10 February 2017
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Overview of comments received by EMA on 'ICH guideline E17 on general principles for planning and design of multi-regional clinical trials - Step 2b' (EMA/CHMP/ICH/453276/2016)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	LEO Pharma A/S
2	Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford
3	ACRO (Association of Clinical Research Organizations)
4	Ekkehard Glimm and Achim Guettner, Novartis
5	Aaron Dane, EFSPI/PSI

Please note that comments will be sent to the **ICH E17 EWG** for consideration in the context of Step 3 of the ICH process.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)
1	LEO Pharma A/S (hereafter referred to as LEO) welcomes the opportunity to give input to this draft guidance document. In general, we agree with the approach taken in this document. Some more detailed comments can be found below.
2	We suggest that you reference the paper in the NEJM (Yusuf S, Wittes J; Interpreting Geographic Variations in Results of Randomized, Controlled Trials. N Engl J Med. 2016, 375(23):2263-2271), which highlights some of the caution required in analysing regional subgroups
3	The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through pivotal studies assessing the safety and effectiveness of new products – as well as post-approval and pharmacovigilance research. With 9,000 employees engaged in research activities in the UK, over 33,000 in Europe, and more than 120,000 worldwide, ACRO member companies advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 pharmaceutical, biotech, and medical device sponsors of clinical trials each year. ACRO welcomes and supports the creation of an ICH guideline on multi-regional clinical trials (MRCTs). This is an important topic for all ACRO member companies and a critical subject for efficient global development of new medicines. ACRO's view is that the draft guideline represents a very well-considered approach to the issues raised by MRCTs and is an excellent step forward in promoting their use. ACRO especially welcomes the recognition that, when scientifically justified, flexibility can be built into a MRCT protocol in terms of regional differences in dosing regimen, active comparators and concomitant medication, endpoint-related subsections, sub-group analysis requirements, non-inferiority margins, regional sample size allocations in rare diseases, etc. In particular, ACRO recognizes and fully agrees that, as noted in section 2.1.1 of the draft guideline, MRCTs can facilitate simultaneous global drug development by reducing the number of clinical trials that need to be conducted separately in each region (but see note 4 under Specific comments on the text, below) and that MRCTs, as part of a carefully planned global regulatory strategy, can "facilitate more rapid availability of drugs to patients." These are key aims for ACRO member companies, but there are two issues that we are concerned may prevent the planned guideline from fully realising these critical targets:

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	1. In order for a MRCT to meet its aims and for its results to be accepted by all of the regulatory authorities involved, it is critical that there is prospective agreement by all of the authorities concerned on the details of the trial protocol. We do not believe that the exhortations in section 2.1.3 that "Sponsors of MRCTs are encouraged to have scientific consultation meetings with regulatory authorities" and "Inter-authority scientific discussions are encouraged to allow for harmonisation of study requirements" are sufficient to achieve this. While recognizing that this may fall outside the ICH remit, ACRO recommends that the regulatory authorities of ICH signatory countries/regions (including those with Observer status) should work to establish an efficient mechanism for inter-authority discussions to accompany the guidance document and provide sponsors with a clear procedure for reaching agreement on a harmonised MRCT protocol with all concerned regulatory authorities. 2. Section 2.2.5 notes that "Any local safety requirement for a 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." Given that a key stated aim of MRCTs is to "facilitate more rapid availability of drug to patients", ACRO recommends that the guideline should address in significantly more detail the MRCT position within a global drug development program, in order to achieve this more rapid availability of new medicines. There may be a need for additional local clinical trials, but such studies may delay the availability of medicines to patients in countries requiring such trials, especially where, if a country is not involved in the MRCT, the regulatory authority of that country requires extensive prior patient exposure elsewhere before approving the conduct of local studies. Additionally, it may, in some cases, be possible to accommodate local regulatory requirements for a minimum number of patients within a MRCT without significantly skewing the stratified global and regional sample sizes necessary for the primary and secondary endpoint analyses. We believe that this is a key issue for MRCTs in the global development of new medicines that is not adequately addressed within the draft guideline. ACRO thanks the EMA for the opportunity to provide comments on the ICH document -- ICH E17 Draft Guideline: General Principles for Planning and Design of Multi-Regional Clinical Trials. Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions.
4	**Consistency of treatment effects** across regions or other subpopulations is an important topic for MRCT. Possible scenarios are in an excellent way illustrated in figure 2 in the section "allocation to regions". These are scenarios where the treatment effects are not consistent across regions due to a differing distribution of influential factors like (a) baseline severity of the disease and (b) ethnic groups across regions. However, these differences can be explained by providing insight into the impact of underlying influential variables (severity of the disease and ethnic group). Here the best could be to form subgroups of similar severity (a) or ethnic groups (b) across regions to achieve subgroups with

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	similar treatment effects. This underlines the importance of identifying influential factors per region very early in drug development. Pre-phase 3 MRCTs could be planned accordingly as is illustrated in figure 1. It is suggested to move figure 2 to an earlier section like 2.1.2 to illustrate matters. Figure 2 can also be used to describe how a pooling can be defined to achieve similar treatment effects without requiring region similarity. (419-420). **Estimands.** It is suggested to include a section on estimands. In the most straightforward case this could be a common concept across regions. Otherwise it could differ by region according to regional regulatory requirements possibly depending on regional specifics of the patient population. **NI trials**. The possibility of differing requirements regarding the NI margin is discussed in the draft guidance. Important further aspects include the impact of increased variation which might make a NI assessment more difficult. The estimand context should also be taken into account.
5	The guidance states in a number of places that the primary objective of an MRCT (and the basis for its sizing) is the overall analysis, but there are a number of statements that trials should ensure sufficient patients in key regions to be able to ascertain clinically significant differences. This suggests studies should be sized for detecting cross-region differences. Although the section entitled "Allocation to Regions" outlines possible approaches, it acknowledges that many of these are not feasible. As such, it is not clear how both of these statements (1-sizing the trial for the overall effect, and 2-ensuring sufficient patients per region to detect differences) can both be true without conducting a much larger trial. Clear statements on the general premise of planning to assume the overall treatment effect applies across region should be added along with the type of approaches required to meet requirements of consistency across regions would be helpful. Discussion of current specific agency requirements, such as those recommended in the PMDA guideline and discussed by Quan et al (2010) is not addressed. As such approaches are not achievable for a number of regions within the same MRCT, this should be addressed. Clarity can then be provided regarding the sample size required in relation to those methods. Given the primary aim of an MRCT is to make conclusions on all patients, and as such requires broad consistency between regions, it is proposed that a clearer statement is made that the key premise is to show general consistency, and to outline the key methods to support this consistency (some of which is outlined on page 12). This should be overlaid with the strength of evidence with any finding, and should consider consistency of the finding, biological plausibility and practical reasons for the finding in that particular

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	study.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
Line 201-202	1	**Comments**: Regarding description of "Inter-authority scientific discussions are encouraged to allow for harmonisation of study requirements," we would like to know the plans to realize inter-authority scientific discussion including three polar countries (EU, US, Japan). Furthermore, it should be clarified if the Sponsor will participate in the Inter-authority scientific discussions – as in a joint advice – or whether reference is made to internal meetings between authorities. **Proposed change**: "Inter-authority scientific discussions should be available to allow for harmonisation of study requirements,"
Line 218-222	1	**Comments**: It is suggested to address view on Standard of Care as part of this section. E.g. considerations with respect to use of standards of care according to national guidelines as comparator in relation to palliative treatment in end stage cancer – or Standard of care (according to national guidelines) as background treatment for e.g. use of emollient in skin disease) Discussion or clarification on when Standard of Care, which may be different in each country is acceptable, and if Standard of Care sometimes can be considered acceptable in the comparator arm. Examples of standard of care which could be very different in each country, emollium treatment in Eczema versus palliative treatment in end stage cancer. Comments also relevant for section 2.2.8
Line 228-229	1	**Comment**: As there is a cultural difference in the use of contraceptive , standard practice in each country should be allowed if appropriate. **Proposed change**: "Cultural differences, such as use of contraceptives, should also be considered, and standard practice in each country should be allowed if appropriate."

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Line 455-458	1	**Comments**: Even if local safety data is considered at a program level, pooling of safety data in relevant subpopulation should be acceptable if scientifically justified.
Line 468-480 & Line 498-502	1	**Comments**: For "pooled subpopulation", it is mentioned in the guideline that analysis of pooled subpopulations considering the similarity of intrinsic and/or extrinsic factors may provide a basis for the regulatory decision-making for relevant regulatory authorities. Furthermore it is mentioned that pooled subpopulations may provide practical ways to maintain the total sample size. Since in some countries (for instance: South Korea), at present only local patients' data will be acceptable for regulatory purposes, this will frequently lead to issues with the local sample size requirements, study design and costs. Therefore we would like to suggest having a stricter message in this guideline on the acceptance of pooled subpopulations in each regulatory authority. **Proposed change (477-478)**: "… how the analysis of pooled regions and/or pooled subpopulations can provide a basis for the regulatory decision-making for relevant regulatory authorities."
Line 655-659	1	**Comments**: It is indicated that bioequivalence data is required if the product is sources from different sources to document sameness. It is proposed that it will be acceptable to demonstrate sameness by documenting that the comparator from different sources originate from from same sponsor. It seems unethical if companies should perform bioequivalence trials for products, which in practise are identical, and where the authorities have the required information to have it confirmed (e.g via inter-authority communication) **Proposed change**: "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 or a statement that the product is from same sponsor

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		even if sourced from different countries and that excipient list is identical, to support the differently sourced comparators.”
Line 719	1	3. Glossary - pooled regions **Proposed change**: It is proposed to add examples of pooled regions that have a commonality of intrinsic and/or extrinsic factors for purpose of regulatory decision making – either in the glossary or in the actual guidance.
Line 104-108	2	**Comments**: There appears to be an inherent contradiction throughout the document about overall and regional sample size requirements. This text illustrates the point from the introduction: 104 The guiding principle for determining the overall sample size in MRCTs is that the test of the primary 105 hypothesis can be assessed, based on combining data from all regions in the trial. The sample size 106 allocation to regions or pooled regions should be determined such that clinically meaningful differences 107 in treatment effects among regions can be described without substantially increasing the sample size 108 requirements based on the primary hypothesis. How can you reliably address the main question in defined subgroups (e.g. different regions) without substantially increasing the sample size? This either requires correction or needs proper explanation.
Section 1.1	3	**Comments**: ACRO recommends that a statement is included in Section 1.1 (Objectives of the guideline) to make clear that the guidance is intended to assist sponsors planning to conduct a MRCT and that, while MRCTs are to be encouraged for their potential to reduce development times, the conduct of region-specific clinical trials remains acceptable for regulatory purposes.

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Section 1.3	3	**Comments**: Section 1.3: Rather than simply referencing the Glossary, ACRO recommends that, for clarity, the sentence "In this context, region may refer to a geographical region, country or regulatory region" should be extended. Proposed change (if any): ACRO recommends changing the sentence to read: "In this context, region may refer to a geographical region, country or regulatory region for which a common set of regulatory requirements applies for drug approval".
Section 2.1.1	3	**Comments**: Section 2.1.1 includes the statement "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)". This wording implies that in all other circumstances MRCTs will be considered mandatory, which ACRO does not believe is the intended aim. While recognizing that MRCTs can greatly facilitate global development and are therefore to be encouraged, it is ACRO's view that it is the responsibility of the sponsor developing a new medicine to determine the most appropriate way in which to conduct the required development programme. **Proposed change**: Consequently, ACRO recommends that the statement is re-phrased to read: "In cases 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 will not be justified", and that a clarifying statement, as noted in point 1 above, is included in Section 1.1.
Section 2.1.1	3	**Comments**: Section 2.1.1 also includes the statement "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." While ACRO fully agrees with the first part of this sentence, clinical trials are conducted to answer a multitude of questions and it is not necessarily unethical to perform, with the approval of the relevant local ethics committee(s), region-specific studies (rather than a MRCT) to answer questions specific to the

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		regional population. **Proposed change**: Consequently, ACRO recommends that the second part of the sentence should read simply "….thereby avoiding the unnecessary duplication of studies."
Section 2.2.5	3	**Comments**: ACRO notes the statement in section 2.2.5 that "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 regions may be a more appropriate drug development strategy". Again, it is ACRO's view that there may be other practical and valid reasons why a sponsor would wish to follow a sequential strategy for regional development of the product and that, recognising this may lead to longer development times, it is the sponsor's prerogative to do so. **Proposed change**: Consequently, ACRO recommends deletion of the word "Only" from this sentence, and that a clarifying statement, as noted in point 1 above, is included in Section 1.1.
Section 2.2.8	3	**Comments**: Section 2.2.8 states that "When active comparators from different sources are used in MRCTs, justification should be provided, such as bioequivalence data, to support the differently sourced comparators." ACRO notes that the regulatory authorities of the various ICH signatory countries/regions (including those with Observer status) define "bioequivalence" in different ways. Also, in the case of simple dosage forms with marketing approval, ACRO believes that there are situations where in vitro dissolution data rather than in vivo studies may be suitable to confirm bioequivalence. **Proposed change**: ACRO therefore recommends that the sentence should be clarified by a statement that agreement on any bioequivalence requirements should form part of the pre-trial planning discussions with regulatory authorities.
Section 3	3	**Comments**:

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		Section 3: For consistency with the text of the guideline, ACRO recommends that the Glossary should define a Regulatory region as "a geographical region, country or regulatory region for which a common set of regulatory requirements applies for drug approval". Additionally, with reference to comment 6 on Section 2.2.8 above, ACRO recommends that consideration is given to providing a common definition of the term "bioequivalence."
Lines 87-94	4	**Comments**: The guideline is not sufficiently clear on the difference between geographic region and ethnicity. It seems to implicitly assume that "ethnicity" can be used interchangeably with "region" or at least that ethnicity is nested within region. Unless an unconventional definition of the word "ethnicity" is used, this is not necessarily so. In particular, the last sentence of this paragraph suddenly switches from statements about ethnicity to statements about region.
Lines 104-108 & 385-388	4	**Comments**: The following sentence "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." can be found under 1.4. Basic principles. As this is a very critical aspect (especially the part underlined) it is further elaborated under 2.2.5. I suggest to add a reference to 2.2.5 in 1.4 in order not to leave the reader alone with the statement in 1.4.
Lines 167-169	4	**Comments**: If "*…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*", then why should an adjustment for them be included in the statistical analysis?
Lines 214 - 219	4	**Comments**: Can this paragraph also include a discussion on intrinsic and extrinsic factors?
Lines 217-227	4	**Comments**: The purpose of these two sections is unclear. Is it intended to say that if regional differences can be pinned down to more specific root causes (like use of concomitant medication or genetic differences between populations), then these should (i) replace "region" as stratification factor or (ii) included in stratification / adjustment in addition to region or

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		(iii) just recorded/reported or (iv) any of these measures, depending on other circumstances?
Lines 275-280	4	**Comments**: Is this also true for route of administration, e.g. intravenous versus subcutaneous injection as outlined in line 218
Lines 279-280	4	**Comments**: Obviously, the dose/exposure/response relationship will differ between individual patients, but the root cause for that will rarely be "region" (but rather age, gender, nutrition, …). Hence, it is unclear why for this topic in particular, there is such an emphasis on "region". For example, if patients in a certain region are on average lighter than others and weight has been identified as the key factor for determining the appropriate dose, it seems strange to base dose recommendations on "region" rather than on body weight.
Lines 285-299	4	**Comments**: Can more details be added, or can this paragraph be more specific on two different endpoints, objectives and analysis plans?
Lines 295-296	4	**Comments**: Delete "due to well-justified scientific or regulatory reasons". I do not think the recommendation is intended only for those cases where the disagreement is "due to well-justified scientific or regulatory reasons".
Lines 311-312	4	**Comments**: what precisely qualifies as "experience"? Usage in previous clinical trials? I think well-justified exceptions should be allowed here for newly developed endpoints if they are clearly superior to traditional ones – even if there is no previous experience with this in clinical trials in any of the regions.
Lines 323-324	4	**Comments**: Control of the Type I error across both primary and secondary endpoints may be required by some regulatory authorities." I would appreciate if the guideline could elaborate more on this aspect. If not, I suggest to delete this sentence as it seems not to be specific for MRCTs and therefore does not add value here.

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Lines 359-362	4	**Comments**: Can it be clarified whether stratification can be different across regions if one region mandated to use an additional stratification factor?
Lines 383-385	4	**Comments**: I think this figure is redundant. I would remove it.
Lines 392-409	4	**Comments**: There are 5 approaches described with its own limitations. I am not sure the value of listing these 5 approaches in the guideline with limitation emphasized. There must be lots of challenges for the sample size determination for different scenario. It would be more beneficial if the guidance explicit the points need to consider, rather than the limitations.
Lines 416-417	4	**Comments**: "For purposes of sample size planning and evaluation of consistency of treatment effects across regions, some regions may be pooled, …" I think this should read "some *or all* regions …". Or is it intended to prescribe that "region" *must* be a stratification factor in all MRCTs? I would think that is too strict.
Lines 434-436	4	**Comments**: In 2.2.5 it is stated "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." Theoretically I fully agree to this statement however practically I find it very difficult to justify a certain increase in variability. Therefore, I would appreciate if the guideline could elaborate more on this aspect.
Lines 448 - 455	4	**Comments**: Can it be added that this is also applicable to safety specific exclusion criteria?
Line 484	4	**Comments**: Delete "for well-justified scientific or regulatory reasons". For reasons same as comment on lines 295-296. I suspect

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		that the recommendation is intended to apply to all cases, not just to cases of a certain type.
Lines 487-507	4	**Comments**: There is one section about the 'Evaluation of subgroups defined by intrinsic and extrinsic factors', while another section is about 'Examination of regional consistency'. From my perspective, these two sections are describing some overlapping contents. It is probably better to combine these two sections to provide more clear guidance regarding the subgroups consistency check.
Lines 509 to 514	4	**Comments**: Please clarify how to build the model if stratification was different across regions?
Line 535	4	**Comments**: For the analysis of regional treatment effects the analysis strategy cannot be the same as for the primary analysis if region was used as a stratification factor.
Lines 555 – 558, 573-584	4	**Comments**: Please clarify whether it would be possible to omit an active control from a region if the active control is not registered at all in that region?
Lines 564 - 567	4	**Comments**: Please clarify whether bioequivalence data are sufficient or whether additional information might be needed or must be provided, for example for biologics.
Lines 84, 147, 223, 274, 388	4	**Comments**: Various times in the text the authors refer to "sensitivity of the drug to ethnic or other factors" (e.g. lines 84, 147, 223, 274, 388). Is the sensitivity of the response to the drug or the treatment effect with respect to specific factors meant, or as worded in line 145 " sensitivity to the drug with respect to intrinsic and/or extrinsic factors"? Reference to "influence on the treatment effect of intrinsic/extrinsic factors (lines 348,379) seems to be clearer **Proposed change**:

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		sensitivity of the drug effect to ethnic or other factors
Lines 62-63	5	**Comments**: MRCTs provide earlier access to medicines in specific regions such as Japan without a delay for the rest of the world (e.g. US, EU). **Proposed change**: "Provides earlier access to medicines in **specific region without a delay from the rest of the world**" or "provide **worldwide** earlier access to medicines".
Lines 68-70	5	**Comments**: *"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"* This definition appears inconsistent with that given in the Points to Consider in Defining Region for a Multiregional Clinical Trial (Tanaka, 2011*), which provides the definition of region and emphasized that region should not be limited to geographic boundaries, but should take into consideration "relevant intrinsic genetic and physiological or pathological factors as well as extrinsic factors such as medical practice." *Tanaka, Y et al. "Points to consider in defining region for a multiregional clinical trial: defining region work stream in PhRMA MRCT Key Issue Team." Drug Information Journal 45.5 (2011): 575-585.
Lines 95-96	5	**Comments**: Proposed change (if any): "The consistency of treatment effects should be evaluated **across MRCT region, which is not always geographic region**."
Line 160, figure 1	5	**Comments**: Although the premise of the MRCT making trials run faster is true, it should be acknowledged that this is dependent upon gaining regulatory agreement in each region in a timely manner, and also that any potential increase in variability does not lead to an increase in overall sample size. Also, write "Multi-regional confirmatory clinical trials" in the box, as "MRCT Confirmatory clinical trials" would involve

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		mentioning "clinical trials/CT" twice.
Lines 278-283	5	**Comments**: This paragraph implies that different doses of a drug may be studied in an MRCT across different regions and all data analysed and interpreted together. Although this is reasonable in a number of situations (eg, dose titration studies), it would be helpful to outline if there are any situations where this may be more challenging.
Line 292	5	**Comments**: *"… to ensure that interpretation of the success or failure of the MRCT is consistent across regions and among regulatory authorities…"* Although criteria for results being a success or failure should be consistent across regions, but it should be acknowledged that the implications for clinical care may vary due to factors such as the patient population and available treatment options in each region.
Lines 326-327	5	**Comments**: It should be clarified that control of Type I error across a set of both primary and secondary endpoints for a particular region may be required by the regulatory authority in that region, and not all primary and secondary endpoints across regions. Proposed change (if any): "Control of Type I error across **a set of** both primary and secondary endpoints **for a particular region** may be required by ~~**some**~~ **the** regulatory authority **in that region. As a result, different approaches to multiplicity control for different authorities may be acceptable."**
Lines 350-353	5	**Comments**: Considering the situation where two confirmatory trials are performed, these are often performed in different regions for logistical reasons, without expecting large regional variability. This case should be mentioned as well and the "Only" at the beginning of the sentence in line 350 be deleted.
372, Allocation to	5	**Comments**: Enrollment into a study is usually variable and difficult to plan in detail in advance, so it will generally not be possible to

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regions		enroll patients in the exact proportion planned in each region. It would be helpful if the guideline could discuss the case of differences between planned and actual proportions and how discrepancies are considered within the review.
Lines 485-487	5	**Comments**: *"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".* Some regulatory agencies require specific exploratory analyses, for example, the PMDA usually requires analyses on Japanese patients only. It should be clarified that these region-specific exploratory analyses may be described in regional SAPs, while the overall analysis plan is focused on the analysis of key endpoints of the trial.
Lines 516-517	5	**Comments**: Suggest to soften wording by writing "The most appropriate strategy,…" instead of "The appropriate strategy…". Leaving region and other stratification factors out of a subgroup analysis may also give a sensible analysis, which might sometimes be preferable.
Line 523	5	**Comments**: Suggest adding Galbraith plots as a key approach to help interpret regions, and whether the observed values are beyond what is expected by chance.
Lines 528-529	5	**Comments**: The examination of whether subgroup differences are consistent across regions would amount to a subgroup analysis with two factors. As mentioned in the draft EMA guideline on subgroup analysis these analyses might be especially difficult to interpret due to many subgroups with small sample sizes. Suggest adding a cautionary note along these lines, or to state that an attempt to quantify the effects seen given the number of subgroups explored is important. This comment also has relevance to lines 506-510.
Line 532	5	**Comments**: It is important when exploring subgroups to take account of the number of subgroups explored. Proposed change (if

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		any): ''… as well as the statistical uncertainty **and the number of pre-specified subgroups explored**."
Lines 535-544	5	**Comments**: This section should discuss the premise that, under the situation of no true underlying regional differences, the overall estimate of treatment effect is the most reliable for each region. Therefore, when there is external evidence to support homogeneity of effect across regions, and the data generated from the MRCT suggest consistency, the overall estimate of effect is most appropriate for all regions.
Lines 539-544	5	**Comments**: This sentence is inconsistent with the methods of allocation of overall sample size to region.