Draft comments on Revision 3 of "detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial.

Section 2.2

1. Paragraph 1: not all trials have a sponsor protocol number, and where it does it may not be unique to a particular sponsor. The EudraCT number is unique and should suffice.
2. Paragraph 2: it is not clear what is meant by "particular particularities". Since the protocol will be part of the application, it is unclear what is added if the covering letter gives information that should be readily available in the protocol's summary section. If there are *specific* issues that may have a bearing on the decision to authorize the trial, then it is reasonable to request that they are mentioned briefly in the covering letter, but the suggested guidance about what is to be included will result in much unnecessary material being included (thereby obscuring the most important information).

Section 2.5

1. Paragraph 2: the Community guidelines on Good Clinical Practice describe *guidelines*, and it is not appropriate for this guidance (or any other) to elevate the contents of that document to obligatory rules. Protocols can take many appropriate forms, depending on the context of the trial, and should be acceptable so long as they meet the definition described in paragraph 1 and provide sufficient information for judgments to be made by both competent authorities and ethics committees. Excessively formalistic approaches to a protocol's structure may actually be less informative for such authorities than a well written document that deals with the main elements clearly.
2. Paragraph 2: Again, the sponsor's code may not be unique across sponsors.
3. It is not clear what is gained by having the sponsor and principal investigator sign the protocol. It will not, for example, guarantee that those personnel understand the protocol nor that they have the necessary training to follow it. The chief purpose of this step seems only to be that the signature can easily be audited; this is just one example of rules that are unlikely to improve the quality of trials.
4. Line 8: Replace with "Where appropriate, it should include:"
5. Paragraph 3, final bullet point: If additional care is regarded as necessary, then it suggests that there are continuing safety or other concerns, in which case the trial should be continuing to study such concerns (and shouldn't have "ended").
6. Paragraph 5: This guidance implies that a protocol only needs to address these issues in first-in-human trials, whereas they are relevant in many (if not all) trials.

Section 2.10

1. Second bullet point: Rephrase as “A list of national competent authorities in which the sponsor has already made the same application with details of *any decisions already taken.*” (Otherwise it might be implied that a sponsor has to wait for any outstanding applications before applying for a new authorization.)
2. Fourth bullet point: This contradicts section 2.2, which says that this information should form part of the application and that the covering letter should say where it is.

Section 3.3

1. The definition of “substantial” is vague and even with this clarification will continue to cause a great deal of unnecessary work for sponsors without adding to the safety of patients. (Note 41 is very unclear, does not help, and should be deleted.) Substantial amendments should be “notifiable” (ie, sent for specific approval) *if and only if* they would result in changes to the trial that might conceivably jeopardize its approval status. Improvements in procedures, for example, should not be substantial amendments. Unless a potentially contentious change in protocol is proposed, it should be possible to update a protocol and send a new version for information only. Competent authorities and ethics committees would still see such revised protocols, and would still be able to remove authorization if necessary (and apply sanctions to sponsors that regularly abuse such a system), but the current tendency for defensive over-reporting might be reduced.
2. It is not clear why the examples given in 3.3.1 are *necessarily* substantial (although they might meet the proposed criterion above). For example, reducing the number of clinic visits could be accompanied by an increase in other forms of follow-up, such as through access to reliable registries. If so, patient safety may be *enhanced*, not reduced. In such circumstances, sponsors should be able to choose not to report a substantial amendment. Similarly, extending the end of the trial (with the consent of patients) might well result in additional safety information becoming available, and again sponsors should not necessarily have to await approvals for such measures before implementing such protocol changes. Currently, such changes would have to be urgent (see section 3.7) for this method to be allowed.

Section 4

1. The “end of trial” cannot easily be defined for some trials that involve long-term follow-up, unless it is defined as the time when the last randomized patient dies.

Colin Baigent
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