
 2599 adjustment” or “dose interruption” for individual participants, parts of trial and entire  
 2600 trial.

2601 B.4.7 Accountability procedures for the investigational product(s), including the placebo(s)  
 2602 and other comparator(s), if any.

2603 B.4.8 Maintenance of treatment randomisation codes and procedures for breaking codes.

2604 **B.5 Selection of Participants**

2605 B.5.1 Participant inclusion criteria.

2606 B.5.2 Participant exclusion criteria.

2607 B.5.3 Mechanism for pre-screening, where appropriate, and screening of participants.

2608 **B.6 Withdrawal of Consent or Discontinuation of Participation**

2609 The investigator may choose to discontinue the participant, or the participant may  
 2610 withdraw their consent. The protocol should specify:

2611 (a) when and how to discontinue participants from the trial/investigational product  
 2612 treatment;

2613 (b) the type and timing of the data to be collected for withdrawn/discontinued  
 2614 participants, including the process by which the data are handled, in accordance  
 2615 with applicable regulatory requirements;

2616 (c) whether and how participants are to be replaced;

2617 (d) the follow-up for participants who have discontinued the use of the  
 2618 investigational product.

2619 **B.7 Treatment and Interventions for Participants**

2620 B.7.1 The treatment(s) to be administered, including the name(s) of all the product(s), the  
 2621 dose(s), the dosing schedule(s), the criteria for dose adjustment(s), the route/mode(s)  
 2622 of administration and the treatment period(s), including the follow-up period(s) for  
 2623 participants for each investigational product treatment/trial treatment group/arm of the  
 2624 trial.

2625 B.7.2 Medication(s)/treatment(s) permitted (including concomitant and rescue medication)  
 2626 and not permitted before and/or during the trial.

2627 B.7.3 Strategies to monitor the participant’s adherence to treatment.

2628 **B.8 Assessment of Efficacy**

2629 B.8.1 Specification of the efficacy parameters, where applicable.

2630 B.8.2 Methods and timing for assessing, recording and analysing of efficacy parameters.  
 2631 Where any trial-related committees (e.g., independent data monitoring committee  
 2632 (IDMC)/adjudication committees) are utilised for the purpose of assessing efficacy  
 2633 data, procedures, timing and activities should be described in the protocol or a separate  
 2634 document.

2635 **B.9 Assessment of Safety**

2636 B.9.1 Specification of safety parameters.

2637 B.9.2 The methods, extent and timing for recording and assessing safety parameters. Where  
 2638 any trial-related committees (e.g., IDMC) are utilised for the purpose of assessing  
 2639 safety data, procedures, timing and activities should be described in the protocol or a  
 2640 separate document.

2641 B.9.3 Procedures for obtaining reports of and for recording and reporting adverse event and  
 2642 intercurrent events; see ICH E9(R1).

2643 B.9.4 The type and duration of the follow-up of participants after adverse events.

2644 **B.10 Statistical Considerations**

2645 B.10.1 A description of the statistical methods to be employed, including timing and purpose  
 2646 of any planned interim analysis(es) and the criteria for the stopping of the trial.

2647 B.10.2 The number of participants planned to be enrolled and the reason for the choice of  
 2648 sample size, including reflections on or calculations of the power of the trial and  
 2649 clinical justification.

- 2650 B.10.3 The level of significance to be used or the threshold for success on the posterior  
2651 probability in a Bayesian design.
- 2652 B.10.4 The criteria for the termination of the trial and the criteria for the stopping of the trial.
- 2653 B.10.5 The selection of participants to be included in the planned analyses (e.g., all  
2654 randomised participants, all dosed participants, all eligible participants, all evaluable  
2655 participants).
- 2656 B.10.6 Procedures for accounting for missing, unused and spurious data.
- 2657 B.10.7 Statement that any deviation(s) from the statistical analysis plan will be described and  
2658 justified in the clinical study report.
- 2659 **B.11 Direct Access to Source Records**
- 2660 The sponsor should ensure that it is specified in the protocol or other documented agreement  
2661 that the investigator(s)/institution(s)/service provider(s) will permit trial-related monitoring,  
2662 audits, institutional review board/independent ethics committee (IRB/IEC) review and  
2663 regulatory inspection(s), providing direct access to source records.
- 2664 **B.12 Quality Control and Quality Assurance**
- 2665 B.12.1 Description of identified quality factors and associated risks in the trial unless  
2666 documented elsewhere.
- 2667 B.12.2 Description of the monitoring approaches that are part of the quality control process  
2668 for the clinical trial.
- 2669 B.12.3 Description of the process for the handling of non-compliance with the protocol or  
2670 GCP.
- 2671 **B.13 Ethics**
- 2672 Description of ethical considerations relating to the trial.
- 2673 **B.14 Data Handling and Record Keeping**
- 2674 B.14.1 Specification of data to be collected and the method of its collection. Where necessary,  
2675 additional details should be contained in a clinical trial-related document.
- 2676 B.14.2 The identification of records to be recorded directly into the data acquisition tools  
2677 (i.e., no prior written or electronic record of data) and considered to be source data.
- 2678 B.14.3 A statement that records should be retained in accordance with applicable regulatory  
2679 requirements.
- 2680 **B.15 Financing and Insurance**
- 2681 Financing and insurance, if not addressed in a separate agreement.
- 2682 **B.16 Publication Policy**
- 2683 Publication policy, if not addressed in a separate agreement.

2684 **Appendix C. ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL**2685 **C.1 Introduction**

2686 C.1.1 Many records are generated before and during the conduct of a clinical trial. The  
2687 nature and extent of those records generated and maintained are dependent upon the  
2688 trial design, its conduct, application of proportional approaches and the importance  
2689 and relevance of that record to the trial.

2691 C.1.2 Determining which records are essential will be based upon consideration of the  
2692 guidance in this appendix.

2694 C.1.3 The essential records permit and contribute to the evaluation of the conduct of a trial  
2695 and the reliability of the results produced. They serve to demonstrate the compliance  
2696 of the investigator and sponsor with the standards of Good Clinical Practice (GCP)  
2697 and applicable regulatory requirements. The essential records are used as part of the  
2698 sponsor oversight or investigator supervision of the trial. These records are used by  
2699 the sponsor's independent audit function and during inspections by regulatory  
2700 authority(ies) to assess the trial conduct and the reliability of the trial results. The  
2701 investigator/institution should have access to and the ability to maintain and retain the  
2702 essential records generated by the investigator/institution before, during and after the  
2703 trial.

2704 **C.2 Management of Essential Records**

2705 C.2.1 Records should be identifiable and version controlled, and should include authors,  
2706 reviewers and approvers as appropriate, along with date and signature (electronic or  
2707 wet ink), where necessary.

2709 C.2.2 For activities that are transferred or delegated to service providers by the sponsor or  
2710 investigator/institution respectively, arrangements should be made for the access and  
2711 management of the essential records throughout the trial and for their retention  
2712 following completion of the trial.

2714 C.2.3 These essential records should be maintained in or referred to from repositories,  
2715 including, for example, the trial master file (TMF) or investigator site file (ISF). The  
2716 TMF is held by the sponsor or by the investigator; in the latter case, it is often called  
2717 the ISF.

2719 C.2.4 The sponsor and investigator/institution should maintain a record of where essential  
2720 records are located, including source records. The storage system(s) used during the  
2721 trial and for archiving (irrespective of the type of media used) should provide for  
2722 appropriate identification, version history, search and retrieval of trial records.

2724 C.2.5 The sponsor and investigator/institution should ensure that the essential records are  
2725 collected and filed in a timely manner, including those required to be in place prior to  
2726 the trial start, which can greatly assist in the successful management of a trial.

- 2727 C.2.6 The sponsor and investigator/institution should retain the essential records in a way  
 2728 that ensures that they remain complete, readable and readily available and are directly  
 2729 accessible upon request by regulatory authorities. Alteration to the essential records  
 2730 should be traceable.  
 2731
- 2732 C.2.7 The original version of the essential record should be retained by the responsible party  
 2733 (sponsor or investigator). When a copy is used to permanently replace the original  
 2734 essential record, the copy should fulfil the requirements for certified copies.  
 2735
- 2736 C.2.8 In order to fulfil their responsibilities in the conduct of the trial, the sponsor and  
 2737 investigator/institution may need access to or copies of one another's relevant  
 2738 essential records before, during and after the trial is completed. This will determine  
 2739 whether the record resides in the repositories of the sponsor, the  
 2740 investigator/institution, or both. There should be careful consideration of sharing of  
 2741 records subject to data protection legislation and blinding considerations in line with  
 2742 applicable regulatory requirements. For the sharing of essential records with service  
 2743 providers, see section C.2.2.  
 2744
- 2745 C.2.9 Certain essential records may not be specific to a trial but may be related to the  
 2746 systems and processes involved in running multiple trials and retained outside the  
 2747 trial-specific repositories (e.g., standard operating procedures validation records,  
 2748 master services agreements).
- 2749 **C.3 Essentiality of Trial Records**
- 2750 C.3.1 Whether a specific clinical trial record generated before, during and after the trial is  
 2751 essential and needs to be retained should be based on the following criteria:
- 2752 (a) Is a document that is submitted to or issued by the regulatory authority or  
 2753 IRB/IEC, including related correspondence and those documenting regulatory  
 2754 decisions or approvals/favourable opinions;
  - 2755 (b) Is a trial-specific procedure or plan;
  - 2756 (c) Is relevant correspondence or documentation of meetings related to important  
 2757 discussions and/or trial-related decisions that have been made related to the  
 2758 conduct of the trial and the processes being used;
  - 2759 (d) Documents the conduct of relevant trial procedures;
  - 2760 (e) Documents the arrangements between parties and insurance/indemnity  
 2761 arrangements;
  - 2762 (f) Documents the compliance with the requirements and any conditions of  
 2763 approval from the regulatory authority or the favourable opinion of the  
 2764 institutional review board/independent ethics committee (IRB/IEC);
  - 2765 (g) Documents the composition and, where appropriate, the functions,  
 2766 correspondence and decisions of any committees involved in the trial approval  
 2767 or its conduct.

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- 2768 (h) Demonstrates that a trial-specific computerised system is validated and that  
2769 non-trial-specific systems have been assessed as fit for purpose for their  
2770 intended use in the trial;
- 2771 (i) Is a document that has been authorised/signed by the sponsor and/or  
2772 investigator to confirm review or approval;
- 2773 (j) Is, where necessary, documentation that demonstrates signatures/initials of staff  
2774 undertaking trial-specific activities; for example, completing data acquisition  
2775 tools;
- 2776 (k) Documents what information was provided to potential trial participants and  
2777 that participants' informed consent was appropriately obtained and maintained;
- 2778 (l) Documents that sponsor personnel involved in the trial conduct and individuals  
2779 performing trial-specific activities on their behalf are qualified by education,  
2780 training and experience to undertake their activities;
- 2781 (m) Documents that the investigator and those individuals delegated trial-specific  
2782 activities by the investigator are qualified by education, training and experience  
2783 to undertake their activities, particularly where the activities are not part of their  
2784 normal role;
- 2785 (n) Contains the data as well as relevant metadata that would be needed to be able  
2786 to reconstruct the trial;
- 2787 (o) Are documents related to the sponsor and investigator oversight of safety of  
2788 trial participants during the trial, including compliance with safety reporting  
2789 requirements between sponsors and investigators, regulatory authorities and  
2790 IRBs/IECs and informing trial participants of safety information as necessary;
- 2791 (p) Documents that service providers are suitably qualified for conducting their  
2792 delegated or transferred activities;
- 2793 (q) Documents that laboratory activities and other tests used in the trial are fit for  
2794 purpose;
- 2795 (r) Documents sponsor oversight of investigator site selection and monitoring and  
2796 audit of the trial, where appropriate, and provides information on arising  
2797 issues/non-compliance and deviations detected and implementation of  
2798 corrective and preventative actions;
- 2799 (s) Documents the compliance with the protocol and/or procedures for  
2800 management and statistical analysis of the data and production of any interim  
2801 report and the final report;
- 2802 (t) Documents the collection, chain of custody, analysis and retention or  
2803 destruction of biological samples;
- 2804 (u) Provides relevant information on the investigational product and its labelling;
- 2805 (v) Provides information about the shipment, storage, packaging, dispensing,  
2806 randomisation and blinding of the investigational product;
- 2807 (w) Provides, where appropriate, traceability and accountability information about  
2808 the investigational product from release from the manufacturer to dispensation,

- 2809 administration to trial participants, and return and destruction, or alternative  
2810 disposition;
- 2811 (x) Provides information on the identity and quality of the investigational product  
2812 used in the trial;
- 2813 (y) Documents processes and activities relating to unblinding;
- 2814 (z) Documents the recruitment, pre-trial screening and consenting process of trial  
2815 participants and their identity and chronological enrolment as appropriate;
- 2816 (aa) Documents the existence of the trial participants and substantiates the integrity  
2817 of trial data collected. Includes source records related to the trial and medical  
2818 treatments and history of the trial participants;
- 2819 (bb) Defines processes/practices in place in the event of a security breach in order to  
2820 protect participants' rights, safety and well-being and the integrity of the data.
- 2821 C.3.2 Applying the criteria in section C.3.1, the trial records for every trial that are  
2822 considered essential, except in justifiable and documented exceptional circumstances,  
2823 are set out in Table 1, and these should be retained.  
2824
- 2825 C.3.3 For other trial records, their presence and nature are dependent upon the trial design,  
2826 its conduct and risk proportional management. Table 2 lists potential trial records that  
2827 when generated, would be considered essential by applying the criteria in section  
2828 C.3.1 and should be retained. This is not an exhaustive list, and other trial records may  
2829 also be considered essential by the sponsor or the investigator.
- 2830

| <b>Table 1 – Essential Records for All Trials</b> |  |
|---|--|
| 1.1   | Investigator's Brochure or basic product information brochure (e.g., summary of product characteristic, package leaflet or labelling) and relevant updates   |
| 1.2   | signed protocol and amendments during the trial  |
| 1.3   | dated, documented approval/favourable opinion of IRB/IEC of information provided to them before and during the trial   |
| 1.4   | IRB/IEC composition  |
| 1.5   | regulatory authority(ies) authorisation, approval and/or notification of the protocol and subsequent protocol amendments during the trial (where required)   |
| 1.6   | completed signed and dated informed consent forms  |
| 1.7   | completed participant identification code list and enrolment log   |
| 1.8   | - notification by originating investigator to sponsor of serious adverse events (SAEs) and related reports, where required<br>- notification by sponsor and/or investigator, where required, to regulatory authority(ies) and IRB(s)/IEC(s) of suspected unexpected serious adverse reactions (SUSARs) and of other safety information<br>- notification by sponsor to investigators of safety information, where required |
| 1.9   | interim or annual reports to IRB/IEC and regulatory authority(ies)   |
| 1.10  | source records   |

| <b>Table 1 – Essential Records for All Trials</b> |  |
|---|--|
| 1.11  | data and relevant metadata (including documentation of data corrections) in the data acquisition tools |
| 1.12  | final report by investigator to IRB/IEC and regulatory authority(ies), where required                  |
| 1.13  | interim (where applicable) and final clinical trial reports  |

2831

| <b>Table 2 – Potential Essential Records</b> |   |
|--|---|
| 2.1  | sample of data acquisition tools (e.g., case report forms (CRFs), diaries, clinical outcome assessments, patient-reported outcomes) that are provided to the investigator and/or IRB/IEC  |
| 2.2  | sample of information given to trial participants and revisions during the trial<br>- informed consent materials (including all applicable translations)<br>- any other documented information, e.g., instructions for use of an investigational product or a device<br>- advertisement for participant recruitment |
| 2.3  | financial aspects of the trial  |
| 2.4  | insurance statement   |
| 2.5  | signed agreement between involved parties, e.g.,<br>- investigator/institution and sponsor<br>- investigator/institution and service providers<br>- sponsor and service providers<br>- sponsor and independent data monitoring committee (IDMC) members   |
| 2.6  | curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub-investigator(s) involved in conducting the trial  |
| 2.7  | trial-specific training records   |
| 2.8  | documentation of delegation of activities by the investigator to investigator site staff  |
| 2.9  | signature sheet documenting signatures and initials of delegated investigator site staff  |
| 2.10   | normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol and updates during the trial conduct   |
| 2.11   | certification or accreditation or established quality control and/or external quality assessment or other validation (where required) of medical/laboratory/technical procedures/tests used during the trial conduct and any updates  |
| 2.12   | documentation of collection, processing and shipment of body fluids/tissue samples  |
| 2.13   | documentation of body fluids/tissue samples storage conditions  |
| 2.14   | record of retained body fluids/tissue samples at the end of the trial   |
| 2.15   | sample of label(s) attached to investigational product container(s)   |
| 2.16   | instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure), for example, pharmacy manual  |
| 2.17   | shipping records for investigational product(s) and trial-related materials   |
| 2.18   | certificate(s) of analysis of investigational product(s) shipped  |



| <b>Table 2 – Potential Essential Records</b> |   |
|--|---|
| 2.19   | investigational product(s) accountability at investigator site  |
| 2.20   | documentation of investigational product storage conditions during shipment and at the trial site   |
| 2.21   | records of relabelling of investigational product at trial site   |
| 2.22   | documentation of investigational product destruction  |
| 2.23   | emergency decoding procedures for blinded trials  |
| 2.24   | master randomisation list   |
| 2.25   | instructions for use for critical trial-specific systems (e.g., interactive response technologies (IRT) user manual, electronic CRF (eCRF) manual)  |
| 2.26   | maintenance and calibration records for critical trial-specific equipment   |
| 2.27   | treatment allocation and decoding documentation   |
| 2.28   | completed participants screening log  |
| 2.29   | site monitoring reports (including site selection, initiation, routine and close-out)   |
| 2.30   | centralised monitoring reports  |
| 2.31   | records and reports of protocol and GCP non-compliance/deviations and corrective and preventative actions   |
| 2.32   | documentation of relevant communications and meetings   |
| 2.33   | audit certificate   |
| 2.34   | documentation relating to data finalisation for analysis (e.g., query resolutions, SAE reconciliation, quality control reports, coding completion, output data sets)                                      |
| 2.35   | documentation of trial-specific computerised system validation (e.g., specifications, testing, validation report, change control)   |
| 2.36   | documentation relating to the statistical considerations and analysis (e.g., sample size calculations, analysis sets decisions, analysis datasets, analysis programs, quality control records and output) |
| 2.37   | trial-specific plans (e.g., risk management, monitoring, safety, data management, data validation and statistical analysis) and procedures  |
| 2.38   | procedures, meeting minutes and submissions to the IDMC   |