

From: Graaf, R. van der <R.vanderGraaf@umcutrecht.nl>
Sent: Wednesday, April 25, 2018 7:50 AM
To: Kaeser, Lisa (NIH/NICHD) [E] <kaeserl@mail.nih.gov>
Subject: input PRGLAC 14 May

Dear Lisa Kaeser,

Thank you for the opportunity to send in comments. I have some comments on the timing of the trials in pregnant women. Please see my specific comments below. I have also attached the paper in which I express some of these concerns.

Kind regards,

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<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2495-9>

Page 9:

Line 351: “if there are limited safety data or other approved treatments are available in this situation it may be more appropriate to complete phase 3 clinical trials in a nonpregnant population”. We agree that safety issues and proper dosing should be addressed before larger groups of (pregnant) women are exposed to a drug. However, by explicitly pointing at phase III trials in nonpregnant population the reader may get the impression that other *design options* are no reasonable alternative. Yet, there are options to earlier include pregnant women in the drug development process while ensuring that sufficient safety and efficacy data are available before more substantial numbers of pregnant women are enrolled. One of these alternatives is the use of an adaptive trial design. Please also see *Roes KCB, van der Zande ISE, van Smeden M, van der Graaf R. [Towards an appropriate framework to facilitate responsible inclusion of pregnant women in drug development programs](#). *Trials*. 2018 Feb 20;19(1):123.*

Line 355: “if there are limited therapeutic options”. Please add: “and inclusion is a reasonable option”

Line 358: “if there are safety data for a drug that has been studied previously for other indications or populations: in these situations, the risk-benefit considerations may favor enrollment of pregnant women in earlier phase trials”: Please reverse the order: “Pregnant women may be enrolled in earlier phase trials provided that the risk-benefit ratio of inclusion is favorable”