28 February 2017

Submission of comments on ' 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
The Royal Statistical Society

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)*
	1. The Royal Statistical Society (RSS) is a learned society and professional body for statisticians and data analysts, which promotes statistics for the public good. Our strategy supports strengthening both the profession and the discipline of statistics, and medical and pharmaceutical trials clearly set an example and a high standard for this, as statistics play a crucial part in reducing the risk of harm. Our commentary which follows focuses on statistical issues for your draft Guideline, and refers to recommendations made by the Royal Statistical Society's (RSS) Working Party on Statistical Issues in First-in-Man Studies[1]. We comment on those aspects that relate strongly to RSS's recommendations, as follows: 2. In the BIAL/Biotrial clinical trial[2], one problem was that the pre-specified decision criteria, as approved by ANSM, were per-cohort, not across-cohorts as the EMA Guidance rightly requires (see Bird et al., 2017[3]). It is important to note where and how this would be addressed by implementing the new draft guidance: 2.1. A clear statement is made at lines 345-346 that: "The starting dose and estimated exposure levels chosen for all cohorts and study parts should be pre-specified and a justification for these steps should be outlined in the study protocol". 2.2. Section 8.2.6 (lines 575-593) of the EMA Guidance should also highlight more precautionary designs, because serious adverse events may not manifest themselves in all participants at the same speed. For example, in Cohort 5 of the Multiple Ascending Dose phase of the BIAL/Biotrial clinical trial, only a third of	

[1] Senn, S. Amin, R. Bailey, A. Bird, S.M., Bogacka, B. Colman, P. Garrett, A. Grieve, A. & Lachmann, P. (2007) 'Statistical issues in first-in-man studies', *Journal of the Royal Statistical Society, Series A* 170: 517–579, or the RSS Report (PDF) available at: http://www.rss.org.uk/Images/PDF/publications/rss-reports-statistical-issues-first-in-man-studies-2007.pdf
[2] Fassbender, M. (2016) "Clear statistical reservations' surround Bial's fatal clinical trial', *in-Pharma*, 2 February 2016. Available at: http://www.in-pharmatechnologist.com/Regulatory-Safety/Clear-statistical-reservations-surround-Bial-s-fatal-clinical-trial
[3] Bird, S.M. Bailey, R.A., Grieve, A.P. & Senn, S. (2017) 'Statistical issues in first-in-human studies on BIA 10-2474: Neglected comparison of protocol against practice', *Pharmaceutical Statistics* 00:1–7. Available at: https://doi.org/10.1002/pst.180

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	actively treated subjects became ill on the fifth day of exposure, while others became ill later. In Section 8.2.6, the EMA Guidance appears to suggest that a single sentinel pair (active; placebo) per cohort is sufficiently precautionary. Please see RSS recommendations to the contrary[4] and note that line 575 "in any cohort" should probably read "in every cohort" to convey more accurately the suggestion that the EMA Guidance makes. 2.3. The draft guidance (sections 7.1-7.4, lines 351-353) stipulates that the methods used and calculations on how doses and estimated exposure levels were determined, including methods for modelling, should be included in the Investigator's Brochure, and summarised in the protocol. We particularly value the requirement for summarisation in the protocol. This is essential to meet RSS 'open protocol' recommendations, since the Investigator's Brochure is not generally in the public domain. Welcome also, in the RSS spirit of 'open protocol', is the requirement (at line 382) that: "Any safety factors used should be justified and detailed in the Investigator's Brochure and protocol". This needs to fulfil RSS's recommendation[5] that "Before proceeding to a first-in-man study, there should be: • Quantitative justification of the starting dose - based on suitable preclinical studies and relevant calculations. • A priori assessment of the risk level for the recommended study dose(s). • Appraisal of the uncertainty about these recommendations." 2.4. In the BIAL/Biotrial clinical trial, the desired effect of the drug in humans was observed at much lower doses than anticipated. The EMA Guidelines should give a clear recommendation to reconsider the planned dose-escalation in such cases.	

[4] Recommendations no. 9 and 10 in Senn *et al*. (2007) say: "Unless arguments have been provided that the risk is so low that simultaneous treatments are acceptable […] a proper, or sufficient, inter-administration interval needs to be proposed and observed", and "First-in-man study protocols should provide justification of the proper interval between administration to successive subjects." Additionally, Bird *et al* (2017) conclude that in some or all cohorts, multiple sentinel-pairs may be necessary, and that regulators should specifically assess how well safeguarding is justified per-cohort.

[5] Recommendation 4 in RSS (2007) 'Statistical issues in first-in-man studies', available at: http://www.rss.org.uk/Images/PDF/publications/rss-reports-statistical-issues-first-in-man-studies-2007.pdf

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	3. We suggest wording needs to be strengthened in section 4.4 and section 6 (lines 235-236) where "the inclusion of a tabulated summary containing an overview of all relevant non-clinical data is encouraged". The findings of non-clinical safety studies that are relevant when designing first-in-human and early clinical trials need to be considered. The EMA's Guidance should explicitly set out that these findings are summarised quantitatively in the protocol. In particular, all animal deaths in the pre-clinical studies should be reported in the protocol (at lines 207-208, 235-236, 280-281 and 329-332). We welcome the principle at lines 280-281 that "A weight-of-evidence approach should involve integration of information from in vivo, ex vivo and in vitro studies into the decision-making process." 4. We particularly value the requirement (line 91) for protocols to nominate and justify a pre-defined maximum dose. The EMA Guidance reiterates (at lines 409-411) that: "A maximum dose or exposure, which should not be exceeded in the study without approval of a substantial amendment, should be pre-defined and justified in the protocol for the full clinical trial and/or each study part." 5. We welcome the clear assertion (at lines 432-433) that: "A trial design using a maximum tolerated dose approach is considered to be unethical for healthy volunteers". 6. In respect of dose escalation, the EMA Guidance rightly highlights non-linear pharmacokinetics (PK), and the reliability with which potential adverse effects can be monitored in humans before they escalate into something serious or irreversible (lines 396-399). In moving from single to multiple dosing, the EMA Guidance correctly requires (lines 438-439) that: "particular attention should be paid to linear versus non-linear PK in the expected concentration range, the PK half-life versus duration of action and the potential for accumulation." 7. The EMA Guidance is correct (at lines 590-593) that more precautionary cohort-designs could be needed at later stages, e.g. on the steep part of dose-response curve or when approaching target	

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	saturation levels or exposure margins. Conversely (at lines 617-618), since the initial doses may be very low, early cohorts may not show any pharmacological effects. 8. The EMA Guidance suggests, but does not insist in Section 8.2.8 on Precautions to apply between study parts, that: "For studies with multiple parts, consideration may be given to submitting an interim report to the competent authorities for review as a substantial amendment prior to the start of further dosing phases" (see lines 634-636). It is not clear whether it is the sponsor or the authorities who are making the substantial amendment. If interim reports are desirable we suggest that it should be clearly stated (a) that they are mandatory, and (b) precisely between which study parts they are needed, and (c) whether the later study parts need to wait on further approval. 9. In the draft guidelines' Executive Summary (lines 71-74), strategies for mitigating and managing risks do not explicitly mention study design separately from the conduct of the clinical trial. In the last twenty years some designs have been proposed which maintain the rule that each cohort corresponds to a dose increment but have more flexibility in the number of subjects on placebo, or even on lower doses, within that cohort[6]. It has been shown that these new designs have several advantages. (1) more information about the effects of the different doses is obtained from the same number of subjects, because there is less confounding of differences between doses with differences between cohorts.	

[6] Some of these are described briefly in
(a) Senn, S. *et al.* [ibid] (2007) 'Statistical issues in first-in-man studies', available at: http://www.rss.org.uk/Images/PDF/publications/rss-reports-statistical-issues-first-in-man-studies-2007.pdf
There are more details in
(b) Senn, S. (1997) *Statistical Issues in Drug Development*. Wiley: Chichester; and
(c) Bailey, R.A. (2009) Designs for dose-escalation trials with quantitative responses (with discussion). *Statistics in Medicine* 28: 3721–3760.

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	(2) They are safer, because the number of subjects given each new dose in the same cohort is smaller. (3) Because it is no longer the case that most subjects in each cohort receive the same dose, blinding is much more effective. On the other hand, there are still issues to discuss about such designs, including the following. (A) If each dose is given to subjects in a number of cohorts, how and when can pharmacokinetic / pharmacodynamic studies be done on that dose to inform the choice of next dose? (B) If we are trying to find a safe dose to give to people, is it more important to compare it with the control or to compare it with the next lowest dose? We believe the EMA guidelines ought to discuss such designs, and encourage investigation into finding better designs for first-in-human trials.	

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)*
		Comment: In the draft guidelines' Executive Summary (lines 71-74), strategies for mitigating and managing risks do not explicitly mention study-design separately from the conduct of the clinical trial. We believe the EMA guidelines ought to discuss new (c. past 20 years) designs which maintain the rule that each cohort corresponds to a dose increment but have more flexibility in the number of subjects on placebo, or even on lower doses, within that cohort[7], and should encourage investigation into finding better designs for first-in-human trials.	
		Comment: In the BIAL/Biotrial clinical trial, the desired effect of the drug in humans was observed at much lower doses than anticipated. The EMA Guidelines should give a clear recommendation to reconsider the planned dose-escalation in such cases.	
		Comment: We suggest wording needs to be strengthened in section 4.4 and section 6 (lines 235-236) where "the inclusion of a tabulated summary containing an overview of all relevant non-clinical data is encouraged". Proposed change (if any): "the inclusion of a tabulated summary containing an overview of all relevant non-clinical data is mandatory".	
		Comment: Section 8.2.6 (lines 575-593) should highlight more precautionary designs, because serious adverse events may not manifest themselves in all participants at the same speed.	

[7] Some of these are described briefly in
(a) Senn, S. *et al.* [ibid] (2007) 'Statistical issues in first-in-man studies', available at: http://www.rss.org.uk/Images/PDF/publications/rss-reports-statistical-issues-first-in-man-studies-2007.pdf
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(c) Bailey, R.A. (2009) Designs for dose-escalation trials with quantitative responses (with discussion). *Statistics in Medicine* 28: 3721–3760.

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		Proposed change (if any): line 575 "in any cohort" should probably read "in every cohort" to convey more accurately the suggestion that the EMA Guidance makes	
		Comment The EMA Guidance suggests at lines 634-636 that: "For studies with multiple parts, consideration may be given to submitting an interim report to the competent authorities for review as a substantial amendment prior to the start of further dosing phases" (see lines 634-636) Proposed change (if any): It is not clear whether it is the sponsor or the authorities who are making the substantial amendment. If interim reports are desirable we suggest that it should be clearly stated (a) that they are mandatory, and (b) precisely between which study parts they are needed, and (c) whether the later study parts need to wait on further approval.	

Please add more rows if needed.