



1 23 July 2015
2 EMA/CHMP/ICH/135/1995
3 Committee for Human Medicinal Products

4 Guideline for good clinical practice E6(R2)

5 Step 2b

Adopted by CHMP for release for consultation	23 July 2015
Start of public consultation	4 August 2015
End of consultation (deadline for comments)	3 February 2016

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Comments should be provided using this [template](#). The completed comments form should be sent to ich@ema.europa.eu

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10 **Document History**

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First Codification	History	Date	New Codification November 2005
E6	Approval by the CPMP under <i>Step 3</i> and release for public consultation.	May 1995	E6
E6	Approval by the CPMP under <i>Step 4</i> and released for information.	July 1996	E6

12 **Step 5 corrected version**

E6	Approval by the CPMP of <i>Post-Step 4</i> editorial corrections.	July 2002	E6(R1)
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13 **Current E6(R2) Addendum Step 2 version**

Code	History	Date
E6	Approval by the Steering Committee under <i>Step 2</i> and release for public consultation. Integrated Addendum to ICH E6(R1) document. Changes are integrated directly into the following sections of the parental Guideline: Introduction, 1.11.1, 1.38.1, 1.39, 1.60.1, 2.10, 4.2.5, 4.2.6, 4.9.0, 5.0, 5.0.1, 5.0.2, 5.0.3, 5.0.4, 5.0.5, 5.0.6, 5.0.7, 5.2.1, 5.2.2, 5.5.3, 5.18.3, 5.18.6, 5.18.7, 5.20.1, 8.1	11 June 2015

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159 **Introduction**

160 Good Clinical Practice (GCP) is an international ethical and scientific quality standard for
161 designing, conducting, recording and reporting trials that involve the participation of human subjects.
162 Compliance with this standard provides public assurance that the rights, safety and well-being of trial
163 subjects are protected, consistent with the principles that have their origin in the Declaration of
164 Helsinki, and that the clinical trial data are credible.

165 The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU),
166 Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory
167 authorities in these jurisdictions.

168 The guideline was developed with consideration of the current good clinical practices of the European
169 Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and
170 the World Health Organization (WHO).

171 This guideline should be followed when generating clinical trial data that are intended to be
172 submitted to regulatory authorities.

173 The principles established in this guideline may also be applied to other clinical investigations that may
174 have an impact on the safety and well-being of human subjects.

175 **ADDENDUM**

176 Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have
177 increased. Evolutions in technology and risk management processes offer new opportunities to
178 increase efficiency and focus on relevant activities. This guideline has been amended to encourage
179 implementation of improved and more efficient approaches to clinical trial design, conduct, oversight,
180 recording and reporting while continuing to ensure human subject protection and data integrity.
181 Standards regarding electronic records and essential documents intended to increase clinical trial
182 quality and efficiency have also been updated.

183 This ICH GCP Guideline addendum provides a unified standard for the European Union (EU), Japan, the
184 United States, Canada and Switzerland to facilitate the mutual acceptance of clinical data by the
185 regulatory authorities in these jurisdictions.

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187

188

189 **1. Glossary**

190 **1.1. Adverse Drug Reaction (ADR)**

191 In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as
192 the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal
193 product related to any dose should be considered adverse drug reactions. The phrase responses to a
194 medicinal product means that a causal relationship between a medicinal product and an adverse event
195 is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

196 Regarding marketed medicinal products: a response to a drug which is noxious and unintended and
197 which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or
198 for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management:
199 Definitions and Standards for Expedited Reporting).

200 **1.2. Adverse Event (AE)**

201 Any untoward medical occurrence in a patient or clinical investigation subject administered a
202 pharmaceutical product and which does not necessarily have a causal relationship with this treatment.
203 An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal
204 laboratory finding), symptom, or disease temporally associated with the use of a medicinal
205 (investigational) product, whether or not related to the medicinal (investigational) product (see the
206 ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited
207 Reporting).

208 **1.3. Amendment (to the protocol)**

209 See Protocol Amendment.

210 **1.4. Applicable regulatory requirement(s)**

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

212 **1.5. Approval (in relation to institutional review boards)**

213 The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at
214 the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice
215 (GCP), and the applicable regulatory requirements.

216 **1.6. Audit**

217 A systematic and independent examination of trial related activities and documents to determine
218 whether the evaluated trial related activities were conducted, and the data were recorded, analyzed
219 and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs),
220 Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

221 **1.7. Audit certificate**

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

223 **1.8. Audit report**

224 A written evaluation by the sponsor's auditor of the results of the audit.

225 **1.9. Audit trail**

226 Documentation that allows reconstruction of the course of events.

227 **1.10. Blinding/masking**

228 A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s).
229 Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to
230 the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the
231 treatment assignment(s).

232 **1.11. Case Report Form (CRF)**

233 A printed, optical, or electronic document designed to record all of the protocol required
234 information to be reported to the sponsor on each trial subject.

235 **ADDENDUM**

236 **1.11.1. Certified copy**

237 A paper or electronic copy of the original record that has been verified (e.g. by a dated signature) or
238 has been generated through a validated process to produce an exact copy having all of the same
239 attributes and information as the original.

240 **1.12. Clinical trial/study**

241 Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or
242 other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse
243 reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and
244 excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The
245 terms clinical trial and clinical study are synonymous.

246 **1.13. Clinical trial/study report**

247 A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in
248 human subjects, in which the clinical and statistical description, presentations, and analyses are fully
249 integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study
250 Reports).

251 **1.14. Comparator (Product)**

252 An investigational or marketed product (i.e., active control), or placebo, used as a reference in a
253 clinical trial.

254 **1.15. Compliance (in relation to trials)**

255 Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and
256 the applicable regulatory requirements.

257

258 **1.16. Confidentiality**

259 Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or
260 of a subject's identity.

261 **1.17. Contract**

262 A written, dated, and signed agreement between two or more involved parties that sets out any
263 arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial
264 matters. The protocol may serve as the basis of a contract.

265 **1.18. Coordinating committee**

266 A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

267 **1.19. Coordinating investigator**

268 An investigator assigned the responsibility for the coordination of investigators at different centres
269 participating in a multicentre trial.

270 **1.20. Contract Research Organization (CRO)**

271 A person or an organization (commercial, academic, or other) contracted by the sponsor to
272 perform one or more of a sponsor's trial-related duties and functions.

273 **1.21. Direct access**

274 Permission to examine, analyze, verify, and reproduce any records and reports that are important to
275 evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's
276 monitors and auditors) with direct access should take all reasonable precautions within the constraints
277 of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and
278 sponsor's proprietary information.

279 **1.22. Documentation**

280 All records, in any form (including, but not limited to, written, electronic, magnetic, and optical
281 records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct,
282 and/or results of a trial, the factors affecting a trial, and the actions taken.

283 **1.23. Essential documents**

284 Documents which individually and collectively permit evaluation of the conduct of a study and the
285 quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

286 **1.24. Good Clinical Practice (GCP)**

287 A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and
288 reporting of clinical trials that provides assurance that the data and reported results are credible and
289 accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

290 **1.25. Independent Data-Monitoring Committee (IDMC) (data and safety
291 monitoring board, monitoring committee, data monitoring committee)**

292 An independent data-monitoring committee that may be established by the sponsor to assess at
293 intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to
294 recommend to the sponsor whether to continue, modify, or stop a trial.

295 **1.26. Impartial witness**

296 A person, who is independent of the trial, who cannot be unfairly influenced by people involved with
297 the trial, who attends the informed consent process if the subject or the subject's legally acceptable
298 representative cannot read, and who reads the informed consent form and any other written
299 information supplied to the subject.

300 **1.27. Independent Ethics Committee (IEC)**

301 An independent body (a review board or a committee, institutional, regional, national, or
302 supranational), constituted of medical professionals and non-medical members, whose responsibility it
303 is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial
304 and to provide public assurance of that protection, by, among other things, reviewing and
305 approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s),
306 facilities, and the methods and material to be used in obtaining and documenting informed consent of
307 the trial subjects.

308 The legal status, composition, function, operations and regulatory requirements pertaining to
309 Independent Ethics Committees may differ among countries, but should allow the Independent Ethics
310 Committee to act in agreement with GCP as described in this guideline.

311 **1.28. Informed consent**

312 A process by which a subject voluntarily confirms his or her willingness to participate in a particular
313 trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to
314 participate. Informed consent is documented by means of a written, signed and dated informed
315 consent form.

316 **1.29. Inspection**

317 The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records,
318 and any other resources that are deemed by the authority(ies) to be related to the clinical trial and
319 that may be located at the site of the trial, at the sponsor's and/or contract research organization's
320 (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

321 **1.30. Institution (medical)**

322 Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

323 **1.31. Institutional Review Board (IRB)**

324 An independent body constituted of medical, scientific, and non-scientific members, whose
325 responsibility is to ensure the protection of the rights, safety and well-being of human subjects
326 involved in a trial by, among other things, reviewing, approving, and providing continuing review of
327 trial protocol and amendments and of the methods and material to be used in obtaining and
328 documenting informed consent of the trial subjects.

329 **1.32. Interim clinical trial/study report**

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

332 **1.33. Investigational product**

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

337 **1.34. Investigator**

338 A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team
339 of individuals at a trial site, the investigator is the responsible leader of the team and may be called
340 the principal investigator. See also Subinvestigator.

341 **1.35. Investigator / institution**

342 An expression meaning "the investigator and/or institution, where required by the applicable
343 regulatory requirements".

344 **1.36. Investigator's brochure**

345 A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to
346 the study of the investigational product(s) in human subjects (see 7. Investigator's Brochure).

347 **1.37. Legally acceptable representative**

348 An individual or juridical or other body authorized under applicable law to consent, on behalf of a
349 prospective subject, to the subject's participation in the clinical trial.

350 **1.38. Monitoring**

351 The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded,
352 and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good
353 Clinical Practice (GCP), and the applicable regulatory requirement(s).

354 **ADDENDUM**

355 **1.38.1. Monitoring plan**

356 A description of the methods, responsibilities and requirements for monitoring the trial.

357 **1.39. Monitoring report**

358 A written report from the monitor to the sponsor after each site visit and/or other trial-related
359 communication according to the sponsor's SOPs.

360 **ADDENDUM**

361 Outcomes of any centralized monitoring should also be reported.

362 **1.40. Multicentre trial**

363 A clinical trial conducted according to a single protocol but at more than one site, and therefore,
364 carried out by more than one investigator.

365 **1.41. Nonclinical study**

366 Biomedical studies not performed on human subjects.

367 **1.42. Opinion (in relation to independent ethics committee)**

368 The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

369 **1.43. Original medical record**

370 See Source Documents.

371 **1.44. Protocol**

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

376 **1.45. Protocol amendment**

377 A written description of a change(s) to or formal clarification of a protocol.

378 **1.46. Quality Assurance (QA)**

379 All those planned and systematic actions that are established to ensure that the trial is performed and
380 the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice
381 (GCP) and the applicable regulatory requirement(s).

382 **1.47. Quality Control (QC)**

383 The operational techniques and activities undertaken within the quality assurance system to verify that
384 the requirements for quality of the trial-related activities have been fulfilled.

385 **1.48. Randomization**

386 The process of assigning trial subjects to treatment or control groups using an element of
387 chance to determine the assignments in order to reduce bias.

388 **1.49. Regulatory authorities**

389 Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities
390 includes the authorities that review submitted clinical data and those that conduct inspections (see
391 1.29). These bodies are sometimes referred to as competent authorities.

392 **1.50. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction**
393 **(Serious ADR)**

394 Any untoward medical occurrence that at any dose:

- 395 - results in death,
- 396 - is life-threatening,
- 397 - requires inpatient hospitalization or prolongation of existing hospitalization,
- 398 - results in persistent or significant disability/incapacity, or
- 399 - is a congenital anomaly/birth defect

400 (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for
401 Expedited Reporting).

402 **1.51. Source data**

403 All information in original records and certified copies of original records of clinical findings,
404 observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the
405 trial. Source data are contained in source documents (original records or certified copies).

406 **1.52. Source documents**

407 Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory
408 notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded
409 data from automated instruments, copies or transcriptions certified after verification as being accurate
410 copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files,
411 and records kept at the pharmacy, at the laboratories and at medico-technical
412 departments involved in the clinical trial).

413 **1.53. Sponsor**

414 An individual, company, institution, or organization which takes responsibility for the initiation,
415 management, and/or financing of a clinical trial.

416 **1.54. Sponsor-Investigator**

417 An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose
418 immediate direction the investigational product is administered to, dispensed to, or used by a subject.

419 The term does not include any person other than an individual (e.g., it does not include a corporation
420 or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of
421 an investigator.

422 **1.55. Standard Operating Procedures (SOPs)**

423 Detailed, written instructions to achieve uniformity of the performance of a specific function.

424 **1.56. Subinvestigator**

425 Any individual member of the clinical trial team designated and supervised by the investigator at a trial
426 site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g.,
427 associates, residents, research fellows). See also Investigator.

428 **1.57. Subject/trial subject**

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

431 **1.58. Subject identification code**

432 A unique identifier assigned by the investigator to each trial subject to protect the subject's identity
433 and used in lieu of the subject's name when the investigator reports adverse events and/or other trial
434 related data.

435 **1.59. Trial site**

436 The location(s) where trial-related activities are actually conducted.

437 **1.60. Unexpected adverse drug reaction**

438 An adverse reaction, the nature or severity of which is not consistent with the applicable product
439 information (e.g., Investigator's Brochure for an unapproved investigational product or package
440 insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical
441 Safety Data Management: Definitions and Standards for Expedited Reporting).

442 **ADDENDUM**

443 **1.60.1. Validation of computerized systems**

444 A process of establishing and documenting that the specified requirements of a computerized system
445 can be consistently fulfilled. Validation should ensure accuracy, reliability and consistent intended
446 performance, from design until decommissioning of the system or transition to a new system.

447 **1.61. Vulnerable subjects**

448 Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the
449 expectation, whether justified or not, of benefits associated with participation, or of a retaliatory
450 response from senior members of a hierarchy in case of refusal to participate. Examples are members
451 of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students,
452 subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of

453 the armed forces, and persons kept in detention. Other vulnerable subjects include patients with
454 incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in
455 emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those
456 incapable of giving consent.

457 **1.62. Well-being (of the trial subjects)**

458 The physical and mental integrity of the subjects participating in a clinical trial.

459

460 **2. The principles of ICH GCP**

461 **2.1.**

462 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the
463 Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

464 **2.2.**

465 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the
466 anticipated benefit for the individual trial subject and society. A trial should be initiated and
467 continued only if the anticipated benefits justify the risks.

468 **2.3.**

469 The rights, safety, and well-being of the trial subjects are the most important considerations and
470 should prevail over interests of science and society.

471 **2.4.**

472 The available nonclinical and clinical information on an investigational product should be adequate to
473 support the proposed clinical trial.

474 **2.5.**

475 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

476 **2.6.**

477 A trial should be conducted in compliance with the protocol that has received prior institutional review
478 board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

479 **2.7.**

480 The medical care given to, and medical decisions made on behalf of, subjects should always be the
481 responsibility of a qualified physician or, when appropriate, of a qualified dentist.

482 **2.8.**

483 Each individual involved in conducting a trial should be qualified by education, training, and
484 experience to perform his or her respective task(s).

485 **2.9.**

486 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

487 **2.10.**

488 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate
489 reporting, interpretation and verification.

490 **ADDENDUM**

491 This principle applies to all records (paper or electronic) referenced in this guideline.

492 **2.11.**

493 The confidentiality of records that could identify subjects should be protected, respecting the privacy
494 and confidentiality rules in accordance with the applicable regulatory requirement(s).

495 **2.12.**

496 Investigational products should be manufactured, handled, and stored in accordance with
497 applicable good manufacturing practice (GMP). They should be used in accordance with the approved
498 protocol.

499 **2.13.**

500 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

501 **3. Institutional Review Board / Independent Ethics**
502 **Committee (IRB/IEC)**

503 **3.1. Responsibilities**

504 **3.1.1.**

505 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention
506 should be paid to trials that may include vulnerable subjects.

507 **3.1.2.**

508 The IRB/IEC should obtain the following documents:

- 509 • trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates
510 that the investigator proposes for use in the trial, subject recruitment procedures (e.g.
511 advertisements), written information to be provided to subjects, Investigator's Brochure (IB),
512 available safety information, information about payments and compensation available to
513 subjects, the investigator's current curriculum vitae and/or other documentation evidencing
514 qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.
- 515 • The IRB/IEC should review a proposed clinical trial within a reasonable time and document its
516 views in writing, clearly identifying the trial, the documents reviewed and the dates for the
517 following:
- 518 ○ approval/favourable opinion;
 - 519 ○ modifications required prior to its approval/favourable opinion;
 - 520 ○ disapproval / negative opinion; and
 - 521 ○ termination/suspension of any prior approval/favourable opinion.

522 **3.1.3.**

523 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented
524 by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

525 **3.1.4.**

526 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to
527 the degree of risk to human subjects, but at least once per year.

528 **3.1.5.**

529 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects
530 when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the
531 protection of the rights, safety and/or well-being of the subjects.

532 **3.1.6.**

533 When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable
534 representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or

535 other document(s) adequately addresses relevant ethical concerns and meets applicable
536 regulatory requirements for such trials.

537 **3.1.7.**

538 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable
539 representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol
540 and/or other document(s) adequately addresses relevant ethical concerns and meets
541 applicable regulatory requirements for such trials (i.e. in emergency situations).

542 **3.1.8.**

543 The IRB/IEC should review both the amount and method of payment to subjects to assure
544 that neither presents problems of coercion or undue influence on the trial subjects. Payments to a
545 subject should be prorated and not wholly contingent on completion of the trial by the subject.

546 **3.1.9.**

547 The IRB/IEC should ensure that information regarding payment to subjects, including the methods,
548 amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form
549 and any other written information to be provided to subjects. The way payment will be prorated should
550 be specified.

551 **3.2. Composition, Functions and Operations**

552 **3.2.1.**

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

- 556 • At least five members.
- 557 • At least one member whose primary area of interest is in a nonscientific area.
- 558 • At least one member who is independent of the institution/trial site.

559 Only those IRB/IEC members who are independent of the investigator and the sponsor of the
560 trial should vote/provide opinion on a trial-related matter.

561 A list of IRB/IEC members and their qualifications should be maintained.

562 **3.2.2.**

563 The IRB/IEC should perform its functions according to written operating procedures, should
564 maintain written records of its activities and minutes of its meetings, and should comply with GCP and
565 with the applicable regulatory requirement(s).

566 **3.2.3.**

567 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated
568 in its written operating procedures, is present.

569 **3.2.4.**

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

572 **3.2.5.**

573 The investigator may provide information on any aspect of the trial, but should not participate in the
574 deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

575 **3.2.6.**

576 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

577 **3.3. Procedures**

578 The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

579 **3.3.1.**

580 Determining its composition (names and qualifications of the members) and the authority under which
581 it is established.

582 **3.3.2.**

583 Scheduling, notifying its members of, and conducting its meetings.

584 **3.3.3.**

585 Conducting initial and continuing review of trials.

586 **3.3.4.**

587 Determining the frequency of continuing review, as appropriate.

588 **3.3.5.**

589 Providing, according to the applicable regulatory requirements, expedited review and
590 approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable
591 opinion of the IRB/IEC.

592 **3.3.6.**

593 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written
594 approval/favourable opinion of the trial.

595 **3.3.7.**

596 Specifying that no deviations from, or changes of, the protocol should be initiated without prior
597 written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to

598 eliminate immediate hazards to the subjects or when the change(s) involves only logistical or
599 administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

600 **3.3.8.**

601 Specifying that the investigator should promptly report to the IRB/IEC:

- 602 • Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial
603 subjects (see 3.3.7, 4.5.2, 4.5.4).
- 604 • Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial
605 (see 4.10.2).
- 606 • All adverse drug reactions (ADRs) that are both serious and unexpected.
- 607 • New information that may affect adversely the safety of the subjects or the conduct of the
608 trial.

609 **3.3.9.**

610 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution
611 concerning:

- 612 • Its trial-related decisions/opinions.
- 613 • The reasons for its decisions/opinions.
- 614 • Procedures for appeal of its decisions/opinions.

615 **3.4. Records**

616 The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of
617 occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence)
618 for a period of at least 3 years after completion of the trial and make them available upon request from
619 the regulatory authority(ies).

620 The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written
621 procedures and membership lists.

622

623 **4. Investigator**

624 **4.1. Investigator's Qualifications and Agreements**

625 **4.1.1.**

626 The investigator(s) should be qualified by education, training, and experience to assume responsibility
627 for the proper conduct of the trial, should meet all the qualifications specified by the applicable
628 regulatory requirement(s), and should provide evidence of such qualifications through up-to-date
629 curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or
630 the regulatory authority(ies).

631 **4.1.2.**

632 The investigator should be thoroughly familiar with the appropriate use of the investigational
633 product(s), as described in the protocol, in the current Investigator's Brochure, in the product
634 information and in other information sources provided by the sponsor.

635 **4.1.3.**

636 The investigator should be aware of, and should comply with, GCP and the applicable regulatory
637 requirements.

638 **4.1.4.**

639 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by
640 the appropriate regulatory authority(ies).

641 **4.1.5.**

642 The investigator should maintain a list of appropriately qualified persons to whom the investigator has
643 delegated significant trial-related duties.

644 **4.2. Adequate Resources**

645 **4.2.1.**

646 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for
647 recruiting the required number of suitable subjects within the agreed recruitment period.

648 **4.2.2.**

649 The investigator should have sufficient time to properly conduct and complete the trial within the
650 agreed trial period.

651 **4.2.3.**

652 The investigator should have available an adequate number of qualified staff and adequate facilities for
653 the foreseen duration of the trial to conduct the trial properly and safely.

654 **4.2.4.**

655 The investigator should ensure that all persons assisting with the trial are adequately informed about
656 the protocol, the investigational product(s), and their trial-related duties and functions.

657 **ADDENDUM**

658 **4.2.5.**

659 The investigator is responsible for supervising any individual or party to whom the investigator
660 delegates study tasks conducted at the trial site.

661 **4.2.6.**

662 If the investigator/institution retains the services of any party to perform study tasks they should
663 ensure this party is qualified to perform those study tasks and should implement procedures to ensure
664 the integrity of the study tasks performed and any data generated.

665 **4.3. Medical Care of Trial Subjects**

666 **4.3.1.**

667 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the
668 trial, should be responsible for all trial-related medical (or dental) decisions.

669 **4.3.2.**

670 During and following a subject's participation in a trial, the investigator/institution
671 should ensure that adequate medical care is provided to a subject for any adverse events, including
672 clinically significant laboratory values, related to the trial. The investigator/institution should inform a
673 subject when medical care is needed for intercurrent illness(es) of which the investigator becomes
674 aware.

675 **4.3.3.**

676 It is recommended that the investigator inform the subject's primary physician about the subject's
677 participation in the trial if the subject has a primary physician and if the subject agrees to the primary
678 physician being informed.

679 **4.3.4.**

680 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial,
681 the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the
682 subject's rights.

683 **4.4. Communication with IRB/IEC**

684 **4.4.1.**

685 Before initiating a trial, the investigator/institution should have written and dated approval/favourable
686 opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates,

687 subject recruitment procedures (e.g., advertisements), and any other written information to be
688 provided to subjects.

689 **4.4.2.**

690 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution
691 should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's
692 Brochure is updated during the trial, the investigator/institution should supply a copy of the updated
693 Investigator's Brochure to the IRB/IEC.

694 **4.4.3.**

695 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to
696 review.

697 **4.5. Compliance with Protocol**

698 **4.5.1.**

699 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the
700 sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable
701 opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an
702 alternative contract, to confirm agreement.

703 **4.5.2.**

704 The investigator should not implement any deviation from, or changes of the protocol without
705 agreement by the sponsor and prior review and documented approval/favourable opinion from the
706 IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial
707 subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g.,
708 change in monitor(s), change of telephone number(s)).

709 **4.5.3.**

710 The investigator, or person designated by the investigator, should document and explain any deviation
711 from the approved protocol.

712 **4.5.4.**

713 The investigator may implement a deviation from, or a change of, the protocol to eliminate an
714 immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as
715 possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed
716 protocol amendment(s) should be submitted:

- 717
- to the IRB/IEC for review and approval/favourable opinion, (b) to the sponsor for agreement
718 and, if required,
 - to the regulatory authority(ies).
- 719

720 **4.6. Investigational Product(s)**

721 **4.6.1.**

722 Responsibility for investigational product(s) accountability at the trial site(s) rests with the
723 investigator/institution.

724 **4.6.2.**

725 Where allowed/required, the investigator/institution may/should assign some or all of the
726 investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an
727 appropriate pharmacist or another appropriate individual who is under the supervision
728 of the investigator/institution.

729 **4.6.3.**

730 The investigator/institution and/or a pharmacist or other appropriate individual, who is
731 designated by the investigator/institution, should maintain records of the product's delivery to the trial
732 site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative
733 disposition of unused product(s). These records should include dates, quantities, batch/serial numbers,
734 expiration dates (if applicable), and the unique code numbers assigned to the investigational
735 product(s) and trial subjects. Investigators should maintain records that document adequately that the
736 subjects were provided the doses specified by the protocol and reconcile all investigational product(s)
737 received from the sponsor.

738 **4.6.4.**

739 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3)
740 and in accordance with applicable regulatory requirement(s).

741 **4.6.5.**

742 The investigator should ensure that the investigational product(s) are used only in accordance with the
743 approved protocol.

744 **4.6.6.**

745 The investigator, or a person designated by the investigator/institution, should explain the correct use
746 of the investigational product(s) to each subject and should check, at intervals appropriate for the trial,
747 that each subject is following the instructions properly.

748 **4.7. Randomization Procedures and Unblinding**

749 The investigator should follow the trial's randomization procedures, if any, and should ensure that the
750 code is broken only in accordance with the protocol. If the trial is blinded, the investigator should
751 promptly document and explain to the sponsor any premature unblinding (e.g., accidental
752 unblinding, unblinding due to a serious adverse event) of the investigational product(s).

753 **4.8. Informed Consent of Trial Subjects**

754 **4.8.1.**

755 In obtaining and documenting informed consent, the investigator should comply with the
756 applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have
757 their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should
758 have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any
759 other written information to be provided to subjects.

760 **4.8.2.**

761 The written informed consent form and any other written information to be provided to subjects should
762 be revised whenever important new information becomes available that may be relevant to the
763 subject's consent. Any revised written informed consent form, and written information should receive
764 the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally
765 acceptable representative should be informed in a timely manner if new information becomes available
766 that may be relevant to the subject's willingness to continue participation in the trial. The
767 communication of this information should be documented.

768 **4.8.3.**

769 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or
770 to continue to participate in a trial.

771 **4.8.4.**

772 None of the oral and written information concerning the trial, including the written informed consent
773 form, should contain any language that causes the subject or the subject's legally acceptable
774 representative to waive or to appear to waive any legal rights, or that releases or appears to
775 release the investigator, the institution, the sponsor, or their agents from liability for negligence.

776 **4.8.5.**

777 The investigator, or a person designated by the investigator, should fully inform the subject or, if the
778 subject is unable to provide informed consent, the subject's legally acceptable representative, of all
779 pertinent aspects of the trial including the written information and the approval/ favourable opinion by
780 the IRB/IEC.

781 **4.8.6.**

782 The language used in the oral and written information about the trial, including the written
783 informed consent form, should be as non-technical as practical and should be understandable to the
784 subject or the subject's legally acceptable representative and the impartial witness, where applicable.

785 **4.8.7.**

786 Before informed consent may be obtained, the investigator, or a person designated by the
787 investigator, should provide the subject or the subject's legally acceptable representative ample time
788 and opportunity to inquire about details of the trial and to decide whether or not to participate in the

789 trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's
790 legally acceptable representative.

791 **4.8.8.**

792 Prior to a subject's participation in the trial, the written informed consent form should be signed and
793 personally dated by the subject or by the subject's legally acceptable representative, and by the
794 person who conducted the informed consent discussion.

795 **4.8.9.**

796 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial
797 witness should be present during the entire informed consent discussion. After the written informed
798 consent form and any other written information to be provided to subjects, is read and explained to
799 the subject or the subject's legally acceptable representative, and after the subject or the subject's
800 legally acceptable representative has orally consented to the subject's participation in the trial and, if
801 capable of doing so, has signed and personally dated the informed consent form, the witness should
802 sign and personally date the consent form. By signing the consent form, the witness attests that the
803 information in the consent form and any other written information was accurately explained to, and
804 apparently understood by, the subject or the subject's legally acceptable representative, and that
805 informed consent was freely given by the subject or the subject's legally acceptable representative.

806 **4.8.10.**

807 Both the informed consent discussion and the written informed consent form and any other written
808 information to be provided to subjects should include explanations of the following:

- 809 • That the trial involves research.
- 810 • The purpose of the trial.
- 811 • The trial treatment(s) and the probability for random assignment to each treatment.
- 812 • The trial procedures to be followed, including all invasive procedures.
- 813 • The subject's responsibilities.
- 814 • Those aspects of the trial that are experimental.
- 815 • The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an
816 embryo, fetus, or nursing infant.
- 817 • The reasonably expected benefits. When there is no intended clinical benefit to the subject,
818 the subject should be made aware of this.
- 819 • The alternative procedure(s) or course(s) of treatment that may be available to the
820 subject, and their important potential benefits and risks.
- 821 • The compensation and/or treatment available to the subject in the event of trial-related injury.
- 822 • The anticipated prorated payment, if any, to the subject for participating in the trial.
- 823 • The anticipated expenses, if any, to the subject for participating in the trial.

- 824 • That the subject's participation in the trial is voluntary and that the subject may refuse to
825 participate or withdraw from the trial, at any time, without penalty or loss of benefits to
826 which the subject is otherwise entitled.
- 827 • That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be
828 granted direct access to the subject's original medical records for verification of clinical trial
829 procedures and/or data, without violating the confidentiality of the subject, to the extent
830 permitted by the applicable laws and regulations and that, by signing a written informed
831 consent form, the subject or the subject's legally acceptable representative is authorizing such
832 access.
- 833 • That records identifying the subject will be kept confidential and, to the extent permitted by
834 the applicable laws and/or regulations, will not be made publicly available. If the results of the
835 trial are published, the subject's identity will remain confidential.
- 836 • That the subject or the subject's legally acceptable representative will be informed in a timely
837 manner if information becomes available that may be relevant to the subject's willingness to
838 continue participation in the trial.
- 839 • The person(s) to contact for further information regarding the trial and the rights of trial
840 subjects, and whom to contact in the event of trial-related injury.
- 841 • The foreseeable circumstances and/or reasons under which the subject's participation in the
842 trial may be terminated.
- 843 • The expected duration of the subject's participation in the trial. (t) The approximate number
844 of subjects involved in the trial.

845 **4.8.11.**

846 Prior to participation in the trial, the subject or the subject's legally acceptable representative should
847 receive a copy of the signed and dated written informed consent form and any other written
848 information provided to the subjects. During a subject's participation in the trial, the subject or the
849 subject's legally acceptable representative should receive a copy of the signed and dated
850 consent form updates and a copy of any amendments to the written information provided to
851 subjects.

852 **4.8.12.**

853 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the
854 trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with
855 severe dementia), the subject should be informed about the trial to the extent compatible with the
856 subject's understanding and, if capable, the subject should sign and personally date the written
857 informed consent.

858 **4.8.13.**

859 Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct
860 clinical benefit to the subject), should be conducted in subjects who personally give consent and who
861 sign and date the written informed consent form.

862 **4.8.14.**

863 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative
864 provided the following conditions are fulfilled:

- 865 • The objectives of the trial cannot be met by means of a trial in subjects who can give informed
866 consent personally.
- 867 • The foreseeable risks to the subjects are low.
- 868 • The negative impact on the subject's well-being is minimized and low. (d) The trial is not
869 prohibited by law.
- 870 • The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such
871 subjects, and the written approval/ favourable opinion covers this aspect.

872 Such trials, unless an exception is justified, should be conducted in patients having a disease or
873 condition for which the investigational product is intended. Subjects in these trials should be
874 particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

875 **4.8.15.**

876 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's
877 legally acceptable representative, if present, should be requested. When prior consent of the subject is
878 not possible, and the subject's legally acceptable representative is not available, enrolment of the
879 subject should require measures described in the protocol and/or elsewhere, with documented
880 approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject
881 and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally
882 acceptable representative should be informed about the trial as soon as possible and consent to
883 continue and other consent as appropriate (see 4.8.10) should be requested.

884 **4.9. Records and Reports**

885 **ADDENDUM**

886 **4.9.0.**

887 The investigator should maintain adequate and accurate source documents and trial records that
888 include all pertinent observations on each of the site's trial subjects. Source data should be
889 attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data
890 should be traceable, should not obscure the original entry and should be explained if necessary (e.g.
891 via an audit trail).

892 **4.9.1.**

893 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data
894 reported to the sponsor in the CRFs and in all required reports.

895 **4.9.2.**

896 Data reported on the CRF, that are derived from source documents, should be consistent with the
897 source documents or the discrepancies should be explained.

898 **4.9.3.**

899 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should
900 not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written
901 and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to
902 investigators and/or the investigators' designated representatives on making such corrections.
903 Sponsors should have written procedures to assure that changes or corrections in CRFs made by
904 sponsor's designated representatives are documented, are necessary, and are endorsed by the
905 investigator. The investigator should retain records of the changes and corrections.

906 **4.9.4.**

907 The investigator/institution should maintain the trial documents as specified in Essential Documents for
908 the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s).
909 The investigator/institution should take measures to prevent accidental or premature destruction of
910 these documents.

911 **4.9.5.**

912 Essential documents should be retained until at least 2 years after the last approval of a marketing
913 application in an ICH region and until there are no pending or contemplated marketing applications in
914 an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development
915 of the investigational product. These documents should be retained for a longer period however if
916 required by the applicable regulatory requirements or by an agreement with the sponsor. It is the
917 responsibility of the sponsor to inform the investigator/institution as to when these documents no
918 longer need to be retained (see 5.5.12).

919 **4.9.6.**

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

922 **4.9.7.**

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

925 **4.10. Progress Reports**

926 **4.10.1.**

927 The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more
928 frequently, if requested by the IRB/IEC.

929 **4.10.2.**

930 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and,
931 where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or
932 increasing the risk to subjects.

933 **4.11. Safety Reporting**

934 **4.11.1.**

935 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those
936 SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing
937 immediate reporting. The immediate reports should be followed promptly by detailed, written reports.
938 The immediate and follow-up reports should identify subjects by unique code numbers assigned to the
939 trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses.
940 The investigator should also comply with the applicable regulatory requirement(s) related to the
941 reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the
942 IRB/IEC.

943 **4.11.2.**

944 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety
945 evaluations should be reported to the sponsor according to the reporting requirements and within the
946 time periods specified by the sponsor in the protocol.

947 **4.11.3.**

948 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional
949 requested information (e.g., autopsy reports and terminal medical reports).

950 **4.12. Premature Termination or Suspension of a Trial**

951 If the trial is prematurely terminated or suspended for any reason, the investigator/institution should
952 promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects,
953 and, where required by the applicable regulatory requirement(s), should inform the regulatory
954 authority(ies). In addition:

955 **4.12.1.**

956 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the
957 investigator should inform the institution where applicable, and the investigator/institution should
958 promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a
959 detailed written explanation of the termination or suspension.

960 **4.12.2.**

961 If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform
962 the institution where applicable and the investigator/institution should promptly inform the IRB/IEC
963 and provide the IRB/IEC a detailed written explanation of the termination or suspension.

964 **4.12.3.**

965 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9),
966 the investigator should inform the institution where applicable and the investigator/institution should
967 promptly notify the sponsor and provide the sponsor with a detailed written explanation of the
968 termination or suspension.

969 **4.13. Final Report(s) by Investigator**

970 Upon completion of the trial, the investigator, where applicable, should inform the institution; the
971 investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the
972 regulatory authority(ies) with any reports required.

973

974 **5. Sponsor**

975 **ADDENDUM**

976 **5.0. Quality management**

977 The sponsor should implement a system to manage quality throughout the design, conduct, recording,
978 evaluation, reporting and archiving of clinical trials.

979 Sponsors should focus on trial activities essential to ensuring human subject protection and the
980 reliability of trial results. Quality management includes the efficient design of clinical trial protocols,
981 data collection tools and procedures, and the collection of information that is essential to decision
982 making.

983 The methods used to assure and control the quality of the trial should be proportionate to the risks
984 inherent in the trial and the importance of the information collected. The sponsor should ensure that all
985 aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures and
986 data collection. Protocols, case report forms, and other operational documents should be clear, concise
987 and consistent.

988 The quality management system should use a risk-based approach as described below.

989 **5.0.1. Critical process and data identification**

990 During protocol development, the sponsor should identify those processes and data that are critical to
991 assure human subject protection and the reliability of study results.

992 **5.0.2. Risk identification**

993 Risks to critical study processes and data should be identified. Risks should be considered at both the
994 system level (e.g. facilities, standard operating procedures, computerized systems, personnel,
995 vendors) and clinical trial level (e.g. investigational product, trial design, data collection and
996 recording).

997 **5.0.3. Risk evaluation**

998 The identified risks should be evaluated by considering:

- 999 • The likelihood of errors occurring, given existing risk controls.
- 1000 • The impact of such errors on human subject protection and data integrity.
- 1001 • The extent to which such errors would be detectable.

1002 **5.0.4. Risk control**

1003 The sponsor should identify those risks that should be reduced (through mitigating actions) and/or can
1004 be accepted. Risk mitigation activities may be incorporated in protocol design and implementation,
1005 monitoring plans, agreements between parties defining roles and responsibilities, systematic
1006 safeguards to ensure adherence to standard operating procedures, and training in processes and
1007 procedures.

1008 Predefined quality tolerance limits should be established, taking into consideration the medical and
1009 statistical characteristics of the variables as well as the statistical design of the trial, to identify
1010 systematic issues that can impact subject safety or data integrity. Detection of deviations from the
1011 predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

1012 **5.0.5. Risk communication**

1013 The quality management activities should be documented and communicated to stakeholders to
1014 facilitate risk review and continual improvement during clinical trial execution.

1015 **5.0.6. Risk review**

1016 The sponsor should periodically review risk control measures to ascertain whether the implemented
1017 quality management activities remain effective and relevant, taking into account emerging knowledge
1018 and experience.

1019 **5.0.7. Risk reporting**

1020 The sponsor should describe the quality management approach implemented in the trial and
1021 summarize important deviations from the predefined quality tolerance limits in the clinical study report
1022 (ICH E3, Section 9.6 Data Quality Assurance).

1023 **5.1. Quality assurance and quality control**

1024 **5.1.1.**

1025 The sponsor is responsible for implementing and maintaining quality assurance and quality
1026 control systems with written SOPs to ensure that trials are conducted and data are generated,
1027 documented (recorded), and reported in compliance with the protocol, GCP, and the
1028 applicable regulatory requirement(s).

1029 **5.1.2.**

1030 The sponsor is responsible for securing agreement from all involved parties to ensure direct access
1031 (see 1.21) to all trial related sites, source data/documents, and reports for the purpose of monitoring
1032 and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

1033 **5.1.3.**

1034 Quality control should be applied to each stage of data handling to ensure that all data are reliable and
1035 have been processed correctly.

1036 **5.1.4.**

1037 Agreements, made by the sponsor with the investigator/institution and any other parties involved with
1038 the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

1039 **5.2. Contract Research Organization (CRO)**

1040 **5.2.1.**

1041 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but
1042 the ultimate responsibility for the quality and integrity of the trial data always resides with the
1043 sponsor. The CRO should implement quality assurance and quality control.

1044 **ADDENDUM**

1045 The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf.

1046 **5.2.2.**

1047 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in
1048 writing.

1049 **ADDENDUM**

1050 The sponsor should document approval of any subcontracting of trial-related duties and functions by a
1051 CRO.

1052 **5.2.3.**

1053 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are
1054 retained by the sponsor.

1055 **5.2.4.**

1056 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed
1057 the trial related duties and functions of a sponsor.

1058 **5.3. Medical expertise**

1059 The sponsor should designate appropriately qualified medical personnel who will be readily available
1060 to advise on trial related medical questions or problems. If necessary, outside consultant(s) may
1061 be appointed for this purpose.

1062 **5.4. Trial design**

1063 **5.4.1.**

1064 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and
1065 physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and
1066 CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

1067 **5.4.2.**

1068 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for
1069 Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design,
1070 protocol and conduct.

1071 **5.5. Trial management, data handling, and record keeping**

1072 **5.5.1.**

1073 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the
1074 trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial
1075 reports.

1076 **5.5.2.**

1077 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to
1078 assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at
1079 intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC
1080 should have written operating procedures and 8.1 of all its meetings.

1081 **5.5.3.**

1082 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor
1083 should:

- 1084 • Ensure and document that the electronic data processing system(s) conforms to the sponsor's
1085 established requirements for completeness, accuracy, reliability, and consistent intended
1086 performance (i.e. validation).
- 1087 • Maintains SOPs for using these systems.

1088 **ADDENDUM**

1089 The SOPs should cover system setup, installation and use. The SOPs should describe system
1090 validation and functionality testing, data collection and handling, system maintenance, system
1091 security measures, change control, data backup, recovery, contingency planning and
1092 decommissioning. The responsibilities of the sponsor, investigator and other parties with
1093 respect to the use of these computerized systems should be clear, and the users should be
1094 provided with training in the use of the systems.

- 1095 • Ensure that the systems are designed to permit data changes in such a way that the data
1096 changes are documented and that there is no deletion of entered data (i.e. maintain an audit
1097 trail, data trail, edit trail).
- 1098 • Maintain a security system that prevents unauthorized access to the data. (e) Maintain a list of
1099 the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).
- 1100 • Maintain adequate backup of the data.
- 1101 • Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

1102 **ADDENDUM**

- 1103 • Ensure the integrity of the data including any data that describe the context, content and
1104 structure of the data. This is particularly important when making changes to the computerized
1105 systems, such as software upgrades or migration of data.

1106 **5.5.4.**

1107 If data are transformed during processing, it should always be possible to compare the original data
1108 and observations with the processed data.

1109 **5.5.5.**

1110 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification
1111 of all the data reported for each subject.

1112 **5.5.6.**

1113 The sponsor, or other owners of the data, should retain all of the sponsor- specific essential
1114 documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

1115 **5.5.7.**

1116 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable
1117 regulatory requirement(s) of the country(ies) where the product is approved, and/or where the
1118 sponsor intends to apply for approval(s).

1119 **5.5.8.**

1120 If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all
1121 indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-
1122 specific essential documents for at least 2 years after formal discontinuation or in conformance with
1123 the applicable regulatory requirement(s).

1124 **5.5.9.**

1125 If the sponsor discontinues the clinical development of an investigational product, the sponsor should
1126 notify all the trial investigators/institutions and all the regulatory authorities.

1127 **5.5.10.**

1128 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required
1129 by the applicable regulatory requirement(s).

1130 **5.5.11.**

1131 The sponsor specific essential documents should be retained until at least 2 years after the last
1132 approval of a marketing application in an ICH region and until there are no pending or contemplated
1133 marketing applications in an ICH region or at least 2 years have elapsed since the formal
1134 discontinuation of clinical development of the investigational product. These documents should be
1135 retained for a longer period however if required by the applicable regulatory requirement(s) or if
1136 needed by the sponsor.

1137 **5.5.12.**

1138 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention
1139 and should notify the investigator(s)/institution(s) in writing when the trial related records are no
1140 longer needed.

1141 **5.6. Investigator selection**

1142 **5.6.1.**

1143 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be
1144 qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly
1145 conduct the trial for which the investigator is selected. If organization of a coordinating committee
1146 and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their
1147 organization and/or selection are the sponsor's responsibility.

1148 **5.6.2.**

1149 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should
1150 provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure,
1151 and should provide sufficient time for the investigator/institution to review the protocol and the
1152 information provided.

1153 **5.6.3.**

1154 The sponsor should obtain the investigator's/institution's agreement:

- 1155 • to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see
1156 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion
1157 by the IRB/IEC (see 4.5.1);
- 1158 • to comply with procedures for data recording/reporting;
- 1159 • to permit monitoring, auditing and inspection (see 4.1.4) and
- 1160 • to retain the trial related essential documents until the sponsor informs the
1161 investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12). The
1162 sponsor and the investigator/institution should sign the protocol, or an alternative document,
1163 to confirm this agreement.

1164 **5.7. Allocation of responsibilities**

1165 Prior to initiating a trial, the sponsor should define, establish, and allocate all trial- related duties and
1166 functions.

1167 **5.8. Compensation to subjects and investigators**

1168 **5.8.1.**

1169 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should
1170 indemnify (legal and financial coverage) the investigator/the institution against claims arising from the
1171 trial, except for claims that arise from malpractice and/or negligence.

1172 **5.8.2.**

1173 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the
1174 event of trial-related injuries in accordance with the applicable regulatory requirement(s).

1175 **5.8.3.**

1176 When trial subjects receive compensation, the method and manner of compensation should comply
1177 with applicable regulatory requirement(s).

1178 **5.9. Financing**

1179 The financial aspects of the trial should be documented in an agreement between the sponsor and the
1180 investigator/institution.

1181 **5.10. Notification/submission to regulatory authority(ies)**

1182 Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the
1183 applicable regulatory requirement(s)) should submit any required application(s) to the appropriate
1184 authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory
1185 requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain
1186 sufficient information to identify the protocol.

1187 **5.11. Confirmation of review by IRB/IEC**

1188 **5.11.1.**

1189 **The sponsor should obtain from the investigator/institution:**

- 1190
- The name and address of the investigator's/institution's IRB/IEC.
 - A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.
 - Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.
- 1191
- 1192
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1198 **5.11.2.**

1199 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial,
1200 such as modification(s) of the protocol, written informed consent form and any other written
1201 information to be provided to subjects, and/or other procedures, the sponsor should obtain from
1202 the investigator/institution a copy of the modification(s) made and the date approval/favourable
1203 opinion was given by the IRB/IEC.

1204 **5.11.3.**

1205 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC
1206 reapprovals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of
1207 approval/favourable opinion.

1208 **5.12. Information on investigational product(s)**

1209 **5.12.1.**

1210 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical
1211 studies and/or clinical trials are available to support human exposure by the route, at the dosages, for
1212 the duration, and in the trial population to be studied.

1213 **5.12.2.**

1214 The sponsor should update the Investigator's Brochure as significant new information becomes
1215 available (see 7. Investigator's Brochure).

1216 **5.13. Manufacturing, packaging, labelling, and coding investigational**
1217 **product(s)**

1218 **5.13.1.**

1219 The sponsor should ensure that the investigational product(s) (including active comparator(s) and
1220 placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is
1221 manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that
1222 protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory
1223 requirement(s).

1224 **5.13.2.**

1225 The sponsor should determine, for the investigational product(s), acceptable storage temperatures,
1226 storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and
1227 devices for product infusion, if any. The sponsor should inform all involved parties (e.g.
1228 monitors, investigators, pharmacists, storage managers) of these determinations.

1229 **5.13.3.**

1230 The investigational product(s) should be packaged to prevent contamination and unacceptable
1231 deterioration during transport and storage.

1232 **5.13.4.**

1233 In blinded trials, the coding system for the investigational product(s) should include a mechanism that
1234 permits rapid identification of the product(s) in case of a medical emergency, but does not permit
1235 undetectable breaks of the blinding.

1236 **5.13.5.**

1237 If significant formulation changes are made in the investigational or comparator product(s) during the
1238 course of clinical development, the results of any additional studies of the formulated product(s) (e.g.
1239 stability, dissolution rate, bioavailability) needed to assess whether these changes would
1240 significantly alter the pharmacokinetic profile of the product should be available prior to the use of the
1241 new formulation in clinical trials.

1242 **5.14. Supplying and handling investigational product(s)**

1243 **5.14.1.**

1244 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational
1245 product(s).

1246 **5.14.2.**

1247 The sponsor should not supply an investigator/institution with the investigational product(s) until the
1248 sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and
1249 regulatory authority(ies)).

1250 **5.14.3.**

1251 The sponsor should ensure that written procedures include instructions that the investigator/institution
1252 should follow for the handling and storage of investigational product(s) for the trial and documentation
1253 thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing,
1254 retrieval of unused product from subjects, and return of unused investigational product(s) to the
1255 sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable
1256 regulatory requirement(s)).

1257 **5.14.4.**

1258 The sponsor should:

- 1259 • Ensure timely delivery of investigational product(s) to the investigator(s).
- 1260 • Maintain records that document shipment, receipt, disposition, return, and destruction of the
1261 investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).
- 1262 • Maintain a system for retrieving investigational products and documenting this retrieval (e.g.
1263 for deficient product recall, reclaim after trial completion, expired product reclaim).
- 1264 • Maintain a system for the disposition of unused investigational product(s) and for the
1265 documentation of this disposition.

1266 **5.14.5.**

1267 The sponsor should:

- 1268 • Take steps to ensure that the investigational product(s) are stable over the period of use.
- 1269 • Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm
1270 specifications, should this become necessary, and maintain records of batch sample analyses

1271 and characteristics. To the extent stability permits, samples should be retained either until the
1272 analyses of the trial data are complete or as required by the applicable regulatory
1273 requirement(s), whichever represents the longer retention period.

1274 **5.15. Record access**

1275 **5.15.1.**

1276 The sponsor should ensure that it is specified in the protocol or other written agreement that the
1277 investigator(s)/institution(s) provide direct access to source data/documents for trial-related
1278 monitoring, audits, IRB/IEC review, and regulatory inspection.

1279 **5.15.2.**

1280 The sponsor should verify that each subject has consented, in writing, to direct access to his/her
1281 original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

1282 **5.16. Safety information**

1283 **5.16.1.**

1284 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

1285 **5.16.2.**

1286 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory
1287 authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the
1288 trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

1289 **5.17. Adverse drug reaction reporting**

1290 **5.17.1.**

1291 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the
1292 IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions
1293 (ADRs) that are both serious and unexpected.

1294 **5.17.2.**

1295 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH
1296 Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

1297 **5.17.3.**

1298 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as
1299 required by applicable regulatory requirement(s).

1300 **5.18. Monitoring**

1301 **5.18.1. Purpose**

1302 The purposes of trial monitoring are to verify that:

- 1303 • The rights and well-being of human subjects are protected.
- 1304 • The reported trial data are accurate, complete, and verifiable from source documents.
- 1305 • The conduct of the trial is in compliance with the currently approved protocol/amendment(s),
1306 with GCP, and with the applicable regulatory requirement(s).

1307 **5.18.2. Selection and qualifications of monitors**

- 1308 • Monitors should be appointed by the sponsor.
- 1309 • Monitors should be appropriately trained, and should have the scientific and/or clinical
1310 knowledge needed to monitor the trial adequately. A monitor's qualifications should be
1311 documented.
- 1312 • Monitors should be thoroughly familiar with the investigational product(s), the protocol, written
1313 informed consent form and any other written information to be provided to subjects, the
1314 sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

1315 **5.18.3. Extent and nature of monitoring**

1316 The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the
1317 appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring
1318 should be based on considerations such as the objective, purpose, design, complexity, blinding, size,
1319 and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after
1320 the trial; however in exceptional circumstances the sponsor may determine that central monitoring in
1321 conjunction with procedures such as investigators' training and meetings, and extensive written
1322 guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled
1323 sampling may be an acceptable method for selecting the data to be verified.

1324 **ADDENDUM**

1325 The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials.
1326 The flexibility in the extent and nature of monitoring described in this section is intended to permit
1327 varied approaches that improve the effectiveness and efficiency of monitoring. A combination of on-
1328 site and centralized monitoring activities may be appropriate. The sponsor should document the
1329 rationale for the chosen monitoring strategy (e.g. in the monitoring plan).

1330 *On-site monitoring* is performed at the sites at which the clinical trial is being conducted.

1331 *Centralized monitoring* is a remote evaluation of ongoing and/or cumulative data collected from trial
1332 sites, in a timely manner. Centralized monitoring processes provide additional monitoring capabilities
1333 that can complement and reduce the extent and/or frequency of on-site monitoring by such methods
1334 as:

- 1335 • Routine review of submitted data.
- 1336 • Identification of missing data, inconsistent data, data outliers or unexpected lack of variability
1337 and protocol deviations that may be indicative of systematic or significant errors in data

1338 collection and reporting at a site or across sites, or may be indicative of potential data
1339 manipulation or data integrity problems.

1340 • Using statistical analyses to identify data trends such as the range and consistency of data
1341 within and across sites.

1342 • Analyzing site characteristics and performance metrics.

1343 • Selection of sites and/or processes for targeted on-site monitoring.

1344 **5.18.4. Monitor's responsibilities**

1345 The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted
1346 and documented properly by carrying out the following activities when relevant and necessary to the
1347 trial and the trial site:

1348 • Acting as the main line of communication between the sponsor and the investigator.

1349 • Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6)
1350 and remain adequate throughout the trial period, that facilities, including laboratories,
1351 equipment, and staff, are adequate to safely and properly conduct the trial and remain
1352 adequate throughout the trial period.

1353 • Verifying, for the investigational product(s):

1354 ○ That storage times and conditions are acceptable, and that supplies are sufficient
1355 throughout the trial.

1356 ○ That the investigational product(s) are supplied only to subjects who are eligible to
1357 receive it and at the protocol specified dose(s).

1358 ○ That subjects are provided with necessary instruction on properly using,
1359 handling, storing, and returning the investigational product(s).

1360 ○ That the receipt, use, and return of the investigational product(s) at the trial sites are
1361 controlled and documented adequately.

1362 ○ That the disposition of unused investigational product(s) at the trial sites complies with
1363 applicable regulatory requirement(s) and is in accordance with the sponsor.

1364 • Verifying that the investigator follows the approved protocol and all approved amendment(s), if
1365 any.

1366 • Verifying that written informed consent was obtained before each subject's participation in the
1367 trial.

1368 • Ensuring that the investigator receives the current Investigator's Brochure, all documents,
1369 and all trial supplies needed to conduct the trial properly and to comply with the applicable
1370 regulatory requirement(s).

1371 • Ensuring that the investigator and the investigator's trial staff are adequately informed about
1372 the trial.

1373 • Verifying that the investigator and the investigator's trial staff are performing the specified trial
1374 functions, in accordance with the protocol and any other written agreement between the
1375 sponsor and the investigator/institution, and have not delegated these functions to
1376 unauthorized individuals.

- 1377 • Verifying that the investigator is enrolling only eligible subjects. (j) Reporting the subject
1378 recruitment rate.
- 1379 • Verifying that source documents and other trial records are accurate, complete, kept up-to-
1380 date and maintained.
- 1381 • Verifying that the investigator provides all the required reports, notifications,
1382 applications, and submissions, and that these documents are accurate, complete, timely,
1383 legible, dated, and identify the trial.
- 1384 • Checking the accuracy and completeness of the CRF entries, source documents and other trial-
1385 related records against each other. The monitor specifically should verify that:
 - 1386 ○ The data required by the protocol are reported accurately on the CRFs and are
1387 consistent with the source documents.
 - 1388 ○ Any dose and/or therapy modifications are well documented for each of the trial
1389 subjects.
 - 1390 ○ Adverse events, concomitant medications and intercurrent illnesses are reported in
1391 accordance with the protocol on the CRFs.
 - 1392 ○ Visits that the subjects fail to make, tests that are not conducted, and examinations
1393 that are not performed are clearly reported as such on the CRFs.
 - 1394 ○ All withdrawals and dropouts of enrolled subjects from the trial are reported and
1395 explained on the CRFs.
- 1396 • Informing the investigator of any CRF entry error, omission, or illegibility.
- 1397 The monitor should ensure that appropriate corrections, additions, or deletions are made,
1398 dated, explained (if necessary), and initialled by the investigator or by a member of the
1399 investigator's trial staff who is authorized to initial CRF changes for the investigator. This
1400 authorization should be documented.
- 1401 • Determining whether all adverse events (AEs) are appropriately reported within the time
1402 periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory
1403 requirement(s).
- 1404 • Determining whether the investigator is maintaining the essential documents (see 8. Essential
1405 Documents for the Conduct of a Clinical Trial).
- 1406 • Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory
1407 requirements to the investigator and taking appropriate action designed to prevent
1408 recurrence of the detected deviations.

1409 **5.18.5. Monitoring procedures**

1410 The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that
1411 are specified by the sponsor for monitoring a specific trial.

1412 **5.18.6. Monitoring report**

- 1413 • The monitor should submit a written report to the sponsor after each trial- site visit or trial-
1414 related communication.

- 1415 • Reports should include the date, site, name of the monitor, and name of the investigator or
1416 other individual(s) contacted.
- 1417 • Reports should include a summary of what the monitor reviewed and the monitor's statements
1418 concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken
1419 or to be taken and/or actions recommended to secure compliance.
- 1420 • The review and follow-up of the monitoring report with the sponsor should be documented by
1421 the sponsor's designated representative.

1422 **ADDENDUM**

- 1423 • Monitoring results should be provided to the sponsor (including appropriate management and
1424 staff responsible for trial and site oversight) in a timely manner for review and follow up as
1425 indicated. Results of monitoring activities should be documented in sufficient detail to allow
1426 verification of compliance with the monitoring plan.

1427 **ADDENDUM**

1428 **5.18.7. Monitoring plan**

1429 The sponsor should develop a monitoring plan that is tailored to the specific human subject protection
1430 and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring
1431 responsibilities of all the parties involved, the various monitoring methods to be used and the rationale
1432 for their use. The plan should also emphasize the monitoring of critical data and processes. Particular
1433 attention should be given to those aspects that are not routine clinical practice and that require
1434 additional training. The monitoring plan should reference the applicable policies and procedures.

1435 **5.19. Audit**

1436 If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

1437 **5.19.1. Purpose**

1438 The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or
1439 quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs,
1440 GCP, and the applicable regulatory requirements.

1441 **5.19.2. Selection and qualification of auditors**

- 1442 • The sponsor should appoint individuals, who are independent of the clinical trials/systems, to
1443 conduct audits.
- 1444 • The sponsor should ensure that the auditors are qualified by training and experience to
1445 conduct audits properly. An auditor's qualifications should be documented.

1446 **5.19.3. Auditing procedures**

- 1447 • The sponsor should ensure that the auditing of clinical trials/systems is conducted in
1448 accordance with the sponsor's written procedures on what to audit, how to audit, the frequency
1449 of audits, and the form and content of audit reports.

- 1450 • The sponsor's audit plan and procedures for a trial audit should be guided by the importance of
1451 the trial to submissions to regulatory authorities, the number of subjects in the trial, the type
1452 and complexity of the trial, the level of risks to the trial subjects, and any identified
1453 problem(s).
- 1454 • The observations and findings of the auditor(s) should be documented.
- 1455 • To preserve the independence and value of the audit function, the regulatory authority(ies)
1456 should not routinely request the audit reports. Regulatory authority(ies) may seek access to an
1457 audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in
1458 the course of legal proceedings.
- 1459 • When required by applicable law or regulation, the sponsor should provide an audit certificate.

1460 **5.20. Noncompliance**

1461 **5.20.1.**

1462 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an
1463 investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the
1464 sponsor to secure compliance.

1465 **ADDENDUM**

1466 When significant noncompliance is discovered, the sponsor should perform a root cause analysis and
1467 implement appropriate corrective and preventive actions. If required by applicable law or regulation
1468 the sponsor should inform the regulatory authority(ies) when the noncompliance is a serious breach of
1469 the trial protocol or GCP.

1470 **5.20.2.**

1471 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an
1472 investigator/institution, the sponsor should terminate the investigator's/institution's participation in the
1473 trial. When an investigator's/institution's participation is terminated because of
1474 noncompliance, the sponsor should notify promptly the regulatory authority(ies).

1475 **5.21. Premature termination or suspension of a trial**

1476 If a trial is prematurely terminated or suspended, the sponsor should promptly inform the
1477 investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the
1478 reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and
1479 provided the reason(s) for the termination or suspension by the sponsor or by the investigator /
1480 institution, as specified by the applicable regulatory requirement(s).

1481 **5.22. Clinical trial/study reports**

1482 Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical
1483 trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable
1484 regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing
1485 applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study
1486 Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that
1487 abbreviated study reports may be acceptable in certain cases.)

1488 **5.23. Multicentre trials**

1489 For multicentre trials, the sponsor should ensure that:

1490 **5.23.1.**

1491 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if
1492 required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

1493 **5.23.2.**

1494 The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators
1495 who are collecting additional data, supplemental CRFs should also be provided that are designed to
1496 capture the additional data.

1497 **5.23.3.**

1498 The responsibilities of coordinating investigator(s) and the other participating investigators are
1499 documented prior to the start of the trial.

1500 **5.23.4.**

1501 All investigators are given instructions on following the protocol, on complying with a uniform set of
1502 standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

1503 **5.23.5.**

1504 Communication between investigators is facilitated.

1505

1506 **6. Clinical trial protocol and protocol amendment(s)**

1507 The contents of a trial protocol should generally include the following topics. However, site specific
1508 information may be provided on separate protocol page(s), or addressed in a separate agreement, and
1509 some of the information listed below may be contained in other protocol referenced documents, such
1510 as an Investigator's Brochure.

1511 **6.1. General Information**

1512 **6.1.1.**

1513 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the
1514 amendment number(s) and date(s).

1515 **6.1.2.**

1516 Name and address of the sponsor and monitor (if other than the sponsor).

1517 **6.1.3.**

1518 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the
1519 sponsor.

1520 **6.1.4.**

1521 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when
1522 appropriate) for the trial.

1523 **6.1.5.**

1524 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address
1525 and telephone number(s) of the trial site(s).

1526 **6.1.6.**

1527 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who
1528 is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

1529 **6.1.7.**

1530 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical
1531 department(s) and/or institutions involved in the trial.

1532 **6.2. Background Information**

1533 **6.2.1.**

1534 Name and description of the investigational product(s).

1535 **6.2.2.**

1536 A summary of findings from nonclinical studies that potentially have clinical significance and from
1537 clinical trials that are relevant to the trial.

1538 **6.2.3.**

1539 Summary of the known and potential risks and benefits, if any, to human subjects.

1540 **6.2.4.**

1541 Description of and justification for the route of administration, dosage, dosage regimen, and treatment
1542 period(s).

1543 **6.2.5.**

1544 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable
1545 regulatory requirement(s).

1546 **6.2.6.**

1547 Description of the population to be studied.

1548 **6.2.7.**

1549 References to literature and data that are relevant to the trial, and that provide background for the
1550 trial.

1551 **6.3. Trial objectives and purpose**

1552 A detailed description of the objectives and the purpose of the trial.

1553 **6.4. Trial design**

1554 The scientific integrity of the trial and the credibility of the data from the trial depend substantially on
1555 the trial design. A description of the trial design, should include:

1556 **6.4.1.**

1557 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured
1558 during the trial.

1559 **6.4.2.**

1560 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel
1561 design) and a schematic diagram of trial design, procedures and stages.

1562 **6.4.3.**

1563 A description of the measures taken to minimize/avoid bias, including:

- 1564
 - Randomization.

1565 • Blinding.

1566 **6.4.4.**

1567 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational
1568 product(s). Also include a description of the dosage form, packaging, and labelling of the
1569 investigational product(s).

1570 **6.4.5.**

1571 The expected duration of subject participation, and a description of the sequence and duration of all
1572 trial periods, including follow-up, if any.

1573 **6.4.6.**

1574 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial
1575 and entire trial.

1576 **6.4.7.**

1577 Accountability procedures for the investigational product(s), including the placebo(s) and
1578 comparator(s), if any.

1579 **6.4.8.**

1580 Maintenance of trial treatment randomization codes and procedures for breaking codes.

1581 **6.4.9.**

1582 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic
1583 record of data), and to be considered to be source data.

1584 **6.5. Selection and withdrawal of subjects**

1585 **6.5.1.**

1586 Subject inclusion criteria.

1587 **6.5.2.**

1588 Subject exclusion criteria.

1589 **6.5.3.**

1590 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and
1591 procedures specifying:

- 1592 • When and how to withdraw subjects from the trial/ investigational product treatment.
- 1593 • The type and timing of the data to be collected for withdrawn subjects.
- 1594 • Whether and how subjects are to be replaced.

- 1595 • The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

1596 **6.6. Treatment of Subjects**

1597 **6.6.1.**

1598 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s),
1599 the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including
1600 the follow-up period(s) for subjects for each investigational product treatment/trial treatment
1601 group/arm of the trial.

1602 **6.6.2.**

1603 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or
1604 during the trial.

1605 **6.6.3.**

1606 Procedures for monitoring subject compliance.

1607 **6.7. Assessment of Efficacy**

1608 **6.7.1.**

1609 Specification of the efficacy parameters.

1610 **6.7.2.**

1611 Methods and timing for assessing, recording, and analysing of efficacy parameters.

1612 **6.8. Assessment of Safety**

1613 **6.8.1.**

1614 Specification of safety parameters.

1615 **6.8.2.**

1616 The methods and timing for assessing, recording, and analysing safety parameters.

1617 **6.8.3.**

1618 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent
1619 illnesses.

1620 **6.8.4.**

1621 The type and duration of the follow-up of subjects after adverse events.

1622

1623 **6.9. Statistics**

1624 **6.9.1.**

1625 A description of the statistical methods to be employed, including timing of any planned interim
1626 analysis(es).

1627 **6.9.2.**

1628 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects
1629 projected for each trial site should be specified. Reason for choice of sample size, including reflections
1630 on (or calculations of) the power of the trial and clinical justification.

1631 **6.9.3.**

1632 The level of significance to be used.

1633 **6.9.4.**

1634 Criteria for the termination of the trial.

1635 **6.9.5.**

1636 Procedure for accounting for missing, unused, and spurious data.

1637 **6.9.6.**

1638 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the
1639 original statistical plan should be described and justified in protocol and/or in the final report, as
1640 appropriate).

1641 **6.9.7.**

1642 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed
1643 subjects, all eligible subjects, evaluable subjects).

1644 **6.10. Direct access to source data/documents**

1645 The sponsor should ensure that it is specified in the protocol or other written agreement that the
1646 investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory
1647 inspection(s), providing direct access to source data/documents.

1648 **6.11. Quality control and quality assurance**

1649 **6.12. Ethics**

1650 Description of ethical considerations relating to the trial.

1651 **6.13. Data handling and record keeping**

1652 **6.14. Financing and insurance**

1653 Financing and insurance if not addressed in a separate agreement.

1654 **6.15. Publication policy**

1655 Publication policy, if not addressed in a separate agreement.

1656 **6.16. Supplements**

1657 (NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant
1658 information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

1659

1660 **7. Investigator's brochure**

1661 **7.1. Introduction**

1662 The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the
1663 investigational product(s) that are relevant to the study of the product(s) in human subjects. Its
1664 purpose is to provide the investigators and others involved in the trial with the information to facilitate
1665 their understanding of the rationale for, and their compliance with, many key features of the protocol,
1666 such as the dose, dose frequency/interval, methods of administration: and safety monitoring
1667 procedures. The IB also provides insight to support the clinical management of the study subjects
1668 during the course of the clinical trial. The information should be presented in a concise, simple,
1669 objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to
1670 understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the
1671 proposed trial. For this reason, a medically qualified person should generally participate in the editing
1672 of an IB, but the contents of the IB should be approved by the disciplines that generated the described
1673 data.

1674 This guideline delineates the minimum information that should be included in an IB and provides
1675 suggestions for its layout. It is expected that the type and extent of information available will vary with
1676 the stage of development of the investigational product. If the investigational product is marketed and
1677 its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary.
1678 Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or
1679 labelling may be an appropriate alternative, provided that it includes current, comprehensive, and
1680 detailed information on all aspects of the investigational product that might be of importance to the
1681 investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB
1682 specific to that new use should be prepared. The IB should be reviewed at least annually and revised
1683 as necessary in compliance with a sponsor's written procedures. More frequent revision may be
1684 appropriate depending on the stage of development and the generation of relevant new information.
1685 However, in accordance with Good Clinical Practice, relevant new information may be so important that
1686 it should be communicated to the investigators, and possibly to the Institutional Review Boards
1687 (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a
1688 revised IB.

1689 Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the
1690 investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible
1691 IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine
1692 whether a brochure is available from the commercial manufacturer. If the investigational product is
1693 provided by the sponsor-investigator, then he or she should provide the necessary information to the
1694 trial personnel. In cases where preparation of a formal IB is impractical, the sponsor- investigator
1695 should provide, as a substitute, an expanded background information section in the trial protocol that
1696 contains the minimum current information described in this guideline.

1697 **7.2. General considerations**

1698 The IB should include:

1699 **7.2.1. Title page**

1700 This should provide the sponsor's name, the identity of each investigational product (i.e., research
1701 number, chemical or approved generic name, and trade name(s) where legally permissible and desired

1702 by the sponsor), and the release date. It is also suggested that an edition number, and a reference to
1703 the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

1704 **7.2.2. Confidentiality statement**

1705 The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a
1706 confidential document for the sole information and use of the investigator's team and the IRB/IEC.

1707 **7.3. Contents of the investigator's brochure**

1708 The IB should contain the following sections, each with literature references where appropriate:

1709 **7.3.1. Table of contents**

1710 An example of the Table of Contents is given in Appendix 2

1711 **7.3.2. Summary**

1712 A brief summary (preferably not exceeding two pages) should be given, highlighting the significant
1713 physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and
1714 clinical information available that is relevant to the stage of clinical development of the investigational
1715 product.

1716 **7.3.3. Introduction**

1717 A brief introductory statement should be provided that contains the chemical name (and generic and
1718 trade name(s) when approved) of the investigational product(s), all active ingredients, the
1719 investigational product (s) pharmacological class and its expected position within this class (e.g.
1720 advantages), the rationale for performing research with the investigational product(s), and the
1721 anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement
1722 should provide the general approach to be followed in evaluating the investigational product.

1723 **7.3.4. Physical, chemical, and pharmaceutical properties and formulation**

1724 A description should be provided of the investigational product substance(s) (including the chemical
1725 and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical,
1726 and pharmaceutical properties.

1727 To permit appropriate safety measures to be taken in the course of the trial, a description of the
1728 formulation(s) to be used, including excipients, should be provided and justified if clinically relevant.
1729 Instructions for the storage and handling of the dosage form(s) should also be given.

1730 Any structural similarities to other known compounds should be mentioned.

1731 **7.3.5. Nonclinical studies**

1732 Introduction:

1733 The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational
1734 product metabolism studies should be provided in summary form. This summary should address the
1735 methodology used, the results, and a discussion of the relevance of the findings to the investigated
1736 therapeutic and the possible unfavourable and unintended effects in humans.

- 1737 • The information provided may include the following, as appropriate, if known/available:
- 1738 • Species tested
- 1739 • Number and sex of animals in each group
- 1740 • Unit dose (e.g., milligram/kilogram (mg/kg))
- 1741 • Dose interval
- 1742 • Route of administration
- 1743 • Duration of dosing
- 1744 • Information on systemic distribution
- 1745 • Duration of post-exposure follow-up
- 1746 • Results, including the following aspects:
 - 1747 ○ Nature and frequency of pharmacological or toxic effects
 - 1748 ○ Severity or intensity of pharmacological or toxic effects
 - 1749 ○ Time to onset of effects
 - 1750 ○ Reversibility of effects
 - 1751 ○ Duration of effects
 - 1752 ○ Dose response

1753 Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

1754 The following sections should discuss the most important findings from the studies, including the dose
1755 response of observed effects, the relevance to humans, and any aspects to be studied in humans. If
1756 applicable, the effective and nontoxic dose findings in the same animal species should be compared
1757 (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed
1758 human dosing should be addressed. Whenever possible, comparisons should be made in terms of
1759 blood/tissue levels rather than on a mg/kg basis.

1760 **7.3.5.1. Nonclinical pharmacology**

1761 A summary of the pharmacological aspects of the investigational product and, where appropriate, its
1762 significant metabolites studied in animals, should be included. Such a summary should incorporate
1763 studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and
1764 specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions
1765 other than the intended therapeutic effect(s)).

1766 **7.3.5.2. Pharmacokinetics and product metabolism in animals**

1767 A summary of the pharmacokinetics and biological transformation and disposition of the investigational
1768 product in all species studied should be given. The discussion of the findings should address the
1769 absorption and the local and systemic bioavailability of the investigational product and its metabolites,
1770 and their relationship to the pharmacological and toxicological findings in animal species.

1771 **7.3.5.3. Toxicology**

1772 A summary of the toxicological effects found in relevant studies conducted in different animal species
1773 should be described under the following headings where appropriate:

- 1774 • Single dose
- 1775 • Repeated dose
- 1776 • Carcinogenicity
- 1777 • Special studies (e.g. irritancy and sensitisation)
- 1778 • Reproductive toxicity
- 1779 • Genotoxicity (mutagenicity)

1780 **7.3.6. Effects in humans**

1781 Introduction:

1782 A thorough discussion of the known effects of the investigational product(s) in humans should be
1783 provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response,
1784 safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed
1785 clinical trial should be provided. Information should also be provided regarding results of any use of
1786 the investigational product(s) other than from in clinical trials, such as from experience during
1787 marketing.

1788 **7.3.6.1. Pharmacokinetics and product metabolism in humans**

- 1789 • A summary of information on the pharmacokinetics of the investigational product(s) should be
1790 presented, including the following, if available:
- 1791 • Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein
1792 binding, distribution, and elimination).
- 1793 • Bioavailability of the investigational product (absolute, where possible, and/or relative) using a
1794 reference dosage form.
- 1795 • Population subgroups (e.g., gender, age, and impaired organ function).
- 1796 • Interactions (e.g., product-product interactions and effects of food).
- 1797 • Other pharmacokinetic data (e.g., results of population studies performed within clinical
1798 trial(s)).

1799 **7.3.6.2. Safety and efficacy**

1800 A summary of information should be provided about the investigational product's/products' (including
1801 metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were
1802 obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this
1803 information should be discussed. In cases where a number of clinical trials have been completed, the
1804 use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide
1805 a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials
1806 (including those for all the studied indications) would be useful. Important differences in adverse drug
1807 reaction patterns/incidences across indications or subgroups should be discussed.

1808 The IB should provide a description of the possible risks and adverse drug reactions to be anticipated
1809 on the basis of prior experiences with the product under investigation and with related products. A
1810 description should also be provided of the precautions or special monitoring to be done as part of the
1811 investigational use of the product(s).

1812 **7.3.6.3. Marketing experience**

1813 The IB should identify countries where the investigational product has been marketed or approved.
1814 Any significant information arising from the marketed use should be summarised (e.g., formulations,
1815 dosages, routes of administration, and adverse product reactions). The IB should also identify all the
1816 countries where the investigational product did not receive approval/registration for marketing or was
1817 withdrawn from marketing/registration.

1818 **7.3.7. Summary of Data and Guidance for the Investigator**

1819 This section should provide an overall discussion of the nonclinical and clinical data, and should
1820 summarise the information from various sources on different aspects of the investigational product(s),
1821 wherever possible. In this way, the investigator can be provided with the most informative
1822 interpretation of the available data and with an assessment of the implications of the information for
1823 future clinical trials.

1824 Where appropriate, the published reports on related products should be discussed. This could help the
1825 investigator to anticipate adverse drug reactions or other problems in clinical trials.

1826 **The overall aim of this section is to provide the investigator with a clear understanding of**
1827 **the possible risks and adverse reactions, and of the specific tests, observations, and**
1828 **precautions that may be needed for a clinical trial. This understanding should be based on**
1829 **the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical**
1830 **information on the investigational product(s). Guidance should also be provided to the**
1831 **clinical investigator on the recognition and treatment of possible overdose and adverse drug**
1832 **reactions that is based on previous human experience and on the pharmacology of the**
1833 **investigational product.**

1834

1835 **7.4. Appendix 1:**

1836
1837 **TITLE PAGE (Example)**

1838 **SPONSOR'S NAME**

1839 **Product:**

1840
1841 **Research Number:**

1842
1843 **Name(s):** Chemical, Generic (if approved)

1844
1845 Trade Name(s) (if legally permissible and desired by the sponsor)

1846

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INVESTIGATOR'S BROCHURE

Edition Number:

Release Date:

Replaces Previous Edition Number: Date:

1859 **7.5. Appendix 2:**

1860
1861 **TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (*Example*)**
1862

1863
1864
1865 - Confidentiality Statement (optional)
1866 - Signature Page (optional)
1867 1 Table of Contents
1868 2 Summary
1869 3 Introduction
1870 4 Physical, Chemical, and Pharmaceutical Properties and Formulation
1871 5 Nonclinical Studies
1872 5.1 Nonclinical Pharmacology
1873 5.2 Pharmacokinetics and Product Metabolism in Animals
1874 5.3 Toxicology
1875 6 Effects in Humans
1876 6.1 Pharmacokinetics and Product Metabolism in Humans
1877 6.2 Safety and Efficacy
1878 6.3 Marketing Experience
1879 7 Summary of Data and Guidance for the Investigator
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- 1897 NB: References on 1. Publications
1898 2. Reports

1899 These references should be found at the end of each chapter
1900

1901 Appendices (if any)
1902
1903
1904
1905

1906 **8. Essential documents for the conduct of a clinical trial**

1907 **8.1. Introduction**

1908 Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.
1909 These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all
1910 applicable regulatory requirements.

1911 Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely
1912 manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are
1913 usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the
1914 trial conduct and the integrity of data collected.

1915 The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the
1916 trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after
1917 completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the
1918 investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

1919 Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a
1920 trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the
1921 appropriate files.

1922 Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the
1923 regulatory authority(ies).

1924 **ADDENDUM**

1925 The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents. The storage system (irrespective of
1926 the media used) should provide for document identification, search and retrieval.

1927 Depending on the activities being carried out, individual trials may require additional documents not specifically mentioned in the essential document list. The
1928 sponsor and/or investigator/institution should include these as part of the trial master file.

1929 The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have
1930 exclusive control of those data.

1931 When a copy is used to replace an original document, the copy should fulfill the requirements for certified copies.

1932 The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during and after the
 1933 trial.

1934 **8.2. Before the clinical phase of the trial commences**

1935 During this planning stage the following documents should be generated and should be on file before the trial formally start

1936

1937

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
8.2.1 INVESTIGATOR'S BROCHURE (where required)	To document that relevant and current scientific Information about the investigational product has been provided to the investigator trial-related injury will be available	x	x
8.2.2 SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement	x	x
8.2.3 INFORMATION GIVEN TO TRIAL SUBJECT - INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent	X	x
- ANY OTHER WRITTEN INFORMATION	To document that subject will be given appropriate written information (content and wording)to support their ability to give fully informed consent	x	x
- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.2 FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	x	x

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.5	INSURANCE STATEMENT (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	SIGNED AGREEMENT BETWEEN INVOLVED PARTIES , e.g.: <ul style="list-style-type: none"> - investigator/institution and sponsor - investigator/institution and CRO - sponsor and CRO - investigator/institution and authority(ies) (where required) 	To document agreements	X X	X X (where required)
8.2.7	DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: <ul style="list-style-type: none"> - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/favourable opinion 	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.8	INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/NOTIFICATION OF PROTOCOL (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and/or ranges of the tests	X	X
8.2.12	MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s) , and support reliability of results	X (where required)	X

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
8.2.13 SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14 INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial- related materials	X	X
8.2.15 SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16 CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17 DECODING PROCEDURES FOR BLINDED TRIALS	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)

Title of Document	Purpose	Located in Files of Investigator/ Institution Sponsor	
8.2.18 MASTER RANDOMISATION LIST	To document method for randomisation of trial population		X (third party if applicable)
8.2.19 PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20 TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

8.3. During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

8.3.1 INVESTIGATOR'S BROCHURE UPDATES	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
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Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
<p>8.3.2 ANY REVISION TO:</p> <ul style="list-style-type: none"> - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used) 	<p>To document revisions of these trial related documents that take effect during trial</p>	X	X
<p>8.3.3 DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</p> <ul style="list-style-type: none"> - protocol amendment(s) - revision(s) of: <ul style="list-style-type: none"> - informed consent form - any other written information to be provided to the subject - advertisement for subject recruitment (if used) - any other documents given approval/favourable opinion - continuing review of trial (where required) 	<p>To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).</p>	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.4	REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATI ONS WHERE REQUIRED FOR: - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB- INVESTIGATOR(S)	(see 8.2.10)	X	X
8.3.6	UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT	(see 8.2.15.)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.9	CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS	(see 8.2.16)		X
8.3.10	MONITORING VISIT REPORTS	To document site visits by, and findings of, the monitor		X
8.3.11	RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	SIGNED INFORMED CONSENT FORMS	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	SOURCE DOCUMENTS	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
8.3.14 SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)	To document that the investigator or authorised member of the investigator’s staff confirms the observations recorded	X (copy)	X (original)
8.3.15 DOCUMENTATION OF CRF CORRECTIONS	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16 NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17 NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2	X (where required)	X
8.3.18 NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19 INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
8.3.20 SUBJECT SCREENING LOG	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21 SUBJECT IDENTIFICATION CODE LIST	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22 SUBJECT ENROLMENT LOG	To document chronological enrolment of subjects by trial number	X	
8.3.23 INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24 SIGNATURE SHEET	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25 RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)	To document location and identification of retained samples if assays need to be repeated	X	X

8.4. After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.4.1	INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	COMPLETED SUBJECT IDENTIFICATION CODE LIST	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	AUDIT CERTIFICATE (if available)	To document that audit was performed		X
8.4.5	FINAL TRIAL CLOSE-OUT MONITORING REPORT	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	TREATMENT ALLOCATION AND DECODING DOCUMENTATION	Returned to sponsor to document any decoding that may have occurred		X

Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.4.7 FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)	To document completion of the trial	X	
8.4.8 CLINICAL STUDY REPORT	To document results and interpretation of trial	X (if applicable)	X