INTERVIEW

Planning and Performing Clinical Trials in Children and Adolescents

Jaypreet Dhillon: We are receiving an increasing number of queries from our readers asking us to publish more information relating to running paediatric clinical trials. Is this a phenomenon that you as a centralised laboratory are aware of?

Hermann Schulz: Indeed, the current regulatory climate and the need to meet FDA and EMA paediatric regulations has increased the burden on pharmaceutical companies wanting to register new medications. The development of paediatric investigation plans (PIP) requires that scientists writing clinical protocols take the needs of children in the various age groups into consideration.[1]

JD: You refer to the age groups. Can you provide more details?

HS: When talking about children we should have in mind that "children" is not just a homogenous population. The various age groups significantly differ in their organ maturity and metabolic patterns, and therefore will respond unequally to drug treatment depending on the organ functions affected by the drug's pharmacokinetic and dynamic effects. When planning study protocols and study drug production, the galenic formulation of the study medication plays a significant role. In summary, paediatric trials require a more individualised approach to study planning and performance when compared to studies in the adult population (also refer to Table 1).

JD: Why are paediatric trials coming into focus now?

HS: Unfortunately, it has been and still is standard medical practice to treat children with drugs that have been approved for use in adults only. In the past, clinical trials did not include children and children were not considered to be a target population when planning clinical trials. Unfortunately, we should be aware that children are not just small adults. As children significantly differ from adults in their metabolism patterns they consequently should not be treated with drugs simply by extrapolating dosing information developed for adults. This therapeutic approach followed so far may cause a number of problems, such as a possible lack of efficacy due to underdosing or toxic effects due to overdosing, or just no therapeutic effect at all. With regard to health risks associated to over- or underdosing, off-label use of drugs in the paediatric environment should be avoided.

JD: When did regulatory bodies implement these changes?

HS: To improve the health of children, both the US FDA (BPCA Best Pharmaceuticals for Children Act and PREA Paediatric Research Equity Act) and the European Parliament implemented appropriate regulations in 2002 and 2007, respectively. The authorities' goal was and still is to increase the involvement of children when developing new medications.

JD: The administrative logistics behind a clinical trial should not be much different between a study in adults and a study with children, should they?

HS: Well, the logistics involved in collecting and handling blood samples in paediatric trials do significantly differ from the standards used in "adult" studies. And this is the reason why central laboratories are playing an increasing role in this new type of trial.

JD: Is there a way for pharma companies to avoid running paediatric studies and hence avoid this extra workload and costs?

HS: This is an important issue. Yes, the requirement to submit a PIP may be waived for specific medicinal products or classes of medicinal products that are likely to be ineffective or unsafe in one or more paediatric age groups, that are intended for conditions that occur only in the adult population, or that do not present a significant therapeutic benefit to paediatric patients compared to existing therapies.

JD: Let me return to the more practical issues. Embarking on paediatric clinical trials also means additional headache in obtaining informed consent.

HS: Participation of a child in a clinical trial follows the same rules as adults. These rules are based on an inclusion/exclusion criteria. Regulation and laws foresee additional safeguards when children are participating in clinical trials to ensure the safe and ethical treatment of this population. The standards for obtaining parental consent for a child to participate in a clinical trial vary geographically. While consent can be given at the age of 16 in one country, this may only be possible in another country if the adolescent is over 21 years of age. Children below this age limit may give their assent.

JD: Is there a difference between consent and assent?

HS: Granting "assent" expresses a willingness to participate in research by persons who are too young (as defined by law or regulation) to give informed consent, but who are old enough to generally understand the proposed research, the expected risks and possible benefits, and the activities expected of them as study participants. If assent is granted, informed consent must still be obtained from the child's parents or guardian.

JD: I can imagine that collecting blood samples from lactates or small children brings limitation to the study design with respect to the number of control visits and blood collections.

HS: Absolutely. The most challenging

aspect of running clinical trials in children below two or three years is their overall reduced total blood volume. Consequently, when treating children, blood cannot be drawn in the same quantities or using the same type of tubes as used for adults. It is therefore critical to identify appropriate sampling techniques. The critical questions are a) how much blood can be collected, and b) which sampling techniques are available.

JD: But what does this mean for practical purposes? How much blood can be withdrawn with minimal risk to children?

HS: Institutional review boards (IRBs) or ethical review committees tend to consider a single blood draw equivalent to 1-2% of the child's total blood volume as minimal risk. But one blood draw is generally not sufficient when running a clinical trial. Therefore, other experts define it as safe if the cumulative blood volume collected over an eight-week period does not exceed ten per cent of the child's total blood volume. Unfortunately literature about this item is not consistent.

JD: Can you give an example?

HS: Most publications recommend the total blood volume to be drawn in a 24-hour period to be below 3-5% of the total blood volume. This would mean approximately 10ml blood for a newborn child with an average weight of 3kg and a total blood volume of 270ml, or approximately 3ml in case of a premature baby with less than 1kg body weight and a total blood volume of up to 90ml.

JD: I guess the individual medical situation must be taken into account, too?

HS: Correct!

JD: Is there a way to avoid collecting blood from babies in the ml-range?

HS: An alternative sampling method to the conventional blood withdrawal is Dried Blood Spot (DBS; 2). DBS offers significant practical advantages over traditional sampling methods, as the samples are easy to obtain from finger, ear lobe or heel-prick. Suitable commercial sampling papers absorb the blood sample and distribute evenly through the paper to leave a spot of blood which is allowed to dry in situ. Using the DBS technology, typical sample size is approx. 15µl. Thus, this method could help to overcome the challenge of collecting multiple samples to perform pharmacokinetic and pharmacodynamic evaluations which are also required in paediatric studies. With its well-characterised advantage of low sample volume and the relatively non-invasive nature of the DBS sampling method could be ideally suited for this type of clinical trials.

Table1: Different age classes due to ICH Guidance E11

Paediatric Age Classes	
< 37th week of gestation	Premature baby
0 to 27 days	Neonates
28 days to 23 months	Baby and small child
2 to 11 years	Children
12 to 16-18	Teenager

JD: But with DBS a laboratory must use different analytical equipment.

HS: Absolutely. There are a number of techniques that can offer significant reductions in the volumes of biological fluids required for each analysis e.g. multiplexing techniques such as Luminex. This method not only reduces the sample volume required, but also improves the efficiency when compared to single analyte methods. This technique allows performing analysis of a large number of analytes on extremely small volumes of approximately 50µl per sample. Another assay using nanotechnology for quantitative assays of macromolecules is Gyrolab. Up to five assays can be run simultaneously on Gyrolab on the same sample. Sample size for this method is as little as 10µl.

JD: One side of the coin is collecting low blood volumes; the other side is to find a laboratory able to handle such minimal blood volumes.

HS: My words. This is of special interest, because most automatic analyzers have a so called "dead volume" which means that the vial which is inserted into the analyzer has to contain more fluid than actually needed for the determination itself. Therefore before planning a paediatric clinical trial an appropriate laboratory should be found which is able not only to run the methods needed, but also to show sufficient expertise in supporting paediatric studies and in handling microvolumes.

JD: Thank you very much, Hermann, for this brilliant insight.

References

1. *K. Neuer-Etscheidt, H. Schulz, "Clinical trials in children challenge central laboratories", Journal for Clinical Studies Vol. 3 Issue 1: 16-19, January 2011*
2. *ICH Guidance E11: "Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population" (CPMP/ICH/2711/99) http://www.ema.europa.eu/pdfs/human/ich/271199en.pdf*

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