

E17 General Principles for Planning and Design of Multi-Regional Clinical Trials

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ICH HARMONISED TRIPARTITE GUIDELINE

General Principles
for Planning and Design of
Multi-Regional Clinical Trials

E17

(DRAFT)



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40 1. INTRODUCTION

41 1.1 Objectives of the Guideline

42 With the increasing globalisation of drug development, it has become important that data
43 from multi-regional clinical trials (MRCTs) can be accepted by regulatory authorities
44 across regions and countries as the primary source of evidence to support marketing
45 approval of drugs (medicinal products). The purpose of this guideline is to describe
46 general principles for the planning and design of MRCTs with the aim of increasing the
47 acceptability of MRCTs in global regulatory submissions. The guideline addresses
48 some strategic programme issues as well as those issues that are specific to the planning
49 and design of confirmatory MRCTs and should be used together with other ICH
50 guidelines, including E2, E3, E4, E5, E6, E8, E9, E10 and E18.

51 1.2 Background

52 Globalisation of drug development has increased the use of MRCTs for regulatory
53 submissions in ICH regions as well as in non-ICH regions. Currently, it may be
54 challenging both operationally and scientifically to conduct a drug development
55 programme globally, in part due to distinct and sometimes conflicting requirements from
56 regulatory authorities. At the same time, regulatory authorities face increasing
57 challenges in evaluating data from MRCTs for drug approval. Data from MRCTs are
58 often submitted to multiple regulatory authorities without a previous harmonised
59 regulatory view on the study plan. There are currently no ICH guidelines that deal with
60 the planning and design of MRCTs, although the ICH E5 Guideline covers issues relating
61 to the bridging of results from one region to another. The present guideline describes the
62 principles for planning and design of MRCTs, in order to increase the acceptability of
63 MRCTs by multiple regulatory authorities.

64

65 MRCTs conducted according to the present guideline will allow investigation of



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66 treatment effects in overall populations with multiple ethnic factors (intrinsic and
67 extrinsic factors as described in the ICH E5 guideline) as well as investigating
68 consistency in treatment effects across populations. Hence, using the present guideline
69 for planning MRCTs may facilitate a more efficient drug development and provide earlier
70 access to medicines. In addition, MRCTs conducted according to the present guideline
71 may enhance scientific knowledge about how treatment effects vary across populations
72 and ethnicities under the umbrella of a single study protocol. This information is
73 essential for simultaneous drug development to treat a broad patient population.

74 **1.3 Scope of the Guideline**

75 MRCT in the present guideline is defined as a clinical trial conducted in more than one
76 region under a single protocol. In this context, region may refer to a geographical region,
77 country or regulatory region (see also section 3. Glossary). The primary focus of this
78 guideline is on MRCTs designed to provide data that will be submitted to multiple
79 regulatory authorities for drug approval (including approval of additional indications,
80 new formulations and new dosing regimens) and for studies conducted to satisfy
81 post-marketing requirements. Certain aspects of this guideline may be relevant to trials
82 conducted early in clinical development or in later phases. The present guideline mainly
83 covers drugs, including biological products, but principles described herein may be
84 applicable to studies of other types of treatments.

85 **1.4 Basic Principles**

86 MRCTs are generally the preferred option for investigating a new drug for which
87 regulatory submission is planned in multiple regions. The underlying assumption of the
88 conduct of MRCTs is that the treatment effect is clinically meaningful and relevant to all
89 regions being studied. This assumption should be based on knowledge of the disease, the
90 mechanism of action of the drug, on *a priori* knowledge about ethnic factors and their
91 potential impact on drug response in each region, as well as any data available from early



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92 exploratory trials with the new drug. The study is intended to describe and evaluate this
93 treatment effect, acknowledging that some sensitivity of the drug with respect to intrinsic
94 and/or extrinsic factors may be expected in different regions and this should not preclude
95 consideration of MRCTs.

96

97 Ethnic factors are a major point of consideration when planning MRCTs. They should
98 be identified during the planning stage, and information about them should also be
99 collected and evaluated when conducting MRCTs. In the ICH E5 guideline, and for
100 purposes of the present document, ethnic factors are defined as those factors relating to
101 the intrinsic (e.g.; genetic, physiological) and the extrinsic (e.g.; medical practice, cultural
102 and environmental) characteristics of a population. Based on the understanding of
103 accumulated knowledge about these intrinsic and extrinsic factors, MRCTs should be
104 designed to provide information to support an evaluation of whether the overall treatment
105 effect applies to subjects from participating regions.

106

107 For purposes of sample size planning and evaluation of consistency of treatment effects
108 across geographic regions, some regions may be pooled at the design stage, if subjects in
109 those regions are thought to be similar enough with respect to intrinsic and/or extrinsic
110 factors relevant to the disease area and/or drug under study. In order to further evaluate
111 consistency of treatment effects consideration could also be given to pooling a subset of
112 the subjects from a particular region with similarly defined subsets from other regions to
113 form a pooled subpopulation whose members share one or more intrinsic or extrinsic
114 factors important for the drug development program. The latter approach may be
115 particularly useful when regulators would like additional data to be available from a
116 relevant subpopulation to allow generalisability to a specific population within their
117 regulatory country or region. Both pooled subpopulations and pooled regions should be
118 specified at the study planning stage and be described in the study protocol. These
119 pooled subpopulations and pooled regions may provide a basis for regulatory



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120 decision-making for relevant regulatory authorities.

121

122 The guiding principle for determining the overall sample size in MRCTs is that the test of
123 the primary hypothesis can be assessed, based on combining data from all regions in the
124 trial. The sample size allocation to regions or pooled regions should be determined such
125 that clinically meaningful differences in treatment effects among regions can be described
126 without substantially increasing the sample size requirements based on the primary
127 hypothesis.

128

129 In the planning and design of MRCTs, it is important to understand the different
130 regulatory requirements in the concerned regions. Efficient communication among
131 sponsors and regulatory authorities at a global level can facilitate future development of
132 drugs. These discussions are encouraged at the planning stage of MRCTs.

133

134 Ensuring trial quality is of paramount importance for MRCTs. This will not only ensure
135 the scientific validity of the trial results, but also enable adequate evaluation of the impact
136 of intrinsic and extrinsic factors by applying the same quality standard for trial conduct in
137 all regions. In addition, planning and conducting high quality MRCTs throughout drug
138 development will build up trial infrastructure and capability, which over time will result
139 in a strong environment for efficient global drug development.

140

141 MRCTs can play an important role in drug development programmes beyond their
142 contribution at the confirmatory stage. For example, exploratory MRCTs can gather
143 scientific data regarding the impact of extrinsic and intrinsic factors on pharmacokinetics
144 and/or pharmacodynamics (PK/PD) and other drug properties, facilitating the planning of
145 confirmatory MRCTs. MRCTs may also serve as the basis for approval in regions not
146 studied at the confirmatory stage through the extrapolation of study results.

147



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148 **2. GENERAL RECOMMENDATIONS IN THE PLANNING AND DESIGN OF**
149 **MRCTs**

150 **2.1 Strategy-related Issues**

151 **2.1.1 *The Value of MRCTs in Drug Development***

152 Historically, drug development focused on regulatory strategies designed for specific
153 regulatory regions. In this model, multiregional clinical trials were particularly useful to
154 enable recruitment of the planned number of study subjects within a reasonable
155 timeframe when either the disease and/or condition was rare (e.g.; enzyme deficiency
156 disorder) or when very large numbers of subjects were required (e.g.; cardiovascular
157 outcome trials). More recently, global regulatory strategies are also used to plan and
158 conduct trials more efficiently to facilitate more rapid availability of drugs to patients
159 worldwide. Proper planning and conduct of MRCT's are critical to this effort.

160

161 MRCTs allow for an examination of the applicability of a treatment to a diverse
162 population. The intrinsic and extrinsic factors that are believed and/or suspected to
163 impact drug responses can be further evaluated based on data from multiple ethnicities in
164 various regions using a single protocol. For example, effects of genetic differences on
165 metabolic enzymes or the molecular target of a drug can be examined in exploratory
166 and/or confirmatory MRCTs with participation of subjects of different ethnicities across
167 regions. Accumulated knowledge of the impact of ethnic factors and experience with
168 global collaboration in various regions will promote inclusion of additional regions in
169 MRCTs.

170

171 Even though the primary interest in performing MRCTs is to describe treatment effect
172 based on data from subjects in all regions, some sensitivity to the drug with respect to
173 intrinsic and/or extrinsic factors may be expected in different regions and should not
174 preclude consideration of MRCTs. Even in the case where a drug is very sensitive to one



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175 or more of these factors, it may still be possible to conduct MRCTs by excluding some
176 regions or populations. Only in rare cases will single-region studies be justified, such as
177 the case where disease prevalence is unique to a single region (e.g., anti-malarial drugs,
178 vaccines specific to local epidemics, or antibiotics for regional-specific strains).

179

180 MRCTs can facilitate simultaneous global drug development by reducing the number of
181 clinical trials that need to be conducted separately in each region, thereby avoiding the
182 ethical issue of unnecessary duplication of studies. Although MRCTs require more
183 coordination during the planning stage and possibly increase start-up time, their use can
184 provide a pathway for earlier access to new drugs worldwide.

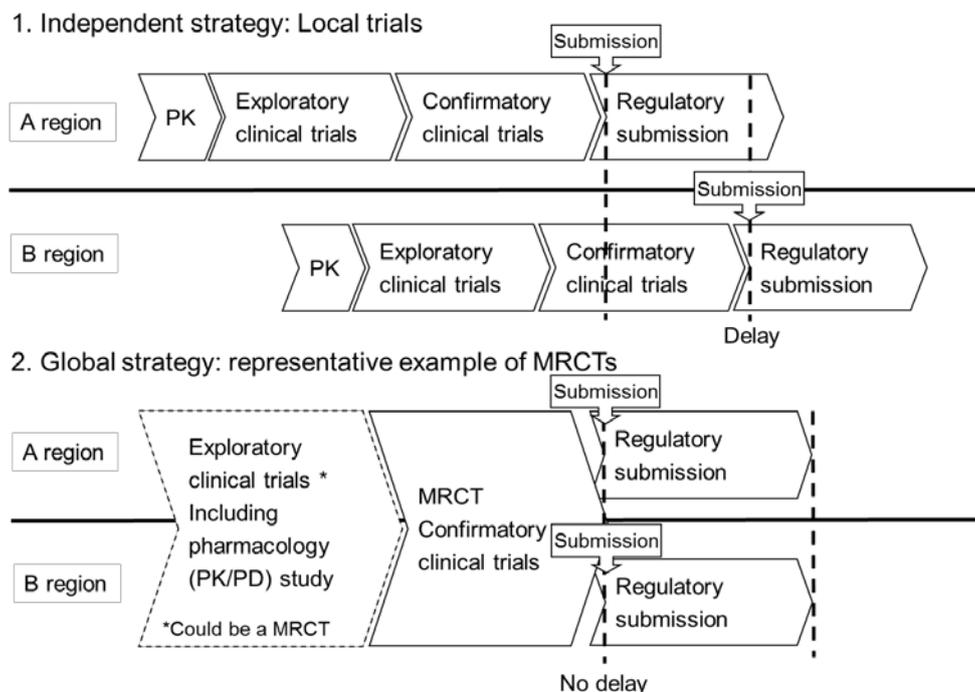
185

186 As shown in the illustrative examples in Figure 1, the timing of clinical drug development
187 across different regions can be synchronised by the use of MRCTs, in comparison to local
188 trials conducted independently in each region. MRCTs may therefore increase the
189 possibility of submitting marketing authorisation applications to multiple regulatory
190 authorities in different regions simultaneously.

191



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192

Figure 1. Time schedules of clinical drug development across regions in independent and global strategies.

193

194 2.1.2 Basic Requirements and Key Considerations

195 In MRCTs, participating regions should share a unified trial hypothesis with common
196 comparators (see Section 2.2.8), and a primary endpoint which is considered clinically
197 meaningful in all regions (see Section 2.2.4). Participating sites should be able to enrol a
198 well-described, well-characterised population of eligible subjects (see Section 2.2.2),
199 where differences between regions with respect to disease and population factors,
200 medical practices and other intrinsic or extrinsic factors (ICH E5) are not expected to
201 substantially impact safety and efficacy results. If major ethnic differences in drug
202 responses are expected, the magnitude of such differences could be examined in
203 exploratory trials (e.g., exploratory MRCTs) before the planning and design of



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204 confirmatory MRCTs.

205

206 It is also a basic requirement that all sites participating in MRCTs should meet applicable
207 quality and regulatory standards. Specifically, MRCTs should be conducted in
208 compliance with ICH E6-GCP standards in all regions and sites, including making sites
209 available for GCP inspections by relevant regulatory authorities. Monitoring plans and
210 other quality checks should be pre-specified and implemented in order to address
211 potential risks to trial integrity. Centralised and risk-based monitoring may be
212 particularly useful for MRCTs in order to monitor and mitigate the impact of emerging
213 regional differences in, for example, retention compliance or adverse event reporting
214 (ICH E6 addendum). Timely and accurate flow of information should occur between the
215 sponsor, trial management team and participating sites. For example, it is critical that
216 important safety information during a trial is provided appropriately to all investigational
217 sites in a timely manner (ICH E2) (see Section 2.2.6).

218

219 To address these basic requirements, it is recommended that investigators and experts
220 representing participating regions are involved in the planning and design of MRCTs.
221 This facilitates taking into consideration differences among regions in extrinsic factors
222 such as local medical practices, administration and interpretation of patient reported
223 outcomes, and endpoint measurements. The impact of some of these factors may be
224 controlled or mitigated via specified clinical management of subjects during the trial, and
225 by relevant inclusion and exclusion criteria. It is also important to have common
226 training for investigators and study personnel in all regions before initiating the trial, in
227 order to ensure that the trial objectives are met through a standardised implementation of
228 the trial protocol, and that an appropriate level of data quality is achieved.

229 ***2.1.3 Scientific Consultation Meetings with Regulatory Authorities***

230 Sponsors of MRCTs are encouraged to have scientific consultation meetings with



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231 regulatory authorities. These interactions should take place during the planning stage of
232 MRCTs to discuss the regulatory requirements for the overall development plan and the
233 acceptability of MRCT data to support marketing authorisations. Conducting such
234 consultation meetings early in the planning stage of MRCTs will enable the comments
235 received from regulatory authorities to be taken into consideration. The sponsor should
236 communicate which authorities are providing regulatory advice and how that advice is
237 being taken into consideration in preparing the relevant documents (e.g., the protocol).
238 Inter-authority scientific discussions are encouraged to allow for harmonisation of study
239 requirements.

240 **2.2 Clinical Trial Design and Protocol-related Issues**

241 **2.2.1 *Pre-consideration of Regional Variability and its Potential Impact on Efficacy*** 242 ***and Safety***

243 In the planning stage, regional variability and the extent to which it can be explained by
244 intrinsic and extrinsic factors should be carefully considered in determining the role
245 MRCTs can play in the development strategy. The most current and relevant data should
246 be used to understand the potential sources of regional variability. If historical data are
247 used, it should be considered whether these data are still relevant in terms of scientific and
248 methodological validity and with respect to current treatment context.

249

250 Factors related to the disease such as prevalence, incidence and natural history are
251 expected to vary across regions, as are disease definitions, methods of diagnosis, and the
252 understanding of certain endpoints. These differences should be minimised by precisely
253 defining inclusion and exclusion criteria and study procedures.

254

255 It is acknowledged that there are almost always small differences in medical practices
256 across regions, and these can be acceptable. However, substantial differences may have
257 a large impact on the study results and/or their interpretation. Common training of



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258 investigators and study personnel in all involved regions before initiating the trial may be
259 able to reduce the impact of these differences.

260

261 Factors, such as distribution of baseline demographics (e.g., body weight or age) may
262 differ between regions, and may potentially impact study results. Additionally, factors
263 such as cultural or socio-economic factors and access to healthcare may impact study
264 results and also recruitment, compliance, and retention, as well as the approaches that
265 could be used to retain subjects. Cultural differences such as use of contraceptives and
266 preferences for a particular route of administration should also be considered.

267

268 It is recognised that different drugs may be more or less sensitive to regional variability
269 based on intrinsic factors, such as genetic polymorphism of drug metabolism or receptor
270 sensitivity (described in ICH E5 Appendix D) which can impact PK/PD, and efficacy and
271 safety of the drug. This applies not only to the investigational drug, but also to
272 comparators and concomitant medications and should be taken into account during
273 planning of MRCTs.

274

275 Often, the degree of variability based on the factors mentioned above can be mitigated by
276 proper design and execution of MRCTs. Providing additional support as needed (e.g.,
277 logistical, infrastructure, laboratory) to specific regions or other mitigation strategies
278 should be considered and implemented to ensure harmonisation.

279 **2.2.2 Subject Selection**

280 In MRCTs, subject selection should be carefully considered to better understand and
281 possibly mitigate potential sources of regional variability and their impact on trial results.
282 Clear and specific inclusion and exclusion criteria that are acceptable and can be applied
283 across all regions should be included in the protocol.

284



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285 To harmonise subject selection, uniform classification and criteria for diagnosis of the
286 disease or definition of the at-risk population should be implemented. When diagnostic
287 tools (e.g., biochemical testing, genetic testing) are needed for the selection of subjects,
288 these should be clearly specified including the degree to which local validated tools and
289 qualified laboratories may be used. In particular, when subject selection is based on
290 subjective criteria (e.g., use of symptom scales in rheumatoid arthritis), the same methods
291 (e.g., validated symptom scales and/or scores in the appropriate language) should be used
292 uniformly across regions. Even so, patient reporting of symptoms may vary by region
293 and may lead to differences in the types of patients included in the trials. This aspect
294 should be considered in the planning stage, in order to implement training requirements
295 and other strategies for potential mitigation of the impact.

296

297 Recommended tools, such as validated imaging instruments and measurements of
298 biomarkers, should be available, or made available, in all regions when these tools are
299 utilised for subject selection. Methods for specimen collection, handling and storage
300 should be specified to the degree required. Methods of imaging need to be clearly
301 defined and are recommended to be standardised throughout the trial.

302 **2.2.3 Selection of Doses for Use in Confirmatory MRCTs**

303 In order to select the dose for confirmatory MRCTs, it is necessary to execute
304 well-planned development programmes during phase I– II that include PK and/or PK/PD
305 studies of applicable parameters, in order to be able to identify important regional
306 differences which may impact dose selection. If PK and/or PK/PD data are needed from
307 different regions, early phase MRCTs should be considered to efficiently gather such data
308 or to better understand PK/ PD prior to initiating confirmatory MRCTs.

309

310 When applicable, PK investigations should be undertaken in subjects from major
311 subpopulations that are intended to be included in MRCTs (e.g., Asian, Black and



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312 Caucasian). Adequate PK comparisons between subpopulations will allow for decisions
313 with respect to the need for pharmacodynamics studies and dose-response studies in
314 different regions and/or subpopulations. It is encouraged to collect genetic data (e.g.,
315 genotypes of metabolising enzymes) from subjects enrolled in the early trials to examine
316 the effects of genetic factors on PK and PD. Such early data may provide useful
317 information when determining optimal dosing regimen(s) for further studies.

318

319 Population PK approaches and/or model-based approaches (e.g., exposure-response
320 models) may be useful to identify important factors affecting drug responses in different
321 populations, and to set an appropriate dose range for further dose-response studies.
322 Dose response studies should cover a broad range of doses and generally include the
323 subpopulations to be studied in MRCTs. However, it may not be necessary to obtain
324 PK/PD or dose-response data from subjects in all regions planned to be included in
325 confirmatory MRCTs, if important regional differences in PK/PD and dose-response are
326 not anticipated (e.g., the drug is unlikely to be sensitive to intrinsic and extrinsic factors).
327 The acceptability of such a strategy should be discussed in advance with relevant
328 regulatory authorities. If substantial differences are anticipated (e.g., the drug is
329 sensitive to intrinsic and/or extrinsic factors), further investigations may be needed.
330 These could include a dose-response study conducted in a particular region or additional
331 dose-response or PK/PD studies conducted for a broader population that would allow
332 further evaluation of the impact of intrinsic and extrinsic factors on dose-response.

333

334 The dose regimens in confirmatory MRCTs (based on data from studies mentioned
335 above) should in principle be the same in all participating regions. However, if early
336 trial data show a clearly defined dose/exposure/response relationship that differs for a
337 region, it may be appropriate to use a different dosing regimen in that region, provided
338 that the regimen is expected to produce similar therapeutic effects with an acceptable
339 safety margin, and is fully justified and clearly described in the study protocol.



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340

341 **2.2.4 Choice of Endpoints**

342 The general principles for endpoint selection and definitions, which are provided in ICH
343 E9, apply. The aspects of particular importance to MRCTs are described here.

344 ***Primary Endpoint***

345 An ideal study endpoint is one that is clinically meaningful, accepted in medical practice
346 (by regulatory guidance or professional society guidelines) and sufficiently sensitive and
347 specific to detect the anticipated effect of the treatment. For MRCTs, the primary
348 endpoint, whether efficacy or safety, should satisfy these criteria as well as being
349 acceptable to all concerned regulatory authorities to ensure that interpretation of the
350 success or failure of the MRCT is consistent across regions and among regulatory
351 authorities. Agreement on the primary endpoint ensures that the overall sample size and
352 power can be determined for a single (primary) endpoint based on the overall study
353 population and also agreed upon by the regulatory authorities. If, in rare instances,
354 agreement cannot be reached due to well-justified scientific or regulatory reasons, a
355 single protocol should be developed with endpoint-related sub-sections tailored to meet
356 the respective requirements of the regulatory authorities. In this case, since regulatory
357 approvals are based on different primary endpoints by different authorities, no
358 multiplicity adjustment is needed for regulatory decision-making. As stated in ICH E9,
359 the primary endpoint should be relevant to the patient population. In MRCTs, this
360 relevance needs to be considered for all regions in the trial and with respect to the various
361 drug, disease and population characteristics represented in those regions (see Section
362 2.2.1).

363

364 MRCTs may introduce the need for further consideration regarding the definition of the
365 primary endpoint. While endpoints like mortality or other directly measurable outcomes
366 are self-explanatory, others may require precise and uniform definitions (e.g.,



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367 progression-free survival). Of specific concern in MRCTs are those endpoints that could
368 be understood and/or measured differently across regions. Examples are hospitalisation,
369 psychometric scales, assessment of quality of life, and pain scales. To guarantee that
370 such scales can be properly interpreted, the scales should be validated and their
371 applicability to all relevant regions justified before starting the MRCT. Furthermore, it
372 should be ensured that the outcome is relevant to all regions.

373

374 The primary endpoint of MRCTs should be one for which experience is already available
375 in the participating regions. In cases where prior experience with an endpoint only exists
376 in one or a subset of regions involved in the MRCT, its adoption as primary endpoint will
377 require discussion and agreement with regulatory authorities regarding the basis for the
378 evidence, keeping in mind that the forthcoming trial can add information about clinical
379 relevance of the agreed endpoints.

380

381 In addition to endpoint selection and definition, regulatory agreement should also be
382 obtained on the timing and methods of the primary endpoint assessment, as discussed in
383 Section 2.2.6.

384 *Secondary Endpoints*

385 Where possible, harmonisation of secondary endpoints is encouraged to maintain the
386 feasibility and improve the quality of trial conduct. However, in some cases, individual
387 regulatory authorities may propose different secondary endpoints relevant to their
388 interests and experience. Even in such cases, all secondary endpoints including those
389 selected only for a particular regulatory authority should be described in the protocol. It
390 is in the interest of the sponsor to describe the specific advantages of the investigational
391 product in terms of secondary endpoints as precisely as possible during the planning stage
392 of MRCTs, to reduce the need for (and impact of) multiplicity adjustments for multiple
393 endpoints, thereby improving the chance for successfully demonstrating the intended



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394 effect. Control of the Type I error across both primary and secondary endpoints may be
395 required by some regulatory authorities.

396 *Other Considerations*

397 Although endpoints may not require formal validation, some endpoints may be subject to
398 subtle differences in understanding, when used in different cultural settings. For
399 example, certain types of adverse events may be more sensitively reported (e.g., more
400 frequently) in some regions and not in others, resulting in differences in reporting patterns
401 due to cultural variation rather than true differences in incidence. Use of these variables
402 as endpoints in MRCTs will require careful planning. Approaches to minimise the impact
403 of this variation in data collection and interpretation of the study results should be
404 described and justified in the study protocol.

405

406 Endpoints that are only of interest for one or a few regions could be considered for a
407 regional sub-trial of the MRCT. However, care should be taken to ensure that
408 ascertainment of regional sub-trial endpoints do not hamper in any way the conduct of the
409 main trial. In particular, consideration should be given to the impact of additional
410 patient burden, and the potential to induce reporting bias with respect to other endpoints
411 in determining whether regional sub-trials can be conducted or whether a separate trial is
412 needed.

413 **2.2.5 Estimation of an Overall Sample Size and Allocation to Regions**

414 *General considerations and overall sample size*

415 The overall sample-size for MRCTs is determined by a treatment effect that is
416 considered clinically meaningful and relevant to all regions based on knowledge of the
417 disease, the mechanism of action of the drug, on *a priori* knowledge about ethnic factors
418 and their potential impact on drug response in each region, as well as any data available
419 from early exploratory trials with the new drug. However, the treatment effect may be



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420 influenced by intrinsic and/or extrinsic factors that vary across regions. The MRCT
421 should therefore also be designed to provide sufficient information for an evaluation of
422 the extent to which the overall treatment effect applies to subjects from different regions.
423 Only if regional variation is known or suspected *a priori* to be of such a high degree that
424 the treatment effect will be difficult to interpret, then conducting separate trials in at least
425 some of the regions may be a more appropriate drug development strategy.

426

427 The ICH E9 provides general principles for determining sample sizes of clinical trials and
428 a detailed description of the factors impacting that determination. The same principles
429 apply to MRCTs. As stated in E9, the overall sample size is usually determined by the
430 primary objective of the trial, stated in terms of study endpoints and specific hypotheses,
431 as well as the size of the treatment effect to be detected, background and/or control group
432 mean values or event rates, variability of the primary outcome, test statistics, Type I error
433 control, multiplicity, and missing data considerations. In addition to these factors, the
434 overall sample size calculation for the MRCT should take into consideration the potential
435 for increased variability due to the inclusion of multiple regions and a possibly more
436 heterogeneous population, compared to a single-region trial. Also with MRCTs, even
437 after attempts at reaching consensus among regional authorities, it may be the case that
438 different regulatory requirements (e.g., regarding the trial's endpoints, subgroup analysis
439 requirements, non-inferiority margins, etc.) will impact the overall sample size.

440

441 Where the primary objective of MRCTs is to assess non-inferiority (or equivalence) of
442 two drugs, the margin is a critical factor in determining the overall sample size and should
443 be pre-specified in the study protocol. Ideally, the same margin would be acceptable to
444 all regulatory authorities, but if different margins are required for different regulatory
445 regions, the rationale should be provided in the protocol. The protocol should clearly
446 specify which margin is in effect for which region involved in the trial, and the sample
447 size calculation should take into consideration the most stringent margin.



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448

449 *Allocation to Regions*

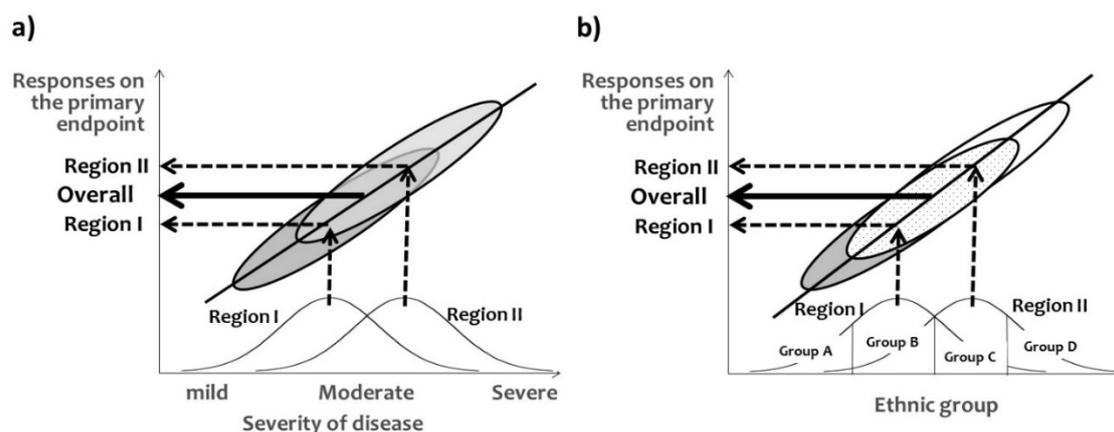
450 Although knowledge of intrinsic and extrinsic factors accumulates as drug development
451 moves from the exploratory to confirmatory stage (see Section 2.2.1), empirical evidence
452 exists that region is a feasible and valuable indicator for unknown and important
453 differences in intrinsic and/or extrinsic factors, which may exist among populations.
454 Figure 2 illustrates that the primary endpoint may be modulated by known intrinsic and/or
455 extrinsic factors such as disease severity (Figure 2a) or ethnicity (Figure 2b) across
456 regions. Consequently, the treatment effect of the primary endpoint may be influenced
457 by those known factors, along with other potential unknown factors across regions.
458 When these factors have different distributions among the regions, some variation in
459 treatment effect among regions may be observed. Therefore proper planning for sample
460 size allocation to region is needed in order to describe the treatment effect in the
461 multi-regional setting.

462



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463



464

Figure 2. Illustration of primary endpoint responses modulated by
intrinsic and extrinsic factors across regions;
(2a) by severity of disease, (2b) by ethnic group.

465

466 Understanding the treatment effect in the multi-regional setting is an important objective
467 of MRCTs, and for that purpose, MRCTs are usually stratified by region to reflect the
468 similarity of patients within a region regarding genetics, medical practice, and other
469 intrinsic and extrinsic factors. Without substantially increasing the overall sample size
470 required for the primary hypothesis, the sample size allocation to regions should be
471 determined such that clinically meaningful differences in treatment effects estimated in
472 different regions can be described.

473

474 There are several approaches that could be considered for allocating the overall sample
475 size to regions each with its own limitations, and a few are described below. One
476 approach is to determine the regional sample sizes needed to be able to show similar
477 trends in treatment effects across regions. Allocating equal numbers of patients to each
478 region would increase the likelihood of showing similar trends; however, such an
479 allocation strategy may not be feasible or efficient in terms of enrolment and trial conduct.



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480 Another approach is to determine the sample size needed in one or more regions based on
481 the ability to show that the region-specific treatment effect preserves some pre-specified
482 proportion of the overall treatment effect. This allocation strategy, however, would be
483 difficult if all regions have this requirement. A third approach is to enrol subjects in
484 proportion to region size and disease prevalence without adhering to a fixed allocation
485 strategy for regions. This allocation strategy will likely result in very small sample sizes
486 within some countries and/or regions and therefore be insufficient alone to support any
487 evaluation of consistency among region specific effects. A fourth approach is to
488 determine the regional sample sizes to be able to achieve significant results within one or
489 more regions. This allocation strategy brings into question the reasons for conducting
490 MRCTs and should be discouraged. A fifth approach is to require a fixed minimum
491 number of subjects in one or more regions. Any local safety requirement for minimum
492 number of subjects to be exposed to the drug is generally a programme level
493 consideration and should not be a key determinant of the regional sample size in MRCTs.
494

495 Because there is no uniformly acceptable or standardised approach to regional sample
496 size allocation, a balanced approach is needed to ensure that the trial is feasible but also
497 provides sufficient information to evaluate the drug in its regional context. Therefore,
498 sample size allocation should take into consideration region size, the commonality of
499 enrolled subjects across regions based on intrinsic and extrinsic factors and patterns of
500 disease prevalence, as well as other logistical considerations to ensure enrolment is able
501 to be completed in a timely fashion.

502

503 For purposes of sample size planning and evaluation of consistency of treatment effects
504 across regions, some regions may be pooled, if subjects in those regions are thought to be
505 similar with respect to intrinsic and/or extrinsic factors, which are relevant to the disease
506 area and/or drug under study. Consideration could also be given to pooling a subset of
507 the subjects from a particular region with similarly defined subsets from other regions to



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508 form a pooled subpopulation whose members share one or more intrinsic or extrinsic
509 factors important for the drug development programme. Use of this pooled
510 subpopulation can further support the evaluation of consistency of treatment effects
511 across regional populations. It should be discussed at the planning stage how the
512 analyses of *pooled regions and/or pooled subpopulations* may provide a basis for the
513 regulatory decision-making for relevant regulatory authorities. This should also be
514 specified and be described in the study protocol in advance.

515

516 As an example of a pooled subpopulation; in Figure 2b, an ethnic group B that can largely
517 be enrolled from region I could alternatively be enrolled globally (e.g.; region I and II) to
518 facilitate scientific evaluation of the impact of ethnic factors and regulatory decision
519 making. At the same time the allocation should provide a minimally sufficient amount
520 of information within each region to support assessment of consistency in treatment
521 effects. Examples of pooled subpopulations include Hispanics living in North and South
522 America, or Caucasians living in Europe and North America. Examples of pooled
523 regions include East Asia, Europe, and North America.

524

525 The above considerations for sample size planning to assess regional variation apply to
526 assessing consistency of treatment effect with respect to other intrinsic and/or extrinsic
527 factors. It may be possible to pool regions or subpopulations in these assessments in
528 order to increase the ability to evaluate consistency.

529

530 In general, comparing with sample size requirements in regional or local trials, the
531 potential increase of the overall sample size in MRCTs should be due primarily to the
532 increased variability and/or decreased overall treatment effect anticipated for a
533 multi-regional population. Based on accumulated information about intrinsic and/or
534 extrinsic factors, the use of pooled regions and pooled subpopulations may provide
535 practical ways to maintain the total sample size while allowing the descriptions of



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536 treatment effect in its regional context. Discussion with regulatory authorities on the
537 proposed sample allocation is highly recommended at the planning stage.

538

539 In certain situations (e.g.; rare diseases, unmet medical needs), sample size allocation in
540 regions could generally be allowed more flexibility. If prevalence of the disease is
541 substantially different in one or more regions, scientific consultation with the relevant
542 regulatory authority in advance is recommended. Acceptability of the trial should be
543 discussed with the authorities, as recruitment may be heavily skewed towards the more
544 prevalent region, and this may limit the ability to characterise regional differences in
545 safety and efficacy.

546 **2.2.6 Collecting and Handling of Efficacy and Safety Information**

547 Collecting and handling methods of efficacy and safety information should be
548 standardised across participating regions. Safety reporting should be conducted in
549 accordance with ICH E2. When local regulations specify different requirements, such as
550 timelines for expedited reporting, these should also be adhered to locally. The specific
551 timeframe for safety reporting should be described in the protocol, and the investigators
552 should be trained appropriately. In the case of MRCTs, important safety information
553 should be handled both with adherence to any local regulations, and also in adherence to
554 ICH E2A. Important safety information should always be provided to the relevant
555 stakeholders (e.g., investigators, ethics committees) in a timely manner.

556

557 In MRCTs of long duration, where special concerns have been identified, and/or where
558 operational regions are quite large, the use of a central independent data monitoring
559 committee (with representation from major regions, as applicable) should be considered,
560 in order to monitor the accumulating efficacy and/or safety information from the MRCT.
561 If adjudication of endpoints and/or events is planned, a centralised assessment by a single
562 adjudication committee should be considered.



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563

564 Endpoint ascertainment should also be harmonised as far as possible (see Section 2.2.4).

565 If subjective endpoints are used, coordinated training of investigators and clinical site

566 personnel is particularly important for the handling of data in a standardised manner. If

567 laboratory data are used in key primary and secondary endpoints, centralised laboratory

568 tests should be considered.

569

570 Coordinated site initiation is particularly important in MRCTs to ensure proper conduct,

571 completion and reporting of results without any delays among regions. To comply with

572 the quality management described in ICH E6, the sponsor should implement a system to

573 manage quality throughout the design, conduct, evaluation, reporting and archiving of

574 MRCTs. It could be considered to use electronic data capturing and reporting, to gather

575 information and data (including relevant ethnic factors) from all regions in a standardised

576 way without delays. If a case report form and other related documents are translated to

577 the local language, consistency of documents between languages should be ensured.

578 **2.2.7 Statistical Analysis Planning to Address Specific Features of MRCTs**

579 ICH E9 provides general statistical principles for planning and conducting statistical

580 analyses of randomised clinical trials. Aspects of analysis planning that are particularly

581 important for MRCTs are described below.

582 ***Obtaining Regulatory Input on Analysis Strategy***

583 It is recommended to have early discussions with the different regulatory authorities
584 involved in the MRCT, and to obtain their agreement with the proposed analysis strategy.

585 The standard is to specify a single primary analysis approach in the statistical section of
586 the study concept to be agreed upon with the authorities in advance of starting the trial.

587 If different analysis strategies are required by different authorities for well-justified
588 scientific or regulatory reasons, they should be described in the trial protocol. If, in

589 addition, a statistical analysis plan is developed as a separate document for the MRCT, a



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590 single comprehensive analysis plan describing the analytical approaches to be used to
591 meet the different regulatory requirements should be developed. For blinded studies, the
592 statistical analysis plan should be finalised prior to unblinding of treatment assignments
593 (at interim or final report) and submitted to regulatory agencies upon request.

594 *Evaluation of Subgroups Defined by Intrinsic and Extrinsic Factors*

595 To investigate observed differences in treatment effects among regions, which may be
596 due to differences in intrinsic and/or extrinsic factors, it is recommended that subgroup
597 analyses be planned during the design stage and pre-specified in the protocol and
598 statistical analysis plan. Of most interest are subgroups defined according to intrinsic
599 and extrinsic factors likely to be prognostic for the course of the disease or plausibly
600 predictive of differential response to treatment. Examples include subgroups defined by
601 disease stage (e.g., mild, moderate, or severe), race and/or ethnicity (e.g., Asian, Black or
602 Caucasian), medical practice/therapeutic approach (e.g., different doses used in clinical
603 practice) or genetic factors (e.g., polymorphisms of drug metabolising enzymes), that are
604 well-established for the disease or therapy and suggested from early stages of
605 investigation.

606

607 Well-reasoned and prospective planning of the analysis of the impact of intrinsic and
608 extrinsic factors on treatment effects can potentially minimise the need for data-driven
609 investigations of subgroup findings and can establish a good foundation for evaluating
610 the consistency of region specific treatment effects. Furthermore, pre-specified
611 subgroup analyses for relevant study subpopulations that are defined beyond
612 geographical boundaries and based on common intrinsic and /or extrinsic factors may be
613 useful for generating key scientific evidence to support regional or national marketing
614 authorisation.

615



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616 The statistical analysis section of the protocol should describe the analytical approach for
617 assessment of subgroup differences. In addition to summarising the key efficacy and
618 safety endpoints by subgroup, model-based analyses can be useful to assess consistency
619 of treatment effects with respect to one or more subgroup factors. Forest plots or other
620 graphical methods that depict treatment effects for a series of subgroups may also be
621 useful in assessing consistency of subgroup-specific treatment effects.

622 *Considering Regions in the Primary Analysis*

623 If randomisation is stratified by region, then following the ICH E9 principle, the primary
624 efficacy analysis designed to test hypotheses about the overall treatment effects should
625 adjust for regions using appropriate statistical methods. If some regions were combined
626 based on intrinsic and/or extrinsic factors, then the pooled regions would be used as
627 stratification factors in the primary analysis. The appropriate strategy for subgroup
628 analyses is to follow the primary analysis model of the trial, including stratification by
629 region.

630 *Examination of Regional Consistency*

631 The statistical analysis plan should include a strategy for evaluating consistency of
632 treatment effects across regions, and for evaluating how any observed differences across
633 regions may be explained by intrinsic and/or extrinsic factors. Various analytical
634 approaches to this evaluation, possibly used in combination, include but are not limited to
635 (1) descriptive summaries, (2) graphical displays (e.g., Forest plots, funnel plots), (3)
636 model-based estimation including covariate-adjusted analysis, and (4) test of treatment
637 by region interaction, although it is recognised that such tests often have very low power.
638 The assessment of the consistency of treatment effects across regions, considering the
639 plausibility of the findings, should be done with diligence before concluding that
640 potential differences between treatment effects in regions are a chance finding.

641

642 If subgroup differences (e.g., by gender) in treatment effects are observed, then an



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643 examination of whether the subgroup differences are consistent across regions or pooled
644 regions is recommended. In general, the credibility of subgroup and/or regional findings
645 should also take into consideration biological plausibility, consistency (internal and/or
646 external) of findings, the strength of evidence, as well as the statistical uncertainty. The
647 analyses and evaluation of treatment effects should be planned to enable the qualitative
648 and/or quantitative evaluation of benefit/risk across subgroups and across regions.

649 *Estimation of Regional Treatment Effects*

650 The statistical analysis section of the protocol should describe appropriate statistical
651 methods for estimating and reporting treatment effects and associated measures of
652 variance for individual regions, if sample sizes allow. The same analysis strategy should
653 be used as planned for the primary analysis. This plan should include a determination of
654 the adequacy of sample sizes to support accurate estimation within each region or pooled
655 region for which reporting of treatment effect is of interest. If the sample size in a region
656 is so small that the estimates of effect are unreliable, the use of other methods should be
657 considered, including the search for options to pool regions based on commonalities, or
658 borrowing information from other regions or pooled regions using an appropriate
659 statistical model.

660 *Monitoring and Mitigation of MRCT Conduct*

661 Centralised and risk-based monitoring may be particularly useful for MRCTs to identify
662 variability across regions and sites in protocol compliance, e.g., differences in follow-up,
663 compliance with study medications, adverse event reporting, and/or extent of missing
664 data. Mitigation approaches should take regional differences into consideration.

665

666 **2.2.8** *Selection of Comparators*

667 The choice of control groups should be considered in the context of the available standard
668 therapies, the adequacy of the evidence to support the chosen design, and ethical



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669 considerations. Comparators in MRCTs should in principle be the same in all
670 participating regions. Due to the complexity in setting up MRCTs, some keypoints are
671 addressed in the following paragraphs, focusing on practical and ethical issues associated
672 with the use of comparators:

- 673 • Appropriateness of the choice of comparators should be justified based on
674 scientific and other relevant information, including international treatment
675 guidelines.
- 676 • Active controls should in principle be dosed and administered in the same way in
677 all regions. If the approved doses of active comparators are different among
678 regions, the impact of such difference on analysis and evaluation of data should be
679 considered, and relevant scientific reasons, such as different drug exposure
680 induced by intrinsic factors, should be justified in the protocol.
- 681 • The same dosage form (e.g., capsules vs tablets) for active comparators should
682 generally be used among regions participating in MRCTs to ensure consistency of
683 treatment effects. Different dosage forms can cause problems for maintenance of
684 the blinding and data interpretability. Unless the effect of the different dosage
685 forms on the dissolution profiles, bioavailability and blinding are
686 well-characterised and negligible the same dosage form should be used.
- 687 • In order to ensure the quality of the investigational drugs, it is recommended to
688 use the same source of the active comparators in all participating regions. When
689 active comparators from different sources are used in MRCTs, justification should
690 be provided, such as bioequivalence data, to support the differently sourced
691 comparators.
- 692 • The product information used in the region where the product is sourced should be
693 used consistently in all participating regions. If the sourced product information
694 differs from local product information, this should be explained in the protocol
695 and the informed consent form (e.g., there may be differences in the adverse event
696 reporting and/or display between the package inserts).



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698 In addition, active comparators in MRCTs should ideally be approved in all participating
699 regions. However, there could be situations where active comparators used in MRCTs
700 are not approved or not available in specific regions, but have been approved and
701 available in some ICH regions. Therefore the appropriateness of the selected control(s)
702 may vary between the regions. The reason for the use of an unapproved drug vs the
703 current standard of the region should therefore be described in the protocol based on
704 scientific information, such as a guideline and other relevant documents, to justify the
705 choice of comparator. Development status of the unapproved drug in the region should
706 also be described in the protocol. Pre-consideration is also necessary regarding how
707 such an unapproved drug may affect subjects in the region, especially regarding safety.
708 A plan for how to address the issue of non-approved control treatment(s) should be
709 explained in the protocol. In these circumstances, design of MRCTs should involve
710 consultation with the relevant regulatory authorities to determine the appropriateness of
711 such trial designs as part of the overall drug approval strategy.

712 **2.2.9 Handling Concomitant Medications**

713 In general, drugs not allowed in the protocol should be the same throughout the regions to
714 the extent possible, but there may be some differences in the drugs actually used due to
715 different medical practices. This could be acceptable if not expected to substantially
716 impact results.

717

718 Concomitant medications may be required as an important part of the treatment. In
719 circumstances where approved drugs are combined with an investigational drug (e.g., a
720 combination regimen of anticancer drugs) the same dosage regimen in all regions should
721 generally be applied. If required by protocol, concomitant medications that are not
722 approved in a region should have their use justified based on scientific information,
723 treatment guidelines and other relevant documents. This could include documentation



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724 that the concomitant medication is approved in at least one of the participating regions.
725 It should be allowed to use an unapproved concomitant drug; however the impact of using
726 the unapproved drug vs the approved standard in the relevant regions should be discussed
727 with regulatory authorities and described in the protocol (see section 2.2.8). The
728 medication will need to be supplied in regions in which it is otherwise not available.

729

730 For concomitant medications that are not required by protocol, classes of medications that
731 are not allowed during the study should be identified. The effects of differences in
732 concomitant medications on drug responses should be considered in advance. Changes
733 in dosage of concomitant medications that may impact the study endpoints should be
734 carefully documented within each subject and explained throughout the trial period as
735 specified in the protocol.

736

737 To ensure a subject's condition is stable before starting the investigational drug, a prior
738 observation period may be useful for control of some concomitant medications.
739 Changes in concomitant medications or doses of medications that may be expected to
740 impact the study endpoints during the trial may be allowed, based on pre-specified
741 criteria. If a major impact on drug responses is expected, based on differences in
742 concomitant medications, additional measures to minimise impact should be considered,
743 such as additional PK or subgroup analyses.

744

745 3. GLOSSARY

746 • Regulatory region:

747 A region for which a common set of regulatory requirements applies for drug
748 approval (e.g., European Union, Japan).

749 • Pooled regions:

750 A subset of enrolled subjects where data can be pooled together within and/or



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751 across geographical regions, countries or regulatory regions based on a
752 commonality of intrinsic and/or extrinsic factors for purpose of regulatory
753 decision-making.
754