Paediatric research and the regulation "better medicines for the children in Europe"

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The main driver in paediatric clinical research is ethics. All other and subsequent aspects will depend on keeping this obligation at the highest possible and acceptable level of quality. Indeed, research is necessary in children in order to improve their health whereas the past situation where such investigations were deemed not feasible or avoided at any price can no longer be considered ethical. Children have the right to benefit from the improvement in therapy and diagnostic tools whilst one knows nowadays that deriving doses and dosing schedules on rough methodologies (linear extrapolations based on body weight or surface) do not hold true but may expose them to risky or inefficient treatments. Children at various ages are exposed to different risk-benefit ratios. These variables can only be defined if a better knowledge of both the dangers and advantages of the drugs are assessed. One has also to recognize that such characteristics can be perceived differently across cultural backgrounds in Europe. These divergences should be smoothened or even erased on the basis of the principle of equality in the European Union indicating the need for further discussion aiming at achieving harmonization. We might still be far some such ideal goal but the next step (see article Altavilla) should strive to lead to European Ethical Recommendations, facilitating the work of researchers for the benefit of children as a whole.

Concomitantly, researchers should perform any effort to simplify studies performed in children by limiting sampling and related pain, by reducing the burden and psychological stress for the patients whilst probably increasing the sophistication of the methodologies used in these same investigations. Such approach implies to develop the methodological research, to be innovative in that field and test and validate such novel approaches continuously. It is obvious that children are not small adults, already but not only, because growth is not a linear variable. The role of population PK-PD modeling using non-linear mixed effect (see article Danhof et al) should be emphasized as a tool to confirm rational, patient tailored dosing schemes. Indeed absorption, distribution, metabolism and excretion of a medicinal product may all differ at variable degrees between adults and children confirming the need for PK data in these younger age groups. The task is even rendered more difficult due to the need to limit the blood sample volumes implying to develop validated techniques for micro-analyses. The development of a model means to develop first suitable methodology to create such constructs. These are per nature always "wrong" but useful: indeed if internally validated and externally confirmed (using similar sets of data found in the published literature or creating new datasets by splitting a sufficient initial sample size), such models need to demonstrate their reliability in prospective clinical trials. Whatsoever the exercise implies a proper design requiring its power calculation leading hopefully to a final validation. In case of positive outcome, one can further consider a future cross validation of the model in which

the parameters of influence defined in the PK-PD model (and these might not be age, gender, body weight or surface only but liver size, lung capacity or seated height for example) can be applied and evaluated in a similar drug belonging to the same class for instance, or sharing the same metabolism or mechanism of action.

In this latter context, the genetic background of the patient may play a role, sometimes important. Acknowledging that the genetic expression (phenotype) evidently starts to act from birth suggests that the fields of pharmaco-genetics/genomics should have pushed the interest of researchers in the paediatric age range first or in parallel with the adult investigations. This has obviously not been the case so far (see article Russo et al). Back again, in terms of PK-PD, the variability of drug response does not only happen to be a consequence of the genetic polymorphism but also of the maturation of the gene-related phenotype expression. So rather than observing the variability in exposures or responses, the identification and understanding of the genetic inheritance could contribute to predict part of the drug response and anticipate some individual potential toxicity. Although promising, this field has still to be explored and data available were so far underused with few exceptions only.

Similarly the standard use of double-blind randomized controlled trials (RCT) can be challenged in some circumstances. Whilst acknowledging their incomparable value to assess efficacy in ideal circumstances to limit bias or external influences, such design are often limited in terms of sample size and duration, particularly in children when the comparator is placebo hampering a sound safety assessment. Pharmaco-epidemiology is an option to fill the gap, bridging the contribution of each. Indeed whereas the RCT assess efficacy in stringent if not somewhat artificial conditions, effectiveness and long-term safety can be monitored in the field using a bunch of study designs: case reports or series mainly delivering signals, cross-sectional studies exploring links (not surely causality) between exposure and disease, retro/pro-spective cohort studies to estimate incidences rates, particularly of supposed risk(s), (nested) case control studies… (see article Verhamme et al). Clearly these approaches are not limited to children, on the contrary but are of high interest in their age group where both, overall exposure of a drug is low and incidence of (specific) adverse events often rarer than in adults. The extension of safety databases, the last and recent EU-legal provisions implemented during the last decade allow to expect that automated databases will produce within reasonable timelines more accurate and reliable data on the safe use of drugs in children. These databases are not only collected by Health Care providers but some also managed within the EU regulatory system. Their size is supposed to enable detecting rare events occurring after long periods of or after remote exposure. This is particularly important to generate signals and evidence in children or adolescents having been exposed to medicinal products during pregnancy or infancy. Currently the data-mining is underexploited and research projects insufficient. But one can expect that at the time when the information will be properly standardized, new tools to conduct research will emerge needing validation but opening probably the door to interesting perspectives, particularly in paediatric pharmaco-vigilance.

Indeed one could imagine following the expression of the gene profiles from birth on. Anyway blood sampling at a very young age is a challenge as exemplified by the reluctance from parents and families to let clinical trials be conducted in their newborn children even when being sick (see paper from Ligi et al). The specificities of neonatal

development linked to maturation (particularly in preterms) concern all organs but in particular in the current context those involve in drug handling :skin, lungs or digestive tract mainly for absorption, heart function, residual fetal circulation and fluid compartments for distribution, liver for metabolism and kidney and GI tract for elimination should be looked at differently than those exposed to toxicity like the brain and acoustic nerve or the immune system taking on top of this into consideration some intercurrent disease (sepsis, glucose instability…). Further readjustment of several components of multi-drug therapy takes place not only due to an ongoing maturation process but also following the evolution of the clinical condition, both being closely interrelated. The main issue is probably the experience of the investigator, of the team and of the institution as a whole being themselves closely supported by a safety monitoring board. Anyway major difficulties remain in terms of the heterogeneity of small samples and the need to call upon less classical statistical methods using active comparator in the design relying mostly on add on treatment compared head-to-head with standard of care.

One of the key issues relates to the fact that the standard of care is not always as standard as one could wish, leading to have to define strict endpoints requiring due to the rarity of the disease multicentre clinical trials to enroll a sufficient number of patients. However most of the common endpoints used in the design of trials have been validated in adults but rarely in children if ever in neonates.

One of the most tempting approaches in paediatric designs, namely the option to study different dosing in different combinations at variable time points adding interim analyses often using different endpoints still to be validated in (age) subgroups leads to the multiplicity interferences

In paediatric oncology it might be less often the case. Indeed the number of studies is limited as are their sizes. In any case hard endpoints like time-to-death are out of question to be achieved whereas cure rate remains the most relevant endpoint (see article Paolo Paolucci) whilst other parameters like quality of life are poorly explored. Similarly the long term monitoring of survival is currently not realistically attainable indicating the need to invest (e.g. creation of registries…) and improve in the field (e.g. coordinate research efforts …)

The overall preferences of regulators for the evaluation (new) medicinal products are well illustrated when grading usual outcome measures in the field of respiratory diseases. Objectives endpoints like lung function (FEV1, peak flow…) are considered the more robust markers of surrogacy followed by less preferred subjective measures like symptom scores or quality of life measurement. Health related outcomes like reduction in needs for drugs or for hospitalizations and better compliance to therapy are surely also considered well and supportive as long as of real clinical relevance for the patients and not targeting health economics only (see article de Benedictis et al). At the end it remains paramount to reconcile any surrogate endpoint (objective or subjective) with its clinical relevance to ascertain the use of meaningful and convincing outcome measures reflecting tangible benefit for the patients. Surprisingly the most common and severe respiratory diseases (asthma and cystic fibrosis respectively) still lack well accepted and robust surrogates to demonstrate in a workable manner beneficial long term effects for the former or the eradication of lung colonization for the latter.

The use of composite endpoints can represent a way trying to address problems unresolved so far. This approach has been successful in the field of paediatric rheumatic disease (see article Ruperto et al). The heterogeneity of the clinical manifestations and the development of a wide range of novel medicinal products suggest investigating the response to therapy (improvement, stabilization, remission…) as the most important if not the sole outcome measure. Using a strict methodology (collect first a set of candidate measures defined using the Delphi technique, gather large scale data for an evidence-based evaluation of the candidate measures, conduct a final validation out the best performers) different domains (physician's assessment of disease activity, parent's global assessment, quality of life) were identified as the useful components to construct the composite endpoint enriched by additional measures specific to each disease (JIA, SLE, dermatomyositis).
Addressing the field of subjective symptoms like pain, leads to major hurdles when entering the age-group devoid of any or recognizable verbal expression (see article Ceelie et al). To circumvent the difficulty, pain instrument in terms of scores were developed, validated and widely used in the postoperative pain evaluation. However in some instances (e.g. critically ill and intubated ICU patients, cognitive impaired subjects…), children cannot vocalize their suffering whilst pain should be assessed. Some new tools (e.g. skin conductance, hormonal stress markers…) can contribute and measure pain with more accuracy, helping also to understand better some wide inter-individual variations in response to treatment. But research in this sensitive field is still needed.

Ending with a fully subjective concept, namely "quality of life", the complexity of individual perception is increased by the multiplicity of the items involved and the value attached to them, differing from person to person, from culture to culture, from one social background to another…(see article of Trana). Nonetheless this dimension is important to capture in children because with advance in medical care children intent to survive more chronic and more disabling conditions. Further on, the child's own perception contributes to help parents and physicians in making decisions. In practice the burden of disease, the need for hospital admissions, the intrusive procedures and the psychological uncertainties linked to whether threatening conditions and survival or shortened life expectancy, all impact childhood development. In such circumstances the inclusion of quality of life measurements contributes to compare interventions and outcomes in studies. Still measuring it properly remains a challenge but currently profile scoring systems seem preferable to indexes or total scores. These should be appropriate to the disease concerned and often fine-tuned according to the disease stage (e.g. muscular disorders).

This supplement of the Journal is a valid contribution to a number of issues resurgent from, and actualized by the recent paediatric regulation. The need to update the methodology used to conduct clinical trials in children and the importance to define validated endpoints as part of this exercise are exemplified in the different articles. Let us hope that researchers supported by industry will take up the challenge.