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# Promoting and developing clinical research with newborns, infants, children and adolescents

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As obvious as it may seem, it is necessary to promote and perform clinical research with the youngest of the children, i.e. newborns and infants. Due to misguided intention of protection through exclusion, the most vulnerable groups (newborns) or the most complex (pregnant women), are not included in clinical trials or studies, or are included much later than young adult males and non-pregnant women.

**Why involve them in research?** Newborns and infants must benefit from medical progress resulting from research. To diagnose, treat or prevent diseases, we must generate scientific data and increase our knowledge about medical or psychological conditions of those newborns and infants, and of their management. Current plans of mandatory paediatric medicines development take many years (decades) and are only too often discontinued before the youngest are included, for reasons of patent expiry, costs and alleged risks of liability.

When they are included last according to paediatric investigation plans, as is still the case to date, newborns and infants are left for years without treatment appropriate for them, and exposed to off-label prescriptions that are not based on demonstrated efficacy and safety. Major physiological differences most often do not allow us to extrapolate data from adults or older children. Many of the newborns and infants' conditions or diseases are specific to them and cannot be studied in adults or even older children. Some conditions, particularly of genetic origin, can manifest themselves before birth and may even require in utero treatments to prevent further degenerative damage. In addition, there is the need for studies of adverse effects or sequelae, in terms of toxicity or chronic burden, from treatments these children may have received. Such sequelae can be specific of the age groups, can be revealed late, must be treated and, if possible, prevented.

Newborns and infants are vulnerable and cannot assent (even less so consent) and should be protected while included in research programmes. The answer to the need for protection is an ethical framework.

To treat children better with effective and safe products, to detect and prevent their diseases and anticipate adverse effects of treatments, there is the need for well managed research and it has been shown that children are safer in clinical trials than when receiving off-label prescriptions.

Conditions to ensure ethical research with the youngest children, as well as with older children and their parents (in legal terms the 'legal representatives', hereafter parents) are both general and specific:

Research must be scientifically justified to be ethical, with a clear and robust rationale, but this is not enough. The main ethics principles must be respected:

- **Autonomy**: requiring informed consent by the parents, supported by prior exchange with the investigators, and at best after a protocol review by parents' associations or concerned parents.
- **Benevolence**: the research objective must be to improve the children's condition; expected progress or benefice due to the research; ensuring confidentiality and respect for cultural differences.
- **Non-malfeasance**: systematic analysis, prevention and minimisation of risks and constraints by measures identified beforehand for predictable risks; setting of a Safety Monitoring Board, stopping rules for unexpected serious risks; equipoise (for ex. no loss of chance for participants by denying them an effective treatment); refusal of pointless research.
- **Distributive justice**: which requires that certain groups are not systematically left out of research (for reasons of age, social or genetic determinants, rare or combined conditions), or conversely over-exploited (chronic diseases).

More specifically in the case of newborns and infants, the research protocols must include ethical protections such as:

- Positive opinion of an ethics committee with paediatric expertise (i.e. by Comité de Protection des Personnes in France)
- Explicit justification for the research scientific objectives and value
- Review of existing data to avoid useless repeats (without ignoring the need for scientific verification)
- Appropriate design of the trial to be able to answer the research question
- Sample size calculation so that results are interpretable, with use of statistical methods appropriate to small samples or rare diseases
- Pharmacokinetic studies with minimal number of sampling, and justification of the sampled blood or CSF volumes
- Need for a Safety Monitoring Board
- Reducing the duration of separating the child from their family and parents
- Effective prevention and management of distress, suffering and pain of children
- Respect for increasing autonomy and psychological maturity

The main objective differences with trials or studies involving newborns and infants can be anticipated.

The differences exist between newborns and infants, and between these two groups and older children, adolescents and adults, and is not limited to weight and height differences:

- Physiological differences including biological differences (for ex. immaturity, slowly changes towards maturity, blood-brain barrier)
- Pharmacodynamic differences (for ex. gut absorption), and pharmacokinetic differences (for ex. distribution volume, kidney function) which are not necessarily height or weight proportional
- Other elements to be considered, for ex. full dependence of newborns and infants for their basic needs, exclusive initial milk-based feeding, metabolic vulnerability (for ex. risk of hypoglycaemia), etc.

Existing non-clinical, animal or in silico data, or data from other age groups should be used to inform research protocols:

- Safety data to identify target organs
- Modelling and simulation data for pharmacodynamics or pharmacokinetics ; dose calculations
- *In silico, in vitro* et *in vivo* activity and safety data;
- Data from models, from other studies or systematic reviews for similar approaches or products.

But in no case should the absence of pre-existing data be an excuse for excluding newborns and infants.

At the end of the research, research results must be published systematically, including in cases of inefficacy or small samples, and for medicines the corresponding product information must be updated regularly.

There are many research priorities, which cannot be all listed here. However, there are clear and urgent priorities to improve the health and well-being of newborns and infants who have been neglected for too long. Those urgent priorities include paediatric cancers, genetic, metabolic and degenerative neurologic diseases, the conditions linked to physical and psychological immaturity, and those relating to dependence (abandoned children or victims of violence).

Older children, including adolescents, also deserve the benefits of medical progress through research. For the same ethical reasons as mentioned above, studying different children's age groups is necessary, when extrapolating data from adults cannot be justified. However, common therapeutic targets can and must be taken into consideration in diseases of adults and children, even if they bear different names or symptoms. Paediatric development should be then based on this common target independently of the child's age.

- There is no justification nor physiological basis to exclude from trials participants aged less than 18 years when affected by the same disease as adults. Very often minors aged 16, 14 or even 12 can be included while there are many examples of similar kinetic and safety profiles between adults and adolescents. In that case, access to the

trials, including early ones, should not be prevented unless there is a scientific justification.

- While admittedly adolescents are not followed by the same carers in the same centres, it is possible to study adolescents like adults, using similar endpoints and tests, and often similar doses, while ensuring that the paediatric investigators are trained, that the investigation sites, parents' information and consent forms as well as assent forms for adolescents are appropriate and recognise the right for adolescents to refuse participation.

This does not exclude the need for specific trials with adolescents, for example related to puberty or sexual or psychological maturation, or any conditions limited to that age group. Adolescents request to be actively involved in research and consulted when drafting the protocol. Investigators must combine respect for growing autonomy, for privacy and access to education, while recognising their often-hidden fragility or vulnerability. They must be informed about the treatment, and about confidentiality of their personal data. In addition, there should be the possibility for discussions with investigators, with and without the parents, taking into consideration the fact that they are still minors. Contraception is required for many studies, and private discussions between male or female adolescents and the investigators should be planned.

Finally, research with children who are neither newborns or infants nor adolescents (those between 3 and 10 years old) is necessary and well justified from the ethical perspective. Information should take into consideration the fact the youngest cannot read. Protocols should be designed for this age group as endpoints will be different, doses will have to be established based on weight or body surface area, and safety and management of the trial require trained personnel and dedicated premises. Here again prior consultation of parents' associations and of the young patients regarding the protocol is highly recommended.

*Children whichever their age cannot wait any longer!*