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## ICH guideline E19 on optimisation of safety data collection

### Step 2b

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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL  
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

**ICH HARMONISED GUIDELINE**

**Optimisation of Safety Data Collection  
E19**

Draft version

*Currently under public consultation*

*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 Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.*

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## 32 1 INTRODUCTION

### 33 *1.1 Objective of the Guideline*

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

### 40 *1.2 Background*

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

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

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

### 59 *1.3 Scope of the Guideline*

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

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

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

71

## 72 2 GENERAL PRINCIPLES

### 73 2.1 *Types of Data for Which Selective Safety Data Collection May be* 74 *Appropriate*

#### 75 2.1.1 **Types of Safety Data Where It May be Appropriate to Limit or Stop** 76 **Collection**

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

#### 82 2.1.2 **Types of Safety Data That Should Generally be Collected under All** 83 **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 want  
99 to proactively collect concomitant antithrombotic therapy across the entire study  
100 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 of

107 demographics, baseline disease characteristics, coexisting illnesses, or concomitant therapies;  
108 analyses of such information can be important in considering the benefit-risk profile of the drug.

## 109 **2.2 When May Selective Safety Data Collection Be Considered?**

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

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

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

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

### 138 **2.2.1 Benefit-Risk Considerations for Selective Safety Data Collection**

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

145 advanced disease may be appropriate to ensure that the benefits outweigh the risks in the less  
146 severely affected population.

### 147 **2.2.2 Extent of Exposure**

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

### 156 **2.3 Examples Where Selective Safety Data Collection May be Considered**

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

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

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

### 172 **2.4 Ensuring Patient Safety within Studies**

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



184 in the CRF and reported to the sponsor if stipulated in the protocol, e.g., as an adverse event of  
185 special interest, associated with a serious adverse event.

## 186 ***2.5 Changes in Approach to Safety Data Collection***

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

## 192 ***2.6 Early Consultation with Regulatory Authorities***

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

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

## 204 **3 METHODS OF IMPLEMENTATION**

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

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

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

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

### 222 ***3.1 Selective Safety Data Collection for All Patients in the Study***

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

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

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

### 240 ***3.2 Comprehensive Safety Data Collection for a Specific Subset(s) of the*** 241 ***Population, with Selective Safety Data Collection for Other Patients***

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

### 249 ***3.3 Comprehensive Safety Data Collection in a Representative Subset of the*** 250 ***Population, with Selective Safety Data Collection for Other Patients***

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

### 257 ***3.4 Comprehensive Safety Data Collection for the Initial Portion of the Study,*** 258 ***with Selective Data Collection Thereafter***

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

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

#### 274 **4 RELATIONSHIP WITH OTHER GUIDELINES/REGULATIONS**

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