INTERNATIONAL CONCIL 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

Current *Step 2 v*ersion

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At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions (the European Union, Japan, the USA, Health Canada and Switzerland) for internal and external consultation, according to national or regional procedures.

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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 some strategic programme issues as well as those issues that are specific to the planning and design of confirmatory MRCTs and should be used together with other ICH guidelines, including E2, E3, E4, E5, E6, E8, E9, E10 and E18.

1.2 Background

Globalisation of drug development has increased the use of MRCTs for regulatory submissions in ICH regions as well as in non-ICH regions. Currently, it may be challenging both operationally and scientifically 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 previous harmonised regulatory view on the study plan. There are currently no ICH guidelines that deal 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. The present guideline describes the principles for planning and design of MRCTs, in order to increase the acceptability of MRCTs by multiple regulatory authorities.

MRCTs conducted according to the present guideline will allow investigation of treatment effects in overall populations with multiple ethnic factors (intrinsic and extrinsic factors as described in the ICH E5 guideline) as well as investigating consistency in treatment effects across populations. Hence, using the present guideline for planning MRCTs may facilitate a more efficient drug development and provide earlier access to medicines. In addition, MRCTs conducted according to the present

guideline may enhance scientific knowledge about how treatment effects vary across populations and ethnicities under the umbrella of a single study protocol. This information is essential for simultaneous drug development to treat a broad patient population.

1.3 Scope of the Guideline

MRCT in the present guideline is defined as a clinical trial conducted in more than one region under a single protocol. In this context, region may refer to a geographical region, country or regulatory region (see also 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 be relevant to trials conducted early in clinical development or in later phases. The present guideline mainly covers drugs, including biological products, but principles described herein may be applicable to studies of other types of treatments.

1.4 Basic Principles

MRCTs are generally the preferred option for investigating a new drug for which regulatory submission is planned in multiple regions. The underlying assumption of the conduct of MRCTs is that the treatment effect is clinically meaningful and relevant to all regions being studied. This assumption should be based on knowledge of the disease, the mechanism of action of the drug, on *a priori* knowledge about ethnic factors and their potential impact on drug response in each region, as well as any data available from early exploratory trials with the new drug. The study is intended to describe and evaluate this treatment effect, acknowledging that some sensitivity of the drug with respect to intrinsic and/or extrinsic factors may be expected in different regions and this should not preclude consideration of MRCTs.

Ethnic factors are a major point of consideration when planning MRCTs. They should be identified during the planning stage, and information about them should also be collected and evaluated when conducting MRCTs. In the ICH E5 guideline, and for purposes of the present document, ethnic factors are defined as those factors relating to the intrinsic (e.g.; genetic, physiological) and the extrinsic (e.g.; medical practice,

cultural and environmental) characteristics of a population. Based on the understanding of accumulated knowledge about these intrinsic and extrinsic factors, MRCTs should be designed to provide information to support an evaluation of whether the overall treatment effect applies to subjects from participating regions.

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

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

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

Ensuring trial quality is of paramount importance for MRCTs. This will not only

ensure the scientific validity of the trial results, but also enable adequate evaluation of the impact of intrinsic and extrinsic factors by applying the same quality standard for trial conduct in all regions. In addition, planning and conducting high quality MRCTs throughout drug development will build up trial infrastructure and capability, which over time will result in a strong environment for efficient global drug development.

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

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 this model, multiregional clinical trials were particularly useful to enable recruitment of the planned number of study subjects within a reasonable timeframe when either the disease and/or condition was rare (e.g.; enzyme deficiency disorder) or when very large numbers of subjects were required (e.g.; cardiovascular outcome trials). More recently, global regulatory strategies are also used to plan and conduct trials more efficiently to facilitate more rapid availability of drugs to patients worldwide. Proper planning and conduct of MRCT's are critical to this effort.

MRCTs allow for an examination of the applicability of a treatment to a diverse population. The intrinsic and extrinsic factors that are believed and/or suspected to impact drug responses can be further evaluated based on data from multiple ethnicities in various regions using a single protocol. For example, effects of genetic differences on metabolic enzymes or the molecular target of a drug can be examined in exploratory

and/or confirmatory MRCTs with participation of subjects of different ethnicities across regions. Accumulated knowledge of the impact of ethnic factors and experience with global collaboration in various regions will promote inclusion of additional regions in MRCTs.

Even though the primary interest in performing MRCTs is to describe treatment effect based on data from subjects in all regions, some sensitivity to the drug with respect to intrinsic and/or extrinsic factors may be expected in different regions and should not preclude consideration of MRCTs. Even in the case where a drug is very sensitive to one or more of these factors, it may still be possible to conduct MRCTs by excluding some regions or populations. Only in rare cases will single-region studies be justified, such as the case where disease prevalence is unique to a single region (e.g., anti-malarial drugs, vaccines specific to local epidemics, or antibiotics for regional-specific strains).

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

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 trials conducted independently in each region. MRCTs may therefore increase the possibility of submitting marketing authorisation applications to multiple regulatory authorities in different regions simultaneously.

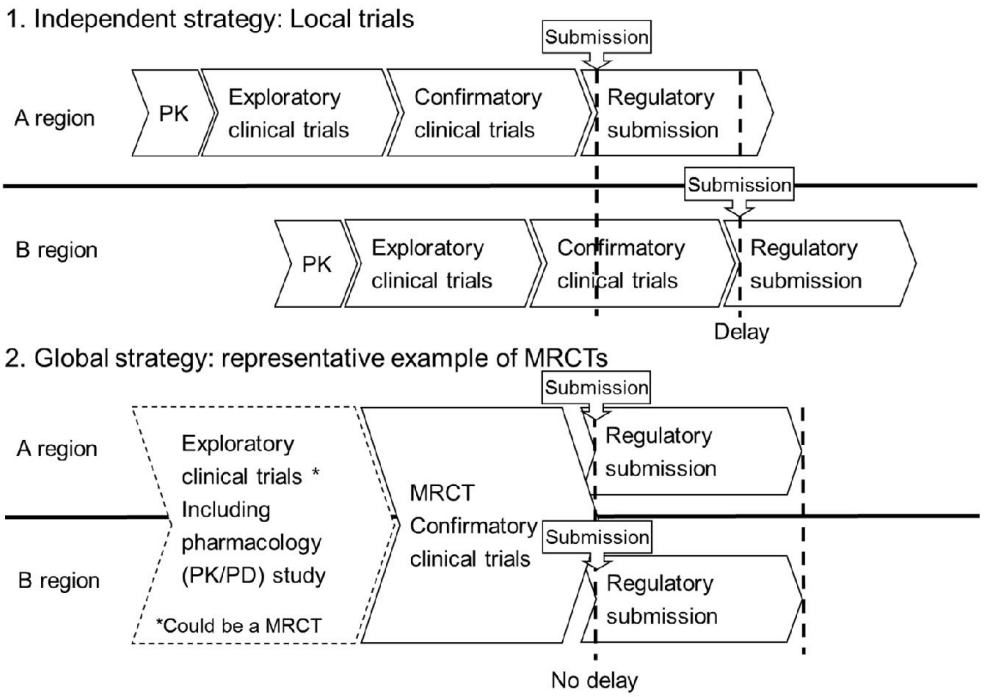

Figure 1. Time schedules of clinical drug development across regions in independent and global strategies.

2.1.2 Basic Requirements and Key Considerations

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

It is also a basic requirement that all sites participating in MRCTs should meet applicable quality 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 relevant regulatory authorities. Monitoring

plans and other quality checks should be pre-specified and implemented in order to address potential risks to trial integrity. 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, retention compliance or adverse event reporting (ICH E6 addendum). Timely and accurate flow of information should occur between the sponsor, trial management team and participating sites. For example, it is critical that important safety information during a trial is provided appropriately to all investigational sites in a timely manner (ICH E2) (see Section 2.2.6).

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

2.1.3 Scientific Consultation Meetings with Regulatory Authorities

Sponsors of MRCTs are encouraged to have scientific consultation meetings with 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 communicate which authorities are providing regulatory advice and how that advice is being taken into consideration in preparing the relevant documents (e.g., the protocol). 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

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

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

It is acknowledged that there are almost always small differences in medical practices across regions, and these can be acceptable. However, substantial differences may have a large impact on the study results and/or their interpretation. Common training of investigators and study personnel in all involved regions before initiating the trial may be able to reduce the impact of these differences.

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

It is recognised that different drugs may be more or less sensitive to regional variability based on intrinsic factors, such as genetic polymorphism of drug metabolism or receptor sensitivity (described in ICH E5 Appendix D) which can impact PK/PD, and 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.

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 ensure harmonisation.

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 all 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. 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, patient reporting of symptoms may vary by region and may lead to differences in the types of patients included in the trials. 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. Methods for specimen collection, handling and storage should be specified to the degree required. Methods of imaging need to be clearly defined and are recommended to be standardised throughout the trial.

2.2.3 Selection of Doses for Use in Confirmatory MRCTs

In order to select the dose for confirmatory MRCTs, it is necessary to execute

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

When applicable, PK investigations should be undertaken in subjects from major subpopulations that are intended to be included in MRCTs (e.g., Asian, Black and Caucasian). Adequate PK comparisons between subpopulations will allow for decisions with respect to the need for pharmacodynamics studies and dose-response studies in different regions and/or subpopulations. It is encouraged to collect genetic data (e.g., genotypes of metabolising enzymes) from subjects enrolled in the early trials to examine the effects of genetic factors on PK and PD. Such early data may provide useful information when determining optimal dosing regimen(s) for further studies.

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 subpopulations to be studied in 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/PD and dose-response are not anticipated (e.g., the drug is unlikely to be sensitive to intrinsic and extrinsic factors). The acceptability of such a strategy should be discussed in advance with relevant regulatory authorities. If substantial differences are anticipated (e.g., the drug is sensitive to intrinsic and/or extrinsic factors), further investigations may be needed. These could include a dose-response study conducted in a particular region or additional dose-response or PK/PD 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 regions. However, if early trial data show a clearly defined dose/exposure/response relationship that differs for a

region, it may be appropriate to use a different dosing regimen in that region, provided that the regimen is expected to produce similar therapeutic effects with an acceptable safety margin, and is fully justified and clearly described in the study protocol.

2.2.4 Choice of Endpoints

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

Primary Endpoint

An ideal study endpoint is one that is clinically meaningful, accepted in medical practice (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 study population and also agreed upon by the regulatory authorities. If, in rare instances, 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, since regulatory approvals are based on different primary endpoints by different authorities, no multiplicity adjustment is needed for regulatory decision-making. As stated in ICH E9, the primary endpoint should be relevant to the patient 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).

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. Furthermore, it should be ensured that the outcome is relevant to all regions.

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 endpoints.

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

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 regulatory authority should be described in the protocol. It is in the interest of the sponsor to describe the specific advantages of the investigational product 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. Control of the Type I error across both primary and secondary endpoints may be required by some regulatory authorities.

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 frequently) in some regions and not in 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 study results should be described and justified in the study protocol.

Endpoints that are only of interest for 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 in any way the conduct of the main trial. In particular, consideration should be given to the impact of additional patient burden, 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 Estimation of an Overall Sample Size and Allocation to Regions

General considerations and overall sample size

The overall sample-size for MRCTs is determined by a treatment effect that is considered clinically meaningful and relevant to all regions based on knowledge of the disease, the mechanism of action of the drug, on *a priori* knowledge about ethnic factors and their potential impact on drug response in each region, as well as any data available from early exploratory trials with the new drug. However, the treatment effect may be influenced by intrinsic and/or extrinsic factors that vary across regions. The MRCT should therefore also be designed to provide sufficient information for an evaluation of the extent to which the overall treatment effect applies to subjects from different regions. Only if regional variation is known or suspected *a priori* to be of such a high degree that the treatment effect will be difficult to interpret, then conducting separate trials in at least some of the regions may be a more appropriate drug development strategy.

The ICH E9 provides general principles for determining sample sizes of clinical trials and a detailed description of the factors impacting that determination. The same principles apply to MRCTs. As stated in E9, the overall sample size is usually determined by the primary objective of the trial, stated in terms of study endpoints and specific hypotheses, as well as the size of the treatment effect to be detected, background and/or control group mean values or event rates, variability of the primary

outcome, test statistics, Type I error control, multiplicity, and missing data considerations. In addition to these factors, the overall sample size calculation for the MRCT should take into consideration the potential for increased variability due to the inclusion of multiple regions and a possibly more heterogeneous population, compared to a single-region trial. Also with MRCTs, even after attempts at reaching consensus among regional authorities, it may be the case that different regulatory requirements (e.g., regarding the trial's endpoints, subgroup analysis requirements, non-inferiority margins, etc.) will impact the overall sample size.

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

Allocation to Regions

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

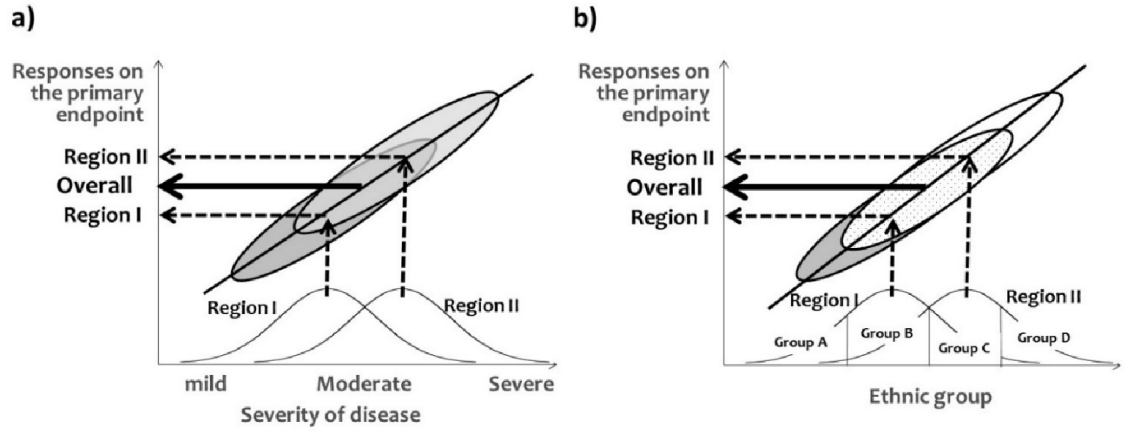

Figure 2. Illustration of primary endpoint responses modulated by intrinsic and extrinsic factors across regions; (2a) by severity of disease, (2b) by ethnic group.

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

There are several approaches that could be considered for allocating the overall sample size to regions each with its own limitations, and a few are described below. One approach is to determine the regional sample sizes needed to be able to show similar trends in treatment effects across regions. Allocating equal numbers of patients to each region would increase the likelihood of showing similar trends; however, such an allocation strategy may not be feasible or efficient in terms of enrolment and trial conduct. Another approach is to determine the sample size needed in one or more regions based on the ability to show that the region-specific treatment effect preserves some pre-specified proportion of the overall treatment effect. This allocation strategy, however, would be difficult if all regions have this requirement. A third approach is to enrol subjects in proportion to region size and disease prevalence without adhering to a fixed allocation strategy for regions. This allocation strategy will likely result in very

small sample sizes within some countries and/or regions and therefore be insufficient alone to support any evaluation of consistency among region specific effects. A fourth approach is to determine the regional sample sizes to be able to achieve significant results within one or more regions. This allocation strategy brings into question the reasons for conducting MRCTs and should be discouraged. A fifth approach is to require a fixed minimum number of subjects in one or more regions. Any local safety requirement for minimum number of subjects to be exposed to the drug is generally a programme level consideration and should not be a key determinant of the regional sample size in MRCTs.

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

For purposes of sample size planning and evaluation of consistency of treatment effects across regions, some regions may be pooled, if subjects in those regions are thought to be similar with respect to intrinsic and/or extrinsic factors, which are relevant to the disease area and/or drug under study. Consideration could also be given to pooling a subset of the subjects from a particular region with similarly defined subsets from other regions to form a pooled subpopulation whose members share one or more intrinsic or extrinsic factors important for the drug development programme. Use of this pooled subpopulation can further support the evaluation of consistency of treatment effects across regional populations. It should be discussed at the planning stage how the analyses of *pooled regions and/or pooled subpopulations* may provide a basis for the regulatory decision-making for relevant regulatory authorities. This should also be specified and be described in the study protocol in advance.

As an example of a pooled subpopulation; in Figure 2b, an ethnic group B that can largely be enrolled from region I could alternatively be enrolled globally (e.g.; region I

and II) to facilitate scientific evaluation of the impact of ethnic factors and regulatory decision making. At the same time the allocation should provide a minimally sufficient amount of information within each region to support assessment of consistency in treatment effects. Examples of pooled subpopulations include Hispanics living in North and South America, or Caucasians living in Europe and North America. Examples of pooled regions include East Asia, Europe, and North America.

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

In general, comparing with sample size requirements in regional or local trials, the potential increase of the overall sample size in MRCTs should be due primarily to the increased variability and/or decreased overall treatment effect anticipated for a multi-regional population. Based on accumulated information about intrinsic and/or extrinsic factors, the use of pooled regions and pooled subpopulations may provide practical ways to maintain the total sample size while allowing the descriptions of treatment effect in its regional context. Discussion with regulatory authorities on the proposed sample allocation is highly recommended at the planning stage.

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

2.2.6 Collecting and Handling of Efficacy and Safety Information

Collecting and handling methods of efficacy and safety information should be standardised across participating regions. Safety reporting should be conducted in accordance with ICH E2. When local regulations specify different requirements, such as timelines 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 be trained appropriately. In the case of MRCTs, important safety information should be handled both with adherence to any local regulations, and also 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 have been identified, and/or where operational regions are quite large, the use of a central independent data monitoring committee (with representation from major regions, as applicable) should be considered, in order to monitor the accumulating efficacy and/or safety information from the MRCT. If adjudication of endpoints and/or events is planned, a centralised assessment by a single adjudication committee should be considered.

Endpoint ascertainment should also be harmonised as far as possible (see Section 2.2.4). If subjective endpoints are used, coordinated training of investigators and clinical site personnel is particularly important for the handling of data in a standardised manner. If laboratory data are used in key primary and secondary endpoints, centralised laboratory tests should be considered.

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 throughout the design, conduct, evaluation, reporting and archiving of MRCTs. It could be considered to use electronic data capturing and reporting, to gather information and data (including relevant ethnic factors) from all regions in a standardised way without delays. If a case report form and other related documents are translated to the local language, consistency of documents between languages should be ensured.

2.2.7 Statistical Analysis Planning to Address Specific Features of MRCTs

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.

Obtaining Regulatory Input on Analysis Strategy

It is recommended to have early discussions with the different regulatory authorities involved in the MRCT, and to obtain their agreement with the proposed analysis strategy. The standard is to specify a single primary analysis approach in the statistical section of the study concept to be agreed upon with the authorities in advance of starting the trial. If different analysis strategies are required by different authorities for well-justified scientific or regulatory reasons, they should be described in the trial protocol. If, in addition, a statistical analysis plan is developed as a separate document for the MRCT, a single comprehensive analysis plan describing the analytical approaches to be used to meet the different regulatory requirements should be developed. For blinded studies, the statistical analysis plan should be finalised prior to unblinding of treatment assignments (at interim or final report) and submitted to regulatory agencies upon request.

Evaluation of Subgroups Defined by Intrinsic and Extrinsic Factors

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

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

authorisation.

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

Considering Regions in the Primary Analysis

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

Examination of Regional Consistency

The statistical analysis plan should include a strategy for evaluating consistency of treatment effects across regions, and for evaluating how any observed differences across regions may be explained by intrinsic and/or extrinsic factors. 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, funnel plots), (3) model-based estimation including covariate-adjusted analysis, and (4) test of treatment by region interaction, although it is recognised that such tests often have very low power. The assessment of the consistency of treatment effects across regions, considering the plausibility of the findings, should be done with diligence before concluding that potential differences between treatment effects in regions are a chance finding.

If subgroup differences (e.g., by gender) in treatment effects are observed, then an examination of whether the subgroup differences are consistent across regions or pooled regions is recommended. In general, the credibility of subgroup and/or regional findings should also take into consideration biological plausibility, consistency (internal

and/or external) of findings, the strength of evidence, as well as the statistical uncertainty. The analyses and evaluation of treatment effects should be planned to enable the qualitative and/or quantitative evaluation of benefit/risk across subgroups and across regions.

Estimation of Regional Treatment Effects

The statistical analysis section of the protocol should describe appropriate statistical methods for estimating and reporting treatment effects and associated measures of variance for individual regions, if sample sizes allow. The same analysis strategy should be used as planned for the primary analysis. This plan should include a determination of the adequacy of sample sizes to support accurate 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 are unreliable, the use of other methods should be considered, including the search for options to pool regions based on commonalities, or borrowing information from other regions or pooled regions using an appropriate statistical model.

Monitoring and Mitigation of MRCT Conduct

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 differences into consideration.

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

- Appropriateness of the choice of comparators should be justified 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 doses of active comparators are different among regions, the impact of such difference on analysis and evaluation of data should be considered, and relevant scientific reasons, such as different drug exposure induced by intrinsic factors, should be justified in the protocol.

- The same dosage form (e.g., capsules vs tablets) for active comparators should generally be used among regions participating in MRCTs to ensure consistency of treatment effects. Different dosage forms can cause problems for maintenance of the blinding and data interpretability. Unless the effect of the different dosage forms on the dissolution profiles, bioavailability and blinding are well-characterised and negligible the same dosage form should be used.
- In order to ensure the quality of the investigational drugs, it is recommended to use the same source of the active comparators in all participating regions. When active comparators from different sources are used in MRCTs, justification should be provided, such as bioequivalence data, to support the differently sourced comparators.
- The product information used in the region where the product is sourced should be used consistently in all participating regions. If the sourced product information differs from local product information, this should be explained in the protocol and the informed consent form (e.g., there may be differences in the adverse event reporting and/or display between the package inserts).

In addition, 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. Therefore the appropriateness of the selected control(s) may vary between the regions. The reason for the use of an unapproved drug vs the current standard of the region should therefore be described in the protocol based on scientific information, such as a guideline and other relevant documents, to justify the choice of comparator. Development status of the unapproved drug in the region should also be described in the protocol. Pre-consideration is also necessary regarding how such an unapproved drug may affect subjects in the region, especially regarding safety. A plan for how to address the issue of non-approved control treatment(s) should be explained in the protocol. In these circumstances,

design of MRCTs should involve consultation with the relevant regulatory authorities to determine the appropriateness of such trial designs as part of the overall drug approval strategy.

2.2.9 Handling Concomitant Medications

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

Concomitant medications may be required 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 participating regions. It should be allowed to use an unapproved concomitant drug; however the impact of using the unapproved drug vs the approved standard in the relevant regions should be discussed with regulatory authorities and described in the protocol (see section 2.2.8). The medication will need to be supplied in regions in which it is otherwise not available.

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

To ensure a subject's condition is stable before starting the investigational drug, a prior observation period may be useful for control of some concomitant medications. Changes in concomitant medications or doses of medications that may be expected to impact the study endpoints during the trial may be allowed, based on pre-specified

criteria. If a major impact on drug responses is expected, based on differences in concomitant medications, additional measures to minimise impact should be considered, such as additional PK or subgroup analyses.

3. GLOSSARY

- Regulatory region:

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

- Pooled regions:

  A subset of enrolled subjects where data can be pooled together within and/or across geographical regions, countries or regulatory regions based on a commonality of intrinsic and/or extrinsic factors for purpose of regulatory decision-making.