

# **E18 GENOMIC SAMPLING AND MANAGEMENT OF GENOMIC DATA**

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

**ICH HARMONISED GUIDELINE**

**GUIDELINE ON GENOMIC SAMPLING AND  
MANAGEMENT OF GENOMIC DATA  
E18**

Current *Step 2* version  
dated 10 December 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 Assembly 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.*

## E18 Document History

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1 **ICH HARMONISED GUIDELINE**

2 **GUIDELINE ON GENOMIC SAMPLING AND**  
3 **MANAGEMENT OF GENOMIC DATA**

4 **E18**

5 **Draft ICH Consensus Guideline**

6 Released for Consultation on 10 December 2015, at *Step 2* of the ICH Process

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35 **1. INTRODUCTION**

36 **1.1. Objectives of the Guideline**

37 The main objective of this guideline is to provide harmonised principles of genomic sampling  
38 and management of genomic data in clinical studies. This guideline will facilitate the  
39 implementation of genomic studies by enabling a common understanding of critical  
40 parameters for the unbiased collection, storage and optimal use of genomic samples and data.  
41 Further objectives of this guideline are to increase awareness and provide considerations  
42 regarding subject privacy, data protection, informed consent and transparency of findings.

43 This guideline is intended to foster interactions amongst stakeholders, including drug  
44 developers, investigators and regulators, and to encourage genomic research within clinical  
45 studies.

46 **1.2. Background**

47 There is growing awareness of, and interest in, genomic data generated from clinical studies.  
48 In particular, genomic research could be used in all phases of drug development to assess  
49 genomic correlates of drug response, disease understanding or mechanism of drug  
50 pharmacology. The identification of genomic biomarkers underlying variability in drug  
51 response may be valuable to optimize patient therapy, inform drug labelling and to design  
52 more efficient studies. Furthermore, the generation and interpretation of genomic data, both  
53 within and across clinical studies and drug development programs, allow for a better  
54 understanding of pharmacological and pathological mechanisms and enable the identification  
55 of new drug targets.

56 Regulatory agencies in the ICH regions have independently published guidelines encouraging  
57 genomic sample collection throughout the life cycle of the drug. The lack of a harmonised  
58 ICH Guideline on genomic sampling and data management from clinical studies makes it  
59 difficult for sponsors and researchers to collect genomic samples and conduct genomic  
60 research in a consistent manner in global clinical studies.

61 Genomic samples may be used for a variety of analyses, including single genes, sets of genes  
62 and whole-genome approaches, that may or may not be pre-specified in the clinical study  
63 objectives at the time of collection.

64 **1.3. Scope of the Guideline**

65 The scope of this guideline pertains to genomic sampling and management of genomic data  
66 from interventional and non-interventional clinical studies. Genomic research can be  
67 conducted during or after a clinical study. It may or may not be pre-specified in the clinical  
68 protocol. This document addresses use of genomic samples and data irrespective of the  
69 timing of analyses and both pre-specified and non-pre-specified use. Genomic samples and  
70 data described in this guideline are consistent with the Desoxyribonucleic Acid (DNA) and  
71 Ribonucleic Acid (RNA) characteristics defined in ICH E15.

72 The focus is on the general principles of collection, processing, transport, storage and  
73 disposition of genomic samples or data, within the scope of an informed consent. Technical  
74 aspects are also discussed when appropriate, recognizing the rapidly evolving technological  
75 advances in genomic sampling and research.

76 No detailed guidance is included on biobanking regulations or ethical aspects as these are  
77 governed by the principles of the Declaration of Helsinki and national rules and regulations.  
78 The principles in this guideline, however, may apply to any genomic research utilising  
79 human-derived materials.

80 **1.4. General Principles**

81 With advances in science and increased awareness of the impact of genomics, there is a need  
82 and an opportunity to maximize the value of the collected samples and the data generated  
83 from them. Therefore, genomic sample acquisition is strongly encouraged in all phases and  
84 studies of clinical development. Moreover, the quality of genomic research is dependent  
85 upon unbiased systematic collection and analysis of samples, ideally, from all subjects in  
86 order to fully represent the study population.

87 Maintaining sample integrity is important and has a major impact on the scientific utility of  
88 genomic samples. The overall quality of these samples, and technical performance of the  
89 assay (e.g., accuracy, precision, sensitivity, specificity, reproducibility) will determine the  
90 reliability of genomic data. Establishing standardized practice for handling and processing  
91 of genomic samples will foster integration of data from different analytical platforms and  
92 facilitate clinical decision making.

93 Genomic samples and data should be securely stored, maintained, and access controlled  
94 similar to non-genomic samples and health information.

95 **2. GENOMIC SAMPLING**

96 Genomic research encompasses a wide variety of methods and applications. These may  
97 include, but are not limited to, nucleic acid sequencing and genotyping; analysis of various  
98 types of RNAs; gene expression or regulation; and detection of epigenetic modifications.  
99 Ever evolving technological advancements are expected to yield novel applications. The  
100 scope of the research will determine the specimen type, the analytes to be assessed and the  
101 methodologies used to extract, stabilize and store well-annotated samples for genomic testing.  
102 Sample quality and amount can influence the accuracy and reliability of the generated data.  
103 Therefore, handling and preparation of the biological samples are critical steps in the process.

104 Pre-analytical variation should be minimized by developing standardized procedures for  
105 genomic sample collection, processing, transport, and storage. Such procedures and quality  
106 monitoring should be tailored to the types of specimens, the analytes and the tests to be  
107 performed. The pre-analytical process for specimen handling and preparation should be  
108 defined, documented and verified prior to implementation. It is important that the timing,  
109 method, location and conditions under which samples are collected are recorded. Any  
110 deviations in procedures should be well documented in the appropriate inventory database  
111 linked to the samples. The chain of custody at all stages of collection, handling and analysis  
112 including the timing of each step should be recorded for all samples. Implementation of  
113 quality control programs is highly recommended. In general, instructions for collection,  
114 processing, transport and storage should be adopted to ensure the stability of the biological  
115 samples at each step from the time of acquisition to the time of testing.

116 **2.1. Collection and Processing of Samples**

117 A number of pre-analytical variables should be considered when developing a strategy for  
118 sample collection and processing to ensure suitability of samples for genomic testing. If  
119 sites participating in a clinical study use different sample collection and handling procedures,  
120 then the subsequent test performance may differ by site. This may affect the interpretability  
121 and combinability of the data and may lead to unreliable results. Staff at all participating  
122 sites should be properly trained to use standardized procedures. Specimens should be  
123 collected and labelled in accordance with appropriate biosafety practices, subject privacy  
124 regulations and the informed consent.

125 **2.1.1. Specimen Type**

126 Nucleic acids may be extracted from a variety of clinical specimen types and matrices (e.g.,  
127 whole blood, tissue, buccal swabs, saliva, bone marrow aspirate, urine, feces). Novel  
128 sources of tissue-derived nucleic acids (e.g., cell-free DNA and liquid biopsies) are emerging  
129 and might require distinct isolation methods. The principles detailed herein also apply to  
130 these sources. The type of specimens to be collected should be compatible with the  
131 intended use. For example, some types of specimens could be used for both DNA and RNA  
132 studies while other specimen types may not be suitable for RNA analysis due to the lack of  
133 analyte stability.

134 **2.1.2. Timing of Specimen Collection**

135 Inter- and intra-subject variability should be considered in the context of the clinical study  
136 objectives when defining the sample collection strategy. For example, diurnal variation or  
137 administered treatments can influence gene expression and should be considered when  
138 selecting sampling time points. While the sequence of germline DNA is relatively stable  
139 and does not change with time, information obtained from tumor DNA and RNA can be  
140 affected by the source, method and/or timing of the sample collection.

141 **2.1.3. Specimen Preservation Conditions**

142 The collection container and the need for an additive, stabilizing agent or preservative will  
143 depend upon the nucleic acid target, the specimen type, the size or volume of sample required,  
144 and the potential analytical assay and technology. For example, blood or bone marrow  
145 aspirate specimens are collected in tubes containing anticoagulants or additives appropriate  
146 for the intended nucleic acid type. Tissue samples may be snap-frozen in liquid nitrogen or  
147 placed in an appropriate preservative.

148 Tissues are often fixed for long-term storage. Parameters that should be carefully  
149 considered for tissue fixation are the type of fixative, fixation time, humidity, oxygenation  
150 and temperature, as well as the compatibility with the downstream nucleic acid extraction  
151 method. It is recommended to evaluate the impact of fixation and additives on the analytes  
152 of interest and the types of tests to be carried out prior to sample collection in a clinical study.  
153 In addition, the specimen tissue type and volume may affect the optimal duration of fixation  
154 and therefore should be taken into account. Handling subsequent to initial fixation could  
155 also impact the integrity of the specimens.



156 **2.1.4. Specimen Stability and Degradation**

157 Appropriate handling measures should be taken to prevent nucleic acid degradation and  
158 genomic profile alterations during sample collection and processing. Nucleic acid  
159 fragmentation and apparent changes in gene expression can occur and are dependent on  
160 conditions related to pH, hypoxia, the presence of endonucleases, and/or other tissue specific  
161 parameters. In addition, the time from specimen collection to freezing, fixation, or  
162 processing, as well as the storage time, should be optimized as needed. The parameters  
163 employed should be documented in sample collection and handling instructions, training  
164 materials and the sample reports. It is recommended that conditions of storage and  
165 processing are monitored. For example, the temperature should be monitored for possible  
166 variations and documented to ensure consistency across samples.

167 **2.1.5. Specimen Volume and Composition**

168 Collection volume for liquid samples is an issue that requires careful consideration. For  
169 example, in pediatric subjects, limited amounts of blood or other tissues may be available and  
170 therefore non-invasive alternatives, such as saliva, dried blood spot or skin scrapings (or tape)  
171 could be considered. Care should be taken when buccal swabs, saliva or other material is  
172 used, as they may bear the risk for contamination with other than host DNA and RNA.

173 Consideration should be given to the minimum tissue or cell content needed for the intended  
174 purposes. The optimal amount of tissue may be dependent upon the cellularity of the tissue  
175 (e.g., smaller amounts may be sufficient for highly cellular tissue types) and the relative  
176 proportion of particular cell types in the entire specimen (e.g., tumor area or disease aspects  
177 represented in a biopsy). As tumor tissue may exhibit molecular heterogeneity (mosaicism),  
178 a documented pathological evaluation of the sample may be helpful prior to genomic analysis.  
179 In circumstances when paired samples are collected (e.g., tumor versus normal tissue, pre-  
180 versus post-treatment samples or prenatal versus maternal specimens), additional  
181 considerations (e.g., matched samples, cell types) may be needed to allow comparison.

182 **2.1.6. Parameters Influencing Genomic Sample Quality**

183 The quality and yield of the extracted nucleic acids are affected by the quality of the source  
184 specimens amongst other factors. As a result, the extraction procedures should be defined  
185 and validated for the handling conditions and the specimen type to be used. Specimen types  
186 have different characteristics and components that can affect the recovery of nucleic acids,  
187 and these should be considered when selecting a methodology for nucleic acid extraction.

188 For example, the procedures for cell lysis may vary for different tissue and body fluid  
189 specimens. The process for removing specific cell constituents may also differ depending  
190 on the composition of the specimens. If both DNA and RNA will be extracted from the  
191 same specimen it should be determined whether extraction is best performed simultaneously  
192 or if the tissue specimen should be divided at the time of collection. Due to the labile nature  
193 of RNA compared to DNA, additional precautions are needed when isolating RNA, such as  
194 the use of RNase-free equipment and reagents. Repeated freezing and thawing of specimens  
195 prior to nucleic acid extraction can affect genomic sample integrity and should be avoided  
196 when possible or otherwise evaluated. To determine if the quality and quantity of the  
197 extracted nucleic acid targets are adequate for the defined downstream genomic testing to be  
198 performed, appropriate quality control methods should be applied, such as  
199 spectrophotometric Optical Density (OD) 260/280 measurement.

#### 200 **2.1.7. Sources of Interference**

201 Potential sources of interference and contamination can affect the performance of genomic  
202 tests and these include endogenous and exogenous substances. The identification of  
203 endogenous substances normally present in a specimen type (e.g., hemoglobin from blood or  
204 melanin from skin may affect Polymerase Chain Reaction (PCR) efficiency) and exogenous  
205 substances (e.g., anticoagulant, other additives, fixative, reagents used for nucleic acid  
206 isolation) that interfere with specific testing methods is important to ensure reliable genomic  
207 datasets. The effects of potential interferents on assay performance should be addressed  
208 during assay development.

### 209 **2.2. Transport and Storage of Samples**

210 Transport and storage conditions will vary according to the specimen type and the nucleic  
211 acid target. In general, samples should not be exposed to conditions that may affect the  
212 stability of the nucleic acid targets during transport and storage.

#### 213 **2.2.1. Transport of Samples**

214 The appropriate transport conditions should be established prior to sample shipment. To  
215 ensure that specimens and/or extracted samples are shipped under acceptable conditions, the  
216 dates of shipment and receipt should be documented, as well as the approximate temperature  
217 of the specimens when received. Where possible, samples should be transported at the  
218 intended storage temperature appropriate for the sample type and the analyte of interest.  
219 Deviations from the intended shipment parameters should be documented.

### 220 **2.2.2. Storage of Samples**

221 It is highly recommended that samples are stored long-term, i.e., over the course of and  
222 beyond a drug development program, to enable re-use and/or future use. The conditions  
223 under which specimens or extracted nucleic acids are archived should be suitable for the  
224 intended genomic testing application. It is recommended that samples and extracted nucleic  
225 acids are stored as multiple aliquots to avoid repeated freeze and thaw cycles, and potential  
226 contamination. If a sample is re-used and undergoes freeze/thaw cycles, then each  
227 freeze/thaw cycle, including the temperature and time at each step, should be recorded.

228 Storage of samples requires a physical infrastructure, as well as a robust laboratory  
229 information and data management system. Considerations when depositing samples into  
230 biorepositories include adherence to quality assurance and quality control programs, sample  
231 tracking systems, local legislations, and informed consent. It is highly recommended that  
232 samples are stored in a physical infrastructure built with appropriate electrical backup  
233 systems and disaster plans. It is of the utmost importance that the party responsible for  
234 samples is clearly identified at all times and that the chain of custody is documented.  
235 Samples should not be stored longer than the allowed total retention time as described in the  
236 informed consent document. Furthermore, procedures should be in place to ensure  
237 appropriate destruction of the sample(s) when a subject withdraws consent or at the end of  
238 the declared retention period.

### 239 **2.2.3. Curation of Sample Inventory**

240 Sample inventory should be monitored and curated relative to the following: consent for use  
241 of the samples, length of storage relative to the sample retention policy, and requests to  
242 withdraw samples from the biorepository. Reconciliation of all samples relative to the  
243 aforementioned aspects should be performed prior to the use of each sample.

## 244 **3. GENOMIC DATA**

245 Human genomic data can be derived from germline (inherited from parents), somatic (e.g.,  
246 mutations in tumor tissues) or mitochondrial (e.g., for traceability of maternal lineage)  
247 sources. Biological specimens from humans may also include non-human genomic  
248 molecules (e.g., microbial DNA or other potentially infectious agents). The type of genomic  
249 data generated depends on the analytes and the applied technology platform(s). For  
250 comprehensive genomic comparisons it may be appropriate to have multiple DNA or RNA  
251 samples collected from a single subject taken from healthy and disease tissue and/or at

252 different time points.

### 253 **3.1. Generation of Genomic Data**

254 Genomic data can be generated by using many different and rapidly evolving technology  
255 platforms and methods. Broad genomic profiling of subjects is technologically feasible  
256 such that the generated data may be stored and used repeatedly over time. It is important to  
257 choose the appropriate platform and method in light of the intended purpose of the genomic  
258 data. Therefore, it is relevant to understand whether research grade or validated methods are  
259 to be used during data generation. Under exploratory settings genomic data can be  
260 generated using research grade reagents and instruments that may not have been validated to  
261 support clinical use. When genomic data are to be used for clinical decision making,  
262 appropriate level of assay validation should be considered in accordance with local  
263 regulations and policies.

264 For genomic research, the processing and analysis workflow (pipeline) details (e.g., reference  
265 genome build, annotation database and parameters) used for mapping purposes should be  
266 documented. The use of standard, publicly available annotation (e.g., GenBank, dbSNP)  
267 and cross-referencing is highly recommended to enable cross-platform comparisons and  
268 integration of genomic and non-genomic (e.g., proteomic) results from different studies.  
269 The database version(s) used for annotation should be recorded to allow for data  
270 compatibility. In addition, bioinformatic algorithms used for treatment decisions should be  
271 documented appropriately.

272 Sponsors should ensure compliant use of samples and genomic data in alignment with  
273 purposeful and permitted use of samples for genomic data generation. The use of the  
274 genomic data should be in alignment with the protocol, the consent and, if applicable, legal or  
275 regulatory requirements.

### 276 **3.2. Handling and Storage of Genomic Data**

277 It is important to understand how different types of genomic data are generated, handled,  
278 analyzed and stored. In general, an instrument generates a raw data file, which is then  
279 processed and converted into an analysis-ready format using appropriate Quality Control  
280 (QC) procedures, followed by the application of analytical software to generate the results  
281 (often referred to as data and analysis pipeline, respectively). It is recommended to retain  
282 data files that maintain the complete features of the raw data; these could be either the raw  
283 data files or derived analysis-ready files along with pipeline documentation, which should

284 allow for reconstruction of the primary data. These data sources would form the basis to  
285 integrate genomic data generated from different technology platforms. Genomic data files  
286 should be stored in secured long-term media. In addition, there should be a possibility to  
287 link the genomic data to other clinical data to allow for current and future use, as appropriate.  
288 Whereas genomic samples may be destroyed upon participant request, destruction of data  
289 contradicts the principles of scientific integrity, particularly in the context of clinical studies.

#### 290 **4. PRIVACY AND CONFIDENTIALITY**

291 Processing and handling of genomic samples and data should be conducted in a manner that  
292 protects the confidentiality of subjects' individual data. For genomic data, like other clinical  
293 data, coding techniques as well as security and access procedures help maintain  
294 confidentiality. Appropriate security measures using coding schemata and restriction of  
295 access should be implemented at each step of analysis and storage. Suitable consideration  
296 should also be given to data protection and confidentiality legislation and policies in each  
297 jurisdiction.

##### 298 **4.1. Coding of Samples and Data**

299 Genomic data should be treated with the same high standards of confidentiality as other  
300 clinical data, which are single-coded and do not carry any personal identifiers. ICH E15  
301 describes various ways for coding of genomic samples and data, including single and double  
302 coding. To decrease complexity and likelihood of error, single coding is recommended for  
303 genomic samples and data, but should be consistent with local regulation or legislation.  
304 Anonymization, as defined in ICH E15, is not recommended for genomic samples or data,  
305 because the process renders the ability to connect previously unlinked genomic data to  
306 phenotypic data impossible. In addition, anonymization does not allow for sample  
307 destruction pursuant to withdrawal of consent or for long term clinical monitoring.

##### 308 **4.2. Access to Genomic Samples and Data**

309 Use of genomic samples and data may involve repeated access over time in accordance with  
310 the informed consent. Therefore, strategies and procedures involving systems that ensure  
311 strict control of access rights with access logs should be established for all genomic samples  
312 and data, similar to that for other clinical data. When outsourcing sample storage, genomic  
313 analysis or data storage, contractual agreements should specify that the responsible party will  
314 supervise the outsourced facility in an appropriate manner to ensure that the samples and/or  
315 data are properly safeguarded.

316 **5. INFORMED CONSENT**

317 Informed consent should be obtained in accordance with ICH E6. Consent for genomic  
318 research may be either included in the consent for the clinical study or obtained separately.  
319 Genomic research has to be conducted in accordance with applicable local legislation and  
320 within the scope of informed consent, which includes collection and storage of genomic  
321 samples and data. Specific considerations should be given to subjects who can only be  
322 enrolled in the study with the consent of the subjects' legal representatives or guardians (e.g.,  
323 minors, subjects with severe dementia).

324 Whereas local regulations currently guide informed consent practices, the identification of  
325 common and essential elements for a globally acceptable informed consent for genomic  
326 sampling would greatly enable genomic research.

327 Ideally, informed consent for the collection and use of genomic samples should permit broad  
328 analysis of the samples (e.g., sets of genes, transcriptome, whole genome sequencing)  
329 regardless of the timing of analysis. Additional elements might include the possibility to  
330 use the samples for assay development, disease research, or pharmacovigilance.

331 **6. TRANSPARENCY AND COMMUNICATION OF FINDINGS**

332 Subjects, their families and/or healthcare providers may wish to receive their results as  
333 related to the intended objectives of the genomic research as with any other clinical study  
334 data. Research, including genomic research, may on occasion generate data or reveal  
335 findings that are incidental to the main objective of the intended research question, but may  
336 be of potential clinical relevance. Some of these incidental findings may also be clinically  
337 actionable. For example, *BRCA1* mutations may be identified with whole genome  
338 sequencing during research that was not intended to investigate cancer risk.

339 It is therefore appropriate that research institutions and sponsors who generate genomic data  
340 in a study adopt a position regarding return of findings to subjects and their primary  
341 healthcare providers. The position should articulate whether the intended research findings,  
342 incidental findings, neither or both will be communicated. Ideally, the position would  
343 describe the timing of such communication (during or after the clinical study) and to whom  
344 (subject or in case of children and incapacitated individuals the primary care giver and the  
345 primary health care provider) as appropriate. If results are communicated, the applied assay  
346 and its level of validation should also be considered. The person(s) responsible for

347 communicating the findings will also need consideration and usually this would be the  
348 investigator, with a link to the informed consent. The subject's desire and consent to receive  
349 such information or not should be respected. Local and regional considerations as well as  
350 guidances may apply.