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5 Step 2b

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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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165 **Introduction**

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

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

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

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

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

181 **ADDENDUM**

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

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

192

193

194

195 **1. Glossary**

196 **1.1. Adverse Drug Reaction (ADR)**

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

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

206 **1.2. Adverse Event (AE)**

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

214 **1.3. Amendment (to the protocol)**

215 See Protocol Amendment.

216 **1.4. Applicable regulatory requirement(s)**

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

218 **1.5. Approval (in relation to institutional review boards)**

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

222 **1.6. Audit**

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

227 **1.7. Audit certificate**

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

229 **1.8. Audit report**

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

231 **1.9. Audit trail**

232 Documentation that allows reconstruction of the course of events.

233 **1.10. Blinding/masking**

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

238 **1.11. Case Report Form (CRF)**

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

241 **ADDENDUM**

242 **1.11.1. Certified copy**

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

246 **1.12. Clinical trial/study**

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

252 **1.13. Clinical trial/study report**

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

257 **1.14. Comparator (Product)**

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

260 **1.15. Compliance (in relation to trials)**

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

263

264 **1.16. Confidentiality**

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

267 **1.17. Contract**

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

271 **1.18. Coordinating committee**

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

273 **1.19. Coordinating investigator**

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

276 **1.20. Contract Research Organization (CRO)**

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

279 **1.21. Direct access**

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

285 **1.22. Documentation**

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

289 **1.23. Essential documents**

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

292 **1.24. Good Clinical Practice (GCP)**

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

296 **1.25. Independent Data-Monitoring Committee (IDMC) (data and safety
297 monitoring board, monitoring committee, data monitoring committee)**

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

301 **1.26. Impartial witness**

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

306 **1.27. Independent Ethics Committee (IEC)**

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

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

317 **1.28. Informed consent**

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

322 **1.29. Inspection**

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

327 **1.30. Institution (medical)**

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

329 **1.31. Institutional Review Board (IRB)**

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

335 **1.32. Interim clinical trial/study report**

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

338 **1.33. Investigational product**

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

343 **1.34. Investigator**

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

347 **1.35. Investigator / institution**

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

350 **1.36. Investigator's brochure**

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

353 **1.37. Legally acceptable representative**

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

356 **1.38. Monitoring**

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

360 **ADDENDUM**

361 **1.38.1. Monitoring plan**

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

363 **1.39. Monitoring report**

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

366 **ADDENDUM**

367 Outcomes of any centralized monitoring should also be reported.

368 **1.40. Multicentre trial**

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

371 **1.41. Nonclinical study**

372 Biomedical studies not performed on human subjects.

373 **1.42. Opinion (in relation to independent ethics committee)**

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

375 **1.43. Original medical record**

376 See Source Documents.

377 **1.44. Protocol**

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

382 **1.45. Protocol amendment**

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

384 **1.46. Quality Assurance (QA)**

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

388 **1.47. Quality Control (QC)**

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

391 **1.48. Randomization**

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

394 **1.49. Regulatory authorities**

395 Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities
396 includes the authorities that review submitted clinical data and those that conduct inspections (see
397 1.29). These bodies are sometimes referred to as competent authorities.

398 **1.50. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction**
399 **(Serious ADR)**

400 Any untoward medical occurrence that at any dose:

401 - results in death,

402 - is life-threatening,

403 - requires inpatient hospitalization or prolongation of existing hospitalization,

404 - results in persistent or significant disability/incapacity, or

405 - is a congenital anomaly/birth defect

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

408 **1.51. Source data**

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

412 **1.52. Source documents**

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

419 **1.53. Sponsor**

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

422 **1.54. Sponsor-Investigator**

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

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

428 **1.55. Standard Operating Procedures (SOPs)**

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

430 **1.56. Subinvestigator**

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

434 **1.57. Subject/trial subject**

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

437 **1.58. Subject identification code**

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

441 **1.59. Trial site**

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

443 **1.60. Unexpected adverse drug reaction**

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

448 **ADDENDUM**

449 **1.60.1. Validation of computerized systems**

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

453 **1.61. Vulnerable subjects**

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

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

463 **1.62. Well-being (of the trial subjects)**

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

465

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

467 **2.1.**

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

470 **2.2.**

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

474 **2.3.**

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

477 **2.4.**

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

480 **2.5.**

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

482 **2.6.**

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

485 **2.7.**

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

488 **2.8.**

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

491 **2.9.**

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

493 **2.10.**

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

496 **ADDENDUM**

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

498 **2.11.**

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

501 **2.12.**

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

505 **2.13.**

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

507 **3. Institutional Review Board / Independent Ethics**
508 **Committee (IRB/IEC)**

509 **3.1. Responsibilities**

510 **3.1.1.**

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

513 **3.1.2.**

514 The IRB/IEC should obtain the following documents:

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

528 **3.1.3.**

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

531 **3.1.4.**

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

534 **3.1.5.**

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

538 **3.1.6.**

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

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

543 **3.1.7.**

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

548 **3.1.8.**

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

552 **3.1.9.**

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

557 **3.2. Composition, Functions and Operations**

558 **3.2.1.**

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

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

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

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

568 **3.2.2.**

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

572 **3.2.3.**

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

575 **3.2.4.**

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

578 **3.2.5.**

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

581 **3.2.6.**

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

583 **3.3. Procedures**

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

585 **3.3.1.**

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

588 **3.3.2.**

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

590 **3.3.3.**

591 Conducting initial and continuing review of trials.

592 **3.3.4.**

593 Determining the frequency of continuing review, as appropriate.

594 **3.3.5.**

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

598 **3.3.6.**

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

601 **3.3.7.**

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

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

606 **3.3.8.**

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

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

615 **3.3.9.**

616 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution
617 concerning:

- 618 • Its trial-related decisions/opinions.
- 619 • The reasons for its decisions/opinions.
- 620 • Procedures for appeal of its decisions/opinions.

621 **3.4. Records**

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

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

628

629 **4. Investigator**

630 **4.1. Investigator's Qualifications and Agreements**

631 **4.1.1.**

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

637 **4.1.2.**

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

641 **4.1.3.**

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

644 **4.1.4.**

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

647 **4.1.5.**

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

650 **4.2. Adequate Resources**

651 **4.2.1.**

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

654 **4.2.2.**

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

657 **4.2.3.**

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

660 **4.2.4.**

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

663 **ADDENDUM**

664 **4.2.5.**

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

667 **4.2.6.**

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

671 **4.3. Medical Care of Trial Subjects**

672 **4.3.1.**

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

675 **4.3.2.**

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

681 **4.3.3.**

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

685 **4.3.4.**

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

689 **4.4. Communication with IRB/IEC**

690 **4.4.1.**

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

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

695 **4.4.2.**

696 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution
697 should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's
698 Brochure is updated during the trial, the investigator/institution should supply a copy of the updated
699 Investigator's Brochure to the IRB/IEC.

700 **4.4.3.**

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

703 **4.5. Compliance with Protocol**

704 **4.5.1.**

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

709 **4.5.2.**

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

715 **4.5.3.**

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

718 **4.5.4.**

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

- 723 • to the IRB/IEC for review and approval/favourable opinion, (b) to the sponsor for agreement
724 and, if required,
- 725 • to the regulatory authority(ies).

726 **4.6. Investigational Product(s)**

727 **4.6.1.**

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

730 **4.6.2.**

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

735 **4.6.3.**

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

744 **4.6.4.**

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

747 **4.6.5.**

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

750 **4.6.6.**

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

754 **4.7. Randomization Procedures and Unblinding**

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

759 **4.8. Informed Consent of Trial Subjects**

760 **4.8.1.**

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

766 **4.8.2.**

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

774 **4.8.3.**

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

777 **4.8.4.**

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

782 **4.8.5.**

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

787 **4.8.6.**

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

791 **4.8.7.**

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

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

797 **4.8.8.**

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

801 **4.8.9.**

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

812 **4.8.10.**

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

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

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

851 **4.8.11.**

852 Prior to participation in the trial, the subject or the subject's legally acceptable representative should
853 receive a copy of the signed and dated written informed consent form and any other written
854 information provided to the subjects. During a subject's participation in the trial, the subject or the
855 subject's legally acceptable representative should receive a copy of the signed and dated
856 consent form updates and a copy of any amendments to the written information provided to
857 subjects.

858 **4.8.12.**

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

864 **4.8.13.**

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

868 **4.8.14.**

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

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

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

881 **4.8.15.**

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

890 **4.9. Records and Reports**

891 **ADDENDUM**

892 **4.9.1.**

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

898 **4.9.2.**

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

901 **4.9.3.**

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

904 **4.9.4.**

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

912 **4.9.5.**

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

917 **4.9.6.**

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

925 **4.9.7.**

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

928 **4.9.8.**

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

931 **4.10. Progress Reports**

932 **4.10.1.**

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

935 **4.10.2.**

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

939 **4.11. Safety Reporting**

940 **4.11.1.**

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

949 **4.11.2.**

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

953 **4.11.3.**

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

956 **4.12. Premature Termination or Suspension of a Trial**

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

961 **4.12.1.**

962 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the
963 investigator should inform the institution where applicable, and the investigator/institution should
964 promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a
965 detailed written explanation of the termination or suspension.

966 **4.12.2.**

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

970 **4.12.3.**

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

975 **4.13. Final Report(s) by Investigator**

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

979

980 5. Sponsor

981 ADDENDUM

982 5.1. *Quality management*

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

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

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

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

995 5.1.1. **Critical process and data identification**

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

998 5.1.2. **Risk identification**

999 Risks to critical study processes and data should be identified. Risks should be considered at both the
1000 system level (e.g. facilities, standard operating procedures, computerized systems, personnel,
1001 vendors) and clinical trial level (e.g. investigational product, trial design, data collection and
1002 recording).

1003 5.1.3. **Risk evaluation**

1004 The identified risks should be evaluated by considering:

- 1005 • The likelihood of errors occurring, given existing risk controls.
- 1006 • The impact of such errors on human subject protection and data integrity.
- 1007 • The extent to which such errors would be detectable.

1008 5.1.4. **Risk control**

1009 The sponsor should identify those risks that should be reduced (through mitigating actions) and/or can
1010 be accepted. Risk mitigation activities may be incorporated in protocol design and implementation,
1011 monitoring plans, agreements between parties defining roles and responsibilities, systematic
1012 safeguards to ensure adherence to standard operating procedures, and training in processes and
1013 procedures.

1014 Predefined quality tolerance limits should be established, taking into consideration the medical and
1015 statistical characteristics of the variables as well as the statistical design of the trial, to identify
1016 systematic issues that can impact subject safety or data integrity. Detection of deviations from the
1017 predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

1018 **5.1.5. Risk communication**

1019 The quality management activities should be documented and communicated to stakeholders to
1020 facilitate risk review and continual improvement during clinical trial execution.

1021 **5.1.6. Risk review**

1022 The sponsor should periodically review risk control measures to ascertain whether the implemented
1023 quality management activities remain effective and relevant, taking into account emerging knowledge
1024 and experience.

1025 **5.1.7. Risk reporting**

1026 The sponsor should describe the quality management approach implemented in the trial and
1027 summarize important deviations from the predefined quality tolerance limits in the clinical study report
1028 (ICH E3, Section 9.6 Data Quality Assurance).

1029 ***5.2. Quality assurance and quality control***

1030 **5.2.1.**

1031 The sponsor is responsible for implementing and maintaining quality assurance and quality
1032 control systems with written SOPs to ensure that trials are conducted and data are generated,
1033 documented (recorded), and reported in compliance with the protocol, GCP, and the
1034 applicable regulatory requirement(s).

1035 **5.2.2.**

1036 The sponsor is responsible for securing agreement from all involved parties to ensure direct access
1037 (see 1.21) to all trial related sites, source data/documents, and reports for the purpose of monitoring
1038 and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

1039 **5.2.3.**

1040 Quality control should be applied to each stage of data handling to ensure that all data are reliable and
1041 have been processed correctly.

1042 **5.2.4.**

1043 Agreements, made by the sponsor with the investigator/institution and any other parties involved with
1044 the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

1045 **5.3. Contract Research Organization (CRO)**

1046 **5.3.1.**

1047 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but
1048 the ultimate responsibility for the quality and integrity of the trial data always resides with the
1049 sponsor. The CRO should implement quality assurance and quality control.

1050 **ADDENDUM**

1051 The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf.

1052 **5.3.2.**

1053 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in
1054 writing.

1055 **ADDENDUM**

1056 The sponsor should document approval of any subcontracting of trial-related duties and functions by a
1057 CRO.

1058 **5.3.3.**

1059 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are
1060 retained by the sponsor.

1061 **5.3.4.**

1062 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed
1063 the trial related duties and functions of a sponsor.

1064 **5.4. Medical expertise**

1065 The sponsor should designate appropriately qualified medical personnel who will be readily available
1066 to advise on trial related medical questions or problems. If necessary, outside consultant(s) may
1067 be appointed for this purpose.

1068 **5.5. Trial design**

1069 **5.5.1.**

1070 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and
1071 physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and
1072 CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

1073 **5.5.2.**

1074 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for
1075 Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design,
1076 protocol and conduct.

1077 **5.6. Trial management, data handling, and record keeping**

1078 **5.6.1.**

1079 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the
1080 trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial
1081 reports.

1082 **5.6.2.**

1083 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to
1084 assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at
1085 intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC
1086 should have written operating procedures and 8.1 of all its meetings.

1087 **5.6.3.**

1088 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor
1089 should:

- 1090 • Ensure and document that the electronic data processing system(s) conforms to the sponsor's
1091 established requirements for completeness, accuracy, reliability, and consistent intended
1092 performance (i.e. validation).
- 1093 • Maintains SOPs for using these systems.

1094 **ADDENDUM**

1095 The SOPs should cover system setup, installation and use. The SOPs should describe system
1096 validation and functionality testing, data collection and handling, system maintenance, system
1097 security measures, change control, data backup, recovery, contingency planning and
1098 decommissioning. The responsibilities of the sponsor, investigator and other parties with
1099 respect to the use of these computerized systems should be clear, and the users should be
1100 provided with training in the use of the systems.

- 1101 • Ensure that the systems are designed to permit data changes in such a way that the data
1102 changes are documented and that there is no deletion of entered data (i.e. maintain an audit
1103 trail, data trail, edit trail).
- 1104 • Maintain a security system that prevents unauthorized access to the data. (e) Maintain a list of
1105 the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).
- 1106 • Maintain adequate backup of the data.
- 1107 • Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

1108 **ADDENDUM**

- 1109 • Ensure the integrity of the data including any data that describe the context, content and
1110 structure of the data. This is particularly important when making changes to the computerized
1111 systems, such as software upgrades or migration of data.

1112 **5.6.4.**

1113 If data are transformed during processing, it should always be possible to compare the original data
1114 and observations with the processed data.

1115 **5.6.5.**

1116 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification
1117 of all the data reported for each subject.

1118 **5.6.6.**

1119 The sponsor, or other owners of the data, should retain all of the sponsor- specific essential
1120 documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

1121 **5.6.7.**

1122 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable
1123 regulatory requirement(s) of the country(ies) where the product is approved, and/or where the
1124 sponsor intends to apply for approval(s).

1125 **5.6.8.**

1126 If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all
1127 indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-
1128 specific essential documents for at least 2 years after formal discontinuation or in conformance with
1129 the applicable regulatory requirement(s).

1130 **5.6.9.**

1131 If the sponsor discontinues the clinical development of an investigational product, the sponsor should
1132 notify all the trial investigators/institutions and all the regulatory authorities.

1133 **5.6.10.**

1134 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required
1135 by the applicable regulatory requirement(s).

1136 **5.6.11.**

1137 The sponsor specific essential documents should be retained until at least 2 years after the last
1138 approval of a marketing application in an ICH region and until there are no pending or contemplated
1139 marketing applications in an ICH region or at least 2 years have elapsed since the formal
1140 discontinuation of clinical development of the investigational product. These documents should be
1141 retained for a longer period however if required by the applicable regulatory requirement(s) or if
1142 needed by the sponsor.

1143 **5.6.12.**

1144 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention
1145 and should notify the investigator(s)/institution(s) in writing when the trial related records are no
1146 longer needed.

1147 **5.7. Investigator selection**

1148 **5.7.1.**

1149 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be
1150 qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly
1151 conduct the trial for which the investigator is selected. If organization of a coordinating committee
1152 and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their
1153 organization and/or selection are the sponsor's responsibility.

1154 **5.7.2.**

1155 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should
1156 provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure,
1157 and should provide sufficient time for the investigator/institution to review the protocol and the
1158 information provided.

1159 **5.7.3.**

1160 The sponsor should obtain the investigator's/institution's agreement:

- 1161 • to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see
1162 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion
1163 by the IRB/IEC (see 4.5.1);
- 1164 • to comply with procedures for data recording/reporting;
- 1165 • to permit monitoring, auditing and inspection (see 4.1.4) and
- 1166 • to retain the trial related essential documents until the sponsor informs the
1167 investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12). The
1168 sponsor and the investigator/institution should sign the protocol, or an alternative document,
1169 to confirm this agreement.

1170 **5.8. Allocation of responsibilities**

1171 Prior to initiating a trial, the sponsor should define, establish, and allocate all trial- related duties and
1172 functions.

1173 **5.9. Compensation to subjects and investigators**

1174 **5.9.1.**

1175 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should
1176 indemnify (legal and financial coverage) the investigator/the institution against claims arising from the
1177 trial, except for claims that arise from malpractice and/or negligence.

1178 **5.9.2.**

1179 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the
1180 event of trial-related injuries in accordance with the applicable regulatory requirement(s).

1181 **5.9.3.**

1182 When trial subjects receive compensation, the method and manner of compensation should comply
1183 with applicable regulatory requirement(s).

1184 **5.10. Financing**

1185 The financial aspects of the trial should be documented in an agreement between the sponsor and the
1186 investigator/institution.

1187 **5.11. Notification/submission to regulatory authority(ies)**

1188 Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the
1189 applicable regulatory requirement(s)) should submit any required application(s) to the appropriate
1190 authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory
1191 requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain
1192 sufficient information to identify the protocol.

1193 **5.12. Confirmation of review by IRB/IEC**

1194 **5.12.1.**

1195 **The sponsor should obtain from the investigator/institution:**

- 1196
- 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.
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1199
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1204 **5.12.2.**

1205 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial,
1206 such as modification(s) of the protocol, written informed consent form and any other written
1207 information to be provided to subjects, and/or other procedures, the sponsor should obtain from
1208 the investigator/institution a copy of the modification(s) made and the date approval/favourable
1209 opinion was given by the IRB/IEC.

1210 **5.12.3.**

1211 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC
1212 reapprovals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of
1213 approval/favourable opinion.

1214 **5.13. Information on investigational product(s)**

1215 **5.13.1.**

1216 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical
1217 studies and/or clinical trials are available to support human exposure by the route, at the dosages, for
1218 the duration, and in the trial population to be studied.

1219 **5.13.2.**

1220 The sponsor should update the Investigator's Brochure as significant new information becomes
1221 available (see 7. Investigator's Brochure).

1222 **5.14. Manufacturing, packaging, labelling, and coding investigational**
1223 **product(s)**

1224 **5.14.1.**

1225 The sponsor should ensure that the investigational product(s) (including active comparator(s) and
1226 placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is
1227 manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that
1228 protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory
1229 requirement(s).

1230 **5.14.2.**

1231 The sponsor should determine, for the investigational product(s), acceptable storage temperatures,
1232 storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and
1233 devices for product infusion, if any. The sponsor should inform all involved parties (e.g.
1234 monitors, investigators, pharmacists, storage managers) of these determinations.

1235 **5.14.3.**

1236 The investigational product(s) should be packaged to prevent contamination and unacceptable
1237 deterioration during transport and storage.

1238 **5.14.4.**

1239 In blinded trials, the coding system for the investigational product(s) should include a mechanism that
1240 permits rapid identification of the product(s) in case of a medical emergency, but does not permit
1241 undetectable breaks of the blinding.

1242 **5.14.5.**

1243 If significant formulation changes are made in the investigational or comparator product(s) during the
1244 course of clinical development, the results of any additional studies of the formulated product(s) (e.g.
1245 stability, dissolution rate, bioavailability) needed to assess whether these changes would
1246 significantly alter the pharmacokinetic profile of the product should be available prior to the use of the
1247 new formulation in clinical trials.

1248 **5.15. *Supplying and handling investigational product(s)***

1249 **5.15.1.**

1250 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational
1251 product(s).

1252 **5.15.2.**

1253 The sponsor should not supply an investigator/institution with the investigational product(s) until the
1254 sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and
1255 regulatory authority(ies)).

1256 **5.15.3.**

1257 The sponsor should ensure that written procedures include instructions that the investigator/institution
1258 should follow for the handling and storage of investigational product(s) for the trial and documentation
1259 thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing,
1260 retrieval of unused product from subjects, and return of unused investigational product(s) to the
1261 sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable
1262 regulatory requirement(s)).

1263 **5.15.4.**

1264 The sponsor should:

- 1265 • Ensure timely delivery of investigational product(s) to the investigator(s).
- 1266 • Maintain records that document shipment, receipt, disposition, return, and destruction of the
1267 investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).
- 1268 • Maintain a system for retrieving investigational products and documenting this retrieval (e.g.
1269 for deficient product recall, reclaim after trial completion, expired product reclaim).
- 1270 • Maintain a system for the disposition of unused investigational product(s) and for the
1271 documentation of this disposition.

1272 **5.15.5.**

1273 The sponsor should:

- 1274 • Take steps to ensure that the investigational product(s) are stable over the period of use.
- 1275 • Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm
1276 specifications, should this become necessary, and maintain records of batch sample analyses

1277 and characteristics. To the extent stability permits, samples should be retained either until the
1278 analyses of the trial data are complete or as required by the applicable regulatory
1279 requirement(s), whichever represents the longer retention period.

1280 **5.16. Record access**

1281 **5.16.1.**

1282 The sponsor should ensure that it is specified in the protocol or other written agreement that the
1283 investigator(s)/institution(s) provide direct access to source data/documents for trial-related
1284 monitoring, audits, IRB/IEC review, and regulatory inspection.

1285 **5.16.2.**

1286 The sponsor should verify that each subject has consented, in writing, to direct access to his/her
1287 original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

1288 **5.17. Safety information**

1289 **5.17.1.**

1290 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

1291 **5.17.2.**

1292 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory
1293 authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the
1294 trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

1295 **5.18. Adverse drug reaction reporting**

1296 **5.18.1.**

1297 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the
1298 IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions
1299 (ADRs) that are both serious and unexpected.

1300 **5.18.2.**

1301 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH
1302 Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

1303 **5.18.3.**

1304 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as
1305 required by applicable regulatory requirement(s).

1306 **5.19. Monitoring**

1307 **5.19.1. Purpose**

1308 The purposes of trial monitoring are to verify that:

- 1309 • The rights and well-being of human subjects are protected.
- 1310 • The reported trial data are accurate, complete, and verifiable from source documents.
- 1311 • The conduct of the trial is in compliance with the currently approved protocol/amendment(s),
1312 with GCP, and with the applicable regulatory requirement(s).

1313 **5.19.2. Selection and qualifications of monitors**

- 1314 • Monitors should be appointed by the sponsor.
- 1315 • Monitors should be appropriately trained, and should have the scientific and/or clinical
1316 knowledge needed to monitor the trial adequately. A monitor's qualifications should be
1317 documented.
- 1318 • Monitors should be thoroughly familiar with the investigational product(s), the protocol, written
1319 informed consent form and any other written information to be provided to subjects, the
1320 sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

1321 **5.19.3. Extent and nature of monitoring**

1322 The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the
1323 appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring
1324 should be based on considerations such as the objective, purpose, design, complexity, blinding, size,
1325 and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after
1326 the trial; however in exceptional circumstances the sponsor may determine that central monitoring in
1327 conjunction with procedures such as investigators' training and meetings, and extensive written
1328 guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled
1329 sampling may be an acceptable method for selecting the data to be verified.

1330 **ADDENDUM**

1331 The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials.
1332 The flexibility in the extent and nature of monitoring described in this section is intended to permit
1333 varied approaches that improve the effectiveness and efficiency of monitoring. A combination of on-
1334 site and centralized monitoring activities may be appropriate. The sponsor should document the
1335 rationale for the chosen monitoring strategy (e.g. in the monitoring plan).

1336 *On-site monitoring* is performed at the sites at which the clinical trial is being conducted.

1337 *Centralized monitoring* is a remote evaluation of ongoing and/or cumulative data collected from trial
1338 sites, in a timely manner. Centralized monitoring processes provide additional monitoring capabilities
1339 that can complement and reduce the extent and/or frequency of on-site monitoring by such methods
1340 as:

- 1341 • Routine review of submitted data.
- 1342 • Identification of missing data, inconsistent data, data outliers or unexpected lack of variability
1343 and protocol deviations that may be indicative of systematic or significant errors in data

1344 collection and reporting at a site or across sites, or may be indicative of potential data
1345 manipulation or data integrity problems.

1346 • Using statistical analyses to identify data trends such as the range and consistency of data
1347 within and across sites.

1348 • Analyzing site characteristics and performance metrics.

1349 • Selection of sites and/or processes for targeted on-site monitoring.

1350 **5.19.4. Monitor's responsibilities**

1351 The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted
1352 and documented properly by carrying out the following activities when relevant and necessary to the
1353 trial and the trial site:

1354 • Acting as the main line of communication between the sponsor and the investigator.

1355 • Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6)
1356 and remain adequate throughout the trial period, that facilities, including laboratories,
1357 equipment, and staff, are adequate to safely and properly conduct the trial and remain
1358 adequate throughout the trial period.

1359 • Verifying, for the investigational product(s):

1360 ○ That storage times and conditions are acceptable, and that supplies are sufficient
1361 throughout the trial.

1362 ○ That the investigational product(s) are supplied only to subjects who are eligible to
1363 receive it and at the protocol specified dose(s).

1364 ○ That subjects are provided with necessary instruction on properly using,
1365 handling, storing, and returning the investigational product(s).

1366 ○ That the receipt, use, and return of the investigational product(s) at the trial sites are
1367 controlled and documented adequately.

1368 ○ That the disposition of unused investigational product(s) at the trial sites complies with
1369 applicable regulatory requirement(s) and is in accordance with the sponsor.

1370 • Verifying that the investigator follows the approved protocol and all approved amendment(s), if
1371 any.

1372 • Verifying that written informed consent was obtained before each subject's participation in the
1373 trial.

1374 • Ensuring that the investigator receives the current Investigator's Brochure, all documents,
1375 and all trial supplies needed to conduct the trial properly and to comply with the applicable
1376 regulatory requirement(s).

1377 • Ensuring that the investigator and the investigator's trial staff are adequately informed about
1378 the trial.

1379 • Verifying that the investigator and the investigator's trial staff are performing the specified trial
1380 functions, in accordance with the protocol and any other written agreement between the
1381 sponsor and the investigator/institution, and have not delegated these functions to
1382 unauthorized individuals.

- 1383 • Verifying that the investigator is enrolling only eligible subjects. (j) Reporting the subject
1384 recruitment rate.
- 1385 • Verifying that source documents and other trial records are accurate, complete, kept up-to-
1386 date and maintained.
- 1387 • Verifying that the investigator provides all the required reports, notifications,
1388 applications, and submissions, and that these documents are accurate, complete, timely,
1389 legible, dated, and identify the trial.
- 1390 • Checking the accuracy and completeness of the CRF entries, source documents and other trial-
1391 related records against each other. The monitor specifically should verify that:
 - 1392 ○ The data required by the protocol are reported accurately on the CRFs and are
1393 consistent with the source documents.
 - 1394 ○ Any dose and/or therapy modifications are well documented for each of the trial
1395 subjects.
 - 1396 ○ Adverse events, concomitant medications and intercurrent illnesses are reported in
1397 accordance with the protocol on the CRFs.
 - 1398 ○ Visits that the subjects fail to make, tests that are not conducted, and examinations
1399 that are not performed are clearly reported as such on the CRFs.
 - 1400 ○ All withdrawals and dropouts of enrolled subjects from the trial are reported and
1401 explained on the CRFs.
- 1402 • Informing the investigator of any CRF entry error, omission, or illegibility.
- 1403 The monitor should ensure that appropriate corrections, additions, or deletions are made,
1404 dated, explained (if necessary), and initialled by the investigator or by a member of the
1405 investigator's trial staff who is authorized to initial CRF changes for the investigator. This
1406 authorization should be documented.
- 1407 • Determining whether all adverse events (AEs) are appropriately reported within the time
1408 periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory
1409 requirement(s).
- 1410 • Determining whether the investigator is maintaining the essential documents (see 8. Essential
1411 Documents for the Conduct of a Clinical Trial).
- 1412 • Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory
1413 requirements to the investigator and taking appropriate action designed to prevent
1414 recurrence of the detected deviations.

1415 **5.19.5. Monitoring procedures**

1416 The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that
1417 are specified by the sponsor for monitoring a specific trial.

1418 **5.19.6. Monitoring report**

- 1419 • The monitor should submit a written report to the sponsor after each trial- site visit or trial-
1420 related communication.

- 1421 • Reports should include the date, site, name of the monitor, and name of the investigator or
1422 other individual(s) contacted.
- 1423 • Reports should include a summary of what the monitor reviewed and the monitor's statements
1424 concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken
1425 or to be taken and/or actions recommended to secure compliance.
- 1426 • The review and follow-up of the monitoring report with the sponsor should be documented by
1427 the sponsor's designated representative.

1428 **ADDENDUM**

- 1429 • Monitoring results should be provided to the sponsor (including appropriate management and
1430 staff responsible for trial and site oversight) in a timely manner for review and follow up as
1431 indicated. Results of monitoring activities should be documented in sufficient detail to allow
1432 verification of compliance with the monitoring plan.

1433 **ADDENDUM**

1434 **5.19.7. Monitoring plan**

1435 The sponsor should develop a monitoring plan that is tailored to the specific human subject protection
1436 and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring
1437 responsibilities of all the parties involved, the various monitoring methods to be used and the rationale
1438 for their use. The plan should also emphasize the monitoring of critical data and processes. Particular
1439 attention should be given to those aspects that are not routine clinical practice and that require
1440 additional training. The monitoring plan should reference the applicable policies and procedures.

1441 **5.20. Audit**

1442 If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

1443 **5.20.1. Purpose**

1444 The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or
1445 quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs,
1446 GCP, and the applicable regulatory requirements.

1447 **5.20.2. Selection and qualification of auditors**

- 1448 • The sponsor should appoint individuals, who are independent of the clinical trials/systems, to
1449 conduct audits.
- 1450 • The sponsor should ensure that the auditors are qualified by training and experience to
1451 conduct audits properly. An auditor's qualifications should be documented.

1452 **5.20.3. Auditing procedures**

- 1453 • The sponsor should ensure that the auditing of clinical trials/systems is conducted in
1454 accordance with the sponsor's written procedures on what to audit, how to audit, the frequency
1455 of audits, and the form and content of audit reports.

- 1456 • The sponsor's audit plan and procedures for a trial audit should be guided by the importance of
1457 the trial to submissions to regulatory authorities, the number of subjects in the trial, the type
1458 and complexity of the trial, the level of risks to the trial subjects, and any identified
1459 problem(s).
- 1460 • The observations and findings of the auditor(s) should be documented.
- 1461 • To preserve the independence and value of the audit function, the regulatory authority(ies)
1462 should not routinely request the audit reports. Regulatory authority(ies) may seek access to an
1463 audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in
1464 the course of legal proceedings.
- 1465 • When required by applicable law or regulation, the sponsor should provide an audit certificate.

1466 **5.21. Noncompliance**

1467 **5.21.1.**

1468 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an
1469 investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the
1470 sponsor to secure compliance.

1471 **ADDENDUM**

1472 When significant noncompliance is discovered, the sponsor should perform a root cause analysis and
1473 implement appropriate corrective and preventive actions. If required by applicable law or regulation
1474 the sponsor should inform the regulatory authority(ies) when the noncompliance is a serious breach of
1475 the trial protocol or GCP.

1476 **5.21.2.**

1477 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an
1478 investigator/institution, the sponsor should terminate the investigator's/institution's participation in the
1479 trial. When an investigator's/institution's participation is terminated because of
1480 noncompliance, the sponsor should notify promptly the regulatory authority(ies).

1481 **5.22. Premature termination or suspension of a trial**

1482 If a trial is prematurely terminated or suspended, the sponsor should promptly inform the
1483 investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the
1484 reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and
1485 provided the reason(s) for the termination or suspension by the sponsor or by the investigator /
1486 institution, as specified by the applicable regulatory requirement(s).

1487 **5.23. Clinical trial/study reports**

1488 Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical
1489 trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable
1490 regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing
1491 applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study
1492 Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that
1493 abbreviated study reports may be acceptable in certain cases.)

1494 **5.24. Multicentre trials**

1495 For multicentre trials, the sponsor should ensure that:

1496 **5.24.1.**

1497 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if
1498 required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

1499 **5.24.2.**

1500 The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators
1501 who are collecting additional data, supplemental CRFs should also be provided that are designed to
1502 capture the additional data.

1503 **5.24.3.**

1504 The responsibilities of coordinating investigator(s) and the other participating investigators are
1505 documented prior to the start of the trial.

1506 **5.24.4.**

1507 All investigators are given instructions on following the protocol, on complying with a uniform set of
1508 standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

1509 **5.24.5.**

1510 Communication between investigators is facilitated.

1511

1512 **6. Clinical trial protocol and protocol amendment(s)**

1513 The contents of a trial protocol should generally include the following topics. However, site specific
1514 information may be provided on separate protocol page(s), or addressed in a separate agreement, and
1515 some of the information listed below may be contained in other protocol referenced documents, such
1516 as an Investigator's Brochure.

1517 **6.1. General Information**

1518 **6.1.1.**

1519 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the
1520 amendment number(s) and date(s).

1521 **6.1.2.**

1522 Name and address of the sponsor and monitor (if other than the sponsor).

1523 **6.1.3.**

1524 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the
1525 sponsor.

1526 **6.1.4.**

1527 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when
1528 appropriate) for the trial.

1529 **6.1.5.**

1530 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address
1531 and telephone number(s) of the trial site(s).

1532 **6.1.6.**

1533 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who
1534 is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

1535 **6.1.7.**

1536 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical
1537 department(s) and/or institutions involved in the trial.

1538 **6.2. Background Information**

1539 **6.2.1.**

1540 Name and description of the investigational product(s).

- 1541 **6.2.2.**
- 1542 A summary of findings from nonclinical studies that potentially have clinical significance and from
1543 clinical trials that are relevant to the trial.
- 1544 **6.2.3.**
- 1545 Summary of the known and potential risks and benefits, if any, to human subjects.
- 1546 **6.2.4.**
- 1547 Description of and justification for the route of administration, dosage, dosage regimen, and treatment
1548 period(s).
- 1549 **6.2.5.**
- 1550 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable
1551 regulatory requirement(s).
- 1552 **6.2.6.**
- 1553 Description of the population to be studied.
- 1554 **6.2.7.**
- 1555 References to literature and data that are relevant to the trial, and that provide background for the
1556 trial.
- 1557 **6.3. Trial objectives and purpose**
- 1558 A detailed description of the objectives and the purpose of the trial.
- 1559 **6.4. Trial design**
- 1560 The scientific integrity of the trial and the credibility of the data from the trial depend substantially on
1561 the trial design. A description of the trial design, should include:
- 1562 **6.4.1.**
- 1563 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured
1564 during the trial.
- 1565 **6.4.2.**
- 1566 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel
1567 design) and a schematic diagram of trial design, procedures and stages.
- 1568 **6.4.3.**
- 1569 A description of the measures taken to minimize/avoid bias, including:
- 1570
 - Randomization.

1571 • Blinding.

1572 **6.4.4.**

1573 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational
1574 product(s). Also include a description of the dosage form, packaging, and labelling of the
1575 investigational product(s).

1576 **6.4.5.**

1577 The expected duration of subject participation, and a description of the sequence and duration of all
1578 trial periods, including follow-up, if any.

1579 **6.4.6.**

1580 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial
1581 and entire trial.

1582 **6.4.7.**

1583 Accountability procedures for the investigational product(s), including the placebo(s) and
1584 comparator(s), if any.

1585 **6.4.8.**

1586 Maintenance of trial treatment randomization codes and procedures for breaking codes.

1587 **6.4.9.**

1588 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic
1589 record of data), and to be considered to be source data.

1590 **6.5. Selection and withdrawal of subjects**

1591 **6.5.1.**

1592 Subject inclusion criteria.

1593 **6.5.2.**

1594 Subject exclusion criteria.

1595 **6.5.3.**

1596 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and
1597 procedures specifying:

- 1598 • When and how to withdraw subjects from the trial/ investigational product treatment.
- 1599 • The type and timing of the data to be collected for withdrawn subjects.
- 1600 • Whether and how subjects are to be replaced.

1601 • The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

1602 **6.6. Treatment of Subjects**

1603 **6.6.1.**

1604 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s),
1605 the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including
1606 the follow-up period(s) for subjects for each investigational product treatment/trial treatment
1607 group/arm of the trial.

1608 **6.6.2.**

1609 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or
1610 during the trial.

1611 **6.6.3.**

1612 Procedures for monitoring subject compliance.

1613 **6.7. Assessment of Efficacy**

1614 **6.7.1.**

1615 Specification of the efficacy parameters.

1616 **6.7.2.**

1617 Methods and timing for assessing, recording, and analysing of efficacy parameters.

1618 **6.8. Assessment of Safety**

1619 **6.8.1.**

1620 Specification of safety parameters.

1621 **6.8.2.**

1622 The methods and timing for assessing, recording, and analysing safety parameters.

1623 **6.8.3.**

1624 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent
1625 illnesses.

1626 **6.8.4.**

1627 The type and duration of the follow-up of subjects after adverse events.

1628

1629 **6.9. Statistics**

1630 **6.9.1.**

1631 A description of the statistical methods to be employed, including timing of any planned interim
1632 analysis(es).

1633 **6.9.2.**

1634 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects
1635 projected for each trial site should be specified. Reason for choice of sample size, including reflections
1636 on (or calculations of) the power of the trial and clinical justification.

1637 **6.9.3.**

1638 The level of significance to be used.

1639 **6.9.4.**

1640 Criteria for the termination of the trial.

1641 **6.9.5.**

1642 Procedure for accounting for missing, unused, and spurious data.

1643 **6.9.6.**

1644 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the
1645 original statistical plan should be described and justified in protocol and/or in the final report, as
1646 appropriate).

1647 **6.9.7.**

1648 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed
1649 subjects, all eligible subjects, evaluable subjects).

1650 **6.10. Direct access to source data/documents**

1651 The sponsor should ensure that it is specified in the protocol or other written agreement that the
1652 investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory
1653 inspection(s), providing direct access to source data/documents.

1654 **6.11. Quality control and quality assurance**

1655 **6.12. Ethics**

1656 Description of ethical considerations relating to the trial.

1657 **6.13. Data handling and record keeping**

1658 **6.14. Financing and insurance**

1659 Financing and insurance if not addressed in a separate agreement.

1660 **6.15. Publication policy**

1661 Publication policy, if not addressed in a separate agreement.

1662 **6.16. Supplements**

1663 (NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant
1664 information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

1665

1666 **7. Investigator's brochure**

1667 **7.1. Introduction**

1668 The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the
1669 investigational product(s) that are relevant to the study of the product(s) in human subjects. Its
1670 purpose is to provide the investigators and others involved in the trial with the information to facilitate
1671 their understanding of the rationale for, and their compliance with, many key features of the protocol,
1672 such as the dose, dose frequency/interval, methods of administration: and safety monitoring
1673 procedures. The IB also provides insight to support the clinical management of the study subjects
1674 during the course of the clinical trial. The information should be presented in a concise, simple,
1675 objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to
1676 understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the
1677 proposed trial. For this reason, a medically qualified person should generally participate in the editing
1678 of an IB, but the contents of the IB should be approved by the disciplines that generated the described
1679 data.

1680 This guideline delineates the minimum information that should be included in an IB and provides
1681 suggestions for its layout. It is expected that the type and extent of information available will vary with
1682 the stage of development of the investigational product. If the investigational product is marketed and
1683 its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary.
1684 Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or
1685 labelling may be an appropriate alternative, provided that it includes current, comprehensive, and
1686 detailed information on all aspects of the investigational product that might be of importance to the
1687 investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB
1688 specific to that new use should be prepared. The IB should be reviewed at least annually and revised
1689 as necessary in compliance with a sponsor's written procedures. More frequent revision may be
1690 appropriate depending on the stage of development and the generation of relevant new information.
1691 However, in accordance with Good Clinical Practice, relevant new information may be so important that
1692 it should be communicated to the investigators, and possibly to the Institutional Review Boards
1693 (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a
1694 revised IB.

1695 Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the
1696 investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible
1697 IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine
1698 whether a brochure is available from the commercial manufacturer. If the investigational product is
1699 provided by the sponsor-investigator, then he or she should provide the necessary information to the
1700 trial personnel. In cases where preparation of a formal IB is impractical, the sponsor- investigator
1701 should provide, as a substitute, an expanded background information section in the trial protocol that
1702 contains the minimum current information described in this guideline.

1703 **7.2. General considerations**

1704 The IB should include:

1705 **7.2.1. Title page**

1706 This should provide the sponsor's name, the identity of each investigational product (i.e., research
1707 number, chemical or approved generic name, and trade name(s) where legally permissible and desired

1708 by the sponsor), and the release date. It is also suggested that an edition number, and a reference to
1709 the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

1710 **7.2.2. Confidentiality statement**

1711 The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a
1712 confidential document for the sole information and use of the investigator's team and the IRB/IEC.

1713 **7.3. Contents of the investigator's brochure**

1714 The IB should contain the following sections, each with literature references where appropriate:

1715 **7.3.1. Table of contents**

1716 An example of the Table of Contents is given in Appendix 2

1717 **7.3.2. Summary**

1718 A brief summary (preferably not exceeding two pages) should be given, highlighting the significant
1719 physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and
1720 clinical information available that is relevant to the stage of clinical development of the investigational
1721 product.

1722 **7.3.3. Introduction**

1723 A brief introductory statement should be provided that contains the chemical name (and generic and
1724 trade name(s) when approved) of the investigational product(s), all active ingredients, the
1725 investigational product (s) pharmacological class and its expected position within this class (e.g.
1726 advantages), the rationale for performing research with the investigational product(s), and the
1727 anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement
1728 should provide the general approach to be followed in evaluating the investigational product.

1729 **7.3.4. Physical, chemical, and pharmaceutical properties and formulation**

1730 A description should be provided of the investigational product substance(s) (including the chemical
1731 and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical,
1732 and pharmaceutical properties.

1733 To permit appropriate safety measures to be taken in the course of the trial, a description of the
1734 formulation(s) to be used, including excipients, should be provided and justified if clinically relevant.
1735 Instructions for the storage and handling of the dosage form(s) should also be given.

1736 Any structural similarities to other known compounds should be mentioned.

1737 **7.3.5. Nonclinical studies**

1738 Introduction:

1739 The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational
1740 product metabolism studies should be provided in summary form. This summary should address the
1741 methodology used, the results, and a discussion of the relevance of the findings to the investigated
1742 therapeutic and the possible unfavourable and unintended effects in humans.

- 1743 • The information provided may include the following, as appropriate, if known/available:
- 1744 • Species tested
- 1745 • Number and sex of animals in each group
- 1746 • Unit dose (e.g., milligram/kilogram (mg/kg))
- 1747 • Dose interval
- 1748 • Route of administration
- 1749 • Duration of dosing
- 1750 • Information on systemic distribution
- 1751 • Duration of post-exposure follow-up
- 1752 • Results, including the following aspects:
 - 1753 ○ Nature and frequency of pharmacological or toxic effects
 - 1754 ○ Severity or intensity of pharmacological or toxic effects
 - 1755 ○ Time to onset of effects
 - 1756 ○ Reversibility of effects
 - 1757 ○ Duration of effects
 - 1758 ○ Dose response

1759 Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

1760 The following sections should discuss the most important findings from the studies, including the dose
1761 response of observed effects, the relevance to humans, and any aspects to be studied in humans. If
1762 applicable, the effective and nontoxic dose findings in the same animal species should be compared
1763 (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed
1764 human dosing should be addressed. Whenever possible, comparisons should be made in terms of
1765 blood/tissue levels rather than on a mg/kg basis.

1766 **7.3.5.1. Nonclinical pharmacology**

1767 A summary of the pharmacological aspects of the investigational product and, where appropriate, its
1768 significant metabolites studied in animals, should be included. Such a summary should incorporate
1769 studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and
1770 specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions
1771 other than the intended therapeutic effect(s)).

1772 **7.3.5.2. Pharmacokinetics and product metabolism in animals**

1773 A summary of the pharmacokinetics and biological transformation and disposition of the investigational
1774 product in all species studied should be given. The discussion of the findings should address the
1775 absorption and the local and systemic bioavailability of the investigational product and its metabolites,
1776 and their relationship to the pharmacological and toxicological findings in animal species.

1777 **7.3.5.3. Toxicology**

1778 A summary of the toxicological effects found in relevant studies conducted in different animal species
1779 should be described under the following headings where appropriate:

- 1780 • Single dose
- 1781 • Repeated dose
- 1782 • Carcinogenicity
- 1783 • Special studies (e.g. irritancy and sensitisation)
- 1784 • Reproductive toxicity
- 1785 • Genotoxicity (mutagenicity)

1786 **7.3.6. Effects in humans**

1787 Introduction:

1788 A thorough discussion of the known effects of the investigational product(s) in humans should be
1789 provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response,
1790 safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed
1791 clinical trial should be provided. Information should also be provided regarding results of any use of
1792 the investigational product(s) other than from in clinical trials, such as from experience during
1793 marketing.

1794 **7.3.6.1. Pharmacokinetics and product metabolism in humans**

- 1795 • A summary of information on the pharmacokinetics of the investigational product(s) should be
1796 presented, including the following, if available:
- 1797 • Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein
1798 binding, distribution, and elimination).
- 1799 • Bioavailability of the investigational product (absolute, where possible, and/or relative) using a
1800 reference dosage form.
- 1801 • Population subgroups (e.g., gender, age, and impaired organ function).
- 1802 • Interactions (e.g., product-product interactions and effects of food).
- 1803 • Other pharmacokinetic data (e.g., results of population studies performed within clinical
1804 trial(s)).

1805 **7.3.6.2. Safety and efficacy**

1806 A summary of information should be provided about the investigational product's/products' (including
1807 metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were
1808 obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this
1809 information should be discussed. In cases where a number of clinical trials have been completed, the
1810 use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide
1811 a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials
1812 (including those for all the studied indications) would be useful. Important differences in adverse drug
1813 reaction patterns/incidences across indications or subgroups should be discussed.

1814 The IB should provide a description of the possible risks and adverse drug reactions to be anticipated
1815 on the basis of prior experiences with the product under investigation and with related products. A
1816 description should also be provided of the precautions or special monitoring to be done as part of the
1817 investigational use of the product(s).

1818 **7.3.6.3. Marketing experience**

1819 The IB should identify countries where the investigational product has been marketed or approved.
1820 Any significant information arising from the marketed use should be summarised (e.g., formulations,
1821 dosages, routes of administration, and adverse product reactions). The IB should also identify all the
1822 countries where the investigational product did not receive approval/registration for marketing or was
1823 withdrawn from marketing/registration.

1824 **7.3.7. Summary of Data and Guidance for the Investigator**

1825 This section should provide an overall discussion of the nonclinical and clinical data, and should
1826 summarise the information from various sources on different aspects of the investigational product(s),
1827 wherever possible. In this way, the investigator can be provided with the most informative
1828 interpretation of the available data and with an assessment of the implications of the information for
1829 future clinical trials.

1830 Where appropriate, the published reports on related products should be discussed. This could help the
1831 investigator to anticipate adverse drug reactions or other problems in clinical trials.

1832 **The overall aim of this section is to provide the investigator with a clear understanding of**
1833 **the possible risks and adverse reactions, and of the specific tests, observations, and**
1834 **precautions that may be needed for a clinical trial. This understanding should be based on**
1835 **the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical**
1836 **information on the investigational product(s). Guidance should also be provided to the**
1837 **clinical investigator on the recognition and treatment of possible overdose and adverse drug**
1838 **reactions that is based on previous human experience and on the pharmacology of the**
1839 **investigational product.**

1840

1841 **7.4. Appendix 1:**

1842
1843 **TITLE PAGE (Example)**

1844 **SPONSOR'S NAME**

1845 **Product:**

1846
1847 **Research Number:**

1848
1849 **Name(s):** Chemical, Generic (if approved)

1850 Trade Name(s) (if legally permissible and desired by the sponsor)

1851

1852

1853

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1855

1856

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Edition Number:

1860

Release Date:

1861

1862

1863

Replaces Previous Edition Number: Date:

1864

INVESTIGATOR'S BROCHURE

1865 **7.5. Appendix 2:**

1866
1867 **TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (Example)**
1868

1869
1870
1871 - Confidentiality Statement (optional)
1872 - Signature Page (optional)
1873 1 Table of Contents
1874 2 Summary
1875 3 Introduction
1876 4 Physical, Chemical, and Pharmaceutical Properties and Formulation
1877 5 Nonclinical Studies
1878 5.1 Nonclinical Pharmacology
1879 5.2 Pharmacokinetics and Product Metabolism in Animals
1880 5.3 Toxicology
1881 6 Effects in Humans
1882 6.1 Pharmacokinetics and Product Metabolism in Humans
1883 6.2 Safety and Efficacy
1884 6.3 Marketing Experience
1885 7 Summary of Data and Guidance for the Investigator
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1903 NB: References on 1. Publications
1904 2. Reports
1905
1906

1907 These references should be found at the end of each chapter
1908

1909 Appendices (if any)
1910
1911

1912 **8. Essential documents for the conduct of a clinical trial**

1913 **8.1. Introduction**

1914 Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.
1915 These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all
1916 applicable regulatory requirements.

1917 Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely
1918 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
1919 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
1920 trial conduct and the integrity of data collected.

1921 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
1922 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
1923 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
1924 investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

1925 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
1926 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
1927 appropriate files.

1928 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
1929 regulatory authority(ies).

1930 **ADDENDUM**

1931 The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents. The storage system (irrespective of
1932 the media used) should provide for document identification, search and retrieval.

1933 Depending on the activities being carried out, individual trials may require additional documents not specifically mentioned in the essential document list. The
1934 sponsor and/or investigator/institution should include these as part of the trial master file.

1935 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
1936 exclusive control of those data.

1937 When a copy is used to replace an original document, the copy should fulfill the requirements for certified copies.

1938 The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during and after the
 1939 trial.

1940 **8.2. Before the clinical phase of the trial commences**

1941 During this planning stage the following documents should be generated and should be on file before the trial formally start

1942

1943

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.: - 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: - 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