EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Submission of comments on 'Draft guideline on adjustment for baseline covariates' (EMA/295050/2013)

Comments from:

Name of organisation or individual
IDeAl (Integrated Design and AnaLysis of small population group trials) FP7 Consortium **(European Union Seventh Framework Programme under grant agreement n° 602552).** (IDEAL Webpage: http://www.ideal.rwth-aachen.de/)

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)*
	We welcome this statement. It yields a very good guideline for the adjustment on covariates. We especially appreciate the claim for justification of every covariate that is included in the study, as well as keeping the total amount of covariates as low as possible by elimination of dependent covariates.	
	We welcome that baseline covariates can be accounted for in two stages of a clinical trial, the randomization and/or the analysis. In particular, we appreciate the explanation, that stratified randomization is the typical approach for handling baseline covariables in the randomization process.	
	We regard it as dangerous, though, to use oversimplified models for the primary analysis. From Senn [2005, 2012] it is known, that all relevant observed baseline covariates must be included in the primary analysis of the study. The credibility of the trial is not compromised by many covariates if their relevance is explained in the study protocol.	
	We recommend the use of a suitable randomization procedure to diminish the increased effects of (selection) bias that might arise due to many strata.	
	We support the claim, that post-hoc testing for baseline-covariates should be avoided in randomized clinical trials if randomization and blinding are properly conducted in the study.	
	The need for randomization and blinding to avoid bias in clinical trials cannot be overstated. In particular, knowing important covariate measurement, may lead to strong selection bias in trials, where the person who recruits the patients is not blinded to previous treatment allocations. We would therefore recommend to further stress this point in the statement.	
	The agency should carefully elaborate on the way the term “imbalance” is used throughout the whole document for covariables as the meaning of the term “imbalance” is twofold and its interpretation is related to the related main objective:	

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	If the interest of covariates is as a main effect, that is to say to adjust the treatment effect for them, it is the degree of imbalance of the covariate between treatment arms that adversely affects power. If the interest is in the covariate as in interaction, then in addition one needs (for a categorical covariate) that each category is well-represented. However, this requirement adversely affects recruitment time and is usually impractical.	

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)*
70-72 (63-65), 283-288		Comment: We have some doubts regarding the statement, where “appropriate categorization of covariables” or simple functional forms for the relationship are mentioned. A loss of information results from categorization and possible erroneous relationships may result in biased treatment estimates. See lines 277-283 Proposed change (if any): We recommend that categorization or linearization of continuous covariables should not be done, apart from the case where well established clinical categorizations are used, meaning that the relationship of the categories to the treatment estimate are established. For exploratory analysis categorized analysis – if in agreement with the results of the primary analysis – may be helpful in interpretation of the data in relevant subgroups.	
147-148, 309-310		Proposed change (if any): Please add references of the relevant regulatory documents. (E.g., it is not clear which guidelines on subgroup analysis are meant.)	
88-89 168-176		Comment: The term “dynamic allocation” could be misleading, because there exist procedures without randomisation element, e.g. minimisation method, Pocock-Simon range method with p=1. In our opinion only “stratified randomization methods” or “baseline adaptive randomization methods” with a true random element should be recommended. Methods without random elements should be avoided. Proposed change (if any):	

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		We recommend to use the term “appropriate random allocation”.	
175-176		Comment: The authors of this comment consider the term “re-randomisation” too vague. Proposed change (if any): Specify what is meant by re-randomisation, e.g. permutation testing.	
225-233		Comment: We welcome the comments on “Change from baseline”. However, in our opinon, a remark on stratification should be given and on reflecting baselines in the randomization process. Proposed change (if any): If baseline values were used as covariates, the measurement scale should be preserved. Consequently, a categorization is not recommended. Further, baseline value could be incorporated in the randomization procedure by using a covariate adaptive randomization procedures, where it is strongly recommended that methods without randomization element (e.g. minimization) are to be avoided.	
243-244 257-261		Comment: The authors along with the IDeAl consortium consider the statement that “In any cases, analyses including many covariates will always be less convincing than analyses with fewer, well-chosen, covariates.” misleading, as all relevant covariates must be included, even though they were many. (See further S. Senn, “Baseline Balance and Valid Statistical Analyses: Common Misunderstandings”, appeared in Applied Clinical Trials, 2005).	

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		Proposed change (if any): Avoid this implication.	
295-297		Comment: The authors along with the IDeAI consortium consider the randomization procedure should be reflected in the nonparametric regression as well. Proposed change (if any): However, in these cases, it is important that the randomization procedure is reflected in the model and appropriate estimates of the size of the treatment effect are still attainable and, not just the calculation of significance levels.	