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ICH HARMONISED GUIDELINE

Optimisation of Safety Data Collection

E19

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35 **1 INTRODUCTION**

36 **1.1 Objective of the Guideline**

37 This Guideline is intended to provide internationally harmonised guidance on an optimised
38 approach to safety data collection in some late-stage pre-approval or post-approval studies
39 when the safety profile of a drug is sufficiently characterised. Optimisation of safety data
40 collection using a selective approach may improve the efficiency of clinical studies while
41 reducing the burden to study participants. Adoption of an internationally harmonised approach
42 to selective safety data collection may facilitate global participation in clinical studies.

43 **1.2 Background**

44 Regulators and industry have a shared interest in reducing the burden to study participants
45 while facilitating the conduct of studies that could yield important new medical knowledge and
46 advance public health. Although safety monitoring of patients during clinical studies remains
47 critically important, unnecessary and burdensome data collection may serve as a disincentive
48 to participation in clinical studies, e.g., frequent and time-consuming patient visits; laboratory
49 tests; and/or physical examinations.

50 Knowledge about a medicinal product's safety profile continually evolves as safety data
51 accumulates. Throughout the course of medicinal product development and subsequently
52 while the drug is marketed, sponsors collect extensive safety-related data, including all vital
53 signs, laboratory data, and adverse events. In the later stages of drug development, and if the
54 safety profile is well-understood and documented, comprehensive collection of all safety data
55 may provide only limited additional knowledge of clinical importance. In such circumstances,
56 a more selective approach to safety data collection may be adequate and optimal, as long as the
57 study objectives and the welfare of study participants are not compromised.

58 Importantly, sponsors and investigators should ensure that routine patient care is not
59 compromised by the selective safety data collection approach outlined in this Guideline. It is
60 recognised that safety monitoring serves to protect individual study participants and will
61 continue to be performed as per standard of care.

62 **1.3 Scope of the Guideline**

63 This guidance is intended to apply to collection of safety data during the late-stage development
64 of medicinal products in interventional and non-interventional studies, in the post-approval
65 setting and, for specific cases, in the pre-approval setting.

66 In the pre-approval setting, comprehensive safety data collection is expected in order to
67 elucidate frequency, severity, seriousness, and dose-response of adverse events, including
68 potential differences across subsets, e.g., demographic; concomitant illnesses; and/or
69 concomitant therapy. However, even before approval of a new medicinal product, if there is
70 agreement with regulatory authorities that sufficient safety data are available or are being
71 collected in ongoing late-stage studies, selective safety data collection may be appropriate in
72 certain studies.

73 Selective safety data collection following the principles of this Guideline does not alter
74 local/regional safety reporting requirements.

75 **2 GENERAL PRINCIPLES**

76 **2.1 Types of Data for Which Selective Safety Data Collection May be Appropriate**

77 *2.1.1 Types of Safety Data Where It May be Appropriate to Limit or Stop Collection*

- 78 1. Non-serious adverse events
- 79 2. Routine laboratory tests
- 80 3. Information on concomitant medications
- 81 4. Physical examinations (including vital signs)
- 82 5. Electrocardiograms

83 *2.1.2 Types of Safety Data That Should Generally be Collected under All Circumstances*

84 For the following types of events/data, comprehensive details should generally be provided to
85 allow adequate assessment of the event/data, e.g., history; associated adverse events; relevant
86 laboratory values; concomitant medications; vital signs; and/or follow-up outcome.

- 87 1. Deaths
- 88 2. Serious adverse events
- 89 3. Significant adverse events that led to an intervention, including withdrawal or dose
90 reduction of investigational medicinal product or addition of concomitant therapy
- 91 4. Marked laboratory abnormalities (other than those meeting the definition of serious)
- 92 5. Overdose
- 93 6. Pregnancies
- 94 7. Adverse events of special interest (if defined). These adverse events may warrant
95 collection of additional information across the entire study population to better
96 characterise these events (e.g., particular laboratory parameters; vital signs; risk
97 factors; concomitant therapies; and/or concomitant illnesses). For example, if
98 gastrointestinal haemorrhage was an adverse event of special interest, one might
99 want to proactively collect concomitant antithrombotic therapy across the entire
100 study population
- 101 8. Laboratory data, vital signs, electrocardiograms of special interest (if defined)

102 *2.1.3 Baseline Data*

103 Use of a selective safety data collection approach does not change considerations for baseline
104 data collection. Baseline data are needed to ensure that subjects meet inclusion and exclusion
105 criteria for study enrolment and are important in the assessment of safety. For example,
106 particular serious adverse events may occur more frequently in subgroups defined on the basis
107 of demographics, baseline disease characteristics, coexisting illnesses, or concomitant
108 therapies; analyses of such information can be important in considering the benefit-risk profile
109 of the drug.

110 2.2 When May Selective Safety Data Collection Be Considered?

111 When sponsors choose to implement selective safety data collection for a clinical study, a
112 scientific justification should be provided. Factors that contribute to a determination that
113 selective safety data collection would be appropriate include:

- 114 1. The medicinal product has received marketing authorisation from a regulatory
115 authority for the indication under investigation
- 116 2. Availability of post-approval safety data and findings
- 117 3. The dose, dosing regimen, dosage form, route of administration and treatment
118 duration used in the previously conducted studies are comparable to the planned use
119 of the drug in the proposed study
- 120 4. The patient population from previously conducted studies is representative of
121 subjects in the planned study regarding demographic characteristics, underlying
122 medical conditions, concomitant drugs, and other important factors (e.g.,
123 Cytochrome P450 enzymes (CYP) metabolizer status)
- 124 5. Exposure in previously conducted (or ongoing, if applicable) studies that contribute
125 to the overall safety database, i.e., number exposure to drug, treatment duration
- 126 6. Consistency of the safety profile across previous studies
- 127 7. Characteristics of previous studies, e.g., study design; study conduct; adequacy of
128 safety monitoring/safety data collection; availability of protocols; statistical analysis
129 plan; and/or access to data
- 130 8. Knowledge of the mechanism of action of the medicinal product under study
- 131 9. Knowledge of the safety profile of approved drugs in the same pharmacologic class

132 The above factors should be considered in determining whether the safety of the medicinal
133 product has been sufficiently characterised to provide justification for selective safety data
134 collection in the proposed study.

135 In the pre-approval setting, selective safety data collection may be justifiable if sufficient safety
136 data are available from completed studies. Moreover, when sufficient safety data will be
137 forthcoming from one or more ongoing late-stage study(ies), selective safety data collection
138 may be appropriate for a concurrently conducted study-initiated pre-approval.

139 2.2.1 Benefit-Risk Considerations for Selective Safety Data Collection

140 It should be recognised that the contribution of non-serious adverse events to the benefit-risk
141 profile of a drug may differ depending on the indication of use and patient characteristics (e.g.,
142 age and/or cardiovascular risk factors). These factors should be considered when accepting the
143 comparability of patient populations and the applicability of selective safety data collection.
144 For example, even when safety of a drug is sufficiently characterised in a patient population
145 with advanced disease, comprehensive safety data collection in a patient population with less
146 advanced disease may be appropriate to ensure that the benefits outweigh the risks in the less
147 severely affected population.

148 2.2.2 *Extent of Exposure*

149 Selective safety data collection could be considered for studies using lower doses and/or shorter
150 durations than in previous studies. Conversely, selective safety data collection would generally
151 not be acceptable if higher doses and/or longer treatment durations than previously studied are
152 planned. Nonetheless, even when exposure is greater in the planned study, there may be
153 circumstances where selective safety data collection is still appropriate, e.g., a study designed
154 to characterise infrequent serious adverse events (e.g., renal toxicity; myocardial infarction;
155 and/or stroke) associated with longer term use of the medicinal product within the labelled
156 indication; a planned five-year study when a one-year study has been completed.

157 2.3 **Examples Where Selective Safety Data Collection May be Considered**

158 Selective safety data collection may be appropriate in studies used to evaluate some of the
159 following objectives. These are not the only circumstances where selective safety data
160 collection may be appropriate.

- 161 1. New indications of approved drugs
- 162 2. To study additional endpoints, e.g., patient-reported outcome for symptomatic
163 improvement; quality of life; and/or outcome studies (e.g., mortality; morbidity; and/or
164 specific safety issues)
- 165 3. To study comparative effectiveness/efficacy
- 166 4. Demonstration of superiority when non-inferiority has been demonstrated
- 167 5. Characterisation of adverse events of special interest
- 168 6. Fulfilment of post-approval requirements, post-authorisation safety studies based on
169 data collection from registries or electronic health records
- 170 7. Late-stage premarketing outcome study in a large population

171 Additional examples and situations for applying selective safety data collection may be found
172 in Section 3, Methods of Implementation.

173 2.4 **Ensuring Patient Safety within Studies**

174 Patient safety monitoring serves two purposes: 1) to protect the welfare of individual study
175 participants; and 2) to accumulate safety information to be used in the assessment of benefit-
176 risk for the proposed indication. The recommendations in this Guideline do not obviate the
177 need for monitoring to protect individual patient welfare. Although certain safety data, e.g.,
178 non-serious adverse events, would not need to be recorded in the case report form (CRF) when
179 selective safety data collection is determined to be appropriate, the protocol should stipulate
180 that patients are monitored per standard of care. For example, for a medicinal product known
181 to cause hyperglycaemia, where routine blood glucose monitoring is recommended in labeling,
182 glucose should be monitored in patients participating in a study. If hyperglycaemia is well-
183 characterised with this medicinal product, the glucose data do not need to be recorded in the
184 CRF or reported to the sponsor in studies using selective safety data collection. Glucose levels
185 would be recorded in the CRF and reported to the sponsor if stipulated in the protocol, e.g., as
186 an adverse event of special interest, associated with a serious adverse event.

187 **2.5 Changes in Approach to Safety Data Collection**

188 When an unexpected safety issue arises during the course of a study, e.g., a postmarketing
189 safety signal; a finding from a nonclinical study; higher than expected withdrawals; and/or
190 concern from a data monitoring committee; a change in the selective safety data collection
191 approach may be warranted, e.g., denoting a new adverse event of special interest; and/or
192 reverting to comprehensive safety data collection.

193 **2.6 Early Consultation with Regulatory Authorities**

194 Studies must be conducted according to local and regional laws and regulatory requirements.
195 When sponsors are considering selective safety data collection in interventional studies, they
196 should discuss their scientific rationale and planned methods with regulatory authorities prior
197 to initiating the study(ies). The same applies to non-interventional studies that are being
198 conducted to address requests from regulatory authorities.

199 It is possible to conduct a multi-regional clinical study using a single protocol with selective
200 safety data collection if the safety profile of the product is considered to be sufficiently
201 characterised, and all regulatory authorities agree with the proposed approach. A well-
202 designed multi-regional clinical study that takes this Guideline into account will help the
203 sponsor reach agreement with regulatory authorities in multiple regions (See ICH E17 –
204 General Principles for Planning and Design of Multi-Regional Clinical Trials).

205 **3 METHODS OF IMPLEMENTATION**

206 Having considered the principles outlined in Section 2, General Principles, with respect to
207 when it may be appropriate to limit or stop collection of certain types of safety data, a number
208 of approaches for selective safety data collection may be considered.

209 Use of selective safety data collection can introduce important complexities in study conduct
210 and safety analysis. The specific approaches should be carefully planned and clearly delineated
211 within the relevant study documents, e.g., protocol; monitoring plan; and/or statistical analysis
212 plan, with a reference to this Guideline.

213 Regardless of the method chosen, it is essential to ensure patient safety and adhere to local and
214 regional laws and regulations. When the selective safety data collection approach is used for
215 a clinical study, the approach should be described in the appropriate document(s) when safety
216 findings are presented, e.g., the Clinical Study Report (CSR); Development Safety Update
217 Report (DSUR); Periodic Benefit-Risk Evaluation Report (PBRER); Periodic Safety Update
218 Report (PSUR); and/or Common Technical Document (CTD).

219 The following examples of methods of implementation are not meant to be all-inclusive. These
220 approaches can be applied in both the pre- and post-approval settings and require a scientific
221 rationale and justification. The data supporting these approaches are more likely to be available
222 in the post-approval setting than in the pre-approval setting.

223 3.1 Selective Safety Data Collection for All Patients in the Study

224 For all patients in the study, parameters listed in Section 2.1.2, General Principles, are collected
225 throughout the study, e.g., serious adverse events; adverse events of special interest; and/or
226 deaths. Conversely, the parameters listed in Section 2.1.1, General Principles, are not
227 collected, e.g., non-serious adverse events; routine laboratory values; concomitant
228 medications; physical examination data; vital signs; and/or electrocardiograms.

229 In the post-approval setting, this approach may be useful to address a specific safety concern,
230 for example, to meet a post-authorisation commitment, when safety in other regards has been
231 sufficiently characterised.

232 In the pre-approval setting, this approach may be also used. For example, consider a
233 development programme for a lipid-lowering drug, where a decrease in low-density lipoprotein
234 (LDL) cholesterol will serve as the basis of approval, but the impact on cardiovascular risk is
235 being investigated. In addition to the completed Phase 2 programme, two Phase 3 studies are
236 ongoing with LDL cholesterol as the primary endpoint, which will provide adequate exposure
237 to assess safety sufficiently. The sponsor wishes to initiate a third study with major adverse
238 cardiovascular events as the primary endpoint. For the third study, a selective safety data
239 collection approach could be justified considering the data available in light of the principles
240 above.

**241 3.2 Comprehensive Safety Data Collection for a Specific Subset(s) of the Population,
242 with Selective Safety Data Collection for Other Patients**

243 Comprehensive safety data are collected for specific subset(s) of the patient population where
244 additional information is deemed important, whereas selective safety data are collected for
245 other patients. For example, if the patient population in previous studies included few patients
246 over the age of 65, it could be of value to collect full data on this population in a new study in
247 the same indication or in a related indication. Other examples of specific subsets include those
248 based on geographic location; ethnicity; sex; baseline disease status (renal/hepatic impairment),
249 CYP status; or genetics.

**250 3.3 Comprehensive Safety Data Collection in a Representative Subset of the
251 Population, with Selective Safety Data Collection for Other Patients**

252 In some cases, efficacy studies must enrol many thousands of patients in order to achieve
253 adequate statistical power. In such settings, such as a large clinical outcomes study, the number
254 of patients planned for enrolment may greatly exceed the number needed to assess the non-
255 serious adverse events adequately. In this setting, comprehensive safety data could be collected
256 for only a representative subset of patients, for example, full data collection could be
257 undertaken at randomly selected sites.

**258 3.4 Comprehensive Safety Data Collection for the Initial Portion of the Study, with
259 Selective Data Collection Thereafter**

260 Comprehensive safety data are collected from baseline through some pre-determined interval
261 of the study, with selective safety data collection thereafter. A data monitoring committee

262 could consider the safety data and provide agreement with selective safety data collection for
263 the subsequent portion of the study. These approaches can be useful for studies designed to
264 assess important long-term drug effects, where safety would be adequately characterised in the
265 early part of the study, e.g., one year, through comprehensive safety data collection. For
266 example, consider a study to prevent an important outcome such as dementia, end-stage kidney
267 disease, and/or hepatic failure. Assuming it would take three years to collect adequate events
268 to have adequate statistical power for efficacy, it may be appropriate to utilize a selective
269 approach to safety data collection once data have been analysed for all patients followed
270 through one year and non-serious adverse events have been deemed to be adequately
271 characterised. The selective approach would discontinue collection of non-serious adverse
272 events, vital signs, laboratory tests, etc., and utilize less frequent study visit intervals. The
273 protocol should include a prospective plan for concurrence of a data monitoring committee
274 prior to the change to selective safety data collection.

275 **4 RELATIONSHIP WITH OTHER GUIDELINES/REGULATIONS**

276 This guideline should be considered in conjunction with other ICH guidelines relevant to the
277 conduct of clinical studies and clinical safety data management, e.g., E2A (Clinical Safety Data
278 Management: Definitions and Standards for Expedited Reporting); E2F (Development Safety
279 Update Report); E3 (Structure and Content of Clinical Study Reports); E6(R2) (Good Clinical
280 Practice: Integrated Addendum to ICH E6(R1)); E8 (General Considerations for Clinical
281 Trials); and/or E17 (General Principles for Planning and Design of Multi-Regional Clinical
282 Trials). Evaluation of the information generated through post-approval pharmacovigilance
283 activities is also important for all products to ensure their safe use, e.g. E2E (Pharmacovigilance
284 Planning); E2D (Post-Approval Safety Data Management: Definitions and Standards for
285 Expedited Reporting); and E2C(R2) (Periodic Benefit-Risk Evaluation Report).