

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

**INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD
CLINICAL PRACTICE**

E6(R2)

Current *Step 2* version

dated 11 June 2015

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the ICH regions (the European Union, Japan, the USA, Health Canada and Switzerland) for internal and external consultation, according to national or regional procedures.

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ICH HARMONISED GUIDELINE
INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR
GOOD CLINICAL PRACTICE ICH

E6(R2)

Draft ICH Consensus Guideline
Released for Consultation on 11 June 2015, at *Step 2* of the ICH Process

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1 **INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR**
2 **GOOD CLINICAL PRACTICE ICH**

3 **E6(R2)**

4 **INTRODUCTION**

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

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

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

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

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

20 **ADDENDUM**

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

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

31 **1. GLOSSARY**

32 **1.1 Adverse Drug Reaction (ADR)**

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

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

43 **1.2 Adverse Event (AE)**

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

51 **1.3 Amendment (to the protocol)**

52 See Protocol Amendment.

53 **1.4 Applicable Regulatory Requirement(s)**

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

56 **1.5 Approval (in relation to Institutional Review Boards)**

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

60 **1.6 Audit**

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

66 **1.7 Audit Certificate**

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

68 **1.8 Audit Report**

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

70

71 **1.9 Audit Trail**

72 Documentation that allows reconstruction of the course of events.

73 **1.10 Blinding/Masking**

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

78 **1.11 Case Report Form (CRF)**

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

81 **ADDENDUM**

82 **1.11.1 Certified Copy**

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

86 **1.12 Clinical Trial/Study**

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

93 **1.13 Clinical Trial/Study Report**

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

98 **1.14 Comparator (Product)**

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

101 **1.15 Compliance (in relation to trials)**

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

104 **1.16 Confidentiality**

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

107 **1.17 Contract**

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

111

112 **1.18 Coordinating Committee**

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

114 **1.19 Coordinating Investigator**

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

117 **1.20 Contract Research Organization (CRO)**

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

120 **1.21 Direct Access**

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

126 **1.22 Documentation**

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

130 **1.23 Essential Documents**

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

134 **1.24 Good Clinical Practice (GCP)**

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

139 **1.25 Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring
140 Board, Monitoring Committee, Data Monitoring Committee)**

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

144 **1.26 Impartial Witness**

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

149 **1.27 Independent Ethics Committee (IEC)**

150 An independent body (a review board or a committee, institutional, regional, national, or
151 supranational), constituted of medical professionals and non-medical members, whose
152 responsibility it is to ensure the protection of the rights, safety and well-being of human

153 subjects involved in a trial and to provide public assurance of that protection, by, among other
154 things, reviewing and approving/providing favourable opinion on, the trial protocol, the
155 suitability of the investigator(s), facilities, and the methods and material to be used in
156 obtaining and documenting informed consent of the trial subjects.

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

160 **1.28 Informed Consent**

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

165 **1.29 Inspection**

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

171 **1.30 Institution (medical)**

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

174 **1.31 Institutional Review Board (IRB)**

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

180 **1.32 Interim Clinical Trial/Study Report**

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

183 **1.33 Investigational Product**

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

188 **1.34 Investigator**

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

192 **1.35 Investigator/Institution**

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

195 **1.36 Investigator's Brochure**

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

199 **1.37 Legally Acceptable Representative**

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

202 **1.38 Monitoring**

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

206 **ADDENDUM**

207 **1.38.1 Monitoring Plan**

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

209 **1.39 Monitoring Report**

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

212 **ADDENDUM**

213 Outcomes of any centralized monitoring should also be reported.

214 **1.40 Multicentre Trial**

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

217 **1.41 Nonclinical Study**

218 Biomedical studies not performed on human subjects.

219 **1.42 Opinion (in relation to Independent Ethics Committee)**

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

221 **1.43 Original Medical Record**

222 See Source Documents.

223 **1.44 Protocol**

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

228 **1.45 Protocol Amendment**

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

230

231 **1.46 Quality Assurance (QA)**

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

235 **1.47 Quality Control (QC)**

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

238 **1.48 Randomization**

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

241 **1.49 Regulatory Authorities**

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

245 **1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)**

246 Any untoward medical occurrence that at any dose:

247 - results in death,

248 - is life-threatening,

249 - requires inpatient hospitalization or prolongation of existing hospitalization,

250 - results in persistent or significant disability/incapacity,

251 or

252 - is a congenital anomaly/birth defect

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

255 **1.51 Source Data**

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

260 **1.52 Source Documents**

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

267 **1.53 Sponsor**

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

270 **1.54 Sponsor-Investigator**

271 An individual who both initiates and conducts, alone or with others, a clinical trial, and under
272 whose immediate direction the investigational product is administered to, dispensed to, or
273 used by a subject. The term does not include any person other than an individual (e.g., it does
274 not include a corporation or an agency). The obligations of a sponsor-investigator include both
275 those of a sponsor and those of an investigator.

276 **1.55 Standard Operating Procedures (SOPs)**

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

278 **1.56 Subinvestigator**

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

282 **1.57 Subject/Trial Subject**

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

285 **1.58 Subject Identification Code**

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

289 **1.59 Trial Site**

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

291 **1.60 Unexpected Adverse Drug Reaction**

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

297 **ADDENDUM**

298 **1.60.1 Validation of computerized systems**

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

303 **1.61 Vulnerable Subjects**

304 Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the
305 expectation, whether justified or not, of benefits associated with participation, or of a
306 retaliatory response from senior members of a hierarchy in case of refusal to participate.
307 Examples are members of a group with a hierarchical structure, such as medical, pharmacy,
308 dental, and nursing students, subordinate hospital and laboratory personnel, employees of the
309 pharmaceutical industry, members of the armed forces, and persons kept in detention. Other
310 vulnerable subjects include patients with incurable diseases, persons in nursing homes,

311 unemployed or impoverished persons, patients in emergency situations, ethnic minority
312 groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

313 **1.62 Well-being (of the trial subjects)**

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

315 **2. THE PRINCIPLES OF ICH GCP**

316 **2.1** Clinical trials should be conducted in accordance with the ethical principles that have
317 their origin in the Declaration of Helsinki, and that are consistent with GCP and the
318 applicable regulatory requirement(s).

319 **2.2** Before a trial is initiated, foreseeable risks and inconveniences should be weighed
320 against the anticipated benefit for the individual trial subject and society. A trial
321 should be initiated and continued only if the anticipated benefits justify the risks.

322 **2.3** The rights, safety, and well-being of the trial subjects are the most important
323 considerations and should prevail over interests of science and society.

324 **2.4** The available nonclinical and clinical information on an investigational product should
325 be adequate to support the proposed clinical trial.

326 **2.5** Clinical trials should be scientifically sound, and described in a clear, detailed
327 protocol.

328 **2.6** A trial should be conducted in compliance with the protocol that has received prior
329 institutional review board (IRB)/independent ethics committee (IEC)
330 approval/favourable opinion.

331 **2.7** The medical care given to, and medical decisions made on behalf of, subjects should
332 always be the responsibility of a qualified physician or, when appropriate, of a
333 qualified dentist.

334 **2.8** Each individual involved in conducting a trial should be qualified by education,
335 training, and experience to perform his or her respective task(s).

336 **2.9** Freely given informed consent should be obtained from every subject prior to clinical
337 trial participation.

338 **2.10** All clinical trial information should be recorded, handled, and stored in a way that
339 allows its accurate reporting, interpretation and verification.

340 **ADDENDUM**

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

342 **2.11** The confidentiality of records that could identify subjects should be protected,
343 respecting the privacy and confidentiality rules in accordance with the applicable
344 regulatory requirement(s).

- 345 **2.12** Investigational products should be manufactured, handled, and stored in accordance
346 with applicable good manufacturing practice (GMP). They should be used in
347 accordance with the approved protocol.
- 348 **2.13** Systems with procedures that assure the quality of every aspect of the trial should be
349 implemented.
- 350 **3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE**
351 **(IRB/IEC)**
- 352 **3.1 Responsibilities**
- 353 **3.1.1** An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects.
354 Special attention should be paid to trials that may include vulnerable subjects.
- 355 **3.1.2** The IRB/IEC should obtain the following documents:
356 trial protocol(s)/amendment(s), written informed consent form(s) and consent form
357 updates that the investigator proposes for use in the trial, subject recruitment
358 procedures (e.g., advertisements), written information to be provided to subjects,
359 Investigator's Brochure (IB), available safety information, information about payments
360 and compensation available to subjects, the investigator's current curriculum vitae
361 and/or other documentation evidencing qualifications, and any other documents that
362 the IRB/IEC may need to fulfil its responsibilities.
- 363 The IRB/IEC should review a proposed clinical trial within a reasonable time and
364 document its views in writing, clearly identifying the trial, the documents reviewed
365 and the dates for the following:
- 366 - approval/favourable opinion;
- 367 - modifications required prior to its approval/favourable opinion;
- 368 - disapproval / negative opinion; and
- 369 - termination/suspension of any prior approval/favourable opinion.
- 370 **3.1.3** The IRB/IEC should consider the qualifications of the investigator for the proposed
371 trial, as documented by a current curriculum vitae and/or by any other relevant
372 documentation the IRB/IEC requests.
- 373 **3.1.4** The IRB/IEC should conduct continuing review of each ongoing trial at intervals
374 appropriate to the degree of risk to human subjects, but at least once per year.
- 375 **3.1.5** The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be
376 given to subjects when, in the judgement of the IRB/IEC, the additional information
377 would add meaningfully to the protection of the rights, safety and/or well-being of the
378 subjects.
- 379 **3.1.6** When a non-therapeutic trial is to be carried out with the consent of the subject's
380 legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine

381 that the proposed protocol and/or other document(s) adequately addresses relevant
382 ethical concerns and meets applicable regulatory requirements for such trials.

383 3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's
384 legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should
385 determine that the proposed protocol and/or other document(s) adequately addresses
386 relevant ethical concerns and meets applicable regulatory requirements for such trials
387 (i.e., in emergency situations).

388 3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to
389 assure that neither presents problems of coercion or undue influence on the trial
390 subjects. Payments to a subject should be prorated and not wholly contingent on
391 completion of the trial by the subject.

392 3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including
393 the methods, amounts, and schedule of payment to trial subjects, is set forth in the
394 written informed consent form and any other written information to be provided to
395 subjects. The way payment will be prorated should be specified.

396 **3.2 Composition, Functions and Operations**

397 3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively
398 have the qualifications and experience to review and evaluate the science, medical
399 aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should
400 include:

401 (a) At least five members.

402 (b) At least one member whose primary area of interest is in a nonscientific area.

403 (c) At least one member who is independent of the institution/trial site.

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

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

407 3.2.2 The IRB/IEC should perform its functions according to written operating procedures,
408 should maintain written records of its activities and minutes of its meetings, and
409 should comply with GCP and with the applicable regulatory requirement(s).

410 3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a
411 quorum, as stipulated in its written operating procedures, is present.

412 3.2.4 Only members who participate in the IRB/IEC review and discussion should
413 vote/provide their opinion and/or advise.

414 3.2.5 The investigator may provide information on any aspect of the trial, but should not
415 participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

416 3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

417 **3.3 Procedures**

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

420 3.3.1 Determining its composition (names and qualifications of the members) and the
421 authority under which it is established.

422 3.3.2 Scheduling, notifying its members of, and conducting its meetings.

423 3.3.3 Conducting initial and continuing review of trials.

424 3.3.4 Determining the frequency of continuing review, as appropriate.

425 3.3.5 Providing, according to the applicable regulatory requirements, expedited review and
426 approval/favourable opinion of minor change(s) in ongoing trials that have the
427 approval/favourable opinion of the IRB/IEC.

428 3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its
429 written approval/favourable opinion of the trial.

430 3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated
431 without prior written IRB/IEC approval/favourable opinion of an appropriate
432 amendment, except when necessary to eliminate immediate hazards to the subjects or
433 when the change(s) involves only logistical or administrative aspects of the trial (e.g.,
434 change of monitor(s), telephone number(s)) (see 4.5.2).

435 3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

436 (a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the
437 trial subjects (see 3.3.7, 4.5.2, 4.5.4).

438 (b) Changes increasing the risk to subjects and/or affecting significantly the conduct
439 of the trial (see 4.10.2).

440 (c) All adverse drug reactions (ADRs) that are both serious and unexpected.

441 (d) New information that may affect adversely the safety of the subjects or the
442 conduct of the trial.

443 3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution
444 concerning:

445 (a) Its trial-related decisions/opinions.

446 (b) The reasons for its decisions/opinions.

447 (c) Procedures for appeal of its decisions/opinions.

448 **3.4 Records**

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

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

455 **4. INVESTIGATOR**

456 **4.1 Investigator's Qualifications and Agreements**

457 *4.1.1* The investigator(s) should be qualified by education, training, and experience to
458 assume responsibility for the proper conduct of the trial, should meet all the
459 qualifications specified by the applicable regulatory requirement(s), and should
460 provide evidence of such qualifications through up-to-date curriculum vitae and/or
461 other relevant documentation requested by the sponsor, the IRB/IEC, and/or the
462 regulatory authority(ies).

463 *4.1.2* The investigator should be thoroughly familiar with the appropriate use of the
464 investigational product(s), as described in the protocol, in the current Investigator's
465 Brochure, in the product information and in other information sources provided by the
466 sponsor.

467 *4.1.3* The investigator should be aware of, and should comply with, GCP and the applicable
468 regulatory requirements.

469 *4.1.4* The investigator/institution should permit monitoring and auditing by the sponsor, and
470 inspection by the appropriate regulatory authority(ies).

471 *4.1.5* The investigator should maintain a list of appropriately qualified persons to whom the
472 investigator has delegated significant trial-related duties.

473 **4.2 Adequate Resources**

474 *4.2.1* The investigator should be able to demonstrate (e.g., based on retrospective data) a
475 potential for recruiting the required number of suitable subjects within the agreed
476 recruitment period.

477 *4.2.2* The investigator should have sufficient time to properly conduct and complete the trial
478 within the agreed trial period.

479 *4.2.3* The investigator should have available an adequate number of qualified staff and
480 adequate facilities for the foreseen duration of the trial to conduct the trial properly and
481 safely.

482 *4.2.4* The investigator should ensure that all persons assisting with the trial are adequately
483 informed about the protocol, the investigational product(s), and their trial-related
484 duties and functions.

485

486 **ADDENDUM**

487 4.2.5 The investigator is responsible for supervising any individual or party to whom the
488 investigator delegates study tasks conducted at the trial site.

489 4.2.6 If the investigator/institution retains the services of any party to perform study tasks
490 they should ensure this party is qualified to perform those study tasks and should
491 implement procedures to ensure the integrity of the study tasks performed and any
492 data generated.

493 **4.3 Medical Care of Trial Subjects**

494 4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-
495 investigator for the trial, should be responsible for all trial-related medical (or dental)
496 decisions.

497 4.3.2 During and following a subject's participation in a trial, the investigator/institution
498 should ensure that adequate medical care is provided to a subject for any adverse
499 events, including clinically significant laboratory values, related to the trial. The
500 investigator/institution should inform a subject when medical care is needed for
501 intercurrent illness(es) of which the investigator becomes aware.

502 4.3.3 It is recommended that the investigator inform the subject's primary physician about
503 the subject's participation in the trial if the subject has a primary physician and if the
504 subject agrees to the primary physician being informed.

505 4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing
506 prematurely from a trial, the investigator should make a reasonable effort to ascertain
507 the reason(s), while fully respecting the subject's rights.

508 **4.4 Communication with IRB/IEC**

509 4.4.1 Before initiating a trial, the investigator/institution should have written and dated
510 approval/favourable opinion from the IRB/IEC for the trial protocol, written informed
511 consent form, consent form updates, subject recruitment procedures (e.g.,
512 advertisements), and any other written information to be provided to subjects.

513 4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the
514 investigator/institution should provide the IRB/IEC with a current copy of the
515 Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the
516 investigator/institution should supply a copy of the updated Investigator's Brochure to
517 the IRB/IEC.

518 4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all
519 documents subject to review.

520 **4.5 Compliance with Protocol**

521 4.5.1 The investigator/institution should conduct the trial in compliance with the protocol
522 agreed to by the sponsor and, if required, by the regulatory authority(ies) and which
523 was given approval/favourable opinion by the IRB/IEC. The investigator/institution

524 and the sponsor should sign the protocol, or an alternative contract, to confirm
525 agreement.

526 4.5.2 The investigator should not implement any deviation from, or changes of the protocol
527 without agreement by the sponsor and prior review and documented
528 approval/favourable opinion from the IRB/IEC of an amendment, except where
529 necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s)
530 involves only logistical or administrative aspects of the trial (e.g., change in
531 monitor(s), change of telephone number(s)).

532 4.5.3 The investigator, or person designated by the investigator, should document and
533 explain any deviation from the approved protocol.

534 4.5.4 The investigator may implement a deviation from, or a change of, the protocol to
535 eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC
536 approval/favourable opinion. As soon as possible, the implemented deviation or
537 change, the reasons for it, and, if appropriate, the proposed protocol amendment(s)
538 should be submitted:

539 (a) to the IRB/IEC for review and approval/favourable opinion,

540 (b) to the sponsor for agreement and, if required,

541 (c) to the regulatory authority(ies).

542 **4.6 Investigational Product(s)**

543 4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with
544 the investigator/institution.

545 4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of
546 the investigator's/institution's duties for investigational product(s) accountability at the
547 trial site(s) to an appropriate pharmacist or another appropriate individual who is under
548 the supervision of the investigator/institution..

549 4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is
550 designated by the investigator/institution, should maintain records of the product's
551 delivery to the trial site, the inventory at the site, the use by each subject, and the
552 return to the sponsor or alternative disposition of unused product(s). These records
553 should include dates, quantities, batch/serial numbers, expiration dates (if applicable),
554 and the unique code numbers assigned to the investigational product(s) and trial
555 subjects. Investigators should maintain records that document adequately that the
556 subjects were provided the doses specified by the protocol and reconcile all
557 investigational product(s) received from the sponsor.

558 4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2
559 and 5.14.3) and in accordance with applicable regulatory requirement(s).

560 4.6.5 The investigator should ensure that the investigational product(s) are used only in
561 accordance with the approved protocol.

562 4.6.6 The investigator, or a person designated by the investigator/institution, should explain
563 the correct use of the investigational product(s) to each subject and should check, at
564 intervals appropriate for the trial, that each subject is following the instructions
565 properly.

566 **4.7 Randomization Procedures and Unblinding**

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

572 **4.8 Informed Consent of Trial Subjects**

573 4.8.1 In obtaining and documenting informed consent, the investigator should comply with
574 the applicable regulatory requirement(s), and should adhere to GCP and to the ethical
575 principles that have their origin in the Declaration of Helsinki. Prior to the beginning
576 of the trial, the investigator should have the IRB/IEC's written approval/favourable
577 opinion of the written informed consent form and any other written information to be
578 provided to subjects.

579 4.8.2 The written informed consent form and any other written information to be provided to
580 subjects should be revised whenever important new information becomes available
581 that may be relevant to the subject's consent. Any revised written informed consent
582 form, and written information should receive the IRB/IEC's approval/favourable
583 opinion in advance of use. The subject or the subject's legally acceptable
584 representative should be informed in a timely manner if new information becomes
585 available that may be relevant to the subject's willingness to continue participation in
586 the trial. The communication of this information should be documented.

587 4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject
588 to participate or to continue to participate in a trial.

589 4.8.4 None of the oral and written information concerning the trial, including the written
590 informed consent form, should contain any language that causes the subject or the
591 subject's legally acceptable representative to waive or to appear to waive any legal
592 rights, or that releases or appears to release the investigator, the institution, the
593 sponsor, or their agents from liability for negligence.

594 4.8.5 The investigator, or a person designated by the investigator, should fully inform the
595 subject or, if the subject is unable to provide informed consent, the subject's legally
596 acceptable representative, of all pertinent aspects of the trial including the written
597 information and the approval/ favourable opinion by the IRB/IEC.

598 4.8.6 The language used in the oral and written information about the trial, including the
599 written informed consent form, should be as non-technical as practical and should be
600 understandable to the subject or the subject's legally acceptable representative and the
601 impartial witness, where applicable.

- 602 4.8.7 Before informed consent may be obtained, the investigator, or a person designated by
603 the investigator, should provide the subject or the subject's legally acceptable
604 representative ample time and opportunity to inquire about details of the trial and to
605 decide whether or not to participate in the trial. All questions about the trial should be
606 answered to the satisfaction of the subject or the subject's legally acceptable
607 representative.
- 608 4.8.8 Prior to a subject's participation in the trial, the written informed consent form should
609 be signed and personally dated by the subject or by the subject's legally acceptable
610 representative, and by the person who conducted the informed consent discussion.
- 611 4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read,
612 an impartial witness should be present during the entire informed consent discussion.
613 After the written informed consent form and any other written information to be
614 provided to subjects, is read and explained to the subject or the subject's legally
615 acceptable representative, and after the subject or the subject's legally acceptable
616 representative has orally consented to the subject's participation in the trial and, if
617 capable of doing so, has signed and personally dated the informed consent form, the
618 witness should sign and personally date the consent form. By signing the consent
619 form, the witness attests that the information in the consent form and any other written
620 information was accurately explained to, and apparently understood by, the subject or
621 the subject's legally acceptable representative, and that informed consent was freely
622 given by the subject or the subject's legally acceptable representative.
- 623 4.8.10 Both the informed consent discussion and the written informed consent form and any
624 other written information to be provided to subjects should include explanations of the
625 following:
- 626 (a) That the trial involves research.
- 627 (b) The purpose of the trial.
- 628 (c) The trial treatment(s) and the probability for random assignment to each treatment.
- 629 (d) The trial procedures to be followed, including all invasive procedures.
- 630 (e) The subject's responsibilities.
- 631 (f) Those aspects of the trial that are experimental.
- 632 (g) The reasonably foreseeable risks or inconveniences to the subject and, when
633 applicable, to an embryo, fetus, or nursing infant.
- 634 (h) The reasonably expected benefits. When there is no intended clinical benefit to the
635 subject, the subject should be made aware of this.
- 636 (i) The alternative procedure(s) or course(s) of treatment that may be available to the
637 subject, and their important potential benefits and risks.
- 638 (j) The compensation and/or treatment available to the subject in the event of trial-
639 related injury.
- 640 (k) The anticipated prorated payment, if any, to the subject for participating in the
641 trial.
- 642 (l) The anticipated expenses, if any, to the subject for participating in the trial.

- 643 (m) That the subject's participation in the trial is voluntary and that the subject may
644 refuse to participate or withdraw from the trial, at any time, without penalty or loss
645 of benefits to which the subject is otherwise entitled.
- 646 (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies)
647 will be granted direct access to the subject's original medical records for
648 verification of clinical trial procedures and/or data, without violating the
649 confidentiality of the subject, to the extent permitted by the applicable laws and
650 regulations and that, by signing a written informed consent form, the subject or the
651 subject's legally acceptable representative is authorizing such access.
- 652 (o) That records identifying the subject will be kept confidential and, to the extent
653 permitted by the applicable laws and/or regulations, will not be made publicly
654 available. If the results of the trial are published, the subject's identity will remain
655 confidential.
- 656 (p) That the subject or the subject's legally acceptable representative will be informed
657 in a timely manner if information becomes available that may be relevant to the
658 subject's willingness to continue participation in the trial.
- 659 (q) The person(s) to contact for further information regarding the trial and the rights
660 of trial subjects, and whom to contact in the event of trial-related injury.
- 661 (r) The foreseeable circumstances and/or reasons under which the subject's
662 participation in the trial may be terminated.
- 663 (s) The expected duration of the subject's participation in the trial.
- 664 (t) The approximate number of subjects involved in the trial.
- 665 4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable
666 representative should receive a copy of the signed and dated written informed consent
667 form and any other written information provided to the subjects. During a subject's
668 participation in the trial, the subject or the subject's legally acceptable representative
669 should receive a copy of the signed and dated consent form updates and a copy of any
670 amendments to the written information provided to subjects.
- 671 4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only
672 be enrolled in the trial with the consent of the subject's legally acceptable
673 representative (e.g., minors, or patients with severe dementia), the subject should be
674 informed about the trial to the extent compatible with the subject's understanding and,
675 if capable, the subject should sign and personally date the written informed consent.
- 676 4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e., a trial in which there is no
677 anticipated direct clinical benefit to the subject), should be conducted in subjects who
678 personally give consent and who sign and date the written informed consent form.
- 679 4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally
680 acceptable representative provided the following conditions are fulfilled:
- 681 (a) The objectives of the trial can not be met by means of a trial in subjects who can
682 give informed consent personally.
- 683 (b) The foreseeable risks to the subjects are low.

- 684 (c) The negative impact on the subject's well-being is minimized and low.
685 (d) The trial is not prohibited by law.
686 (e) The approval/favourable opinion of the IRB/IEC is expressly sought on the
687 inclusion of such subjects, and the written approval/ favourable opinion covers
688 this aspect.

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

693 4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent
694 of the subject's legally acceptable representative, if present, should be requested. When
695 prior consent of the subject is not possible, and the subject's legally acceptable
696 representative is not available, enrolment of the subject should require measures
697 described in the protocol and/or elsewhere, with documented approval/favourable
698 opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and
699 to ensure compliance with applicable regulatory requirements. The subject or the
700 subject's legally acceptable representative should be informed about the trial as soon as
701 possible and consent to continue and other consent as appropriate (see 4.8.10) should
702 be requested.

703 4.9 Records and Reports

704 ADDENDUM

705 4.9.0 The investigator should maintain adequate and accurate source documents and trial
706 records that include all pertinent observations on each of the site's trial subjects.
707 Source data should be attributable, legible, contemporaneous, original, accurate, and
708 complete. Changes to source data should be traceable, should not obscure the original
709 entry and should be explained if necessary (e.g., *via* an audit trail).

710 4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness
711 of the data reported to the sponsor in the CRFs and in all required reports.

712 4.9.2 Data reported on the CRF, that are derived from source documents, should be
713 consistent with the source documents or the discrepancies should be explained.

714 4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if
715 necessary) and should not obscure the original entry (i.e., an audit trail should be
716 maintained); this applies to both written and electronic changes or corrections (see
717 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators'
718 designated representatives on making such corrections. Sponsors should have written
719 procedures to assure that changes or corrections in CRFs made by sponsor's designated
720 representatives are documented, are necessary, and are endorsed by the investigator.
721 The investigator should retain records of the changes and corrections.

722 4.9.4 The investigator/institution should maintain the trial documents as specified in
723 Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the
724 applicable regulatory requirement(s). The investigator/institution should take measures
725 to prevent accidental or premature destruction of these documents.

726 4.9.5 Essential documents should be retained until at least 2-years after the last approval of a
727 marketing application in an ICH region and until there are no pending or contemplated
728 marketing applications in an ICH region or at least 2-years have elapsed since the
729 formal discontinuation of clinical development of the investigational product. These
730 documents should be retained for a longer period however if required by the applicable
731 regulatory requirements or by an agreement with the sponsor. It is the responsibility of
732 the sponsor to inform the investigator/institution as to when these documents no
733 longer need to be retained (see 5.5.12).

734 4.9.6 The financial aspects of the trial should be documented in an agreement between the
735 sponsor and the investigator/institution.

736 4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the
737 investigator/institution should make available for direct access all requested trial-
738 related records.

739 **4.10 Progress Reports**

740 4.10.1 The investigator should submit written summaries of the trial status to the IRB/IEC
741 annually, or more frequently, if requested by the IRB/IEC.

742 4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC
743 (see 3.3.8) and, where applicable, the institution on any changes significantly affecting
744 the conduct of the trial, and/or increasing the risk to subjects.

745 **4.11 Safety Reporting**

746 4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor
747 except for those SAEs that the protocol or other document (e.g., Investigator's
748 Brochure) identifies as not needing immediate reporting. The immediate reports
749 should be followed promptly by detailed, written reports. The immediate and follow-
750 up reports should identify subjects by unique code numbers assigned to the trial
751 subjects rather than by the subjects' names, personal identification numbers, and/or
752 addresses. The investigator should also comply with the applicable regulatory
753 requirement(s) related to the reporting of unexpected serious adverse drug reactions to
754 the regulatory authority(ies) and the IRB/IEC.

755 4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to
756 safety evaluations should be reported to the sponsor according to the reporting
757 requirements and within the time periods specified by the sponsor in the protocol.

758 4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with
759 any additional requested information (e.g., autopsy reports and terminal medical
760 reports).

761 **4.12 Premature Termination or Suspension of a Trial**

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

766 4.12.1 If the investigator terminates or suspends a trial without prior agreement of the
767 sponsor, the investigator should inform the institution where applicable, and the
768 investigator/institution should promptly inform the sponsor and the IRB/IEC, and
769 should provide the sponsor and the IRB/IEC a detailed written explanation of the
770 termination or suspension.

771 4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should
772 promptly inform the institution where applicable and the investigator/institution
773 should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written
774 explanation of the termination or suspension.

775 4.12.3 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see
776 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and
777 the investigator/institution should promptly notify the sponsor and provide the sponsor
778 with a detailed written explanation of the termination or suspension.

779 **4.13 Final Report(s) by Investigator**

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

783 **5. SPONSOR**

784 **ADDENDUM**

785 **5.0 Quality Management**

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

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

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

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

798 *5.0.1 Critical Process and Data Identification*

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

801 *5.0.2 Risk Identification*

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

806

- 807 5.0.3 *Risk Evaluation*
808 The identified risks should be evaluated by considering:
809 (a) The likelihood of errors occurring, given existing risk controls.
810 (b) The impact of such errors on human subject protection and data integrity.
811 (c) The extent to which such errors would be detectable.
- 812 5.0.4 *Risk Control*
813 The sponsor should identify those risks that should be reduced (through mitigating
814 actions) and/or can be accepted. Risk mitigation activities may be incorporated in
815 protocol design and implementation, monitoring plans, agreements between parties
816 defining roles and responsibilities, systematic safeguards to ensure adherence to
817 standard operating procedures, and training in processes and procedures.
- 818 Predefined quality tolerance limits should be established, taking into consideration
819 the medical and statistical characteristics of the variables as well as the statistical
820 design of the trial, to identify systematic issues that can impact subject safety or data
821 integrity. Detection of deviations from the predefined quality tolerance limits should
822 trigger an evaluation to determine if action is needed.
- 823 5.0.5 *Risk Communication*
824 The quality management activities should be documented and communicated to
825 stakeholders to facilitate risk review and continual improvement during clinical trial
826 execution.
- 827 5.0.6 *Risk Review*
828 The sponsor should periodically review risk control measures to ascertain whether
829 the implemented quality management activities remain effective and relevant, taking
830 into account emerging knowledge and experience.
- 831 5.0.7 *Risk Reporting*
832 The sponsor should describe the quality management approach implemented in the
833 trial and summarize important deviations from the predefined quality tolerance limits
834 in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).
- 835 **5.1 Quality Assurance and Quality Control**
- 836 5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and
837 quality control systems with written SOPs to ensure that trials are conducted and data
838 are generated, documented (recorded), and reported in compliance with the protocol,
839 GCP, and the applicable regulatory requirement(s).
- 840 5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure
841 direct access (see 1.21) to all trial related sites, source data/documents, and reports for
842 the purpose of monitoring and auditing by the sponsor, and inspection by domestic and
843 foreign regulatory authorities.
- 844 5.1.3 Quality control should be applied to each stage of data handling to ensure that all data
845 are reliable and have been processed correctly.
- 846 5.1.4 Agreements, made by the sponsor with the investigator/institution and any other
847 parties involved with the clinical trial, should be in writing, as part of the protocol or
848 in a separate agreement.

849 **5.2 Contract Research Organization (CRO)**

850 5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a
851 CRO, but the ultimate responsibility for the quality and integrity of the trial data
852 always resides with the sponsor. The CRO should implement quality assurance and
853 quality control.

854 **ADDENDUM**

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

857 5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should
858 be specified in writing.

859 **ADDENDUM**

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

862 5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a
863 CRO are retained by the sponsor.

864 5.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a
865 CRO has assumed the trial related duties and functions of a sponsor.

866 **5.3 Medical Expertise**

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

870 **5.4 Trial Design**

871 5.4.1 The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical
872 pharmacologists, and physicians) as appropriate, throughout all stages of the trial
873 process, from designing the protocol and CRFs and planning the analyses to analyzing
874 and preparing interim and final clinical trial reports.

875 5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the
876 ICH Guideline for Structure and Content of Clinical Study Reports, and other
877 appropriate ICH guidance on trial design, protocol and conduct.

878

879 **5.5 Trial Management, Data Handling, and Record Keeping**

880 5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall
881 conduct of the trial, to handle the data, to verify the data, to conduct the statistical
882 analyses, and to prepare the trial reports.

883 5.5.2 The sponsor may consider establishing an independent data-monitoring committee
884 (IDMC) to assess the progress of a clinical trial, including the safety data and the
885 critical efficacy endpoints at intervals, and to recommend to the sponsor whether to
886 continue, modify, or stop a trial. The IDMC should have written operating procedures
887 and maintain written records of all its meetings.

888 5.5.3 When using electronic trial data handling and/or remote electronic trial data systems,
889 the sponsor should:

890 (a) Ensure and document that the electronic data processing system(s) conforms to the
891 sponsor's established requirements for completeness, accuracy, reliability, and
892 consistent intended performance (i.e., validation).

893 (b) Maintains SOPs for using these systems.

894 **ADDENDUM**

895 The SOPs should cover system setup, installation and use. The SOPs should
896 describe system validation and functionality testing, data collection and handling,
897 system maintenance, system security measures, change control, data backup,
898 recovery, contingency planning and decommissioning. The responsibilities of the
899 sponsor, investigator and other parties with respect to the use of these
900 computerized systems should be clear, and the users should be provided with
901 training in the use of the systems.

902
903 (c) Ensure that the systems are designed to permit data changes in such a way that the
904 data changes are documented and that there is no deletion of entered data (i.e.,
905 maintain an audit trail, data trail, edit trail).

906 (d) Maintain a security system that prevents unauthorized access to the data.

907 (e) Maintain a list of the individuals who are authorized to make data changes (see
908 4.1.5 and 4.9.3).

909 (f) Maintain adequate backup of the data.

910 (g) Safeguard the blinding, if any (e.g., maintain the blinding during data entry and
911 processing).

912 **ADDENDUM**

913 (h) Ensure the integrity of the data including any data that describe the context,
914 content and structure of the data. This is particularly important when making
915 changes to the computerized systems, such as software upgrades or migration of
916 data.

917 5.5.4 If data are transformed during processing, it should always be possible to compare the
918 original data and observations with the processed data.

- 919 5.5.5 The sponsor should use an unambiguous subject identification code (see 1.58) that
920 allows identification of all the data reported for each subject.
- 921 5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific
922 essential documents pertaining to the trial (see 8. Essential Documents for the Conduct
923 of a Clinical Trial).
- 924 5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance
925 with the applicable regulatory requirement(s) of the country(ies) where the product is
926 approved, and/or where the sponsor intends to apply for approval(s).
- 927 5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e.,
928 for any or all indications, routes of administration, or dosage forms), the sponsor
929 should maintain all sponsor-specific essential documents for at least 2-years after
930 formal discontinuation or in conformance with the applicable regulatory
931 requirement(s).
- 932 5.5.9 If the sponsor discontinues the clinical development of an investigational product, the
933 sponsor should notify all the trial investigators/institutions and all the regulatory
934 authorities.
- 935 5.5.10 Any transfer of ownership of the data should be reported to the appropriate
936 authority(ies), as required by the applicable regulatory requirement(s).
- 937 5.5.11 The sponsor specific essential documents should be retained until at least 2-years after
938 the last approval of a marketing application in an ICH region and until there are no
939 pending or contemplated marketing applications in an ICH region or at least 2-years
940 have elapsed since the formal discontinuation of clinical development of the
941 investigational product. These documents should be retained for a longer period
942 however if required by the applicable regulatory requirement(s) or if needed by the
943 sponsor.
- 944 5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for
945 record retention and should notify the investigator(s)/institution(s) in writing when the
946 trial related records are no longer needed.
- 947 **5.6 Investigator Selection**
- 948 5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each
949 investigator should be qualified by training and experience and should have adequate
950 resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is
951 selected. If organization of a coordinating committee and/or selection of coordinating
952 investigator(s) are to be utilized in multicentre trials, their organization and/or
953 selection are the sponsor's responsibility.
- 954 5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the
955 sponsor should provide the investigator(s)/institution(s) with the protocol and an up-
956 to-date Investigator's Brochure, and should provide sufficient time for the
957 investigator/institution to review the protocol and the information provided.

- 958 5.6.3 The sponsor should obtain the investigator's/institution's agreement:
959 (a) to conduct the trial in compliance with GCP, with the applicable regulatory
960 requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and
961 given approval/favourable opinion by the IRB/IEC (see 4.5.1);
962 (b) to comply with procedures for data recording/reporting;
963 (c) to permit monitoring, auditing and inspection (see 4.1.4) and
964 (d) to retain the trial related essential documents until the sponsor informs the
965 investigator/institution these documents are no longer needed (see 4.9.4 and
966 5.5.12).

967 The sponsor and the investigator/institution should sign the protocol, or an alternative
968 document, to confirm this agreement.

969 **5.7 Allocation of Responsibilities**

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

972 **5.8 Compensation to Subjects and Investigators**

973 5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide
974 insurance or should indemnify (legal and financial coverage) the investigator/the
975 institution against claims arising from the trial, except for claims that arise from
976 malpractice and/or negligence.

977 5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial
978 subjects in the event of trial-related injuries in accordance with the applicable
979 regulatory requirement(s).

980 5.8.3 When trial subjects receive compensation, the method and manner of compensation
981 should comply with applicable regulatory requirement(s).

982 **5.9 Financing**

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

985 **5.10 Notification/Submission to Regulatory Authority(ies)**

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

992 **5.11 Confirmation of Review by IRB/IEC**

993 5.11.1 The sponsor should obtain from the investigator/institution:

- 994 (a) The name and address of the investigator's/institution's IRB/IEC.

- 995 (b) A statement obtained from the IRB/IEC that it is organized and operates according
996 to GCP and the applicable laws and regulations.
- 997 (c) Documented IRB/IEC approval/favourable opinion and, if requested by the
998 sponsor, a current copy of protocol, written informed consent form(s) and any
999 other written information to be provided to subjects, subject recruiting procedures,
1000 and documents related to payments and compensation available to the subjects,
1001 and any other documents that the IRB/IEC may have requested.
- 1002 5.11.2 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any
1003 aspect of the trial, such as modification(s) of the protocol, written informed consent
1004 form and any other written information to be provided to subjects, and/or other
1005 procedures, the sponsor should obtain from the investigator/institution a copy of the
1006 modification(s) made and the date approval/favourable opinion was given by the
1007 IRB/IEC.
- 1008 5.11.3 The sponsor should obtain from the investigator/institution documentation and dates
1009 of any IRB/IEC reapprovals/re-evaluations with favourable opinion, and of any
1010 withdrawals or suspensions of approval/favourable opinion.
- 1011 **5.12 Information on Investigational Product(s)**
- 1012 5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data
1013 from nonclinical studies and/or clinical trials are available to support human exposure
1014 by the route, at the dosages, for the duration, and in the trial population to be studied.
- 1015 5.12.2 The sponsor should update the Investigator's Brochure as significant new information
1016 becomes available (see 7. Investigator's Brochure).
- 1017 **5.13 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)**
- 1018 5.13.1 The sponsor should ensure that the investigational product(s) (including active
1019 comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of
1020 development of the product(s), is manufactured in accordance with any applicable
1021 GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In
1022 addition, the labelling should comply with applicable regulatory requirement(s).
- 1023 5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage
1024 temperatures, storage conditions (e.g., protection from light), storage times,
1025 reconstitution fluids and procedures, and devices for product infusion, if any. The
1026 sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists,
1027 storage managers) of these determinations.
- 1028 5.13.3 The investigational product(s) should be packaged to prevent contamination and
1029 unacceptable deterioration during transport and storage.
- 1030 5.13.4 In blinded trials, the coding system for the investigational product(s) should include a
1031 mechanism that permits rapid identification of the product(s) in case of a medical
1032 emergency, but does not permit undetectable breaks of the blinding.

1033 5.13.5 If significant formulation changes are made in the investigational or comparator
1034 product(s) during the course of clinical development, the results of any additional
1035 studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability)
1036 needed to assess whether these changes would significantly alter the pharmacokinetic
1037 profile of the product should be available prior to the use of the new formulation in
1038 clinical trials.

1039 **5.14 Supplying and Handling Investigational Product(s)**

1040 5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the
1041 investigational product(s).

1042 5.14.2 The sponsor should not supply an investigator/institution with the investigational
1043 product(s) until the sponsor obtains all required documentation (e.g.,
1044 approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

1045 5.14.3 The sponsor should ensure that written procedures include instructions that the
1046 investigator/institution should follow for the handling and storage of investigational
1047 product(s) for the trial and documentation thereof. The procedures should address
1048 adequate and safe receipt, handling, storage, dispensing, retrieval of unused product
1049 from subjects, and return of unused investigational product(s) to the sponsor (or
1050 alternative disposition if authorized by the sponsor and in compliance with the
1051 applicable regulatory requirement(s)).

1052 5.14.4 The sponsor should:

- 1053 (a) Ensure timely delivery of investigational product(s) to the investigator(s).
- 1054 (b) Maintain records that document shipment, receipt, disposition, return, and
1055 destruction of the investigational product(s) (see 8. Essential Documents for the
1056 Conduct of a Clinical Trial).
- 1057 (c) Maintain a system for retrieving investigational products and documenting this
1058 retrieval (e.g., for deficient product recall, reclaim after trial completion, expired
1059 product reclaim).
- 1060 (d) Maintain a system for the disposition of unused investigational product(s) and for
1061 the documentation of this disposition.

1062 5.14.5 The sponsor should:

- 1063 (a) Take steps to ensure that the investigational product(s) are stable over the period
1064 of use.
- 1065 (b) Maintain sufficient quantities of the investigational product(s) used in the trials to
1066 reconfirm specifications, should this become necessary, and maintain records of
1067 batch sample analyses and characteristics. To the extent stability permits, samples
1068 should be retained either until the analyses of the trial data are complete or as
1069 required by the applicable regulatory requirement(s), whichever represents the
1070 longer retention period.

1071

1072 **5.15 Record Access**

1073 5.15.1 The sponsor should ensure that it is specified in the protocol or other written
1074 agreement that the investigator(s)/institution(s) provide direct access to source
1075 data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory
1076 inspection.

1077 5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access
1078 to his/her original medical records for trial-related monitoring, audit, IRB/IEC review,
1079 and regulatory inspection.

1080 **5.16 Safety Information**

1081 5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational
1082 product(s).

1083 5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the
1084 regulatory authority(ies) of findings that could affect adversely the safety of subjects,
1085 impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to
1086 continue the trial.

1087 **5.17 Adverse Drug Reaction Reporting**

1088 5.17.1 The sponsor should expedite the reporting to all concerned
1089 investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the
1090 regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and
1091 unexpected.

1092 5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s)
1093 and with the ICH Guideline for Clinical Safety Data Management: Definitions and
1094 Standards for Expedited Reporting.

1095 5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and
1096 periodic reports, as required by applicable regulatory requirement(s).

1097 **5.18 Monitoring**

1098 *5.18.1 Purpose*

1099 The purposes of trial monitoring are to verify that:

1100 (a) The rights and well-being of human subjects are protected.

1101 (b) The reported trial data are accurate, complete, and verifiable from source
1102 documents.

1103 (c) The conduct of the trial is in compliance with the currently approved
1104 protocol/amendment(s), with GCP, and with the applicable regulatory
1105 requirement(s).

1106 *5.18.2 Selection and Qualifications of Monitors*

1107 (a) Monitors should be appointed by the sponsor.

1108 (b) Monitors should be appropriately trained, and should have the scientific and/or
1109 clinical knowledge needed to monitor the trial adequately. A monitor's
1110 qualifications should be documented.

1111 (c) Monitors should be thoroughly familiar with the investigational product(s), the
1112 protocol, written informed consent form and any other written information to be
1113 provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory
1114 requirement(s).

1115 *5.18.3 Extent and Nature of Monitoring*

1116 The sponsor should ensure that the trials are adequately monitored. The sponsor
1117 should determine the appropriate extent and nature of monitoring. The determination
1118 of the extent and nature of monitoring should be based on considerations such as the
1119 objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In
1120 general there is a need for on-site monitoring, before, during, and after the trial;
1121 however in exceptional circumstances the sponsor may determine that central
1122 monitoring in conjunction with procedures such as investigators' training and
1123 meetings, and extensive written guidance can assure appropriate conduct of the trial in
1124 accordance with GCP. Statistically controlled sampling may be an acceptable method
1125 for selecting the data to be verified.

1126 **ADDENDUM**

1127 The sponsor should develop a systematic, prioritized, risk-based approach to
1128 monitoring clinical trials. The flexibility in the extent and nature of monitoring
1129 described in this section is intended to permit varied approaches that improve the
1130 effectiveness and efficiency of monitoring. A combination of on-site and centralized
1131 monitoring activities may be appropriate. The sponsor should document the rationale
1132 for the chosen monitoring strategy (e.g., in the monitoring plan).

1133 *On-site* monitoring is performed at the sites at which the clinical trial is being
1134 conducted.

1135 Centralized monitoring is a remote evaluation of ongoing and/or cumulative data
1136 collected from trial sites, in a timely manner. Centralized monitoring processes provide
1137 additional monitoring capabilities that can complement and reduce the extent and/or
1138 frequency of on-site monitoring by such methods as:

- 1139 (a) Routine review of submitted data.
- 1140 (b) Identification of missing data, inconsistent data, data outliers or unexpected lack
1141 of variability and protocol deviations that may be indicative of systematic or
1142 significant errors in data collection and reporting at a site or across sites, or may
1143 be indicative of potential data manipulation or data integrity problems.
- 1144 (c) Using statistical analyses to identify data trends such as the range and
1145 consistency of data within and across sites.
- 1146 (d) Analyzing site characteristics and performance metrics.
- 1147 (e) Selection of sites and/or processes for targeted on-site monitoring.

1148

1149 *5.18.4 Monitor's Responsibilities*

1150 The monitor(s) in accordance with the sponsor's requirements should ensure that the
1151 trial is conducted and documented properly by carrying out the following activities
1152 when relevant and necessary to the trial and the trial site:

1153 (a) Acting as the main line of communication between the sponsor and the
1154 investigator.

1155 (b) Verifying that the investigator has adequate qualifications and resources (see 4.1,
1156 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including
1157 laboratories, equipment, and staff, are adequate to safely and properly conduct the
1158 trial and remain adequate throughout the trial period.

1159 (c) Verifying, for the investigational product(s):

1160 (i) That storage times and conditions are acceptable, and that supplies are
1161 sufficient throughout the trial.

1162 (ii) That the investigational product(s) are supplied only to subjects who are
1163 eligible to receive it and at the protocol specified dose(s).

1164 (iii) That subjects are provided with necessary instruction on properly using,
1165 handling, storing, and returning the investigational product(s).

1166 (iv) That the receipt, use, and return of the investigational product(s) at the trial
1167 sites are controlled and documented adequately.

1168 (v) That the disposition of unused investigational product(s) at the trial sites
1169 complies with applicable regulatory requirement(s) and is in accordance
1170 with the sponsor.

1171 (d) Verifying that the investigator follows the approved protocol and all approved
1172 amendment(s), if any.

1173 (e) Verifying that written informed consent was obtained before each subject's
1174 participation in the trial.

1175 (f) Ensuring that the investigator receives the current Investigator's Brochure, all
1176 documents, and all trial supplies needed to conduct the trial properly and to
1177 comply with the applicable regulatory requirement(s).

1178 (g) Ensuring that the investigator and the investigator's trial staff are adequately
1179 informed about the trial.

1180 (h) Verifying that the investigator and the investigator's trial staff are performing the
1181 specified trial functions, in accordance with the protocol and any other written
1182 agreement between the sponsor and the investigator/institution, and have not
1183 delegated these functions to unauthorized individuals.

1184 (i) Verifying that the investigator is enrolling only eligible subjects.

1185 (j) Reporting the subject recruitment rate.

1186 (k) Verifying that source documents and other trial records are accurate, complete,
1187 kept up-to-date and maintained.

- 1188 (l) Verifying that the investigator provides all the required reports, notifications,
1189 applications, and submissions, and that these documents are accurate, complete,
1190 timely, legible, dated, and identify the trial.
- 1191 (m) Checking the accuracy and completeness of the CRF entries, source documents
1192 and other trial-related records against each other. The monitor specifically should
1193 verify that:
- 1194 (i) The data required by the protocol are reported accurately on the CRFs and
1195 are consistent with the source documents.
- 1196 (ii) Any dose and/or therapy modifications are well documented for each of the
1197 trial subjects.
- 1198 (iii) Adverse events, concomitant medications and intercurrent illnesses are
1199 reported in accordance with the protocol on the CRFs.
- 1200 (iv) Visits that the subjects fail to make, tests that are not conducted, and
1201 examinations that are not performed are clearly reported as such on the
1202 CRFs.
- 1203 (v) All withdrawals and dropouts of enrolled subjects from the trial are reported
1204 and explained on the CRFs.
- 1205 (n) Informing the investigator of any CRF entry error, omission, or illegibility. The
1206 monitor should ensure that appropriate corrections, additions, or deletions are
1207 made, dated, explained (if necessary), and initialled by the investigator or by a
1208 member of the investigator's trial staff who is authorized to initial CRF changes
1209 for the investigator. This authorization should be documented.
- 1210 (o) Determining whether all adverse events (AEs) are appropriately reported within
1211 the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the
1212 applicable regulatory requirement(s).
- 1213 (p) Determining whether the investigator is maintaining the essential documents (see
1214 8. Essential Documents for the Conduct of a Clinical Trial).
- 1215 (q) Communicating deviations from the protocol, SOPs, GCP, and the applicable
1216 regulatory requirements to the investigator and taking appropriate action designed
1217 to prevent recurrence of the detected deviations.

1218 *5.18.5 Monitoring Procedures*

1219 The monitor(s) should follow the sponsor's established written SOPs as well as those
1220 procedures that are specified by the sponsor for monitoring a specific trial.

1221 *5.18.6 Monitoring Report*

- 1222 (a) The monitor should submit a written report to the sponsor after each trial-site visit
1223 or trial-related communication.
- 1224 (b) Reports should include the date, site, name of the monitor, and name of the
1225 investigator or other individual(s) contacted.
- 1226 (c) Reports should include a summary of what the monitor reviewed and the monitor's
1227 statements concerning the significant findings/facts, deviations and deficiencies,

1228 conclusions, actions taken or to be taken and/or actions recommended to secure
1229 compliance.

1230 (d) The review and follow-up of the monitoring report with the sponsor should be
1231 documented by the sponsor's designated representative.

1232 **ADDENDUM**

1233 (e) Monitoring results should be provided to the sponsor (including appropriate
1234 management and staff responsible for trial and site oversight) in a timely manner
1235 for review and follow up as indicated. Results of monitoring activities should be
1236 documented in sufficient detail to allow verification of compliance with the
1237 monitoring plan.

1238 **ADDENDUM**

1240 *5.18.7 Monitoring Plan*

1241 The sponsor should develop a monitoring plan that is tailored to the specific human
1242 subject protection and data integrity risks of the trial. The plan should describe the
1243 monitoring strategy, the monitoring responsibilities of all the parties involved, the
1244 various monitoring methods to be used and the rationale for their use. The plan
1245 should also emphasize the monitoring of critical data and processes. Particular
1246 attention should be given to those aspects that are not routine clinical practice and
1247 that require additional training. The monitoring plan should reference the applicable
1248 policies and procedures.

1249 **5.19 Audit**

1250 If or when sponsors perform audits, as part of implementing quality assurance, they should
1251 consider:

1252 *5.19.1 Purpose*

1253 The purpose of a sponsor's audit, which is independent of and separate from routine
1254 monitoring or quality control functions, should be to evaluate trial conduct and
1255 compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

1256 *5.19.2 Selection and Qualification of Auditors*

1257 (a) The sponsor should appoint individuals, who are independent of the clinical
1258 trials/systems, to conduct audits.

1259 (b) The sponsor should ensure that the auditors are qualified by training and
1260 experience to conduct audits properly. An auditor's qualifications should be
1261 documented.

1262 *5.19.3 Auditing Procedures*

1263 (a) The sponsor should ensure that the auditing of clinical trials/systems is conducted
1264 in accordance with the sponsor's written procedures on what to audit, how to audit,
1265 the frequency of audits, and the form and content of audit reports.

1266 (b) The sponsor's audit plan and procedures for a trial audit should be guided by the
1267 importance of the trial to submissions to regulatory authorities, the number of

- 1268 subjects in the trial, the type and complexity of the trial, the level of risks to the
1269 trial subjects, and any identified problem(s).
- 1270 (c) The observations and findings of the auditor(s) should be documented.
- 1271 (d) To preserve the independence and value of the audit function, the regulatory
1272 authority(ies) should not routinely request the audit reports. Regulatory
1273 authority(ies) may seek access to an audit report on a case by case basis when
1274 evidence of serious GCP non-compliance exists, or in the course of legal
1275 proceedings.
- 1276 (e) When required by applicable law or regulation, the sponsor should provide an
1277 audit certificate.

1278 **5.20 Noncompliance**

- 1279 5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory
1280 requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff
1281 should lead to prompt action by the sponsor to secure compliance.

1282 **ADDENDUM**

1283 When significant noncompliance is discovered, the sponsor should perform a root
1284 cause analysis and implement appropriate corrective and preventive actions. If required
1285 by applicable law or regulation the sponsor should inform the regulatory authority(ies)
1286 when the noncompliance is a serious breach of the trial protocol or GCP.

- 1287 5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on
1288 the part of an investigator/institution, the sponsor should terminate the
1289 investigator's/institution's participation in the trial. When an investigator's/institution's
1290 participation is terminated because of noncompliance, the sponsor should notify
1291 promptly the regulatory authority(ies).

1292 **5.21 Premature Termination or Suspension of a Trial**

1293 If a trial is prematurely terminated or suspended, the sponsor should promptly inform the
1294 investigators/institutions, and the regulatory authority(ies) of the termination or suspension
1295 and the reason(s) for the termination or suspension. The IRB/IEC should also be informed
1296 promptly and provided the reason(s) for the termination or suspension by the sponsor or by the
1297 investigator/institution, as specified by the applicable regulatory requirement(s).

1298 **5.22 Clinical Trial/Study Reports**

1299 Whether the trial is completed or prematurely terminated, the sponsor should ensure that the
1300 clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the
1301 applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial
1302 reports in marketing applications meet the standards of the ICH Guideline for Structure and
1303 Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of
1304 Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain
1305 cases.)

1306 **5.23 Multicentre Trials**

1307 For multicentre trials, the sponsor should ensure that:

1308 5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by
1309 the sponsor and, if required, by the regulatory authority(ies), and given
1310 approval/favourable opinion by the IRB/IEC.

1311 5.23.2 The CRFs are designed to capture the required data at all multicentre trial sites. For
1312 those investigators who are collecting additional data, supplemental CRFs should also
1313 be provided that are designed to capture the additional data.

1314 5.23.3 The responsibilities of coordinating investigator(s) and the other participating
1315 investigators are documented prior to the start of the trial.

1316 5.23.4 All investigators are given instructions on following the protocol, on complying with a
1317 uniform set of standards for the assessment of clinical and laboratory findings, and on
1318 completing the CRFs.

1319 5.23.5 Communication between investigators is facilitated.

1320 **6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)**

1321 The contents of a trial protocol should generally include the following topics. However, site
1322 specific information may be provided on separate protocol page(s), or addressed in a separate
1323 agreement, and some of the information listed below may be contained in other protocol
1324 referenced documents, such as an Investigator's Brochure.

1325 **6.1 General Information**

1326 6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also
1327 bear the amendment number(s) and date(s).

1328 6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

1329 6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol
1330 amendment(s) for the sponsor.

1331 6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or
1332 dentist when appropriate) for the trial.

1333 6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial,
1334 and the address and telephone number(s) of the trial site(s).

1335 6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if
1336 applicable), who is responsible for all trial-site related medical (or dental) decisions (if
1337 other than investigator).

1338 6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or
1339 technical department(s) and/or institutions involved in the trial.

1340 **6.2 Background Information**

1341 6.2.1 Name and description of the investigational product(s).

- 1342 6.2.2 A summary of findings from nonclinical studies that potentially have clinical
1343 significance and from clinical trials that are relevant to the trial.
- 1344 6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.
- 1345 6.2.4 Description of and justification for the route of administration, dosage, dosage
1346 regimen, and treatment period(s).
- 1347 6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and
1348 the applicable regulatory requirement(s).
- 1349 6.2.6 Description of the population to be studied.
- 1350 6.2.7 References to literature and data that are relevant to the trial, and that provide
1351 background for the trial.
- 1352 **6.3 Trial Objectives and Purpose**
- 1353 A detailed description of the objectives and the purpose of the trial.
- 1354 **6.4 Trial Design**
- 1355 The scientific integrity of the trial and the credibility of the data from the trial depend
1356 substantially on the trial design. A description of the trial design, should include:
- 1357 6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to
1358 be measured during the trial.
- 1359 6.4.2 A description of the type/design of trial to be conducted (e.g., double-blind, placebo-
1360 controlled, parallel design) and a schematic diagram of trial design, procedures and
1361 stages.
- 1362 6.4.3 A description of the measures taken to minimize/avoid bias, including:
1363 (a) Randomization.
1364 (b) Blinding.
- 1365 6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the
1366 investigational product(s). Also include a description of the dosage form, packaging,
1367 and labelling of the investigational product(s).
- 1368 6.4.5 The expected duration of subject participation, and a description of the sequence and
1369 duration of all trial periods, including follow-up, if any.
- 1370 6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual
1371 subjects, parts of trial and entire trial.
- 1372 6.4.7 Accountability procedures for the investigational product(s), including the placebo(s)
1373 and comparator(s), if any.
- 1374 6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking
1375 codes.

1376 6.4.9 The identification of any data to be recorded directly on the CRFs (i.e., no prior
1377 written or electronic record of data), and to be considered to be source data.

1378 **6.5 Selection and Withdrawal of Subjects**

1379 6.5.1 Subject inclusion criteria.

1380 6.5.2 Subject exclusion criteria.

1381 6.5.3 Subject withdrawal criteria (i.e., terminating investigational product treatment/trial
1382 treatment) and procedures specifying:

1383 (a) When and how to withdraw subjects from the trial/ investigational product
1384 treatment.

1385 (b) The type and timing of the data to be collected for withdrawn subjects.

1386 (c) Whether and how subjects are to be replaced.

1387 (d) The follow-up for subjects withdrawn from investigational product treatment/trial
1388 treatment.

1389 **6.6 Treatment of Subjects**

1390 6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the
1391 dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment
1392 period(s), including the follow-up period(s) for subjects for each investigational
1393 product treatment/trial treatment group/arm of the trial.

1394 6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted
1395 before and/or during the trial.

1396 6.6.3 Procedures for monitoring subject compliance.

1397 **6.7 Assessment of Efficacy**

1398 6.7.1 Specification of the efficacy parameters.

1399 6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

1400 **6.8 Assessment of Safety**

1401 6.8.1 Specification of safety parameters.

1402 6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

1403 6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and
1404 intercurrent illnesses.

1405 6.8.4 The type and duration of the follow-up of subjects after adverse events.

1406

1407 **6.9 Statistics**

1408 6.9.1 A description of the statistical methods to be employed, including timing of any
1409 planned interim analysis(es).

1410 6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of
1411 enrolled subjects projected for each trial site should be specified. Reason for choice of
1412 sample size, including reflections on (or calculations of) the power of the trial and
1413 clinical justification.

1414 6.9.3 The level of significance to be used.

1415 6.9.4 Criteria for the termination of the trial.

1416 6.9.5 Procedure for accounting for missing, unused, and spurious data.

1417 6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any
1418 deviation(s) from the original statistical plan should be described and justified in
1419 protocol and/or in the final report, as appropriate).

1420 6.9.7 The selection of subjects to be included in the analyses (e.g., all randomized subjects,
1421 all dosed subjects, all eligible subjects, evaluable subjects).

1422 **6.10 Direct Access to Source Data/Documents**

1423 The sponsor should ensure that it is specified in the protocol or other written agreement that
1424 the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review,
1425 and regulatory inspection(s), providing direct access to source data/documents.

1426 **6.11 Quality Control and Quality Assurance**

1427 **6.12 Ethics**

1428 Description of ethical considerations relating to the trial.

1429 **6.13 Data Handling and Record Keeping**

1430 **6.14 Financing and Insurance**

1431 Financing and insurance if not addressed in a separate agreement.

1432 **6.15 Publication Policy**

1433 Publication policy, if not addressed in a separate agreement.

1434 **6.16 Supplements**

1435 (NOTE: Since the protocol and the clinical trial/study report are closely related, further
1436 relevant information can be found in the ICH Guideline for Structure and Content of Clinical
1437 Study Reports.)

1438

1439 **7. INVESTIGATOR'S BROCHURE**

1440 **7.1 Introduction**

1441 The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the
1442 investigational product(s) that are relevant to the study of the product(s) in human subjects. Its
1443 purpose is to provide the investigators and others involved in the trial with the information to
1444 facilitate their understanding of the rationale for, and their compliance with, many key features
1445 of the protocol, such as the dose, dose frequency/interval, methods of administration: and
1446 safety monitoring procedures. The IB also provides insight to support the clinical management
1447 of the study subjects during the course of the clinical trial. The information should be
1448 presented in a concise, simple, objective, balanced, and non-promotional form that enables a
1449 clinician, or potential investigator, to understand it and make his/her own unbiased risk-
1450 benefit assessment of the appropriateness of the proposed trial. For this reason, a medically
1451 qualified person should generally participate in the editing of an IB, but the contents of the IB
1452 should be approved by the disciplines that generated the described data.

1453 This guideline delineates the minimum information that should be included in an IB and
1454 provides suggestions for its layout. It is expected that the type and extent of information
1455 available will vary with the stage of development of the investigational product. If the
1456 investigational product is marketed and its pharmacology is widely understood by medical
1457 practitioners, an extensive IB may not be necessary. Where permitted by regulatory
1458 authorities, a basic product information brochure, package leaflet, or labelling may be an
1459 appropriate alternative, provided that it includes current, comprehensive, and detailed
1460 information on all aspects of the investigational product that might be of importance to the
1461 investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB
1462 specific to that new use should be prepared. The IB should be reviewed at least annually and
1463 revised as necessary in compliance with a sponsor's written procedures. More frequent
1464 revision may be appropriate depending on the stage of development and the generation of
1465 relevant new information. However, in accordance with Good Clinical Practice, relevant new
1466 information may be so important that it should be communicated to the investigators, and
1467 possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs)
1468 and/or regulatory authorities before it is included in a revised IB.

1469 Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to
1470 the investigator(s) and the investigators are responsible for providing the up-to-date IB to the
1471 responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator
1472 should determine whether a brochure is available from the commercial manufacturer. If the
1473 investigational product is provided by the sponsor-investigator, then he or she should provide
1474 the necessary information to the trial personnel. In cases where preparation of a formal IB is
1475 impractical, the sponsor-investigator should provide, as a substitute, an expanded background
1476 information section in the trial protocol that contains the minimum current information
1477 described in this guideline.

1478 **7.2 General Considerations**

1479 The IB should include:

1480 *7.2.1 Title Page*

1481 This should provide the sponsor's name, the identity of each investigational product
1482 (i.e., research number, chemical or approved generic name, and trade name(s) where

1483 legally permissible and desired by the sponsor), and the release date. It is also
1484 suggested that an edition number, and a reference to the number and date of the edition
1485 it supersedes, be provided. An example is given in Appendix 1.

1486 **7.2.2 Confidentiality Statement**

1487 The sponsor may wish to include a statement instructing the investigator/recipients to
1488 treat the IB as a confidential document for the sole information and use of the
1489 investigator's team and the IRB/IEC.

1490 **7.3 Contents of the Investigator's Brochure**

1491 The IB should contain the following sections, each with literature references where
1492 appropriate:

1493 **7.3.1 Table of Contents**

1494 An example of the Table of Contents is given in Appendix 2

1495 **7.3.2 Summary**

1496 A brief summary (preferably not exceeding two pages) should be given, highlighting
1497 the significant physical, chemical, pharmaceutical, pharmacological, toxicological,
1498 pharmacokinetic, metabolic, and clinical information available that is relevant to the
1499 stage of clinical development of the investigational product.

1500 **7.3.3 Introduction**

1501 A brief introductory statement should be provided that contains the chemical name
1502 (and generic and trade name(s) when approved) of the investigational product(s), all
1503 active ingredients, the investigational product (s) pharmacological class and its
1504 expected position within this class (e.g., advantages), the rationale for performing
1505 research with the investigational product(s), and the anticipated prophylactic,
1506 therapeutic, or diagnostic indication(s). Finally, the introductory statement should
1507 provide the general approach to be followed in evaluating the investigational product.

1508 **7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation**

1509 A description should be provided of the investigational product substance(s) (including
1510 the chemical and/or structural formula(e)), and a brief summary should be given of the
1511 relevant physical, chemical, and pharmaceutical properties.

1512 To permit appropriate safety measures to be taken in the course of the trial, a
1513 description of the formulation(s) to be used, including excipients, should be provided
1514 and justified if clinically relevant. Instructions for the storage and handling of the
1515 dosage form(s) should also be given.

1516 Any structural similarities to other known compounds should be mentioned.

1517

1518 7.3.5 *Nonclinical Studies*

1519 *Introduction:*

1520 The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and
1521 investigational product metabolism studies should be provided in summary form. This
1522 summary should address the methodology used, the results, and a discussion of the
1523 relevance of the findings to the investigated therapeutic and the possible unfavourable
1524 and unintended effects in humans.

1525 The information provided may include the following, as appropriate, if
1526 known/available:

- 1527 • Species tested
- 1528 • Number and sex of animals in each group
- 1529 • Unit dose (e.g., milligram/kilogram (mg/kg))
- 1530 • Dose interval
- 1531 • Route of administration
- 1532 • Duration of dosing
- 1533 • Information on systemic distribution
- 1534 • Duration of post-exposure follow-up
- 1535 • Results, including the following aspects:
 - 1536 – Nature and frequency of pharmacological or toxic effects
 - 1537 – Severity or intensity of pharmacological or toxic effects
 - 1538 – Time to onset of effects
 - 1539 – Reversibility of effects
 - 1540 – Duration of effects
 - 1541 – Dose response

1542 Tabular format/listings should be used whenever possible to enhance the clarity of the
1543 presentation.

1544 The following sections should discuss the most important findings from the studies,
1545 including the dose response of observed effects, the relevance to humans, and any
1546 aspects to be studied in humans. If applicable, the effective and nontoxic dose findings
1547 in the same animal species should be compared (i.e., the therapeutic index should be
1548 discussed). The relevance of this information to the proposed human dosing should be
1549 addressed. Whenever possible, comparisons should be made in terms of blood/tissue
1550 levels rather than on a mg/kg basis.

1551 (a) *Nonclinical Pharmacology*

1552 A summary of the pharmacological aspects of the investigational product and, where
1553 appropriate, its significant metabolites studied in animals, should be included. Such a
1554 summary should incorporate studies that assess potential therapeutic activity (e.g.,
1555 efficacy models, receptor binding, and specificity) as well as those that assess safety
1556 (e.g., special studies to assess pharmacological actions other than the intended
1557 therapeutic effect(s)).

1558

1559 (b) *Pharmacokinetics and Product Metabolism in Animals*

1560 A summary of the pharmacokinetics and biological transformation and disposition of
1561 the investigational product in all species studied should be given. The discussion of the
1562 findings should address the absorption and the local and systemic bioavailability of the
1563 investigational product and its metabolites, and their relationship to the
1564 pharmacological and toxicological findings in animal species.

1565 (c) *Toxicology*

1566 A summary of the toxicological effects found in relevant studies conducted in different
1567 animal species should be described under the following headings where appropriate:

- 1568 – Single dose
- 1569 – Repeated dose
- 1570 – Carcinogenicity
- 1571 – Special studies (e.g., irritancy and sensitisation)
- 1572 – Reproductive toxicity
- 1573 – Genotoxicity (mutagenicity)

1574 7.3.6 *Effects in Humans*

1575 *Introduction:*

1576 A thorough discussion of the known effects of the investigational product(s) in humans
1577 should be provided, including information on pharmacokinetics, metabolism,
1578 pharmacodynamics, dose response, safety, efficacy, and other pharmacological
1579 activities. Where possible, a summary of each completed clinical trial should be
1580 provided. Information should also be provided regarding results of any use of the
1581 investigational product(s) other than from in clinical trials, such as from experience
1582 during marketing.

1583 (a) *Pharmacokinetics and Product Metabolism in Humans*

- 1584 – A summary of information on the pharmacokinetics of the investigational
1585 product(s) should be presented, including the following, if available:
- 1586 – Pharmacokinetics (including metabolism, as appropriate, and absorption,
1587 plasma protein binding, distribution, and elimination).
- 1588 – Bioavailability of the investigational product (absolute, where possible, and/or
1589 relative) using a reference dosage form.
- 1590 – Population subgroups (e.g., gender, age, and impaired organ function).
- 1591 – Interactions (e.g., product-product interactions and effects of food).
- 1592 – Other pharmacokinetic data (e.g., results of population studies performed
1593 within clinical trial(s)).

1594 (b) *Safety and Efficacy*

1595 A summary of information should be provided about the investigational
1596 product's/products' (including metabolites, where appropriate) safety,
1597 pharmacodynamics, efficacy, and dose response that were obtained from preceding
1598 trials in humans (healthy volunteers and/or patients). The implications of this
1599 information should be discussed. In cases where a number of clinical trials have been
1600 completed, the use of summaries of safety and efficacy across multiple trials by
1601 indications in subgroups may provide a clear presentation of the data. Tabular
1602 summaries of adverse drug reactions for all the clinical trials (including those for all

1603 the studied indications) would be useful. Important differences in adverse drug reaction
1604 patterns/incidences across indications or subgroups should be discussed.

1605 The IB should provide a description of the possible risks and adverse drug reactions to
1606 be anticipated on the basis of prior experiences with the product under investigation
1607 and with related products. A description should also be provided of the precautions or
1608 special monitoring to be done as part of the investigational use of the product(s).

1609 *(c) Marketing Experience*

1610 The IB should identify countries where the investigational product has been marketed
1611 or approved. Any significant information arising from the marketed use should be
1612 summarised (e.g., formulations, dosages, routes of administration, and adverse product
1613 reactions). The IB should also identify all the countries where the investigational
1614 product did not receive approval/registration for marketing or was withdrawn from
1615 marketing/registration.

1616 *7.3.7 Summary of Data and Guidance for the Investigator*

1617 This section should provide an overall discussion of the nonclinical and clinical data,
1618 and should summarise the information from various sources on different aspects of the
1619 investigational product(s), wherever possible. In this way, the investigator can be
1620 provided with the most informative interpretation of the available data and with an
1621 assessment of the implications of the information for future clinical trials.

1622 Where appropriate, the published reports on related products should be discussed. This
1623 could help the investigator to anticipate adverse drug reactions or other problems in
1624 clinical trials.

1625 **The overall aim of this section is to provide the investigator with a clear understanding**
1626 **of the possible risks and adverse reactions, and of the specific tests, observations, and**
1627 **precautions that may be needed for a clinical trial. This understanding should be based**
1628 **on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and**
1629 **clinical information on the investigational product(s). Guidance should also be provided**
1630 **to the clinical investigator on the recognition and treatment of possible overdose and**
1631 **adverse drug reactions that is based on previous human experience and on the**
1632 **pharmacology of the investigational product.**

1633

1634 **7.4 APPENDIX 1:**

1635 **TITLE PAGE** (*Example*)

1636 **SPONSOR'S NAME**

1637 **Product:**

1638 **Research Number:**

1639 **Name(s):** Chemical, Generic (if approved)

1640 Trade Name(s) (if legally permissible and desired by the sponsor)

1641

1642 **INVESTIGATOR'S BROCHURE**

1643

1644 Edition Number:

1645 Release Date:

1646

1647

1648 Replaces Previous Edition Number:

1649 Date:

1650

1651 **7.5 APPENDIX 2:**

1652 **TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (Example)**

1653

1654 - Confidentiality Statement (optional)

1655 - Signature Page (optional)

1656 1 Table of Contents

1657 2 Summary

1658 3 Introduction

1659 4 Physical, Chemical, and Pharmaceutical Properties and Formulation

1660 5 Nonclinical Studies

1661 5.1 Nonclinical Pharmacology

1662 5.2 Pharmacokinetics and Product Metabolism in Animals

1663 5.3 Toxicology

1664 6 Effects in Humans

1665 6.1 Pharmacokinetics and Product Metabolism in Humans

1666 6.2 Safety and Efficacy

1667 6.3 Marketing Experience

1668 7 Summary of Data and Guidance for the Investigator

1669

1670 NB: References on 1. Publications

1671 2. Reports

1672 These references should be found at the end of each chapter

1673 Appendices (if any)

1674

1675 **8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL**

1676 **8.1 Introduction**

1677 Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the
1678 data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good
1679 Clinical Practice and with all applicable regulatory requirements.

1680 Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites
1681 in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also
1682 the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process
1683 to confirm the validity of the trial conduct and the integrity of data collected.

1684 The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to
1685 the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical
1686 conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it
1687 should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the
1688 individual elements are readily identifiable.

1689 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
1690 close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all
1691 necessary documents are in the appropriate files.

1692 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
1693 inspection by the regulatory authority(ies).

1694 **ADDENDUM**

1695 The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents. The storage system
1696 (irrespective of the media used) should provide for document identification, search and retrieval.

1698 Depending on the activities being carried out, individual trials may require additional documents not specifically mentioned in the essential
1699 document list. The sponsor and/or investigator/institution should include these as part of the trial master file.

1700 The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should
 1701 not have exclusive control of those data.
 1702
 1703 When a copy is used to replace an original document, the copy should fulfill the requirements for certified copies.
 1704
 1705 The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during and
 1706 after the trial.

1707 **8.2 Before the Clinical Phase of the Trial Commences**

1708 During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.1	INVESTIGATOR’S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	INFORMATION GIVEN TO TRIAL SUBJECT		X	X
	- INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent		
	- ANY OTHER WRITTEN INFORMATION	To document that subjects 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	
8.2.4	FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
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) X X

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

1710

	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	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
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
Title of Document	Purpose	Located in Files of Investigator/ Institution Sponsor		

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)

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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

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8.3 During the Clinical Conduct of the Trial

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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

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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

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	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.4	REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFIC ATIONS 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

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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	

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	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

1725 **8.4 After Completion or Termination of the Trial**

1726 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
1727 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	Located in Files of Investigator/ Institution Sponsor	
Title of Document	Purpose	X	X	
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

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