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

ICH HARMONISED GUIDELINE

GENERAL PRINCIPLES FOR PLANNING AND DESIGN OF MULTI-REGIONAL CLINICAL TRIALS

E17

Final version

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This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

E17
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E17

ICH Consensus Guideline

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1. INTRODUCTION

1.1. Objectives of the Guideline

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

1.2. Background

In the era of globalisation of drug development, it may be challenging to conduct a drug development programme globally, in part due to distinct and sometimes conflicting requirements from regulatory authorities. At the same time, regulatory authorities face increasing challenges in evaluating data from MRCTs for drug approval. Data from MRCTs are often submitted to multiple regulatory authorities without a previously harmonised regulatory view on the development programme. There are currently no ICH guidelines that deal specifically with the planning and design of MRCTs, although the ICH E5 guideline covers issues relating to the bridging of results from one region to another.

MRCTs conducted according to the present guideline will allow investigation of treatment effects including safety evaluations in the overall population as well as investigations of the potential impact of intrinsic and extrinsic factors (described as ethnic factors in the ICH E5 guideline) on the treatment effect. MRCTs, which are properly designed and executed according to this guideline, may facilitate more efficient drug development and increase the possibility of submitting marketing authorisation applications to multiple regulatory authorities in different regions simultaneously, thus providing earlier access to new drugs worldwide. In addition, MRCTs conducted according to the present guideline

may enhance scientific knowledge about how treatment effects vary across regions and populations under the umbrella of a single study protocol, and how this variation may be explained by intrinsic and extrinsic factors.

1.3. Scope of the Guideline

MRCT is defined in the present guideline as a clinical trial conducted in more than one region under a single protocol. In this context, a region may refer to a geographical region, country or regulatory region (see Section 3. Glossary). The primary focus of this guideline is on MRCTs designed to provide data that will be submitted to multiple regulatory authorities for drug approval (including approval of additional indications, new formulations and new dosing regimens) and for studies conducted to satisfy post-marketing requirements. Certain aspects of this guideline may also be relevant to studies conducted early in clinical development or in later phases. The present guideline mainly covers drugs including biological products, although some sections may not be applicable to all development programmes (e.g., pharmacokinetics (PK) not used for preventive vaccine dose-finding).

1.4. Basic Principles

Basic principles for designing MRCTs are described below. Subsequent sections expand on these principles in more detail.

1. Strategic use of MRCTs in drug development programmes, properly designed and executed according to this guideline, can increase efficiency of drug development. MRCTs may enable simultaneous submission of marketing authorisation applications and support regulatory decision-making in multiple regions, allowing earlier access to new drugs worldwide. Although MRCTs may generally become the preferred option for investigating a new drug for which regulatory submission is planned in multiple regions, the potential for regional differences to impact the interpretability of study results should be carefully considered.
2. The intrinsic and extrinsic factors important to the drug development programme, should be identified early. The potential impact of these factors could be examined in the exploratory phases before the design of confirmatory MRCTs. Infor-

mation about them should also be collected during the confirmatory trial for evaluation of their impact on treatment effects.

3. MRCTs are planned under the assumption that the treatment effect applies to the entire target population, particularly to the regions included in the trial. Strategic allocation of the sample size to regions allows an evaluation of the extent to which this assumption holds.
4. Pre-specified pooling of regions or subpopulations, based on established knowledge about similarities, may help provide flexibility in sample size allocation to regions, facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making.
5. A single primary analysis approach for hypothesis testing and estimation of the overall treatment effect should be planned so that it will be acceptable to all concerned regulatory authorities. A structured exploration to examine the consistency of treatment effects across regions and subpopulations should be planned.
6. In light of diverse regional practices, ensuring high quality of study design and conduct in accordance with ICH E6 in all regions is of paramount importance to ensure the study results are interpretable. Careful attention to quality during trial planning, investigator training, and trial monitoring will help achieve consistently high trial quality required for a successful MRCT.
7. Efficient communication among sponsors and regulatory authorities is encouraged at the planning stage of MRCTs, with the goal of obtaining acceptance of a global approach to study design across the different regulatory regions.

2. GENERAL RECOMMENDATIONS IN THE PLANNING AND DESIGN OF MRCTs

2.1 Strategy-related Issues

2.1.1 The Value of MRCTs in Drug Development

Historically, drug development focused on regulatory strategies designed for specific regulatory regions. In that context, MRCTs had been recognised as an efficient way to enable recruitment of the planned number of trial subjects within a reasonable timeframe when either the disease and/or condition was rare (e.g., an enzyme deficiency disorder), for special (e.g., elderly, paediatric) populations, or when very large numbers of subjects

were required (e.g., cardiovascular outcome studies, vaccine efficacy studies). More recently, global regulatory strategies are also used to plan and conduct studies more efficiently to facilitate more rapid availability of drugs to patients worldwide.

MRCTs allow for an examination of the applicability of a treatment to diverse populations. The intrinsic and/or extrinsic factors that are believed or suspected to impact upon responses to the drug can be further evaluated based on data from various regions using a single protocol. For example, the impact on the treatment effect of genetic differences or different distribution of gene polymorphisms in drug metabolising enzymes or the molecular target of a drug can be examined in exploratory and/or confirmatory MRCTs that include subjects with different intrinsic factors across regions. Accumulated knowledge of the impact of intrinsic and extrinsic factors and global sharing of experiences in various regions may promote inclusion of additional regions in MRCTs.

The primary reason for performing MRCTs is to evaluate the overall treatment effect based on data from subjects in all regions. However, intrinsic and/or extrinsic factors may be expected to impact subjects' responses to drugs differently across regions and should be considered when planning MRCTs. If major differences in treatment effects are expected, available data should be assessed to decide, whether it is appropriate and feasible to conduct the MRCT. Even in the case of expected major differences in treatment effects, it may still be possible, to conduct MRCTs by excluding some regions or a defined subgroup within a region, after careful consideration. Additional strategies to study a disease and/or drug in the excluded regions should be considered (see ICH E5). If MRCTs are the source of data in the bridging strategy based on the ICH E5 guideline, MRCTs could provide more robust evidence than single regional trials for extrapolation of study results. In some cases, single-region studies may be appropriate, such as in the evaluation of drugs to treat or prevent a disease that is prevalent in a single region (e.g., anti-malarial drugs, vaccines specific to local epidemics, or antibiotics for region-specific strains).

MRCTs can facilitate simultaneous global development of a drug and reduce the number of clinical studies conducted separately in each region, thereby minimising unnecessary duplication of studies. Although MRCTs require more coordination during the planning stage and possibly increase start-up time, their use may provide a pathway for earlier

access to new drugs worldwide by facilitating earlier approval across regions, thereby avoiding significant lag in the availability of new drugs in some regions.

As shown in the illustrative examples in Figure 1, the timing of clinical drug development across different regions can be synchronised by the use of MRCTs, in comparison to local studies conducted independently in each region. Figure 1 also illustrates the use of MRCTs in the overall design of the drug development programme, not only in the confirmatory stage, but also as an option in the exploratory stage, where it is feasible. Early identification of relevant intrinsic and extrinsic factors could set a good foundation for planning confirmatory MRCTs.

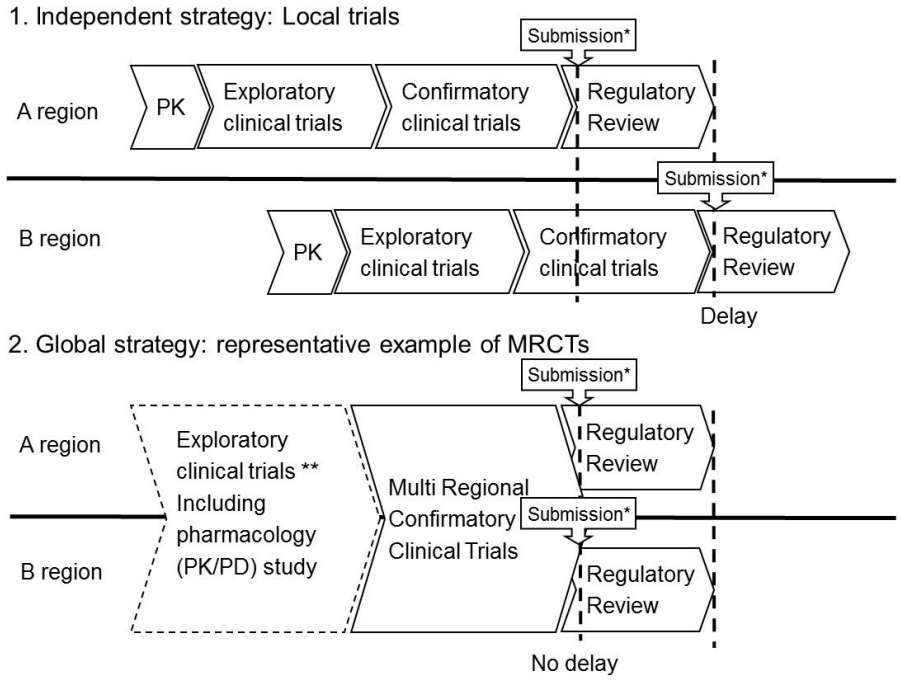

Figure 1. Illustrations of clinical drug development workflow across regions for drug submission and regulatory review in independent and global strategies

*: Marketing Authorization Application/New Drug Application

**: Could be parallel single region trials or MRCTs

It may be plausible and efficient for an MRCT to be the single pivotal trial to support regulatory submission, and if this is the case, it should be designed to provide sufficient and robust evidence to support approval.

In summary, strategic use of MRCTs, properly designed and executed according to this guideline, can increase efficiency of drug development, allow for exploration of the treatment effect to diverse populations, and enable simultaneous submission of marketing authorisation applications and regulatory decision-making in multiple regions. Therefore, MRCTs may generally become the preferred option for investigating a new drug for which regulatory submission is planned in multiple regions.

2.1.2 Good Clinical Practice (GCP) Requirements and MRCTs

All sites participating in MRCTs should meet applicable quality, ethical and regulatory standards. Specifically, MRCTs should be conducted in compliance with ICH E6 GCP standards in all regions and sites, including making sites available for GCP inspections by regulatory authorities. Monitoring plans and other quality checks should be pre-specified and implemented in order to address potential risks to subject rights, safety and well-being, and to the reliability of study results. Centralised and risk-based monitoring may be particularly useful for MRCTs in order to monitor and mitigate the impact of emerging regional differences in, for example, trial subject retention or adverse event reporting (ICH E6). Timely and accurate flow of information should occur between the sponsor, the trial management team and the participating sites.

2.1.3 Scientific Consultation Meetings with Regulatory Authorities

Sponsors of MRCTs are encouraged to have scientific consultation meetings with relevant regulatory authorities. These interactions should take place during the planning stage of MRCTs to discuss the regulatory requirements for the overall development plan and the acceptability of MRCT data to support marketing authorisations. Conducting such consultation meetings early in the planning stage of MRCTs will enable the comments received from regulatory authorities to be taken into consideration. The sponsor should prepare the protocol and other relevant documents, and it may be beneficial to include information as to which authorities are providing regulatory advice, and how that advice is being taken into consideration. Consultation with authorities may happen at various stages affecting different aspects of protocol development. Inter-authority scientific discussions are encouraged to allow for harmonisation of study requirements.

2.2 Clinical Trial Design and Protocol-related Issues

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

At the planning stage, regional variability, the extent to which it can be explained by intrinsic and extrinsic factors, and its potential to influence the study results, should be carefully considered in determining the role MRCTs can play in the drug development strategy. To facilitate taking into consideration differences among regions in intrinsic and extrinsic factors, it is recommended that investigators and experts representing participating regions are consulted in the planning and design of MRCTs.

The most current and relevant data should be used to understand the potential sources of regional variability (e.g., early trials, previous experience of the drug class). If historical data are used, it should be considered whether these data are still relevant in terms of scientific and methodological validity and in the current treatment context. The magnitude of such variability could be examined in exploratory studies before the planning and design of confirmatory MRCTs.

The intrinsic and extrinsic factors important to the drug development programme, should be identified during the planning stage of an MRCT, and information about them should be collected during the confirmatory trial for later evaluation of their impact on treatment effects. The ICH E5 guideline describes intrinsic and extrinsic factors, which may affect the treatment effect. In the MRCT setting, the following factors are particularly important and should be considered to identify regions that are suspected to show differences in treatment effects compared to the overall trial results.

1. Disease definitions, methods of diagnosis and the understanding of certain endpoints may vary between regions. These differences could be mitigated by precisely defining inclusion and exclusion criteria as well as study procedures.
2. There may be differences in medical practices and treatments across regions. Such differences may have an impact on the trial results and/or their interpretation. Standardised protocol and training for investigators and study personnel in each region before initiating the trial in that region may reduce some of the impact of

this variability.

3. Diet, environmental factors, cultural or socio-economic factors (e.g., contraceptive use, preferences for a particular route of administration) and access to healthcare may impact trial results. They may also impact recruitment, compliance, and study subject retention, and may inform relevant mitigation strategies.
4. Subjects' responses to different drugs may be more or less sensitive to intrinsic factors, leading to regional variability. For example, genetic polymorphisms in drug metabolism or receptor sensitivity (described in ICH E5 Appendix D) or body weight and age may impact PK-pharmacodynamics (PD), as well as efficacy and safety of the drug. This applies not only to the investigational drug, but also to comparators and concomitant medications and should be taken into account during planning of MRCTs.

Some sensitivity of the treatment effect to intrinsic and/or extrinsic factors may be expected in different regions, but should not preclude consideration of MRCTs. Often, the degree of variability based on the factors mentioned above can be mitigated by proper design and execution of MRCTs. Providing additional support as needed (e.g., logistical, infrastructure, laboratory) to specific regions or other mitigation strategies should be considered and implemented to reduce variability. However, it is important to consider whether the degree of mitigation may impact the generalizability of the study results.

Even with the mitigation strategies described above, regional differences may still exist, and these differences are usually due to underlying intrinsic and extrinsic factors. In this sense, region is an indicator for other, often unknown (or unanticipated) factors causing regional differences in treatment effects. For this reason, MRCTs are usually stratified by region (see Section 2.2.5). Figure 2 illustrates the way in which intrinsic and/or extrinsic factors such as disease severity (Figure 2a) or ethnicity (Figure 2b) may manifest as regional differences in treatment response. However, these factors may explain such apparent differences across regions. In Figure 2a, response to treatment increases with disease severity, and disease severity differs by region. This scenario is manifested by observed regional differences in response to treatment that are explained by differences in the distribution of the underlying factor (disease severity) among regions. The same phenomenon is illustrated in Figure 2b, where regional differences in response to treatment can be explained by differences in the ethnic distribution of the regions. This type of

investigation is dependent on appropriate stratification and sample size allocation to regions (see Section 2.2.5).

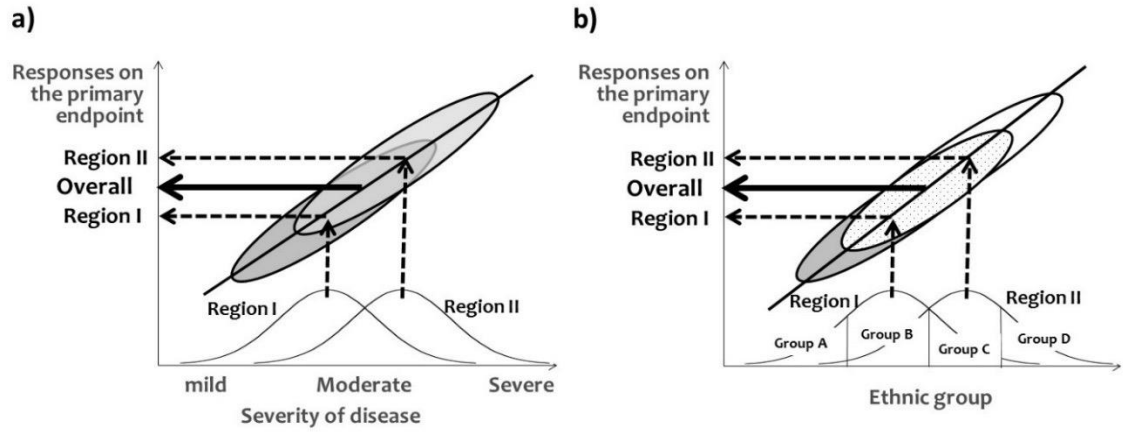

Figure 2. Illustration: primary endpoint modulated by intrinsic and extrinsic factors across regions; (2a) by severity of disease, (2b) by ethnic group.

2.2.2 Subject Selection

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

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

Recommended tools, such as validated imaging instruments and measurements of biomarkers, should be available, or made available, in all regions when these tools are utilised for subject selection. Imaging methods, as well as methods for specimen collection, handling and storage should be clearly defined and standardised across regions to the degree required.

2.2.3 Selection of Doses for Use in Confirmatory MRCTs

It is important to execute well-planned early development programmes that include PK and/or PK-PD studies of applicable parameters, in order to identify regional differences which may impact dose selection. To understand the impact of ethnicity on PK and/or PK-PD, data may be obtained from single-region trials in multiple regions, or a trial with multiple ethnicities conducted in one region. Alternatively, early phase MRCTs may be considered, if they aid in efficiently gathering such data and improve the understanding of regional differences in PK-PD.

PK studies should be undertaken in the major ethnic groups most relevant to the regions to be included in MRCTs, if differences are expected that are not yet adequately understood (see ICH E5). Adequate PK comparisons between subpopulations known to be associated with differences in PK will allow for decisions with respect to the need for pharmacodynamic studies and dose-response studies in different regions and/or subpopulations.

It is encouraged to collect genetic data (e.g., genotypes of drug metabolising enzymes) from subjects enrolled in the early studies to examine the effects of genetic factors on PK and PD. Such early data may provide useful information when determining dosing regimen(s) for future studies, where subjects with specific genotypes may be considered a subpopulation.

A strategy for dose-selection involving population PK approaches and/or model-based approaches (e.g., exposure-response models) may be useful to identify important factors affecting drug responses in different populations, and to set an appropriate dose range for further dose-response studies. Dose-response studies should cover a broad range of doses and generally include the populations to be enrolled in confirmatory MRCTs. However,

it may not be necessary to obtain PK-PD or dose-response data from subjects in all regions planned to be included in confirmatory MRCTs, if important regional differences in PK and/or PD and dose-response are not anticipated (e.g., response to the drug is unlikely to be sensitive to intrinsic and extrinsic factors) (see ICH E5, appendix D).

The acceptability of dose-selection strategies should be discussed in advance with the relevant regulatory authorities. If substantial differences are anticipated (e.g., the drug response is sensitive to intrinsic and/or extrinsic factors), further investigations may be needed. These could include a PK-PD or dose-response study conducted in a particular ethnic population or studies conducted for a broader population, that would allow further evaluation of the impact of intrinsic and extrinsic factors on dose-response.

The dose regimens in confirmatory MRCTs (based on data from studies mentioned above) should in principle be the same in all participating ethnic population. However, if earlier trial data show a clear difference in dose-response and/or exposure-response relationships for an ethnic population, it may be appropriate to use a different dosing regimen, provided that the regimen is expected to produce similar therapeutic effects with an acceptable safety margin, and provided it is scientifically justified in the study protocol. Prospective careful planning of assessment strategies where different doses are used should be tailored to each case and described in the analysis plans.

2.2.4 Choice of Endpoints

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

Primary Endpoint

The primary endpoint should be relevant to the target population. In MRCTs, this relevance needs to be considered for all regions in the trial and with respect to the various drug, disease and population characteristics represented in those regions (see Section 2.2.1). An ideal clinical trial endpoint is one that is clinically relevant, accepted in medical practice (e.g., by regulatory guidance or professional society guidelines) and sufficiently sensitive and specific to detect the anticipated effect of the treatment. For MRCTs, the primary endpoint, whether efficacy or safety, should satisfy these criteria as well as being acceptable to all concerned regulatory authorities, to ensure that interpretation of

the success or failure of the MRCT is consistent across regions and among regulatory authorities. Agreement on the primary endpoint ensures that the overall sample size and power can be determined for a single (primary) endpoint based on the overall population and also agreed upon by the regulatory authorities. If agreement cannot be reached due to well-justified scientific or regulatory reasons, a single protocol should be developed with endpoint-related sub-sections tailored to meet the respective requirements of the regulatory authorities. In this case, because regulatory approvals are based on different primary endpoints by different authorities, no multiplicity adjustment is needed for regulatory decision-making.

Using MRCTs may introduce the need for further consideration regarding the definition of the primary endpoint. While endpoints like mortality or other directly measurable outcomes are self-explanatory, others may require precise and uniform definitions (e.g., progression-free survival). Of specific concern in MRCTs are those endpoints that could be understood and/or measured differently across regions. Examples are hospitalisation, psychometric scales, assessment of quality of life and pain scales. To guarantee that such scales can be properly interpreted, the scales should be validated and their applicability to all relevant regions justified before starting the MRCT.

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

In addition to endpoint selection and definition, regulatory agreement should also be obtained on the timing and methods of the primary endpoint assessment.

Secondary Endpoints

Where possible, harmonisation of secondary endpoints is encouraged to maintain the feasibility and improve the quality of trial conduct. However, in some cases, individual regulatory authorities may propose different secondary endpoints relevant to their interests and experience. Even in such cases, all secondary endpoints, including those selected

only for a particular local stakeholder (e.g., regulatory authority), should be described in the protocol. It is in the interest of the sponsor to describe the specific advantages of the investigational drug, in terms of secondary endpoints as precisely as possible during the planning stage of MRCTs, to reduce the need for (and impact of) multiplicity adjustments for multiple endpoints, thereby improving the chance for successfully demonstrating the intended effect.

Other Considerations

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

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

2.2.5 Sample Size Planning

General Considerations

The key consideration for sample size planning, is ensuring sufficient sample size to be able to evaluate the overall treatment effect, under the assumption that the treatment effect applies to the entire target population, particularly to the regions included in the trial. MRCT offers a unique opportunity to evaluate the extent to which this assumption holds. MRCTs are usually stratified by region for both randomization and analysis. Consistency

of treatment effects across regions is evaluated, and if clinically relevant differences are observed, there should be further exploration to determine if these differences can be attributed to differences in intrinsic or extrinsic factors (see Section 2.2.7). These considerations should be reflected in the overall design of the MRCT and will influence the sample size planning and allocation to regions.

Overall Sample Size

The primary objective of an MRCT generally corresponds to an evaluation (estimation and testing) of the treatment effect averaged across all subjects in all regions of the MRCT. The overall sample-size is determined to ensure that this objective can be met. Examples of commonly defined treatment effects also used in MRCTs, are hazard ratios for morbidity or mortality, differences between treatment groups in average blood pressure levels (adjusted for baseline) and relative risks of either favourable or adverse events.

The same general principles provided in ICH E9 for determining sample sizes of clinical trials apply to MRCTs. Two additional factors are particularly important in the MRCT setting; (i) the size of the treatment effect that is considered clinically relevant to all regions in the trial, and (ii) the expected variability of the primary outcome variables based on combining data across regions. These factors may result in a sample size increase for an MRCT compared to a single trial in one region. The extent of this increase will depend on the specific disease and the mechanism of action of the drug, as well as the intrinsic and extrinsic factors and their potential impact on drug response in each region. Data from early exploratory trials with the investigational drug in relevant populations may inform sample size determination.

Sample Size Allocation to Regions

The MRCT should be planned to include an evaluation of the consistency of treatment effects among regions, where consistency is defined as a lack of clinically relevant differences. If clinically relevant differences among regions are observed, then the MRCT provides a unique opportunity for additional learning about the factors that may explain these differences. Regional allocation should have a scientific basis (rather than arbitrary targets), should support the evaluation of consistency and should provide the information needed to support regulatory decisions.

Sample size allocation to regions should take into consideration patterns of disease prevalence across regions, the size and expected accrual rate of each region, the intrinsic and extrinsic factors understood (or hypothesized) to influence treatment effects, the prevalence of those factors in each region and other logistical considerations thought to impact accrual. A regional allocation strategy that balances these considerations will help to ensure that enrolment can be completed in a timely fashion and that the MRCT objectives are met.

There is no uniformly acceptable or optimal approach to sample size allocation in an MRCT. Some approaches currently in use include:

1. Proportional Allocation: Allocation of subjects to regions in proportion to size of region and disease prevalence.
2. Equal Allocation: Allocation of equal numbers of subjects to each region.
3. Preservation of Effect: Allocation of subjects to one or more regions based on preserving some specified proportion of the overall treatment effect.
4. Local Significance: Allocation of a sufficient number of subjects to be able to achieve significant results within each region.
5. Fixed Minimum Number: Allocation of a fixed minimum number of subjects to a region.

Proportional allocation facilitates recruitment by allocating subjects to the regions with the greatest disease burden, and absent other impediments, will generally minimize the time needed to complete enrolment. The disadvantage is that some regions may end up with too few or no subjects, while other regions may dominate the outcome of the trial. Equal allocation has the advantage of optimizing the power available to detect differences in treatment effects between regions for a given overall sample size target. The disadvantage is that recruitment may be slowed to a possibly unacceptable level, particularly if disease prevalence or ease of recruitment varies substantially among the regions in the MRCT. A balance between proportional and equal allocation is recommended, to ensure that recruitment is feasible and able to be completed in a timely fashion, but also to provide sufficient information to evaluate the drug in its regional context.

Allocation to preserve a proportion of the overall effect is not practical if many regions in the trial have this requirement. Allocation based on achieving local significance of

regional treatment effects is also not practical, as this strategy may inflate the sample size beyond feasibility and brings into question the concept of conducting an MRCT. Allocating a fixed minimum sample size for regions is not recommended, if there is no scientific justification for selecting the minimum.

In practice, sample size allocation deliberations will reflect both scientific and logistical considerations. For example, an initial allocation may be determined that targets the population affected by the disease, taking disease prevalence and regional size into account. This initial allocation should ensure that the overall sample size can be achieved. The allocation would then be modified to reduce any large imbalances in regional sample sizes and to support an evaluation of consistency of treatment effects across regions. This modification could entail pooling some regions (as described below) to provide flexibility in sample size allocation. Minimum regional sample size targets that are scientifically justified could also be taken into consideration at this step. One example would be to specify a minimum sample size to provide meaningful descriptive summaries (e.g., forest plots) with sufficient accuracy and precision.

Alternatively, an equal allocation to regions could be planned as the first step, with modification to better reflect regional sample sizes, disease prevalence and trial logistics at the second step. With either strategy, care should be taken to ensure that no single region or regions dominates enrolment, thereby dominating the trial outcome.

Note that the five approaches discussed above are not exhaustive. New approaches for sample size allocation in MRCTs may be developed in the future, and innovation in this area is encouraged.

Pooled Regions and Pooled Subpopulations

Pre-specified pooling of regions or subpopulations may help provide flexibility in sample size allocation to regions, facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making. For definitions of pooled regions and pooled subpopulations, see 3. Glossary. The pooling strategy should be justified based on the distribution of the intrinsic and extrinsic factors known to affect the treatment response, and the disease under investigation and similarity of those factors across

regions. For example, pooling Canada and the United States into a North American region is often justified because of similar medical practices and similar use of concomitant medications. Pooling strategies should be specified in the study protocol and statistical analysis plan, if applicable.

As discussed earlier, region is often a surrogate for the underlying intrinsic and extrinsic factors that tend to differentiate regions or populations from each other. If there is sufficient knowledge about these factors at the trial design stage, it may be possible to define subpopulations based on those factors, and then incorporate these newly defined subpopulations in the stratification and analysis, in addition to region. Formally, the term pooled subpopulation refers to pooling of a subset of the subjects from one region with similarly defined subsets from other regions whose members share one or more intrinsic or extrinsic factors important for the drug development programme.

Ethnicity usually crosses regional boundaries and can be an important risk factor for the disease or related to treatment response (as the example in Section 2.2.1. Figure 2b illustrates). Pooling ethnic subpopulations across regions in an MRCT provides an opportunity to evaluate the impact of ethnicity on treatment effects. Examples include Hispanics living in North and South America, or Caucasians living in Europe and North America. Pooling across regional boundaries by other intrinsic or extrinsic factors may also be considered (e.g., by genotype).

The sample size allocation should consider the planned analysis of variability of treatment effect among pooled subpopulations, and the principles described above for allocation to regions may also apply to pooled subpopulations. Note that information about the extrinsic and intrinsic factors used to define pooling strategies should be collected for subjects enrolled in the trial to be able to monitor the recruitment strategy and ensure adequate regional and subpopulation representation.

Other Sample Size Considerations

The factors that influence sample size and sample size allocation should be agreed upon in advance with the different regulatory agencies governing the regions represented in the trial. For non-inferiority or equivalence trials, regulatory agreement is also needed on the

relevant margin. If, after extensive attempts to reach consensus among regulatory authorities, it is the case that different regulatory requirements remain due to well-described scientific arguments, the most stringent margin should be considered for sample size calculation.

There are some situations that do not fit into the framework for sample size allocation described above and where more flexibility will be required. In studies of rare diseases or an infectious disease outbreak, for example, disease prevalence may differ substantially between regions, and it may be necessary to allow one or more regions to dominate the trial for recruitment to be feasible. The recruitment strategy should be discussed with the regulatory authorities during planning.

In summary, comparing with sample size requirements in regional or local studies, the potential increase of the overall sample size in MRCTs should be due primarily to the increased variability anticipated for a multi-regional population and not due to overly stringent or arbitrary regional sample size requirements. The use of a well-justified and pre-specified strategy for pooling regions and/or subpopulations in conjunction with a carefully thought out sample allocation plan can facilitate meeting the objectives of the MRCT.

2.2.6 Collecting and Handling of Efficacy and Safety Information

Adherence to GCP, as described in ICH E6, is critical for any clinical trial to meet its stated objectives and is particularly important in an MRCT, because of the coordination required to conduct a trial in diverse geographic regions. Methods of collecting and handling efficacy and safety information should be standardised across participating regions. It is also important to provide standardised training for investigators and study personnel in each region before initiating the trial in that region to ensure that the trial objectives are met through standardised implementation of the study protocol.

Safety reporting should be conducted in accordance with ICH E2. When local regulations specify different requirements, such as timelines and criteria for expedited reporting, these should also be adhered to locally. The specific timeframe for safety reporting

should be described in the protocol, and the investigators should receive sufficient training in accordance with ICH E6 and other relevant guidelines. In the case of MRCTs, important safety information should be handled both with adherence to any local regulations and in adherence to ICH E2A. Important safety information should always be provided to the relevant stakeholders (e.g., investigators, ethics committees) in a timely manner.

In MRCTs of long duration, where special concerns (e.g., serious adverse events) have been identified, and/or where operational regions are quite large (usually Phase III confirmatory studies), the use of a central independent data monitoring committee (with representation from participating regions to adequately assess the context of the trial) should be considered, in order to monitor the accumulating efficacy and/or safety information from the MRCT while maintaining integrity of the ongoing trial. If adjudication of endpoints and/or events is planned, a centralised assessment by a single adjudication committee should be considered.

For endpoints based on laboratory or imaging assessments, it is generally recommended to use a centralised laboratory or centralised adjudication of imaging. If multiple laboratories are used, appropriate cross-validation of methods between laboratories should be conducted before testing clinical samples.

Coordinated site initiation is particularly important in MRCTs to ensure proper conduct, completion and reporting of results without any delays among regions. To comply with the quality management described in ICH E6, the sponsor should implement a system to manage quality in design, conduct, oversight, recording, evaluation, reporting and archiving of MRCTs. In this aspect, centralised and risk-based monitoring may be particularly useful for MRCTs to identify variability across regions and sites in protocol compliance (e.g., differences in follow-up, compliance with study medications, adverse event reporting and/or extent of missing data). Mitigation approaches should take regional variations into consideration. It could also be considered to use electronic data capturing and reporting, to gather information and data (including relevant intrinsic and extrinsic factors) from all regions in a standardised way without delays. If trial related documents (e.g., a case report form) are translated to local languages, consistency of documents between languages should be ensured (e.g., by reverse translation). As described above, careful

attention to quality during trial planning, investigator training and trial monitoring will help achieve the consistently high trial quality required for a successful MRCT.

2.2.7 Statistical Analysis Planning

ICH E9 provides general statistical principles for planning and conducting statistical analyses of randomised clinical trials. Aspects of analysis planning that are particularly important for MRCTs are described below. The analysis strategy should be planned to enable the qualitative and/or quantitative evaluation of benefit/risk (ICH M4E) across regions or important subpopulations represented in the MRCT.

Obtaining Regulatory Input on Analysis Strategy

It is recommended to have early discussions with the regulatory authorities involved in the MRCT, and to obtain their agreement on the proposed analysis strategy. The standard is to specify a single primary analysis approach in the statistical section of the study protocol to be agreed upon with the authorities in advance of initiating the trial. If in an MRCT, regulatory requirements for the primary analysis strategy differ due to well-justified scientific or regulatory reasons, the analysis strategies planned to satisfy the different requirements should be described in the study protocol. If, in addition, a statistical analysis plan is required as a separate document by more than one regulatory authority, a single analysis plan integrating the different regulatory requirements should be developed. The analysis strategy for an MRCT should be finalized prior to unblinding of treatment assignments, if applicable, to ensure trial integrity.

Primary Analysis

In planning an MRCT, the primary analysis strategy should carefully consider (1) the target population, (2) the endpoints/variables of primary interest, (3) the relevant intrinsic and extrinsic factors in the multi-regional, multi-subpopulation context and (4) the population-level summary of data required to describe the treatment effect. For most MRCTs, the primary analysis will correspond to a test of the hypothesis about the treatment effect and the estimation of that effect, considering data from all regions and subpopulations included in the trial.

If randomisation is stratified by region, the primary analysis should adjust for regions

using appropriate statistical methods. If some regions were pooled based on intrinsic and/or extrinsic factors, or if pooled subpopulations were defined for stratification purposes during trial planning, then this pooling should be reflected in the analysis.

Examination of Consistency across Regions and Subpopulations

The statistical analysis strategy should include the evaluation of the consistency of treatment effects across regions and subpopulations. For this purpose, consistency in treatment effects is defined as a lack of clinically relevant differences between treatment effects in different regions or subpopulations. Various analytical approaches to this evaluation, possibly used in combination, include but are not limited to (1) descriptive summaries, (2) graphical displays (e.g., forest plots), (3) model-based estimation including covariate-adjusted analysis and (4) test of treatment-by-region interaction. There are strengths and limitations to any method (e.g., interaction tests often have very low power), and these should be carefully considered during analysis planning.

If clinically relevant differences in treatment effects among regions are observed, a structured exploration of these differences should be planned. The exploration could proceed in the following steps:

1. Factors known a priori to vary among regions and hypothesized to be prognostic or predictive should be planned for and evaluated in the analysis model. Examples of intrinsic and extrinsic factors likely to be prognostic include disease severity, race, other subject characteristics (e.g., smoking status, body mass index), medical practice/therapeutic approach (e.g., different doses of concomitant medications used in clinical practice) or genetic factors (e.g., polymorphisms in drug metabolising enzymes), that are well-established for the disease or therapy and suggested from early stages of investigation.
2. Even with careful planning, unexpected regional differences may be observed, and post-hoc analyses should be used for further investigation. Factors known to be prognostic for the disease would be examined first, because they are often found to be predictive of differential treatment effects as well. If the distribution of a prognostic factor is found to differ between regions, then apparent regional differences in treatment effects may be explained by differences in the prognostic factors.
3. Regional differences not explained by examination of known factors may require

further post-hoc investigation to either identify plausible reasons for the differences or to better understand the observed heterogeneity. In some cases, additional data, including data from other clinical trials, or supportive evidence from other sources, may be needed to understand the regional differences observed.

These eventualities should be carefully considered at the planning stage.

Planned Subgroup Analyses

In addition to analyses intended to investigate any regional or pooled subpopulation differences in treatment effects that may be observed in an MRCT, other subgroup analyses will usually also be of interest, just as they are for any clinical trial (e.g., analyses to investigate differential treatment effects by sex and age) and should be planned. If subgroup differences in overall treatment effects are observed, then exploring whether the subgroup differences are consistent across regions or pooled regions may be informative.

In summary, the assessment of consistency of treatment effects should be done with diligence to inform regulatory decision-making. The credibility of regional, pooled subpopulation, or subgroup findings should take into consideration biological plausibility, internal consistency (e.g., similar patterns of regional variability observed for other secondary endpoints) and/or external consistency (e.g., similar patterns observed in another clinical trial of the same drug), the strength of evidence, the clinical relevance, and the statistical uncertainty. The more of the aforementioned considerations support a potential finding, the greater the likelihood the finding is not false. The evaluation of consistency will benefit from joint clinical and statistical perspectives.

Estimation of Regional Treatment Effects

The statistical analysis section of the protocol should describe appropriate statistical methods for estimating and reporting treatment effects and measures of their uncertainty for individual regions. This plan should include a determination of the adequacy of sample sizes to support robust estimation within each region or pooled region for which reporting of treatment effect is of interest. If the sample size in a region is so small that the estimates of effect will likely be unreliable, the use of other methods should be considered, including the search for options for additional pooling of regions based on commonalities, or borrowing information from other regions or pooled regions using an appropri-

ate statistical model. Covariate adjusted models may be especially important in this setting as a way to account for intrinsic and extrinsic factors. Methods using weighted averages of the overall effect estimate and the estimate using data from individual regions (shrinkage estimates) may be considered, particularly when regional sample sizes are small and outlying values may be overly influential. The choice of model should reflect an understanding of how intrinsic/extrinsic factors affect the regional estimates and be based on appropriate statistical methods. Sensitivity analyses should be planned that vary the assumptions required for the model.

Impact of Trial Quality on Analysis

Differences in trial conduct across regions can negatively impact the power to detect an overall treatment effect as well as the ability to examine consistency of treatment effects at the analysis stage. Important factors impacting the quality of the trial, such as follow-up of study subjects, should be managed consistently across regions, and issues identified during the trial corrected as early as possible.

During the conduct of an MRCT, trial monitoring and blinded data review may uncover various issues that require modifications to be made to the analysis plan for the trial. For example, it might be necessary in an MRCT for better assessment to modify pooling strategies for regions or subpopulations, that were carefully defined during trial planning, after sufficient data have been accumulated on the baseline characteristics (e.g., intrinsic and extrinsic factors) of the multi-regional population. However, such changes should be justified, discussed with the relevant regulatory authorities, and carried out in a way that preserves trial integrity.

2.2.8 Selection of Comparators

The choice of control groups should be considered in the context of the available standard therapies, the adequacy of the evidence to support the chosen design, and ethical considerations. The selection of comparators should be discussed and agreed with the relevant regulatory authorities. Comparators in MRCTs should in principle be the same in all participating regions. Due to the complexity in setting up MRCTs, some key points are addressed in the following paragraphs, focusing on practical and ethical issues associated with the use of comparators:

- The choice of comparators should be justified in the study protocol based on scientific and other relevant information, including international treatment guidelines.
- Active controls should in principle be dosed and administered in the same way in all regions. If the approved dosing regimen of active comparators are different among regions, the proposed study dosing regimen should be justified by available data, and the justification should be included in the study protocol. Additionally, the impact of such a dosage difference on analysis and evaluation of MRCT data should be considered in the planning stage.
- The same dosage form (e.g., liquid drugs vs tablets) for active comparators should generally be used among regions participating in MRCTs to ensure consistency of treatment effects and data interpretability. Different dosage forms could be used if the dissolution profiles and bioavailability are well-characterised, and differences are negligible.
- In order to ensure the consistent quality of the active comparators, it is recommended to use the same source in all participating regions. When active comparators from different sources are used in MRCTs, justification should be provided (e.g., in form of Certification of Analysis or report from the manufacturer on equivalence or dissolution studies), to ensure that the comparator has the same quality in all participating regions.
- The most comprehensive product information used in a region is recommended to be used consistently in all participating regions. If the product information differs from local product information (e.g., differences in the warnings, adverse reactions), this should be explained in the local informed consent form.
- If different drugs in the same or similar drug class are proposed to be used as active comparators, justification should be provided in the protocol based on available scientific evidence.

The above considerations may also be applicable in case of comparators which are selected based on investigator's choice of local standard care.

Active comparators in MRCTs should ideally be approved in all participating regions. However, there could be situations where active comparators used in MRCTs are not approved or not available in specific regions, but have been approved and available in

some ICH regions. The justification (including safety considerations) for the use of an unapproved drug should therefore be described in the protocol based on scientific information, treatment guidelines and other relevant documents. Development status (e.g. no plan for development, under development, under regulatory review) of the unapproved drug in the region should also be described in the protocol. Plans for post-study treatment, including continued access to unapproved comparator, should be considered and provided to the patient in the informed consent.

2.2.9 Handling Concomitant Medications

In general, drugs used concomitantly with the investigational drug should be the same throughout the regions to the extent possible, but there may be some differences in the drugs and/or doses actually used due to variations in medical practices. This could be acceptable if not expected to substantially impact trial results. The clinical trial protocol should specify allowable and not allowable concomitant medications and doses.

Concomitant medications may be required in the protocol as an important part of the treatment. In circumstances where approved drugs are combined with an investigational drug (e.g., a combination regimen of anticancer drugs) the same dosage regimen in all regions should generally be applied. If required by protocol, concomitant medications that are not approved in a region should have their use justified based on scientific information, treatment guidelines and other relevant documents. This could include documentation that the concomitant medication is approved in at least one of the ICH regions. It should generally be allowed to use an unapproved concomitant medication, however the impact of using the unapproved concomitant medication in the relevant regions should be discussed with regulatory authorities and described in the protocol. The medication will need to be supplied in regions in which it is otherwise not available, only available at different strength and/or dosage form, or if a region cannot secure continuous supply during the course of the trial.

Regional differences in the use and dosing of concomitant medications that may have impact on drug responses should be considered in advance and these medications including changes in doses should be documented during the trial. The previous considerations may also be applicable to concomitant therapy other than medications (e.g., compression stockings in the post-operative setting, medical devices).

3. GLOSSARY

Consistency of treatment effect:

A lack of clinically relevant differences between treatment effects in different regions or subpopulations of an MRCT

Multi-Regional Clinical Trial, MRCT:

A clinical trial conducted in more than one region under a single protocol.

Region:

A geographical region, country or regulatory region

Regulatory Region:

A region comprised of countries for which a common set of regulatory requirements applies for drug approval (e.g., EU).

Pooled regions:

Pooling some geographical regions, countries or regulatory regions at the planning stage, if subjects in those regions are thought to be similar enough with respect to intrinsic and/or extrinsic factors relevant to the disease and/or drug under study.

Pooled subpopulations:

Pooling a subset of the subjects from a particular region with similarly defined subsets from other regions whose members share one or more intrinsic or extrinsic factors important for the drug development programme at the planning stage. Pooled subpopulations is assumed as ethnicity-related subgroup particular important in the MRCT setting.