<27th Feb 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
The British Pharmacological Society
The Faculty of Pharmaceutical Medicine

This consultation response was drafted by Professor Michael Eddleston and received comments from Dr Richard Fitzgerald. It was finalised in discussion between selected members of the British Pharmacological Society and the Faculty of Pharmaceutical Medicine, including the Presidents, Professors David Webb and Alan Boyd.

The British Pharmacological Society is a charity with a mission to promote and advance pharmacology and clinical pharmacology. Founded in 1931, the Society now represents over 3,500 members working across academia, industry, regulatory agencies and the health services, many of whom are medically qualified.

The Faculty of Pharmaceutical Medicine is a professional membership organisation and standard-setting body, with 1,500 members who are practising pharmaceutical physicians or those with a professional interest in the specialty. Members work in all stages of drug development, from front line clinical trials, to pharmaceutical marketing and medicines regulation. Founded in 1989, it is a Faculty of the Royal Colleges of Physicians of the UK. The Faculty's mission is to advance the science and practice of pharmaceutical medicine by working to develop and maintain competence, ethics and integrity, and the highest professional standards in the specialty.

In addition, the Joint Specialty Committee on Clinical Pharmacology and Therapeutics of the Royal College of Physicians of London have reviewed and agree to endorse this response.

……..

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received. No objection

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

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	1. This is a helpful and useful document, with advances since the 2007 version that will improve the design of FIH/early CT studies. It is however very long and wordy. Use of bulleted lists for easy checking by the reader could enhance the value to the relatively inexperienced investigator. 2. The document lacks a statement in the Introduction (Section 1.0) concerning the purpose of FIH/early CT studies. The introduction includes the statement: "The aim should always be the safety and well-being of the trial subjects, whether patients or healthy individuals", but this is not an objective. Objectives are offered at various points in the main text (e.g. "assessment of tolerability, PD or PK profile" in Section 7.1 line 337, "maximum tolerated dose" in Section 7.4). It is important that the document states the objectives of these studies early in the introduction section. In	

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	particular, it should state that FIH/early CT trials provide the first opportunity to understand the pharmacology and effects of a drug in humans (i.e. human pharmacology). Safety is not the primary objective of these studies since this approach leads to the MTD being the primary outcome as is currently often the case. The document clearly states this: "A trial design using a MTD approach is considered to be unethical for healthy volunteers." The fact that the MTD cannot be the primary aim of a study also needs to be here in the Introduction, rather than buried in the text. We have proposed changes to account for this. 3. The information on the 'General aspects of planning and conduct of FIH and early clinical trials' currently in Section 8 should comprise the introduction to the document and this should start with the requirement to state clearly what the primary and secondary objectives of the study are. There should then be a section on choice of study population i.e. healthy volunteers / patients including severity of disease, age, sex. This should then be followed by Sections 8.2 to 8.4. By doing this, the clinical	

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	study design and contents, together with the proposed risk minimisation measures sets the tone for the rest of the document. Following this with the Sections on Quality, the Pre-Clinical aspects and Dose Selection will then give a much more logical flow to what is presented and discussed. 4. The document indicates the fundamental importance of pharmacodynamic (PD) measures for the safe introduction of a drug into humans. In places, it clearly emphasises the need for PD outputs e.g.: "The choice of the subsequent dose levels should include some estimate of the potential PD effects …" (section 7.3, line 390-391) However, this is not consistent throughout the whole document. For example, in other parts of that section, only emerging clinical data is required to be considered for dose escalation. We have clarified that all emerging PK and PD data must be considered during dose escalation. The inclusion of PD measures should be given far greater prominence in the document. This should be combined with the development of a PK/PD model whenever possible. 5. The whole question of 'integrated protocols' needs a	

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	separate discussion starting with what is really meant/its definition. Inclusion of a fed / fasted crossover or a healthy elderly group at a particular dose is usually uncontroversial but 5 part studies involving single and multiple doses with various subgroups starts to become a blank cheque from the Regulator and Ethics Committee. Could the EMA provide guidance in general terms of what is reasonable to include in a single study and what is not? Section 8.2.2 really gives the guidance needed – it also should be presented at the beginning of the guidance. 6. The composition of the decision-making group (trial steering committee TSC) is very important to safe and effective trial performance. This is addressed within section 8.3 Documentation of sponsor and investigators' responsibilities on lines 723-727. The section should also include specification of what types of expertise and roles are required in the decision-making group in tandem with a guide to what training those sitting in a decision-making group should have. The inclusion of an independent person on the TSC would be beneficial to all involved in the study. The information is useful and warrants its own section as	

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	8.4 (moving each subsequent section on by .1). Site facilities would then become 8.5, etc. 7. There is much overlap between Sections 4 (4.1 – 4.4) and Section 6 including 6.1 to 6.6. Most of Section 4 should be incorporated within Section 6 and Section 4 could then be deleted. After the introduction to Section 6, there should be a section stating that "In vitro quantitative data on receptor binding affinity, selectivity and reversibility require careful scrutiny with respect to desired and potential undesired effects. Quantitative data should be available in the Investigator's Brochure". 8. The words 'should' and 'must' are used in the document. It would be helpful if these terms were defined at the beginning of the document following the GMC's guidance on Good Medical Practice (http://www.gmc-uk.org/guidance/good_medical_practice/professionalism_in_action.asp). This could simply cite the text from the GMC: "In Good Medical Practice, we use the terms 'you must' and 'you should' in the following ways.	

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	'You must' is used for an overriding duty or principle. 'You should' is used when we are providing an explanation of how you will meet the overriding duty. 'You should' is also used where the duty or principle will not apply in all situations or circumstances, or where there are factors outside your control that affect whether or how you can follow the guidance." 9. This guidance appears to be only directed at FIH and early phase studies in adults. This is not stated. If this is the case, it should be stated. If the EMA considers to exclude paediatric populations from this guidance, then this guidance should also reference a relevant EMA guidance for First-in-Children or early phase studies in children. 10. In the following comments, for clarity and simplicity, the revised text only is presented (without tracked changes). The text should be compared with the current version of the Guidelines sent out for comment (10 November 2016, EMEA/CHMP/SWP/28367/07 Rev. 1).	

2. Specific comments on text

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68.		**Comment:** This guidance should also be addressed to investigators and members of ethics committees as well as sponsors.	
76		**Comment:** The introduction should state why FIH/early CTs are done, rather than providing this information mixed into the main text (e.g. line 337). The comment (currently line 432) that MTD trials are not ethical needs to be stated in the introduction since many trials currently have MTD as the primary outcome. It should also include an explanation as to why some studies are performed in patients rather than healthy volunteers. **Proposed change** (if any): The purpose of FIH trials is to take a medicine into humans for the first time, to study the human pharmacology of the IMP, and to compare it's *in vivo* effects in humans (clinical studies) with it's effects in animal and human tissue studies (non-clinical studies). Safe use results from increased understanding of the IMP. Trials should not be designed to identify the maximum tolerated dose; although there may be studies in which identifying the MTD is justified, it must not be the aim of the study in healthy volunteers. In some cases, FIH trials will be conducted in patients as	

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		opposed to healthy volunteers. Particular circumstances where that may be appropriate include…… Traditionally, FIH CTs were performed with……	
83-84		**Comment:** Safety is not the aim of these studies. The aim (or objective) is to study the pharmacology, pharmacokinetics, safety and tolerability of the IMP in humans for the first time. Safety is a priority for study design and operation but is not the aim of the study (if that was the case FIH studies would never be done since there is always some element of risk, which must be minimised through good design). Therefore, remove the restricting comment. **Proposed change** (if any): … populations. The safety and well-being of the trial subjects, whether patients or healthy individuals, should always be the priority of the researchers and underpin the trial design.	
90-93		**Comment:** This section could be more explicit in emphasising the critical importance of the starting dose and subsequent dose escalations and its basis in non-clinical PK/PD data and previous experience in humans with drugs of similar mechanism or class. **Proposed change:** Special attention must be given ….	

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93-95		**Comment:** It should be emphasised that it is both exposure and effect that should be taken in to consideration **Proposed change** (if any): Therefore, whenever dose is mentioned in this guideline, the expected exposure and effect at that dose must be taken into consideration	
100-102		**Comment:** Emerging clinical trial data should inform the steps of all trials (including cohorts with a SAD component) not just those with an integrated protocol **Proposed change** (if any): … basis. It is important to remember that data generated during the trial must be used to inform the decision processes for the continuation of dosing.	
109-110		**Comment**: It would be useful to expand when and why patients are included into FIH studies with examples instead of stating 'in certain situations' **Proposed change** (if any): These trials are often undertaken in healthy volunteers but can, in certain situations, also include patients. This may include inclusion of a cohort of patients as part of an integrated protocol with healthy volunteers or a FIH study in patients exclusively (for example in oncology, where the drug target is expressed only in patients, or where the principle of minimal risk is not	

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		applicable and FIH trials in healthy subjects not ethically justified')	
152-154		**Comment**: Factors of risk should also include the population being studied – for example in patient groups one might consider the risk posed by even well controlled comorbidities. **Proposed change** (if any): Factors of risk may be derived from … and the population in which the study will be conducted.	
178		**Comment** 'The usefulness of PD data following repeated dosing testing' – correct grammar **Proposed change (if any)** 'The usefulness of PD data following repeated dosing'.	
204		**Comment:** Researchers must also take into account the temporal expression of the target, not just the location. For the Tegenero compound, subsequent research showed that the target was downregulated in some T cell subsets in adults of the monkey species used for non-clinical studies, unlike in humans. Its presence on T cells of the adult volunteers studied in the FIH was one reason for the severe activation of the immune system seen in these volunteers **Proposed change** (if any):	

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		… target, its structural homology, its temporal expression and distribution, age of animals, signal transduction pathways and the nature of …	
207		**Comment:** The findings should come from both toxicology studies and safety pharmacology. **Proposed change:** The findings in non-clinical safety studies, including both toxicology and safety pharmacology, that are considered to be relevant ….	
209-231		**Comment:** The formulations used in non-clinical studies frequently differ from those planned in man (rodents can't take capsules/tablets; exposure to some excipients used in toxicology studies is restricted in man, etc.). The potential impact on exposure and, therefore, effect, at the starting dose should be considered. **Proposed change** (if any): ***5.4 Formulations used in non-clinical studies*** The formulations used in non-clinical studies frequently differ from those planned in humans (for example, rodents can't take capsules/tablets and exposure to some excipients used in toxicology studies is restricted in humans). The potential impact on exposure and, therefore, effect, at the starting dose should be considered.	

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245		**Comment:** This information should also be summarised in the protocol. **Proposed change:** The search for a relevant animal model should be documented, and the model selected justified, in the Investigator's Brochure (IB) and summarised in the Protocol.	
252-284		**Comment:** much of the discussion is relevant to biologicals rather than small molecules. Separate subsections for NBEs and NCE may be useful.	
291		**Comment:** Need to emphasise that both animal and human tissue non-clinical studies are required. **Proposed change** (if any): The primary and secondary PD should be conducted in vitro, using both animal and human-derived material where feasible.	
295		**Comment:** The animal and *ex vivo* human tissue PD data should be compared to better understand the usefulness of the selected animal species, as indicated by line 378 in Section 7.2. This can be added at the end of the paragraph. **Proposed change** (if any): … target. The ex-vivo human PD data should be compared with animal data to illustrate the relevance of the selected non-	

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		clinical animal species to human pharmacology	
302		**Comment:** This section should not include TK data. Mention of TK data should be moved to the toxicology section (6.5)	
311		**Comment:** The importance of safety pharmacology should be stressed and data interpreted in terms of the margins of safety relative to the concentrations required for desired PD effects.	
317		**Comment:** this section should include mention of TK data and of putative margins of safety for NOAEL and NOEL.	
339-341		**Comment:** The use of all available data when making starting dose and dose escalation decisions is critical to the safe conduct of FIH studies. This section could be strengthened by replacement of 'should' with 'must'. **Proposed change** (if any): All available non-clinical information (PD, PK, TK and toxicological profiles, dose or exposure/effect relationships etc.) must be taken into consideration for the calculation of the starting dose, dose escalation steps and maximum dose.	
348-350		**Comment:** It is not just the clinical effects that must be considered during dose escalation, but also the PK and especially the PD. Otherwise, as in the Bial trial, one might	

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		keep increasing the dose far past any maximal pharmacological effect until toxicity occurs **Proposed change** (if any): Substantial amendments will also be needed where dose escalation has reached a pre-defined maximum exposure and PK/PD analysis (and the absence of either adverse or therapeutic clinical effects) leads to a conclusion that further careful escalation is warranted.	
359-363		**Comment:** This paragraph is out of position and should follow the subsequent paragraph (starting Exposure showing …) The default for selection of starting dose should be the Pharmacologically Active Dose / MABEL for small as well as large molecules. The NOAEL provides guidance to the maximum recommended starting dose but the PAD/MABEL will generally provide a much more relevant starting dose, which will be much lower. Lines 374-5 are relevant only to the NOAEL. Generally, a safety factor is not required for doses based on the PAD.	
382		**Comment:** It is unnecessary to duplicate information in both IB and protocol. The IB is not specific to any single CT. At the FIH stage, there are no other CTs. The risk-benefit section of the IB will need updating before any other trial can start, other sections don't. The IB should contain all the information	

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		available; this information and justifications for decisions made should be summarised in the protocol. **Proposed change** (if any): Any safety factors used should be justified and detailed in the protocol.	
385		**Comment:** As above **Proposed change** (if any): Such a justification should be included in the protocol.	
386		**Comment:** meaning of the word 'subject' is unclear. Presumably it means 'participant'. However, this is not needed. The sentence is clear without it. To reinforce the word ideally, an explanation should be requested if this is not planned in the protocol As noted in Section 7.1 (lines 336-338), dose selection should also take into account a reasonably rapid attainment of the trial objectives (…) without exposing large numbers of subjects. The selected should therefore not be far below the expected pharmacological dose. **Proposed change** (if any): In healthy volunteers, the starting dose should ideally result in an exposure that is below, but expected to be close to, that which would be expected to produce a PD response. If this is	

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		not possible, an explanation should be given in the protocol.	
388		**Comment:** It should be made clear from the first sentence of this section that dose escalation must be made on the basis of a comprehensive review of accumulating tolerability, safety, PK and, when relevant, PD data from previous doses.	
392-394		**Comment:** This section should more explicitly state that both PK and PD data from the emerging clinical studies should be incorporated into dose escalation decisions, not just clinical data from an unspecific cohort. **Proposed change** (if any): The dose increment between two dose levels should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in non-clinical studies and by all emerging clinical and pharmacological data, including that from the immediately previous dose cohort and later time points from earlier cohorts.	
399		**Comment:** This advice could be strengthened by changing 'considered' to 'used' and clarification of that higher blood (not lower) concentrations are important. **Proposed change** (if any): Furthermore, if there is evidence of non-linear PK with higher blood concentrations that expected, smaller dose increments	

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		should be used.	
399-402		**Comment:** It should not be just clinical data that should be compared to non-clinical data but also the emerging PK, PD and safety data. **Proposed change** (if any): If emerging PK, PD or safety data reveal significant differences from non-clinical or modelling and simulation data, …	
406		**Comment:** The pharmacological effects in humans (contrasting with non-clinical studies). This could be emphasised for readers. **Proposed change** (if any): The design of FIH or early CTs often aims to determine a dose or exposure-response curve in humans for the most relevant pharmacological effect(s), and…	
418		**Comment:** This should indicate that all previous study parts should be considered. There is no need to state 'once these are completed' since this may permit going ahead with the study without considering these data if that study part is not completed. These words can simply be deleted. **Proposed change** (if any): These criteria should integrate data from all previous study	

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		parts, including all follow up data, and …	
424-5		**Comment:** Dosing may sometimes with justification exceed the maximum PD effect so that the effect of modest increases in dose can be established**.** **Proposed change:** While establishing the maximum (well) tolerated dose should not generally comprise an objective of a Phase I study in healthy volunteers; it is usually reasonable to escalate the dose to a level that produces concentrations a little greater than those associated with the maximum desired pharmacodynamic effect. This can provide reassurance that there is a reasonable therapeutic window and that small increases in drug concentrations are unlikely to result in clinically important adverse events. The dose attaining the maximum desired pharmacodynamics effect will only become clear as data accumulate and are analysed within the FIH study.	
426-428		**Comment:** It may not always be possible to measure relevant PD effects directly, if for example the target enzyme is in the brain (as occurred with the Bial trial where a peripheral leukocyte enzyme assay was proposed). If this is the case, then the consequences of this need to be discussed in this section **Proposed change** (if any):	

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		Target saturation should be taken into account, e.g. if the intended therapeutic effect is linked to enzyme inhibition, then the maximum dose should consider when complete inhibition is achieved and no further therapeutic effect is to be expected by increasing the dose. Where measuring this activity is difficult (as for example with CNS target enzymes), then the consequences/implications of this difficulty need to be discussed in the protocol.	
429-433		**Comment:** The issue that studies with MTD as the primary outcome should never be done in healthy volunteers is fundamentally important as such trials seem to be currently common. This paragraph should be at the top of this section and the patient vs healthy volunteer discussion re-ordered. The comment is given too little emphasis in its current position. **Proposed change** (if any): Consider placing at the top of section 7.4 (currently line 406): A trial design using a maximum tolerated dose (MTD) as the primary objective is unethical for healthy volunteers. For trials or trial parts that include patients, using the MTD as an outcome may be considered but this should be clearly defined and not be exceeded once it has been determined. The potential therapeutic/clinically relevant dose (exposure)	

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		and the expected benefit/risk balance should always be considered when defining the dose range. Where patients are included in a study, consideration should be given to their co-morbidities which may alter the benefit/risk balance. It is important to distinguish between dose-limiting pharmacodynamic effects affecting tolerability e.g. mild undesired but not serious central effects from those with more serious implications for safety.	
441-443		**Comment:** These decisions should not be based around MTDs since there should be no ambition of reaching a MTD in a healthy volunteer study. Instead, previous highest doses should not be exceeded (and the emerging pharmacology should be considered) **Proposed change** (if any): However, previous highest doses should not be exceeded (and the corresponding PK, PD and clinical effects should be carefully considered) unless tolerance occurs on repeated dosing (e.g. with opiates). A maximum duration of dosing should be stated in the protocol for every cohort.	
446		**Comment:** This situation is something that should generally be considered in advance and covered in the protocol. A substantial amendment should not be required.	
451		**Comment:** This statement should be made stronger.	

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		Proposed change: Intravenous infusions should generally be administered slowly. While the duration of infusion will depend to some extent on PK, typical infusion times vary from 1 to 4 hours but may need to be longer. It is rarely justified to administer an IMP as a bolus in early studies, even if such a regimen is ultimately intended in clinical practice.	
456-457		**Comment:** How does one define 'reasonably safe to use'? Better to remove the word 'reasonably'. **Proposed change** (if any): is to identify a dose that is expected to have a minimal pharmacological effect and is safe to use	
462-463		**Comment:** It should rarely be necessary to revert to a single dose design for patients when the safety of multiple doses has been established in healthy volunteers. Use of sentinel (lead subjects) with a defined interval between patients may be justified. **Proposed change** (if any): When moving from healthy volunteers to patients, it is rarely necessary to revert to a SAD design for patients when the safety of multiple doses has been established in healthy volunteers. Use of sentinel (lead subjects) with a defined interval between patients and careful review of PK, PD and safety data may be justified with.	

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468-469		**Comment:** It should be made clearer which other patient groups could be regarded as special populations. **Proposed change** (if any): Furthermore, some special populations, such as populations at the extremes of age (paediatrics, elderly), renal impairment populations and hepatic impairment populations, may deserve additional specific considerations.	
495-496		**Comment:** More information on the decision-making process would be helpful **Proposed change** (if any): If there is an integrated protocol, there should be a decision at a predefined time point on proceeding to the next part. The data required for a decision to escalate should be described, as well as the people who will take this decision.	
502		**Comment:** Please define what is meant by integrated protocols, since they can have several forms.	
511		**Comment:** The overlap should not include higher MAD doses than already studied in the SAD part. This is made explicit in the subsequent two paragraphs (lines 514 and 518), and could usefully be added here.	

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		Proposed change (if any): A certain overlap of SAD and MAD parts may be considered acceptable, provided the dose chosen is equal to or lower than that which was reached in a concluded preceding SAD cohort where all relevant data has been reviewed and no dose escalation stopping criteria were met.	
518-520		**Comment:** This sentence is currently imprecise – it is the IMP doses that should not overlap. I.E. the IMP doses used in other study parts with multiple dosing should not exceed those that have already been studied in a MAD cohort. **Proposed change**: Other study parts that involve multiple dosing (e.g. FI and drug-drug interaction) should not use IMP doses that have not already been studied in an earlier MAD cohort.	
558		**Comment:** 'Justify' is not the right word – of course safety monitoring of any subject would/should be extended until parameters return to normal/baseline; and it should be in the protocol. **Proposed change** (if any): The protocol should describe how safety monitoring should be extended…	
565-566		**Comment:** Little guidance is offered about what to do when PKPD variability is noted within a cohort. Suggest advice to	

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		expand the cohort and/or the next cohort. A substantial amendment is likely to be required. **Proposed change** (if any): The number of subjects per dose increment (the cohort size) depends on the variability of both PK and PD parameters and the trial objectives such as justifying progression to the next cohort. If high variability in PK/PD occurs in any cohort, this cohort should be enlarged to gain better understanding of variability (or the same dose studied in a subsequent cohort).	
575		**Comment:** Make explicit that this relates to both SAD and MAD cohorts and to ALL cohorts. However, allow some flexibility to limit numbers exposed in the sentinel group without specifying that it is exactly one e.g., dose 2 active and 1 placebo and if data are incomplete in one subject, allow continuation if data available on at least 2 (1 active and 1 placebo). The size of the sentinel groups should depend on SAD and earlier MAD cohorts. **Proposed change** (if any): It is considered appropriate to design the administration of the first dose in all SAD or MAD cohort so that usually a single subject receives a single dose of the active IMP. The precise number selected, and the delay before subsequent dosing, should be determined after analysing all information collected from earlier cohorts.	

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590		**Comment:** In the description of the precautions to apply between treating subjects within a cohort, the precautions are said to apply to Any (suggested above to become 'All') cohorts. However, this paragraph then says that the approach may also be appropriate later. This is moot since the precautions should apply to all cohorts. **Proposed change** (if any): Delete the introduction of this paragraph and revise to: Care must be particularly taken in situations such as doses on the steep part of the dose response curve, when approaching target saturation levels or exposure margins to non-clinical NOAELs, in case of non-linear PK, or in light of emerging clinical signs or adverse events that do not meet stopping criteria.	
595		**Comment:** PK and PD results from all previous cohorts must be available before starting the next cohort. Stating 'where available' offers the opportunity to say that they were not available. It is not required. **Proposed change** (if any): Administration in the next cohort should not occur before participants in the previous cohort have been treated and the PK, PD and clinical data, including possible AEs, from those	

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		participants reviewed in accordance with the protocol.	
598-599		**Comment:** Recommend requiring review of all previous cohorts' data in a cumulative manner. **Proposed change** (if any): All previous cohorts' data must be reviewed in a cumulative manner.	
604-605		**Comment:** PD data is essential for understanding the novel human pharmacology of the medicine being tested. There should be no reason for allowing it not to be analysed since it may change with dose. The protocol should clearly specify and justify what data will be reviewed. Multiple different PD tests might be done within a study; the protocol should specify that data from the most robust test will be used and that other PD tests are exploratory and won't be used for the decision. **Proposed change** (if any): Delete: 'While there can be no delay for safety data, a lack of PD information or a reduced PK data set could be justifiable in some cases, such as a short duration of the PD effect.' Insert: 'The protocol should clearly specify and justify what PD data will be reviewed.'	
634-636		**Comment:** We are not sure of the point of this. If there are no issues and no need to change anything, why delay things	

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		by submitting an optional substantial amendment and waiting for a response? If there are issues or a wish to change anything, then the amendment is required. **Proposed change** delete lines 634-636	
638-651		**Comment:** Quality control of the data used for dose escalation needs to be considered. It is vitally important that the data being used for decision making are reliable and represent the source information. **Proposed change** (if any): A statement should be inserted within this section emphasising the necessity for quality control of all data that are being used in the decision to escalate the dose.	
650		**Comment:** PD data is required for safe FIH studies **Proposed change** (if any): All data (e.g. safety, PK, PD, and any other available information) is required …	
671		**Comment:** Missing word – 'the' **Proposed change** (if any): … outline decision points for the situation where stopping rules are met.	

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679		**Comment:** The relevance of the moderate AEs to the medicine's target organ should be taken into account (e.g. the headaches in the Bial trial with a CNS-active medicine) **Proposed change** (if any): and their relation to PD effects, the expected target organ (e.g. CNS), the number of subjects ….	
683-5		**Comment:** In a SAD study, it may be perfectly reasonable to exceed the Cmax at the NOAEL if the pharmacological effects are directly related to it. AUC is usually more important to limit exposure in a MAD study. **Proposed change:** Delete current 683-685, and insert: Plasma concentrations corresponding to those at the NOAEL in the most sensitive species provide a guide to stopping dose-escalation. While it may be reasonable to exceed the NOAEL Cmax in a single-dose escalation if no significant adverse events have been seen, organ toxicity on repeat dosing is usually more closely linked to the exposure in terms of AUC0-24 and it is generally unwise to exceed this.	
692-693		**Comment:** The advice below is vague and not particularly helpful. Can this be made more explicit? 'Additional stopping rules should also be based on what is	

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		known about the PD of the drug (e.g. mode of action, chemical structure and others compounds in class or other classes).'	
700-702		**Comment:** For staffing and supplies of antidotes, allow for the possibility that >1 subject may have the same AR in close proximity. This should include the availability of specific antidotes where they exist and a clear plan of availability of supportive treatment emergency facilities and medical staff to treat multiple patients.	
718-719		**Comment:** It should be made clear that the investigator has the principal responsibility for patient safety and the sponsor for the overall integrity of the trial.	
721-722		**Comment:** It should be made clearer that the decision to un-blind a study in an emergency rests with the Investigator. Line 721-722 does not place sufficient emphasis on this and should be made more explicit. **Proposed change** (if any): It is also the case that unblinding in an emergency may be performed by the Investigator without involvement of the monitor or sponsor, where knowledge of the treatment received is needed for the immediate management of the subject. If unblinding is	

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		needed otherwise, the investigator should discuss with the sponsor, and the investigator has the right to withhold further dosing of the affected and other subjects whilst doing so.	
723-727		**Comment:** This should be a separate section entitled Trial steering group. Consideration should be given to specification of what expertise is required in a Trial Steering Group. For example, this could be related to the nature and action of the IMP or specific expertise in clinical pharmacology. This is particularly important in studies with integrated protocols or studies which are being conducted at smaller research sites or where the sponsor is a small company with no in-house expertise. There should be an independent member of the TSC where possible. **8.4 Trial steering group** The composition of any decision-making group or committee should be documented in the protocol so that their appropriateness to participate in the monitoring and decision-making can be established. Other details to include are the exact remit of the group and the roles of all members in the committee or in relation to the sponsor. The members of the group should also be sufficiently independent from IMP administration and monitoring.	

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726-727		**Comment:** The TSC and trial safety would benefit from limited independent membership, not directly associated with sponsor or study site. **Proposed change** (if any): The members of the group should also be sufficiently independent from IMP administration and monitoring. At least one of the members should be independent of sponsor and study site	
740-742		**Comment:** Whilst FIH / early CTs in healthy volunteers are frequently conducted at a single site, it is important to emphasise that this may not be possible for FIH / early CTs in patient groups. In addition, whilst single site options are advantageous in gaining 'collective experience', it is important to note that when multiple sites are being used there should be adequate procedures in place to share information between sites and that this would not necessarily materially affect the safety or risk of multiple site studies.	

Please add more rows if needed.