Clinical trials in newborns

What is a clinical trial?	A clinical trial is an interventional research study in humans. Clinical trials aim to find out if a new treatment is effective and safe e.g. how well a drug, therapy, diet or technology works. The participants are usually put into different groups and can either receive the new treatment or a placebo/standard treatment.

Frequently used terms concerning clinical trials[1]

Investigators	The people carrying out the clinical trial. This may include doctors, nurses, research coordinators, social workers, and other healthcare professionals. Each clinical trial is led by a principal investigator, who is often a medical doctor.
Blinding or masking	This means that neither the participants nor the investigators of a clinical trial know who will get the treatment and who will get the placebo (see below)/standard treatment until the end of the clinical trial.
Intervention group	A group of people who receive the intervention e.g. medication or a new procedure.
Control group	A group of people who are used for comparing with another group (intervention group) in an experiment/clinical trial. They receive standard treatment or a placebo.
Placebo	A substance or treatment that has no therapeutic value, i.e. not medicine, usually given in a control group to compare the effect observed in this group with the effect observed in the group that receive the drug/treatment.
Informed consent	A process where the participants or their parents/caregivers agree to take part in a clinical trial. The participants and/or parents/caregivers are required to read through a document called an informed consent form which includes the most important information on the clinical trial. This process also includes an oral exchange with the investigator which offers the possibility to ask and clarify questions or concerns.
Interventional study	Another name for a clinical trial.
Participants	Volunteers who participate (enrol) in a clinical trial.
Protocol	Detailed plan of the clinical trial. It describes how the trial will be conducted.
"Off-label" drug usage	Use of a medicine in a way that has not (yet) been approved by regulatory authorities for a specific age group, dosage or how it is given e.g. as an injection or orally.
Observational study	A study where investigators observe the effect of a risk factor, diagnostic test or treatment without intervening. Groups are created based on the existence of a health problem e.g. high blood pressure or obesity.
Randomisation	A way to decide what treatment each person in a clinical trial gets so that there is less chance of bias, e.g. the personal preference of an investigator. It is comparable to flipping a coin or rolling a dice which leads to results which are by chance, not by choice.

Background

Newborn babies and in particular those born preterm are a unique, fragile and vulnerable group. Despite their special needs and demands in care and treatment, up to 90% of drugs used in term born and preterm born babies are used *off-label*, due to a historical reluctance to conduct clinical studies in this group.[2] Therefore, the use of a specific medication sometimes comes with the risk of an unknown optimal dosage, unexpected side effects or a lack of positive impact on the condition or disease. Over the last few years there has been a shift in how clinical trials in newborn babies are viewed by the medical community. Now, these studies are seen as an ethical requirement to ensure suitability and an effective treatment.[3]

What are the aims of trials in newborn babies?

- Treatment tailored to newborns e.g. considering week of pregnancy at birth, risk factors, accompanying illnesses
- Better outcomes of treatment
- Fewer side effects of medication
- Reducing usage of *off-label* medication
- Addressing unknown/unmet medicals needs in newborns

Why can trials in newborns be viewed negatively?

Newborn babies are a unique population with specific ethical and clinical concerns.[4] Trials in newborns can be ethically complicated since the *participants* themselves are not able to give consent. Instead, their parents or caregivers have to make the decision whether to take part in a trial or not - which comes at a particularly difficult and vulnerable time due to the stress of a baby being born sick and/or early. Some trials start directly after birth and decisions have to be made very quickly at a time when parents may be exhausted following the delivery. Added to this is the fact that it can be difficult for adults to accurately interpret or pick up on infant pain and stress cues. Finally, follow-up of an intervention from a clinical trial is often lacking which means that long-term effects of an intervention are difficult to assess.

How can these challenges be addressed?

Early and frequent involvement of parents/caregivers from the very beginning of any planned trial is essential. This means involvement in defining the precise aim(s) of the clinical trial, development of the trial *protocol*, input into developing materials to obtain *informed consent* and then for recruiting patients, definition of results and follow-up. For the study *participants* and their families, there are two key points which merit particular attention and can affect both the short- and long-term success of a clinical trial.
Some recommendations on these points are given below:

1. Informed Consent

- Provision of timely and easily understandable information in a calm environment (Parent and Patient Information Summary of the clinical trial, explanatory videos, links to further information etc.)
- The doctor or other healthcare professional in charge of the child should inform parents about the trial and a trusting, empathetic relationship should be ensured[5]
- Clear discussion of the risks/benefits of the trial with adequate opportunities for the parents/caregivers to ask questions
- Both parents should agree and sign the informed consent form[5]
- Continuous consent process: parents/caregivers' consent is re-affirmed at several time points during the trial (due to the usually initial short window for recruitment in newborn trials)[6]

It is important to note that participation in a clinical trial is always voluntary and a decision not to participate and/or dropping out of an ongoing trial does not come with any negative consequences on the standard of care for the participants.

2. Follow – Up

Historically, follow-up of newborn clinical trials and preterm born children generally over a long period of time has been challenging due to several factors. These include the need for systematic data collection, standardised *protocols* and loss of contact with patients and/or their families. Despite this, many parents or caregivers share positive experiences after their child took part in a trial.[7] Currently, in the field of neonatal research, steps are being taken to address these challenges through various studies and the development of new tools.

The following are examples of follow-up:

- RECAP project: web-based platform bringing together data from more than 20 observational studies that enrolled very preterm babies at birth and follows them into adulthood:
  https://www.efcni.org/wp-content/uploads/2018/03/2017_04_24_EFCNI_RECAP_FLYER_web.pdf
- PARCA-R: free screening questionnaire which assesses children's cognitive and language development at 24 months of age:
  https://le.ac.uk/parca-r

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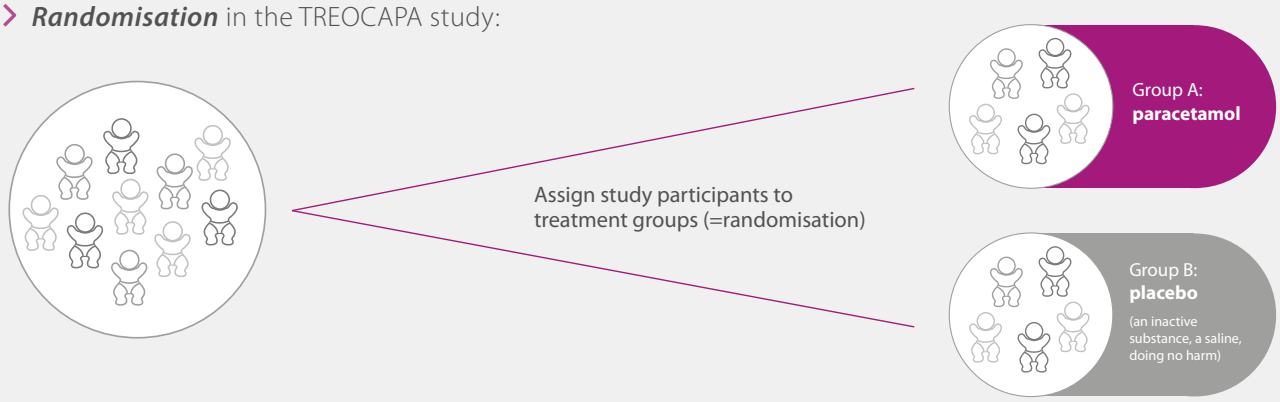
"Until I became a parent to a medically fragile premature baby, I never considered participating in a clinical trial. The opportunity to change another family's experience of premature birth and knowing that my daughter's premature birth experience could advance knowledge and treatments for premature infants in the future was the driving factor that motivated me to consent to participating."

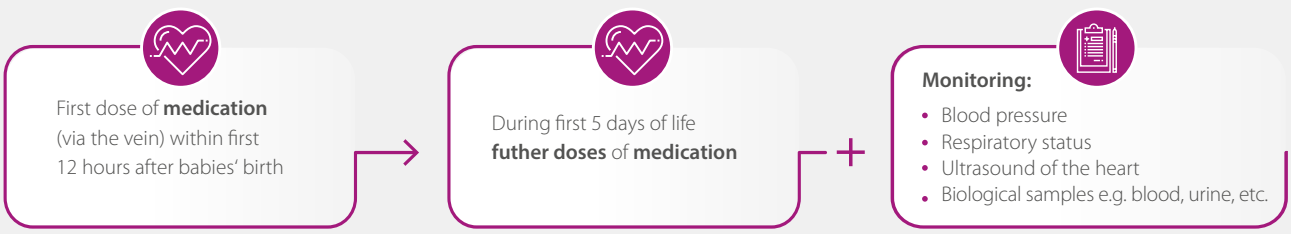
The TREOCAPA study - An example of a clinical trial in preterm born babies

TREOCAPA is a European clinical trial which is done in more than 40 hospitals in a dozen countries. The trial aims to find out more about the preventive use of paracetamol in preterm born babies during the first five days of life. The aim is to find out if the use of paracetamol is safe and effective at closing the *ductus arteriosus* – a blood vessel that bypasses the lungs during life in the womb before birth, but which normally closes shortly after delivery. In preterm babies, this blood vessel sometimes does not close without medical or surgical intervention. Babies participating in this clinical trial are *randomised* to one of two treatment groups so that it is possible to see if the study medication (paracetamol) has the effect that the study investigators think it will have. Randomisation means that some babies receive the study medication and some receive a *placebo*. The process is based on chance and is not influenced by the parents/caregiver, the researchers or doctors.

› ***Randomisation*** in the TREOCAPA study:



› Next steps after ***Randomisation*:**



How is the voice of parents/families included within TREOCAPA?

EFCNI is the Public and Patient Involvement (PPI) partner in the TREOCAPA clinical trial, ensuring that the public, patients and parents/caregivers are involved throughout all phases of the trial. EFCNI reviews and creates understandable information materials (informed consent form, patient information summary, etc.), provides input into follow-up and raises awareness of the clinical trial. The foundation coordinates and manages a Parent Advisory Board (PAB) consisting of parent representatives who give input to the project, e.g. review of patient information materials. Further information on involving parent representatives in neonatal research can be found here: **http://www.efcni.org/wp-content/uploads/2021/06/Involvement-of-parent-representatives-in-neonatal-research.pdf**

EFCNI's main goal is to make sure the aspects important to parents are included in the clinical trial and that parents feel informed and supported throughout the whole trial.

Further information on TREOCAPA: **https://treocapa.inserm.fr**

Where to find further information on clinical trials in newborn babies?

- World Health Organization: **www.who.int/clinical-trials-registry-platform/clinical-trials-in-children**
- Children & Clinical Studies: **www.childrenandclinicalstudies.org**

What ongoing clinical trials might my child be eligible for?

- The European Medicines Agency provides a platform where trials taking place in Europe are listed: **www.clinicaltrialsregister.eu/ctr-search/search**

References:

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Images: Shutterstock /Andrey Zhernovoy

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About EFCNI

The European Foundation for the Care of Newborn Infants (EFCNI) is the first pan-European organisation and network to represent the interests of preterm and newborn infants and their families. It brings together parents, healthcare experts from different disciplines, and scientists with the common goal of improving long-term health of preterm and newborn children. EFCNI's visionis to ensure the best start in life for every baby.

For more information, visit us at: **www.efcni.org**

EFCNI european foundation for the care of newborn infants