EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2017

Submission of comments on Draft Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1)

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 post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world (including 57,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually. ACRO welcomes and supports the draft guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. ACRO considers this to be a comprehensive document that provides sound, detailed guidance to enhance the safety of participants in these studies. In particular, ACRO welcomes:	

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	• The extension of the current guideline to cover early phase clinical trials with integrated protocols that combine a number of different study parts • The strong emphasis on risk identification and mitigation, and especially the recognition that all available information should be taken into account in reaching dosing decisions • The acknowledgement that using a maximum tolerated dose approach is considered to be unethical for healthy volunteers.	

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)*
85 - 102		Comment: These lines (and the rest of the draft guideline) focus on risks posed by the investigational medicinal product (IMP), but risks during early studies do not only come from the IMP. Several healthy volunteers have died due to challenge agents/concomitant medication. For these a similar assessment has to be done as for the IMP. Also, invasive study procedures such as CSF sampling, catheterisation, BAL and endoscopy may involve risks. Proposed change (if any): Add text to clarify that risks associated with study procedures and other medication/challenge agents used in the study must also be evaluated and appropriate mitigations put in place.	
90 - 95		Comment: The words "escalation to a predefined maximum dose" are used and then it is stated that when the guideline says dose it in fact means "expected exposure". This can be simplified. Also, we recommend that the guideline should emphasize that exposure is more relevant than dose. Additionally, evaluation of emerging preclinical data can also lead to the conclusion that the risk of continuation of a FIH study is unacceptable. An example is an IMP with insufficient margin between the highest exposure expected to be needed during the FIH study and exposures at which significant toxicity was observed in animal studies, without sentinel	

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		safety biomarkers or without adequate possible measures for risk mitigation. Proposed change (if any): Replace “escalation to a predefined maximum dose" with "escalation to a predefined maximum expected exposure". Replace "…..is considered important" by "…. is considered more relevant than the relative dose levels between animals and humans". Add text to clarify that continuous evaluation of emerging preclinical data is necessary and that trial design should be altered or the clinical trial stopped in response to newly identified risks.	
118 - 119		Comment: For clarity, ACRO recommends that the text should state that, when Directive 2001/20/EC is repealed by Regulation (EC) 536/2014, this guideline will continue to apply. Proposed change (if any): Make clear that, when Directive 2001/20/EC is repealed by Regulation (EC) 536/2014, this guideline will continue to apply.	
200 - 201		Comment: Section 4.2 concerns the nature of the target, whereas this bullet point concerns off-target effects. ACRO therefore recommends moving this bullet point to the previous section (4.1) on mode of action. Proposed change (if any): Move this bullet point to section	

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		4.1.	
203 - 205		Comment: It is unclear whether the discussion of the relevance of the non-clinical models is applicable to the pharmacodynamic studies and safety studies or to the pharmacodynamic studies alone. ACRO recommends that this is clarified. Proposed change (if any): Add a statement to clarify the scope of the discussion of the relevance of the non-clinical models.	
259 - 261		Comment: It is unclear whether the guidance is advocating the use of transgenic animals or homologous proteins in non-clinical safety studies generally or in pharmacodynamic models alone. ACRO notes that, if the former, interpretation of toxicological outcomes is very complex due to the sparsity of background data and the inherently uncharacterised nature of these models with respect to nonclinical safety endpoints; also, creation of homologous proteins may have unintended and uncharacterised “off target” interactions, not present in the actual drug substance being developed. ACRO therefore recommends that the scope of this discussion is clarified and, if it relates to non-clinical safety studies in general, that these comments about the difficulty of their interpretation are included in the guideline. Proposed change (if any): Add a statement to clarify the scope	

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		of the discussion of the use of transgenic animals or homologous proteins and, if the scope includes non-clinical safety studies, add comments about the difficulty of their interpretation.	
308 - 310		Comment: Toxicokinetics are relevant for all potential safety concerns, whether from primary pharmacodynamic or other toxicity findings. ACRO therefore recommends revising this sentence. Proposed change (if any): Revise the sentence to read "Systemic exposures at pharmacodynamically active doses and toxic doses in the relevant animal models should be determined and considered."	
314 - 316		Comment: The sentence includes the example of low selectivity of the IMP for its primary target, but it is not clear whether this relates to *in vitro* selectivity studies or observed *in vivo* toxicity (or both). For clarity, ACRO recommends an addition to the text. Proposed change (if any): Revise the statement to read: "e.g. in case of low selectivity of the IMP for its primary target or limited margin between anticipated human exposure and significant toxicity."	
327		Comment: ACRO recommends that the term "target organs"	

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		be defined. It is not clear whether this is dependent on the exposure associated with toxicity compared to the exposure expected in humans. If not, there will always be a target organ at sufficiently high doses. Proposed change (if any): Define what is meant by “target organs in the non-clinical studies”.	
333 - 404		Comment: In section 7, PAD is used in some sentences, MABEL is used in others and some sentences use both terms. As PAD and MABEL both refer to the same concept (anticipated exposure/dose resulting in some pharmacological activity), ACRO recommends the use of consistent terminology in order to avoid any potential confusion. Proposed change (if any): Be consistent in use of PAD and/or MABEL.	
334 - 357		Comment: ACRO recommends including mention of pharmacokinetic factors that can have a significant effect on extrapolation of animal to human exposure, e.g. absorption (especially in compounds with low bioavailability), differences in significant routes of clearance, protein binding, etc. Proposed change (if any): Including mention of pharmacokinetic factors that can have a significant effect on extrapolation of animal to human exposure.	

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339 - 344		Comment: To ensure the reliability of information on which dose decisions are made, ACRO recommends that this paragraph should include a statement requiring decisions about starting dose, dose escalation steps and maximum dose to be based on non-clinical and clinical information that has been subject to quality control. Proposed change (if any): Include a statement requiring decisions about starting dose, dose escalation steps and maximum dose to be based on non-clinical and clinical information that has been subject to quality control.	
347		Comment: ACRO is concerned by the term “predefined dosing selection” as not all doses can be determined definitively beforehand. However, if the protocol has predefined decision criteria, doses could be changed, within the margins of these criteria, without a substantial amendment. ACRO therefore recommends revision of the statement. Proposed change (if any): Revise “to adjust the predefined dosing selection” to “to select dose levels outside the margins determined by predefined decision criteria.”	
358 - 387		Comment: ACRO recommends that Section 7.2. would benefit from the use of a flow chart or bullet points, emphasizing the step wise approach.	

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		Proposed change (if any): Include a flow chart or bullet points to emphasize the step wise approach.	
359		Comment: ACRO recommends including a more precise definition of NOAEL, because NOAEL is sometimes interpreted differently, e.g. NOAEL could be the highest dose level that did not produce a toxic effect in preclinical studies or the highest dose that does not produce a toxic effect which would be unacceptable in the first dose in humans. Proposed change (if any): Include a more precise definition of NOAEL.	
359 - 363		Comment: To ensure clarity of decision making for the starting dose, ACRO recommends that the guideline should state that the derivation of the NOAEL and the estimation of equivalent exposure for humans are reported and explained in the Investigator Brochure. Proposed change (if any): Add the following statement: “The derivation of the NOAEL and the estimation of equivalent exposure for humans should be reported and explained in the Investigator Brochure.”	
364 - 375		Comment: To ensure clarity of decision making for the starting dose, ACRO recommends that the guideline should	

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		state that the calculations of MABEL, PAD and/or ATD are reported and explained in the Investigator Brochure. Proposed change (if any): Add the following statement: "The calculations of MABEL, PAD and/or ATD should be reported and explained in the Investigator Brochure."	
367		Comment: ACRO is concerned by the use of "and/or" in this sentence as we consider that the estimation of the anticipated therapeutic dose (ATD) range should not be optional. If possible, the ATD should be compared with the anticipated dose/exposures at which significant toxicities occur in animals since this comparison may reveal that the compound has an insufficient safety margin and further development should not continue. Proposed change (if any): Change "and/or" to "and".	
374 - 375		Comment: ACRO recommends adding clarification as to whether the safety factor should be applied to both the NOAEL and MABEL calculations. Proposed change (if any): Clarify whether the safety factor should be applied to both the NOAEL and MABEL calculations.	
424 - 425		Comment: Limiting the exposure to the (plateau?) of the expected human therapeutic dose range in healthy volunteers	

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		may significantly limit the value of a FIH study. There is no need, and it is not ethical, to proceed to exposures far beyond the plateau of the therapeutic response, ACRO considers that dosing up to 5-10 fold above this anticipated plateau should be allowed if there are no further toxicity concerns since 1) the PD in healthy volunteers cannot always be measured, 2) the exposure-PD relationship in healthy volunteers can be different in patients, 3) supratherapeutic dose levels are needed to reliably detect human toxicity, especially in a limited number of subjects, and to use for instance Concentration Effect Modelling for QTc evaluation according to the ICH-E14 Q&A revision. Similarly, target saturation should be taken into account but a safety margin beyond maximum target saturation (and therapeutic effect) should be assessed. Proposed change (if any): Revise the sentence to read: “The range of exposure at the expected human therapeutic dose range should be scientifically justified. Similarly, target saturation should be taken into account but a safety margin beyond maximum target saturation (and therapeutic effect) should be assessed.”	
428		Comment: ACRO recommends rephrasing the text to more explicitly distinguish from an extended duration of therapeutic effect that may occur with an increased dose, possibly with the penalty of compromised safety or tolerability.	

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		Proposed change (if any): Rephrase the text to read: "...and no increased therapeutic effect is to be expected…"	
459 - 460		Comment: It is not clear whether the statement “If a higher dose is proposed….” refers to the human expected therapeutic dose (which is higher than the typically very low starting dose used in FIH studies) or to a dose that is higher than the human expected therapeutic dose, and ACRO recommends that this is clarified. Proposed change (if any): Make clear what the phrase “If a higher dose is proposed….” refers to.	
471 - 487		Comment: ACRO recommends that formulation (e.g., osmolality and titratable acidity), volume and speed of administration, fed / fasted, be added to the list of bullet points. ACRO also recommends adding a sentence to this section to confirm the importance of adding safety biomarkers that specifically monitor any observed toxicity as a risk mitigation measure. Proposed change (if any): Add formulation, volume and speed of administration, and fed / fasted to the list of bullet points, and add a sentence to confirm the importance of adding safety biomarkers that specifically monitor any observed toxicity as a risk mitigation measure..	

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499		Comment: In order to explain the advantages of a graphical approach, ACRO recommends the following text, in place of the phrase “is encouraged”. Proposed change (if any): Replace “is encouraged” with “is helpful to users and competent authority/ethics committee reviewers”.	
512		Comment: ACRO recommends expanding the statement “supported by a decision-tree” as proposed below. Proposed change (if any): Amend the statement to read “supported by a pre-defined decision-tree”.	
514		Comment: ACRO recommends that, in case exposure is expected to be significantly higher after administration with food (e.g., an IMP with low aqueous solubility and (very) low bioavailability in animals), an additional safety factor should be considered. The experience of ACRO members is that the effect of food on exposure can be up to 30-fold. Proposed change (if any): Add a statement to require that an additional safety factor is used in cases where exposure is expected to be significantly higher after administration with food.	
542 - 543		Comment: The determination of the normal range is a matter	

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		of statistics, e. g. a 90 percentile. Therefore values outside the normal range do not have to be clinically significant and will occur frequently if many parameters are measured. Inclusion / exclusion criteria for healthy volunteers should be allowed to have certain parameters that fall outside normal ranges, if judged to be not clinically significant / acceptable by the investigator. Inclusion and exclusion criteria should take into account the toxicity and safety pharmacology findings from the non-clinical studies and any adverse findings associated with the same pharmacological target and/or drug class. Consequently, ACRO recommends revising the statement. Proposed change (if any): Revise the statement to read: " ...should also be in line with the absence of a clinically significant deviation from normal ranges of vital signs...."	
584 - 587		Comment: The text infers that data from sentinel subjects undergoes formal review before progressing to the rest of the cohort by the dose decision making group/committee ("...in the same manner as the precautions applied between cohorts..."). Whilst we agree that all data should be reviewed, this review is normally undertaken by the investigator, who is responsible for subject safety and who performs a review of all available source data, to enable a prompt and safe transition to the remaining subjects. ACRO recommends that clarification is included to allow the investigator to make the decision to proceed with dosing of the remainder of the cohort.	

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		Proposed change (if any): After "(see also section 8.2.10)" insert the following sentences: "This review may be undertaken either by the investigator or by the dose decision making group/committee. The person or group responsible should be defined in the trial protocol."	
606		Comment: To ensure clarity of decision making, ACRO recommends that the statement below should be added at the end of the paragraph. Proposed change (if any): Add the following statement at the end of the paragraph: "All such justifications should be recorded in the trial master file."	
643 - 647		Comment: For oncology FIH studies it is sometimes the case that discussion on a regular basis regarding emerging adverse events and dose limiting toxicities between the investigator and the sponsor carries the greater weight in terms of decision making at the dose escalation/review meeting. ACRO therefore suggests that all relevant safety data need not be in the clinical database at the time of the dose escalation meeting. Data entered in the CRF should be supplemental to clinical discussion. This allows for a more expeditious review of the current dose, and we recommend that a statement is added to the guideline to acknowledge this.	

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		Proposed change (if any): Add the following sentence at the end of the bullet point: “Clinical discussion/experience should also be a key factor in dose review and should be thoroughly documented.”	
683 - 685		Comment: ACRO considers that the approach described in the draft guideline is overly prescriptive. An exposure cap based on exposure at the NOAEL is mostly unnecessary, e.g. if toxicity observed above the NOAEL is well monitored, transient, not serious and/or species dependent. An exposure cap is needed in the case of: 1) irreversible or severe toxicity, especially without a sentinel biomarker or 2) a risk of exceeding the exposure levels recorded in the general toxicity studies. ACRO also recommends adding a sentence to clarify that this stopping rule may imply a final end of dosing or a possible temporary halt with dose escalation resuming after a full evaluation of all clinical and preclinical data. Proposed change (if any): The sentence should be revised to read: “……should be included in the case of: 1) irreversible or severe toxicity, especially without a sentinel biomarker or 2) a risk of exceeding the exposure levels recorded in the general toxicity studies. This stopping rule may imply a final end of dosing or a possible temporary halt with dose escalation resuming after a full evaluation of all clinical and preclinical data.”	

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686 - 688		Comment: ACRO considers that the approach described in the draft guideline is overly prescriptive. Whilst the approach of limiting exposure based upon individual subjects is a prudent approach for some molecules, we would suggest that the guidance allow for use of mean data if scientifically justified. The draft guideline states that dosing would need to stop if an individual study subject has shown an AUC/Cmax above that associated with the NOAEL in the most sensitive animal species. However, the exposure measurements in the toxicity studies have outliers as well. Therefore, it should be judged on a case by case basis if outliers in exposure in a FIH study fall beyond the range observed in animals, and what the risk is, in view of the observed toxicity and exposure at higher dose cohorts in animals. ACRO recommends revising the current text. Proposed change (if any): Revise the sentence to read: “Comparisons of the non-clinical and clinical exposure should be based either on the maximum clinical exposure in an individual subject within a cohort or the mean (average) clinical exposure in a cohort, whichever is most appropriate to the molecule under study. The method used (with justification) should be defined in the trial protocol.”	
692 - 693		Comment: ACRO considers that stopping criteria should not be only rule based and the study should also be stopped in case the investigator or sponsor decides that the risk to continue is	

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		not acceptable for the trial subjects. ACRO therefore recommends adding a statement to this effect. Proposed change (if any): Add a statement to clarify that the study should also be stopped in any case in which the investigator or sponsor decides that the risk to continue is not acceptable for the trial subjects, and that the justification for this must be thoroughly documented.	
695 - 696		Comment: For clarity, ACRO recommends revising the statement to read as shown below. Proposed change (if any): Revise the sentence to read: "All clinical staff who are in contact with study subjects should be trained to identify adverse reactions and how to respond to these or any other adverse events".	
699 - 700		Comment: As currently written, the guideline could be interpreted as requiring that treatment for all potential adverse events be defined in the protocol. This is unnecessary as most treatments will follow standard medical practice. ACRO therefore recommends replacing the phrase "certain type " with “significant”. Proposed change (if any): Replace "certain type " with “significant”.	

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726 - 727		The principal investigator is ultimately responsible for the safety of trial subjects at the site and therefore should be a member of the decision making group/committee. Consequently, ACRO recommends revising the statement to make this clear. Proposed change (if any): Revise the statement to read: “The principal investigator should be a member of the decision making group/committee. Other members of the group should be sufficiently independent from IMP administration and monitoring".	
734 - 735		Comment: It is not necessary for FIH/early clinical trials to be performed in a hospital setting, as long as appropriate emergency facilities and arrangements are in place. Consequently, ACRO recommends revision of the sentence in order to clarify this. Proposed change (if any): Revise the sentence to read: "FIH/early CTs should take place under controlled conditions in appropriate facilities (e.g. on a hospital campus or within 10 minutes of a hospital with intensive care facilities to facilitate rapid emergency transfer if needed), with the possibility of close supervision of study subjects during and after dosing as required by the protocol."	
738 - 740		Comment: ACRO recommends that this is sufficiently	

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		important that the guideline should clarify specific responsibilities to be defined, as indicated in the proposed change below. Additionally, trial subjects who experience a serious adverse event may be admitted initially to a hospital department other than the intensive care unit for evaluation and/or treatment. Consequently, the text here should not refer specifically to the intensive care unit (ACRO's proposal on lines 734 – 735 above refers to the need for the hospital to have intensive care facilities). Proposed change (if any): Revise the sentence to read as follows: "...regarding the responsibilities and undertakings of each in the transfer and care of patients, and communication of relevant IMP specific information to the hospital and timely communication on clinical findings, which are relevant for other study subjects, from the hospital to the clinical pharmacology unit."	
741 - 742		Comment: ACRO recognizes that the need for an appropriate communication plan between multiple sites involved in a trial is referenced in lines 705 – 710. However, ACRO believes that this is such an important issue with regard to subject safety in FIH trials in healthy volunteers that it should be reiterated here. However, use of multiple sites for patient FIH studies (such as oncology) is standard practice. Additionally, use of multiple sites is also standard for umbrella protocols including both healthy volunteers and patients. ACRO therefore	

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		proposes the following revision. Proposed change (if any): Amend the sentence to read: “All FIH trials (or parts thereof) in healthy volunteers for an IMP should preferably be conducted at a single site (to gather collective experience). When different sites are involved in a FIH healthy volunteer study, this should be justified and a communication plan established for communication of safety data or rapid implementation of corrective or preventive actions at all study sites and investigators.”	
		ACRO thanks the Agency for the opportunity to comment on this Draft Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1). Please contact ACRO (knoonan@acrohealth.org or +1 202 464 9340) if we can provide additional details or answer any questions at all.	

Please add more rows if needed.