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May 28, 2013

Dear Pediatric Investigators,

RE: Pediatric Clinical Research Trials

The Food and Drug Administration (FDA) published a final rule, which went into effect March 28, 2013, pertaining to additional safeguards for children enrolled in FDA regulated clinical investigations, Subpart D of its regulations. The FDA stated in the guidance that it does "not consider the administration of a placebo to offer a prospect of direct benefit" and that the concept of more careful follow-up and safety monitoring, etc., by virtue of enrollment on a clinical trial also does not constitute a prospect of direct benefit.

The most significant clarification provided by the FDA pertained to pediatric studies with more than one arm to which participants might be assigned. Whereas previously IRBs were evaluating the possible benefits and risks of the overall study to make a children's finding, IRBs will now conduct a component analysis of each arm of a multiple arm pediatric trial. The most obvious and most common situation we expect to see will be in the context of placebo controlled clinical trials. Therefore, in studies which previously would have had a children's finding of meeting the requirements under §50.52 (greater than minimal risk but offering the prospect of direct benefit), the placebo arm will now need to be evaluated separately and without a prospect of direct benefit.

The IRB will begin to evaluate studies in accordance with the FDA comments as new and continuing review protocols are submitted. The IRB will need to evaluate if there is a potential for direct benefit to participants randomized to a placebo arm (the answer to which will generally be "no") and evaluate the potential for direct benefit to participants randomized to any investigational product arm or another treatment arm (such as a novel combination chemotherapy arm) separately. This may result in multiple child risk determinations for one protocol. Although the updated interpretation will not have a significant impact on the majority of pediatric research protocols, there will be implications for multiple arm pediatric clinical trials.

As an example, the implications for placebo-controlled pediatric studies will be as follows:

- If all research interventions with the exception of the study product are standard of care and/or do not involve greater than minimal risk, the placebo arm of the study may meet the requirements of §50.51 under Subpart D (no greater than minimal risk).

- Since the placebo arm of the research generally will not offer a prospect of direct benefit to individuals, if the other research interventions present an increased risk (such as additional research procedures which would not be performed as part of clinical care, but only as part of the research study, and which must qualify as a minor increase over minimal risk), then the IRB will generally make the finding that the placebo arm meets the requirements under §50.53 (minor increase over minimal risk and no prospect of direct benefit). Subpart D

requires both parents to provide permission unless one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has legal responsibility for the care and custody of the child under §50.53.

- Any study where the placebo arm would carry more than a minor increase over minimal risk would likely meet the requirements under §50.54 (Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children) which requires review and approval by the Secretary of HHS.

- The intervention arm (or arms) of such a study would likely still meet the requirements under §50.52 (greater than minimal risk with a prospect of direct benefit).

For further guidance, please refer to the following website: https://www.federalregister.gov/articles/2013/02/26/2013-04387/additional-safeguards-for-children-in-clinical-investigations-of-food-and-drug.

Thank you,

Michael D. Amylon, MD
IRB Chairman