EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 September 2016

Submission of comments on Concept paper on the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' (EMEA/CHMP/SWP/28367/07)

Comments from:

Name of organisation or individual
ACRO (Association of Clinical Research Organizations)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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 strongly supports the proposal to revise the current guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. ACRO agrees with the various discussion points identified in section 3 of the Reflection Paper but, as noted below, considers that recommendations in the report of the Temporary Specialist Scientific Committee established by the French competent authority (ANSM) into the BIA 10-2474 clinical trial, conducted in Rennes, in January 2016 should also be addressed specifically in the revised	

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	guideline. Additionally, while recognizing that this is outside the scope of the Concept Paper, which is concerned with revision of the current guideline, ACRO notes that the voluntary accreditation programme for Phase I units in the UK, established by the UK competent authority (MHRA), has led to improvements in the identification and mitigation of risks to subject safety in human pharmacology studies conducted in accredited units. ACRO therefore suggests that the EU regulatory network (EMA, national medicines agencies, and the European Commission) consider studying the utility of the MHRA's voluntary accreditation programme. In addition to an EMA guideline, ACRO asks the Agency to consider if it would be beneficial to harmonise these guidelines globally and include them in, for instance, ICH M3 (R2). The guideline does not mention what risk level, after risk mitigation, is acceptable for FIH studies. This is difficult to define, but ACRO asks the Agency to consider, for example, if it would be helpful to note that the risk resulting from hazard identification and risk mitigation should be minimal and comparable with risk for an activity which is accepted by the society. Before proceeding to "Section 2" of this comment ("Specific Comments on Text"), there are five discussions omitted from the current Concept Paper which ACRO believes merit inclusion in the revised guidance. First, ACRO recommends that the recommendations in	

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	the report of the Temporary Specialist Scientific Committee established by the French competent authority (ANSM) into the BIA 10-2474 clinical trial, conducted in Rennes, in January 2016 should also be addressed specifically in the revised guideline. This can be done via addition of the following bullet points: • "the need for sufficiently comprehensive preclinical pharmacological studies on a sufficiently broad dose range so as to be reasonably predictive of real life, future therapeutic efficacy." • "the need for specific assessments during volunteer screening targeted to the pharmacological profile of the drug, as determined by preclinical and prior human studies." • "dose adjustments in human pharmacology trial protocols based on all of the data previously collected in humans." • "the circumstances in which sequential dosing regimes, currently used in single ascending dose studies in human volunteers, should be extended to multiple ascending dose studies." Second, ACRO asks the Agency to consider the following content on dose escalation. If the inhibition of a biomarker is employed as an indicator of drug activity, then the rationale for dose escalation above the point of complete inhibition of the biomarker should be stated in the protocol. Additionally, ACRO considers that, where a drug shows little or no evidence of toxicity in early human studies, it is not necessary to continue ascending doses (either single or multiple doses) to establish a maximum tolerated dose. ACRO recommends that trial protocols should prospectively establish a multiple of the	

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	anticipated therapeutic dose (sufficient to provide an adequate safety margin) that will not be exceeded in the absence of adverse effects. To achieve this, ACRO suggests the addition of the following statements: "Consideration should be given to creating a requirement for justification of escalation above the dose level at which a relevant biomarker is completely inhibited in the absence of a detectable physiological signal. Consideration should also be given to establishing a multiple of the therapeutic dose (sufficient to provide an adequate safety margin) that will not be exceeded in the absence of adverse effects. This maximum dose should be stated prospectively in the protocol for the human pharmacology trial." Third, a discussion of the use of sentinel dosing would be helpful. ACRO suggests including content stating that all studies involving compounds determined to be at risk include sentinel dosing of 2 subjects for at least the first few cohorts, if not all. And, the sentinel cohort(s) should force randomization to result in an active and placebo treatment assigned within the cohort. Finally, the wash between dosing, safety assessment, and progression to dosing of the balance of the cohort should exceed 24 hours or at least 1 half-life, whichever is longer. Included in this decision should also include careful evaluation of the expected physiologic effects in humans as well as any pre-clinical evidence that suggests the compound may induce or potentiate immunological reactions. Fourth, ACRO asks the Agency to consider a program of enhanced communication with the Member State regulatory authorities. If a previous FIH clinical trial is suspended or terminated due to lack of detectable	

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	activity or due to adverse effects in human volunteers, this information may not be known to the Ethics Committee and regulatory authority in the Member State responsible for reviewing a protocol for another mechanistically-similar agent, or to the sponsor of the trial. However, the information is known to the EMA. ACRO asks the Agency to consider stablishing a process whereby Member States can refer FIH trials to the EMA to ascertain (a) whether previous trials with mechanistically-similar agents have been terminated or suspended, and (b) the reason for that. If the reason relates to lack of detectable activity, despite the use of doses which maximally inhibited the biomarker, then the sponsor of the proposed study should be required to explain the reasons for proceeding with that study. If the reason relates to safety, then the safety considerations from the previous study or studies should be taken into consideration in the design of the proposed study. If an FIH study is suspended or terminated, there is no obvious route whereby that information might become known to the sponsor of another FIH study involving a mechanistically-similar molecule, or to the Ethics Committee and regulatory authority in the Member State which approved the latter study. Would it be possible for the EMA to establish a process whereby FIH which are suspended or terminated can be made known to Ethics Committees and regulatory authorities in all Member States which have approved FIH trials involving agents with similar mechanisms. Would it be possible to create a requirement for Ethics Committees and regulatory authorities which receive such information to review it and provide reasons in writing (to be used in any subsequent investigation should the need arise) for their	

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	decision regarding continuation, modification or termination of the later trial. Fifth, for combined-design studies, e.g., SAD-MAD, the requirements for repeat-dose preclinical studies are ambiguous. ACRO asks the Agency to consider whether particular sections of ICH M3 (R2) should be codified in a manner similar to ICH E6, such that appropriate durations of preclinical exposure are required as a condition of approval for FIH trials. For SAD/MAD designs consider recommendation to require complete safety review prior to escalating to next dose. This is usually included in studies, but on occasion less experienced sponsors will bypass this requirement.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
4 – 6 (title)		Comment: ACRO strongly supports the proposals in lines 35 and 51 – 52 to extend the remit of the guidance beyond single ascending dose first-in-human trials to incorporate other early phase trials and designs. Consequently, ACRO recommends that the title of the revised guideline is changed to reflect its revised scope. Proposed change (if any): Change title to: “Guideline on strategies to identify and mitigate risks for human pharmacology clinical trials with investigational medicinal products”	
35		Comment: Except for FIH studies, identification and mitigation of risks could be done for any study with an anticipated exposure higher than the previous dose in humans. This includes SAD, MAD as well as studies at a later stage when escalating further than done before.	
44-48		Comment: Inclusions of the items on lines 44-48 in the guidelines would be of great value. Proposed change:	

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		ACRO suggests “estimated therapeutic exposure, maximum human exposure level” instead of “estimated therapeutic dose, maximum human dose level”.	
47		Comment: ACRO suggests that the guideline specify identification of the need for an exposure limit for Cmax and/or AUC depending on significant tox or highest exposure in animal studies. In addition to “estimation of the first dose in human,” the guideline could use a section on “determination of the max acceptable dose in human”. ACRO suggests that the guideline specify that not all stopping criteria can be carved in stone -- tolerability depends on duration and reversibility, as well as severity. Therefore the Investigator should always have the discretion to stop escalation. Proposed change (if any):	
48		The bulleted item on line 48 regarding the “identification of safety aspects to monitor” is a very good point, which ACRO strongly supports. Safety assessments should cover vital organs as well as being tailored to detect anticipated risks.	
54		FIH trials by their nature are likely to surface events which were entirely unanticipated, and so an option to suspend trials temporarily to enable review of emerging data should be a standard requirement within protocols. Proposed change (if any):	

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		The current text which reads “overall dose/exposure range and scheme including stopping rules” should be modified to read “overall dose/exposure range and scheme <u>including stopping and suspension/review rules</u>.”	
56		Rather than summaries of tox reports the IB should contain an integrated overview of: 1. The results of tox findings versus exposure 2. The PD versus exposure derived from in vitro/in vivo work 3. The anticipated exposure range in the FIH (instead of in IB this can be included in the protocol)	
56		In the last section, the IB (or protocol) should contain a list of identified risks (based on class, tox, PK properties) and proposed risk mitigation measures (biomarkers, dose schedule, population, exclusion criteria etc)	
72		Specific risk factors: Since most cases of death in healthy volunteers were due to non-IMPs, ACRO suggests mentioning that risk identification should also be done for non-IMPs and any hazardous study procedures.	
72		Specific risk factors: irreversible binding, delayed PD, exposure in case the FiH formulation has a much higher F, there is a considerable FE (30 fold observed recently) or the free fraction in humans is much higher.	
72		Specific risk factors: Preclinical data on specificity is not mentioned in the guideline (nor in any other guideline).	

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		ACRO thanks the Agency for the opportunity to comment on this Concept Paper and looks forward to the Agency's public consultation on the revised draft guideline later this year. Please contact ACRO if we can provide any additional information (knoonan@acrohealth.org).	