

Guidance for IRB Members and Investigators Regarding the Enrollment of Pediatric Patients in Phase 1 Adult Studies

PURPOSE

On June 25, 2008 the Institutional Review Board 3 (IRB3) voted to accept new guidance on the enrollment of pediatric patients in phase 1 research. The purpose of the guidance is to help remove possible barriers to participation of pediatric patients in clinical trials. The guidance was written with the assistance of the IRB Chair and several departments including the Departments of Pediatrics and Investigational Therapeutics. The IRB will use this guidance when reviewing protocols. The IRB encourages investigators to consider this guidance when submitting protocols for IRB review.

Purpose: To remove possible barriers to participation of pediatric patients in clinical trials while serving the best interests of this population and insuring compliance with federal regulations and guideline

GUIDANCE

Background: Pediatric patients were previously excluded from participation in adult clinical trials on the basis that an agent was “too toxic” or that as a “vulnerable population,” it is unfair to expose them to risks of harm. It is now recognized that application of the principle of justice also requires that vulnerable human subjects should not be deprived of potential benefits that they might possibly derive from their participation in a specific research study.

The largest meta-analysis of Phase I trials (N = 460 trials and 11,935 participants) showed a CR/PR rate of 10.6% and an additional less than PR/stable disease rate of 34%, with a toxic death rate of less than 0.5% suggesting that these trials are very safe and that patients derive more benefit than previously reported (NEJM 352:9, 2005).

Another analysis of multiple phase 1 clinical trials (JCO 2005, Vol. 23, pp 843-841) revealed the children generally tolerate drugs better than adults and that the pediatric dose is usually within 30%; and finally that responses, when they occur, often have a longer duration than those of adults receiving the same drug regimen.

Federal regulations do not present a barrier to the inclusion of children. CFR 46.405 states that children are permitted in “research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects” but provided that certain conditions are fulfilled. In the case of CFR 46.405, the “IRB must ascertain that the risk is justified by the anticipated benefit, that the relation of anticipated benefit to risk of harm is at least as favorable to the subjects as that presented by available alternative approaches, and that there are adequate provisions for soliciting assent of children and permission of subjects or guardians as described under CFR 46.408”. The quantitation of the risk and benefit needs to be documented in the protocol or in an IRB approved policy document. Additional procedures that entail risk without benefit as described in CFR 46.406) should be considered by separate component analysis. Examples may include amongst others: PK studies or deep site biopsies that could result in discomfort, pain or bleeding.

CFR 46.405 would apply, for example, to phase 1 clinical trial whereas CFR 46.406 might apply to monitoring studies incorporated into the phase 1 study. The latter might be acceptable if the procedure incurred no more than minimal risk above what might be expected normally. However, in cases where the risk was higher, e.g., core liver biopsies to obtain scientific information of no direct benefit to the subjects, it is preferable that these be made optional.

Specific Recommendations:

1. All pediatric patients under the age of 18 may be included in the eligibility section of Phase I studies unless a specific exclusion has been requested by the FDA.
2. Pediatric patients will be allowed to enter trials after the first dose level has been completed in adults without dose limiting toxicity.
3. Children under 3 years of age should be dosed at mg/kg body weight and not per m2 according to the standard formula used for treatment of these patients.
4. Treatment and outcomes of pediatric patients will be reported separately at the continuing review.
5. Any Phase I trial which includes invasive procedures which hold no direct benefit to the participants should undergo a component analysis by the IRB and the "Opt Out" option must be provided unless this is the primary objective, e.g. PK studies.
6. PIs are requested to inform outside sponsors of this policy. An acceptable explanation should be provided to the IRB in each case when there is no plan to include pediatric patients.

REFERENCES

"OHRP – Secretary’s Advisory Committee on Human Research Protections," Appendix B

REVISIONS

Date	Action	Initials	Description
6/25/2009	IRB	IRB3	IRB3 Approval
6/27/2019	Rev	JH	Updated format