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REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

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E6(R3)
Annex 2

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ICH HARMONISED GUIDELINE
GOOD CLINICAL PRACTICE (GCP)

E6(R3) ANNEX 2

ICH Consensus Guideline

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1 **ANNEX 2**

2 **I. INTRODUCTION**

3 Good Clinical Practice (GCP), as described in ICH E6(R3) Principles and Annex 1, is applicable
4 across clinical trial types, designs and settings, and remains relevant when various operational
5 approaches and data sources are used in a clinical trial. As clinical trial designs evolve and
6 technological advances occur, the appropriate and proportionate application of GCP will support
7 these approaches while safeguarding participants’ rights, safety and well-being, and helping to
8 ensure the reliability of trial results. ICH E6(R3) Annex 2 addresses the GCP considerations that
9 arise from the increased use of a wider range of design elements and data sources. Annex 2
10 provides additional GCP considerations, focusing on examples of trials that incorporate
11 decentralised elements, pragmatic elements and/or real-world data (RWD). Clinical trials may
12 incorporate one or more of the design elements and data sources mentioned above. Annex 2 is not
13 meant to be comprehensive of all design elements since clinical trial ecosystems may continue to
14 evolve, and the operational approaches and data sources utilised may expand. However,
15 considerations provided in this Annex may apply in accordance with local regulatory requirements.
16 This Annex should not be read as an endorsement of any specific trial design elements or data
17 sources and should be read in conjunction with the Principles and Annex 1.

18

19 For the purposes of Annex 2, decentralised elements in a clinical trial are those trial-related
20 activities conducted outside the investigator’s location (e.g., trial visit is conducted in the trial
21 participant’s home, local healthcare centre or mobile medical units or when data acquisition is
22 performed remotely using digital health technologies (DHTs)). Pragmatic elements in clinical
23 trials are those that integrate aspects of clinical practice into the design and conduct of the trial
24 (e.g., simplified protocols with streamlined data collection). Data may be broadly classified into
25 two types, and a trial may make use of both types of data (i.e., data generated specifically for the
26 trial (primary data collection) or data obtained from sources external to the trial that are collected
27 for other purposes (secondary data use)). RWD incorporated in clinical trials include the use of
28 data relating to patient health status collected from a variety of sources outside of clinical trials
29 (e.g., electronic health records (EHRs), registries, claims data). These data from RWD sources

30 may be used in various ways, including, but not limited to, ascertaining endpoints or outcomes or
31 serving as an external control.

32

33 Regardless of the operational approaches and data sources used, a quality by design (QbD)
34 approach should be used in clinical trials as stated in Annex 1. The design elements, DHTs and
35 data sources that are adopted and implemented should be fit for purpose to ensure that the quality
36 and amount of information generated or collected are sufficient to support good decision making.

37 **1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE**
38 **(IRB/IEC)**

39 The ethical principles and standards for the evaluation of clinical trials by IRBs/IECs as described
40 in the Principles and Annex 1, provide a sound basis for the conduct of clinical trials, including
41 those incorporating decentralised elements, pragmatic elements and/or RWD. Particular attention
42 should be given, for example, to privacy and confidentiality of the participants and security of their
43 data.

44 **2. INVESTIGATOR**

45 **2.1 Communication with IRB/IEC**

46 The investigator, in accordance with local regulatory requirements, should provide the IRB/IEC
47 with the information needed for the evaluation of the appropriateness of various operational
48 approaches and data sources being used (see Annex 1, section 1.1).

49 **2.2 Informed Consent Considerations**

50 The informed consent process is an integral part of the conduct of interventional clinical trials.
51 Varied approaches (e.g., text, images, videos and other interactive methods) may be used in the
52 informed consent process, including for providing information to the participant and for supporting
53 the participant's understanding of the trial (see Annex 1, section 2.8).

54 The informed consent materials and process should be tailored to reflect the design elements of
55 the trial (e.g., decentralised or pragmatic elements).

56 2.2.1 Informed consent may be obtained remotely, where appropriate. When informed consent
57 is obtained remotely, the investigator should assure themselves of the identity of the

58 participant (or legally acceptable representative where applicable) in accordance with
59 applicable regulatory requirements.

60 2.2.2 The characteristics of the trial population (e.g., participants may lack familiarity with
61 electronic systems) and the appropriateness of the method and tools used to obtain
62 consent should be taken into consideration when developing the informed consent
63 materials and process. Trial participants may be given the option to use a paper-based
64 approach and/or in-person consent process, to the extent feasible, should they prefer this.

65 2.2.3 The informed consent materials should describe what type of data will be collected, how
66 the data may be used and who will have access to the trial participant’s personal
67 information, such as health records and home address (e.g., when trial-related activities
68 are conducted at the participant’s home or local healthcare centre or when data are
69 collected remotely via DHTs).

70 **2.3 Investigational Product Management**

71 Various approaches to investigational product management (i.e., supply, storage, dispensing,
72 administration, return, accountability documentation, destruction or alternative disposition) may
73 be utilised, as appropriate. The investigational product may be dispensed or supplied to the
74 participant or to an appropriate designee (e.g., caregiver, home nurse, local pharmacist) for
75 administration at the participant’s location (e.g., participant’s home, local healthcare centre) by
76 appropriate parties (e.g., the investigator site staff, the participant, a home nurse or a local
77 pharmacist). These approaches should be arranged and conducted in accordance with applicable
78 regulatory requirements. The level of investigator oversight will depend on a number of factors,
79 including the characteristics of the investigational product, route and complexity of administration,
80 level of existing knowledge about the investigational product’s safety and marketing status (see
81 Annex 1, section 2.10).

82 2.3.1 The investigator may arrange to send the investigational product to the participant (e.g.,
83 the participant’s home) in accordance with applicable regulatory requirements. When
84 shipping investigational products to a participant, the following should be considered:

- 85 (a) The process for protecting the privacy and maintaining the confidentiality of the
86 participant and their disease status.
- 87 (b) That the investigational product is being received by the intended recipient (e.g.,
88 the participant or their appropriate designee, such as a caregiver).
- 89 (c) The process for the receipt, storage, handling, administration, return, destruction
90 or alternative disposition and accountability of the investigational product.
- 91 (d) The process by which blinding (if applicable) is protected.
- 92 (e) The availability of participant support tools, such as online tutorials, information
93 brochures, visual aids and contact details for support (e.g., technical support).
- 94 2.3.2 Certain documentation and processes already used in the institution/healthcare centre
95 may be sufficient for the management of the investigational product, in accordance with
96 local regulatory requirements. For example, existing standard pharmacy practices for
97 product accountability and record of storage conditions that are kept routinely in the
98 pharmacy may be appropriate.
- 99 2.3.3 The investigator should maintain appropriate oversight of the activities related to
100 investigational product management and should ensure that appropriate documentation is
101 maintained. See section 2.3 on the level of oversight. These activities should be under the
102 oversight of the investigator, which include, but are not limited to:
- 103 (a) The receipt, use and return (or alternative disposition) of the investigational
104 product by the trial participants, where appropriate. Receipt and return (or
105 alternative disposition) may be undertaken by an appropriate designee of the
106 participant in accordance with local regulatory requirements.
- 107 (b) Commencement, continuation, dose and dose adjustments of the allocated
108 investigational product in accordance with the protocol.

109 **2.4 Investigator Oversight**

110 Healthcare professionals may be involved in performing trial-related activities that are part of
111 clinical practice.

112 If knowledge about the protocol, investigator’s brochure or other trial-related document is
113 necessary to perform a trial-related activity, this activity should be performed by delegated persons
114 or parties who are under appropriate oversight of investigator and have been appropriately trained,
115 if needed.

116 For trial-related activities conducted in clinical practice by healthcare professionals which do not
117 require knowledge about the protocol, investigators’ brochure, or other trial-related documents,
118 appropriate arrangements and appropriate investigator oversight should be in place. Such
119 arrangements should address plans for making relevant information and records available to the
120 investigator.

121 The level of investigator oversight of the trial-related activities should depend on the nature of the
122 activities and be proportionate to the risks to trial participant safety and data reliability, and the
123 importance of the data being collected. Such oversight should ensure that the resulting records
124 meet the relevant requirements of the protocol and thereby ensure reliable trial results, trial-
125 participant safety and appropriate decision-making.

126 **2.5 Safety Assessment and Reporting**

127 For the safety monitoring of individual trial participants (see Annex 1, section 2.7), the investigator
128 should review and assess information on the health status of participants across the sources of
129 safety-related information (e.g., home nursing, remote trial visits, use of DHTs). See section 3.9
130 and Annex 1, section 3.13.2 for details on how this information will be provided to the investigator.

131 **3. SPONSOR**

132 **3.1 Engagement and Communication**

133 Engagement with relevant stakeholders is particularly important when utilising various operational
134 approaches and data sources in clinical trials. The following considerations are important in
135 communicating with relevant stakeholders and may be undertaken in various ways taking into
136 consideration ICH E8(R1) General Considerations for Clinical Studies.

137 3.1.1 Engaging patients, patient advocacy groups and their communities, as appropriate, can
138 help ensure the successful integration and implementation of various operational
139 approaches and data sources in trials. For example, involving patients early in the design
140 of the trial may help ensure the suitability of DHTs (e.g., mobile apps, wearables) used
141 in trials with decentralised elements. This engagement may bring attention to areas where
142 additional training or support may be needed (e.g., digital literacy, physical ability or lack
143 of access to technology that may require the use of alternative approaches, specialised
144 training or the provision of technology).

145 3.1.2 Engaging healthcare professionals and/or investigators early in the design of a clinical
146 trial that incorporates various operational approaches and data sources is critical for the
147 successful implementation and conduct of a clinical trial. Early engagement can help:

- 148 (a) Address issues related to the infrastructure needed to conduct the trial.
- 149 (b) Develop protocols that incorporate the routine workflow of healthcare
150 professionals, when appropriate, and that allow for the integration of RWD
151 generated in clinical practice when such data are fit for purpose.
- 152 (c) Identify areas where training or support for healthcare professionals and/or
153 investigators is needed.

154 3.1.3 Sponsors are encouraged to engage with regulatory authorities early, especially when
155 designing and planning trials that use various operational approaches (including complex
156 design elements and technological tools) and RWD sources. Early engagement will help
157 address the appropriateness of using such operational approaches and RWD sources in
158 the design of their trial and will allow for timely identification of challenges and strategies
159 for resolution.

160 **3.2 Protocol and Trial Design**

161 Annex 1, Appendix B describes topics that should generally be included in the clinical trial
162 protocol. Additional consideration may need to be given to the protocol and/or protocol-related
163 documents when utilising various operational approaches and/or data sources so that all parties
164 involved in the trial conduct are adequately informed.

165 3.2.1 The specific design elements and data sources should be adequately described in the
166 protocol, and the appropriateness of their use justified. The rationale, fitness for purpose
167 and feasibility of using certain design elements and data sources should be briefly
168 explained. These descriptions can be supplemented in the protocol-related documents
169 (see Annex 1, Appendix B).

170 3.2.2 Since data may originate from different sources or various practice settings (e.g., sources
171 with different timing of data collection), there may be data variability within and/or
172 between data sources/settings. The impact of such data variability should be considered
173 in the trial design and discussed in the protocol or protocol-related documents (e.g.,
174 statistical analysis plan).

175 3.2.3 The design elements and data sources should be considered when determining the need
176 for appropriate training and technical support to be provided to the investigator,
177 investigator site staff and participants (see Annex 1, section 2.3.2).

178 3.2.4 The protocol and, where applicable, protocol-related documents should describe how
179 safety information will be collected from the variety of data sources (e.g., by DHTs, in-
180 person or remote visits), how emerging abnormalities potentially related to participants’
181 safety will be identified and made available to the investigator and what actions should
182 be taken by the investigator in these instances. Such information should be provided to
183 the investigator in a manner that would help inform their decision making (e.g., on
184 eligibility, treatment, continuing participation in the trial and care for the safety of the
185 individual trial participants). See sections 2.5 and 3.9 for more information on safety
186 assessment and reporting.

187 3.2.5 Modalities of the informed consent process (e.g., remote or in-person) should be
188 described in the protocol.

189 **3.3 Communication with IRB/IEC**

190 The sponsor, in accordance with local regulatory requirements, should ensure that the IRB/IEC is
191 provided with the information needed to evaluate the appropriateness of various operational
192 approaches and data sources (see Annex 1, section 1.1).

193 **3.4 Consent or Permission Considerations for RWD**

194 In situations where RWD are used, the sponsor should ensure that appropriate consent or
195 permission for the use of the data has been obtained in accordance with applicable regulatory
196 requirements.

197 **3.5 Data Considerations**

198 The following section provides aspects that should be taken into consideration when utilising a
199 variety of data sources.

200 *3.5.1 Real-World Data Considerations.*

201 (a) A variety of RWD sources may be used in clinical trials (e.g., EHRs, claims data,
202 registry data). The sponsor should apply special considerations to these data
203 sources depending on the data collection and acquisition process and if the data
204 are primary or secondary, since the sponsor may have different levels of control
205 over what and how data elements are collected. These considerations include, but
206 are not limited to:

207 (i) The potential variability of data formats (e.g., different terminologies
208 and/or standards) with data coming from a variety of sources.

209 (ii) Lack of standardised timing of data collection and procedures (e.g., the
210 timing and frequency of clinical assessments in RWD are based on clinical
211 practice and may have been influenced by the participant’s clinical status;
212 therefore, the protocol schedule may not match with those available from
213 the RWD).

214 (iii) Missing data (e.g., due to participants moving to different healthcare
215 systems) or the occurrence of intercurrent events between clinical visits
216 that may be difficult to capture or ascertain when using RWD (e.g.,
217 discontinuation of treatment or the use of an additional or alternative
218 therapy that is not captured in the EHR). See ICH E9(R1) Addendum on
219 Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on
220 Statistical Principles for Clinical Trials.

221 (iv) The overall quality of data collected in clinical practice (e.g., EHR, claims
222 data) or registries, including operational processes and database structure,
223 consistency of vocabularies and coding systems.

224 (v) De-identification methodologies used to protect the privacy and
225 confidentiality of personal information of trial participants.

226 (vi) The validation status of tools used for the acquisition of RWD (e.g.,
227 registries), as appropriate.

228 (b) The sponsor should ensure the fitness for purpose of RWD, which can be
229 described by their reliability and relevance. The term reliability includes accuracy,
230 completeness and traceability; the term relevance includes the availability of key
231 data elements (e.g., exposure, outcomes, covariates) to answer the specific trial
232 question with the specific method.

233 (c) The RWD used in a clinical trial (e.g., data acquired during clinical practice, RWD
234 from a third party) may be owned or controlled by entities other than the sponsor.
235 In such cases, the sponsor should have agreements with those entities in place that
236 allow regulatory authorities to access the source records and data for the purpose
237 of conducting regulatory inspections in accordance with applicable regulatory
238 requirements.

239 (d) Multiple data sources might need to be linked to corroborate information and to
240 improve the completeness and reliability of RWD (e.g., linkage of data from
241 EHRs and claims databases or linkage of a RWD source to a mortality database
242 to confirm outcomes). When data are linked, accurate matching to the individual
243 should be assured and the sponsor should ensure adequate measures to sufficiently
244 protect both data privacy and reliability of trial results. If data are to be linked,
245 this should be pre-specified in the protocol or protocol-related documents.

246 3.5.2 *Remote Data Collection Considerations*

247 (a) Remote data collection in clinical trials that incorporate decentralised and
248 pragmatic elements (e.g., the use of remote visits and DHTs, such as wearables,

249 or the extraction of data from EHRs) requires special attention to be paid to data
250 security vulnerabilities (see Annex 1, section 4.3.3), including cybersecurity and
251 data privacy (see section 3.7).

252 (b) Some of the RWD considerations in section 3.5.1 may also apply to remote
253 clinical trial data collection (e.g., DHTs including wearables).

254 **3.6 Investigational Product Management**

255 Various approaches to investigational product management (i.e., supply, storage, dispensing,
256 administration, return, accountability documentation, destruction or alternative disposition) may
257 be utilised, as appropriate (see section 2.3 and Annex 1, section 3.15.3).

258 3.6.1 The sponsor should assess these approaches to investigational product management
259 during the protocol development process. This assessment should consider, for example,
260 the stability of the investigational product and the requirement for specialised storage
261 conditions, the necessary preparation of the final investigational product for
262 administration (e.g., complex reconstitution or administration) and the route of
263 administration. This assessment should also consider the trial population, the knowledge
264 about the investigational product safety profile, the need for in-person clinical
265 observation in the immediate post-administration period, the measures needed to protect
266 blinding if applicable, and the need for emergency plans related to investigational product
267 administration (e.g., requirement for rescue medication).

268 3.6.2 The sponsor may arrange to send the investigational product to the participant (e.g., to
269 the participant's home) in accordance with applicable regulatory requirements. For
270 specific considerations for investigational product shipping to the participant, see section
271 2.3.1.

272
273 3.6.3 The sponsor may deploy systems (e.g., interactive response technology, DHTs) and assist
274 the investigator to establish processes (e.g., home nurse visits) to ensure that the allocated
275 investigational product was delivered and administered appropriately to the trial
276 participant.

277 3.7 Privacy and Confidentiality Considerations

278 Sponsors should ensure security safeguards, including cybersecurity, are in place to protect the
279 privacy and confidentiality of personal information of trial participants. Participants' personal
280 information may be required by service providers to fulfil their activities (e.g., disclosure of
281 personal information when investigational product is shipped to participants or when a home nurse
282 is deployed, where appropriate). In these circumstances sponsors and service providers should
283 ensure that appropriate informed consent has been provided by the participant, that the personal
284 information is protected from inadvertent disclosure and that access to these data is limited to those
285 authorised. The sponsors should address the risk of potential disclosure of personal information
286 from a data breach when data from DHTs and/or RWD are used.

287 3.8 Sponsor Oversight

288 Sponsor oversight of clinical trials can be more complex with the myriad of data sources, the
289 various operational approaches to the trial design and conduct, and the number of service providers
290 involved. Sponsors should ensure that there are processes in place to provide appropriate level of
291 oversight such that the participants' rights, safety and well-being are protected, and the reliability
292 of the results is ensured. Sponsor oversight includes, but is not limited to, quality control and
293 assurance measures specifically customised to the clinical trial and its critical to quality factors
294 and identified risks. There should be appropriate oversight of service providers including
295 maintenance of their essential records. See Annex 1, sections 3.9, 3.10 and 3.11, and Appendix C.

296 3.9 Safety Assessment and Reporting

297 3.9.1 Safety information in clinical trials with decentralised and/or pragmatic elements may be
298 captured in a variety of ways and may come from multiple sources. For example, some
299 trials may capture information via remote visits, DHTs, EHRs, in-person visits or a
300 combination thereof. In these circumstances, the sponsor should ensure that safety
301 information is appropriately captured and made accessible to the investigator in a timely
302 manner according to the protocol. The safety information should be provided in an
303 actionable manner that provides the investigator with an overview on the health status of
304 the trial participant to allow for medical decision making.

305 3.9.2 The approach to safety management, including any mitigating actions to safeguard
306 participant safety, and to reporting, should be described in the protocol or protocol-related
307 documents. This approach should take into account the trial design, the design elements
308 and the variety of data sources. Where appropriate, consideration should be given to ICH
309 E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval
310 or Post-Approval Clinical Trials.