INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS

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Comments regarding *Draft Guidance for Industry and Food and Drug Administration Staff, Adaptive Designs for Medical Device Clinical Studies, May 2015.*

Guidance Document Section	Comment
Line 17-19	The definition of an adaptive design indicates in these lines that this study design restricts to preplanned modifications and a method that does not 'undermine the trial's integrity and validity'. ***Should the agency also indicate in this definition that this design should also not inflate the type I error rate?*** Later in the draft guidance the Agency indicates that unplanned adaptivity is sometimes possible and that methods should control error rates. It is then confusing to have a section in this document called 'Study design changes that are not adaptive.' ***It is unclear what the Agency's purpose for including this section in the document.***
Line 97	In line 97 and several other places, increasing the sample size because of a small observed effect is recommended. Would the Agency consider it to be a better approach to use a group sequential design powered to detect the effect of interest but able to stop early if a larger effect is observed as this makes it clear what the effect of interest is and does not mean a very large sample size is required for the least promising treatments. ***A better example for sample size reestimation would be when a nuisance parameter such as the variance is unknown.***
Lines 322-328	Lines 322-328 indicate that there may be operational bias if interim information is available and the assignment is unblinded. ***Should the Agency consider using an 'or' in this statement; it can arise in a blinded study with interim analysis or in an unblinded fixed sample size study.***
Line 337: Section 5	***Is the Agency indicating in this section that you cannot inflate the type I error without unblinding?*** If you knew the variance, could you not then get an estimate of the treatment difference from the overall sample variance, so stop when this was large and continue with a very large next stage when it was small?
Line 405	Bayesian methods are mentioned in line 405, but without any substantive explanation of what is meant here and how scientific integrity is maintained. ***If it is intended that even Bayesian methods should control frequentist error rates, we suggest that the Agency address this in more detail.***
Line 455	It is unclear to why SSR methods are listed as requiring breaking the blind. ***Many methods exist that do not require doing so and it seems that that is an example that would be suited better in another section of the document.***

Guidance Document Section	Comment
Line 544: Section F	In Section 6. F, on response adaptive randomization designs: ***Even in a brief description such as given here, we recommend to the Agency to consider the fundamental danger of bias due to confounding with time and to describe it in this section.*** That is, most analyses of RAR trials assume that there is no time effect; if there is, then the time trend could be attributed to the treatment (whose proportion also changes with time).
Line 610: Section J	This is critically important in a trial of a device in an area where the technology is evolving rapidly, and continuing to test the device available at the beginning of the trial would give an evaluation of an outdated device by the end of the trial. ***It would be helpful to have some indication of the extent of device adaptations that might be considered (e.g. change of algorithm used; or change in physical size of device) and appropriate methods to accommodate such changes in the statistical analysis plan.***
Line 934	In line 934 it is suggested that sites are unaware of the randomization ratio. ***Is the Agency indicating that subjects should not be informed of the ratio of the randomization (i.e. 1:1, 2:1 treatment to control)?*** This should be clearer.