

October 26, 2016

ICH Secretariat  
9, chemin des Mines  
1211 Geneva 20  
Switzerland

**RE: ACRO Comment Submission – ICH E17 Draft Guideline:  
*General Principles for Planning and Design of Multi-Regional Clinical Trials***

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.

**General comments**

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:

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.

### **Specific comments on the text**

1. 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.

2. 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 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”.
3. 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. 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.
4. 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 regional population. Consequently, ACRO recommends that the second part of the sentence should read simply “....thereby avoiding the unnecessary duplication of studies.”
5. 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. 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.

6. 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. 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.
  
7. 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”.

ACRO thanks the ICH for this opportunity to provide comment on ICH E17 Draft Guideline: General Principles for Planning and Design of Multi-Regional Clinical Trials. Please do not hesitate to contact ACRO if we can provide additional details or answer any questions.

Respectfully submitted,



Karen A. Noonan  
Vice President, Global Regulatory Policy