
## Paediatric Clinical Research Infrastructure Network

# Procedures for the setup of neonatal trials

# Enrolment into neonatal trials:
# Points to consider during protocol development

V 1.0, 22 March 2021

| | |
|---|---|
| **Description** | This tool provides a list of points to consider during protocol development for improving the enrolment of neonatal trials |
| **Key words** | Neonatal trial, Protocol development, Guidance document, Tool |

**Authors**: Beate Aurich, Eric Vermeulen, Valéry Elie, Naura Mahmoudi, Evelyne Jacqz-Aigrain

Inserm

**Disclaimer:** **Sponsors and researchers unfamiliar with clinical trials in neonates and/or neonatology are advised to seek expert advice due the complexity of neonatology.**

**Correspondence email**: pedcrin@ecrin.org

PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

## Improving the enrolment of neonates into trials

Enrolment in neonatal trials is influenced by a variety of factors including protocol design, parental consent and support by health care professionals.[1,2]

Awareness of how the design of various protocol sections may modify the number of enrolled neonates may help improving recruitment.[3] Effective and repeated communication about the trial in the community may for example support the identification of eligible patients and give future parents time to reflect on the possibility to be approached for the inclusion of their child into a clinical trial.[4-7] Research suggests that most parents prefer to have an initial discussion about the trial inclusion prior to birth.[7] Furthermore, understanding the factors that may influence parental decision making may help improving the number of parents consenting.[8] Parent and patient organisations will provide valuable input into the acceptability of the study design, the practicalities of study procedures and the design of the informed consent form.[9] Obtaining endorsement of a study by a local or national patient organisation may further help with recruitment.[9] Finally, HCPs at planned trial sites may be reluctant to identify patients for a variety of reasons and open discussions about the trial may help anticipate and address these challenges.[8,10] Trial planning should include the provision of sufficient resources to support the conduct of the trial.[11] The Table 1 below lists examples of points to consider during protocol development for improving enrolment in neonatal trials.

Involving parents in neonatal studies has been shown to improve the quality of trial protocols, increase recruitment numbers and reduce costs.[12-13,14,15] Parents will provide valuable input on a variety of topics such as the protocol, study procedures, trial design, follow up, informed consent and outcome assessment.[14,16] It is therefore advisable to consult parent organisations during protocol development.[17] Successful collaboration with parent organisations will depend, for example, on careful planning, and effective communication with all stakeholders.[14,16] For multinational research input should be sought from parents in each participating country. It is important to ensure the expectations of parents with such an initiative are understood, that the role of parents is defined and study results are shared with parents.[16] Table 2 provides examples of parent/patient organisations.

**Competing interests**

All authors consider not having any competing interests for this tool. BA has worked for GlaxoSmithKline between October 2006 and September 2009 and holds company shares. Between October 2009 and May 2015 she has worked for Novartis.



PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

## References


1. DeMauro SB, Cairnie J, D'Ilario J, Kirpalani H, Schmidt B. Honesty, trust, and respect during consent discussions in neonatal clinical trials. Pediatrics. 2014 Jul;134(1):e1-3. doi: 10.1542/peds.2013-3720.
2. Watterberg KL, Fernandez E, Walsh MC, Truog WE, Stoll BJ, Sokol GM, et al. Barriers to enrollment in a randomized controlled trial of hydrocortisone for cardiovascular insufficiency in term and late preterm newborn infants. J Perinatol. 2017 Nov;37(11):1220-1223. doi: 10.1038/jp.2017.131.
3. Huang GD, Bull J, Johnston McKee K, Mahon E, Harper B, Roberts JN et al. Clinical trials recruitment planning: A proposed framework from the Clinical Trials Transformation Initiative. Contemp Clin Trials. 2018 Mar;66:74-79. doi: 10.1016/j.cct.2018.01.003.
4. Ahmed SM, Palermo AG. Community engagement in research: frameworks for education and peer review. Am J Public Health. 2010 Aug;100(8):1380-7. doi: 10.2105/AJPH.2009.178137.
5. Condon DL, Beck D, Kenworthy-Heinige T, Bratcher K, O'Leary M, Asghar A, et al. A cross-cutting approach to enhancing clinical trial site success: The Department of Veterans Affairs' Network of Dedicated Enrollment Sites (NODES) model. Contemp Clin Trials Commun. 2017 Mar 29;6:78-84. doi: 10.1016/j.conctc.2017.03.006. eCollection 2017 Jun.
6. Robinson ET, Baron D, Heise LL, Moffett J, Harlan SV. Communications handbook for clinical trials: strategies, tips, and tools to manage controversy, convey your message, and disseminate results, 2011. URL: https://www.fhi360.org/sites/default/files/ media/documents/Commhandbk_full_ 052314.pdf
7. McCarthy KN, Ryan NC, O'Shea DT, Doran K, Greene R, Livingstone V, et al. Parental opinion of consent in neonatal research. Arch Dis Child Fetal Neonatal Ed. 2019 Jul;104(4):F409-F414. doi: 10.1136/archdischild-2018-315289.
8. Hoberman A, Shaikh N, Bhatnagar S, Haralam MA, Kearney DH, Colborn DK, et al. Factors that influence parental decisions to participate in clinical research: consenters vs nonconsenters. JAMA Pediatr. 2013 Jun;167(6):561-6. doi: 10.1001/jamapediatrics.2013.1050.
9. Vermeulen E, Karsenberg K, van der Lee JH, de Wildt SN. Involve Children and Parents in Clinical Studies. Clin Transl Sci. 2019 Oct 24. doi: 10.1111/cts.12696.
10. Phelps EE, Tutton E, Griffin X, Baird J; TrAFFix study co-applicants. Facilitating trial recruitment: A qualitative study of patient and staff experiences of an orthopaedic trauma trial. Trials. 2019 Aug 9;20(1):492. doi: 10.1186/s13063-019-3597-8.
11. Briel M, Elger B, von Elm E, Satalkar P. Insufficient recruitment and premature discontinuation of clinical trials in Switzerland: qualitative study with trialists and other stakeholders. Swiss Med Wkly. 2017 Nov 16;147:w14556. doi: 10.4414/smw.2017.14556. eCollection 2017.
12. Boote J, Julious S, Horspool M, Elphick H, Smithson WH, Norman P. PPI in the PLEASANT trial: involving children with asthma and their parents in designing an intervention for a randomised controlled trial based within primary care. Prim Health Care Res Dev. 2016 Nov;17(6):536-548.
13. Harvey M, Nongena P, Edwards D, Redshaw M. We knew it was a totally at random thing': parents' experiences of being part of a neonatal trial. Trials. 2017 Aug 1;18(1):361. doi: 10.1186/s13063-017-2112-3.
14. INVOLVE. Briefing notes for researchers: involving the public in NHS, public health and social care research. 2012; INVOLVE, Eastleigh. Available at: https://www.invo.org.uk/wp-content/uploads/2014/11/9938_INVOLVE_Briefing_Notes_WEB.pdf
15. Standards Partnership Development Group (SPDG). National Standards for Public Involvement in Research V1. London, March 2018. Available at:https://www.invo.org.uk/wp-content/uploads/2018/06/Public_Involvement_Standards_v1.pdf
16. Health Research Authority (HRA); INVOLVE. Impact of public involvement on ethical aspects of research. Southampton, 2016. Available at: www.invo.org.uk/posttypepublication/public-involvement-in-researchimpact-on-ethical-aspects-of-research
17. European Foundation for the Care of Newborn Infants (EFCNI). Position paper: Involvement of parent representatives in neonatal research, 2018. Available at: https://www.efcni.org/wp-content/uploads/2018/04/2017_10_26_Parents_In_ Research_web.pdf




PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

**Table 1. PedCRIN Tool: Enrolment into neonatal trials: Points to consider during protocol development**

| Protocol section | Comment | Comment/ rationale | Reference |
|---|---|---|---|
| **Background** | The data presented in this section should support the rationale that the trial is the best way forward to improve the treatment of neonates and that the benefit-risk balance is favourable | Lacking equipoise may reduce the support from health care professionals to include patients | 1,2 |
| | All relevant data on risks for all trial interventions (active and control arm) should be presented | Non-disclosure of risks, including those of the comparator arm may reduce the support from health care professionals and the community to include patients | 3 |
| **Objectives** | Avoid overlap between risk factors for outcome (as an objective) and exclusion criteria | Recruitment may be reduced, if for example the primary objective is neurodevelopmental outcome in a population of neonates with a high incidence of risk factors for neurodevelopmental impairment and the exclusion criteria require the exclusion of all neonates with such risk factors | 4 |
| **Inclusion criteria** | Broad enough to recruit sufficient patients<br>Specific enough to answer the primary objective(s) | Inclusion criteria which are too broad may not provide sufficient data to answer the primary objectives because the neonatal population is very heterogeneous | 5 |
| **Trial procedures** | Parents are concerned about pain and distress caused by trial related procedures | Pain and distress related to trial procedures should be kept to an absolute minimum | 6 |
| | The burden of trial procedures including follow up visits is important for families | Aim to use existing data and procedures where possible and harmonise follow-up with local routine follow-up appointments | 7 |
| **Consent** | Consider reassessing consent | If it is unclear whether the voluntariness of consent may have been compromised, the quality of consent might be improved by seeking continuous consent | 8 |
| | Consent procedures should be adapted to the disease being studied | Different consent procedures can be used to suit the disease being studied | 9,10 |
| | The informed consent form should be written in plain language | Using plain language will facilitate understanding | 11,12 |
| | Consent should be sought in the native language of parents | Understanding will be improved using each parent's native language | 13,14 |



PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

**References**


1. **DeMauro, et al.** Honesty, trust, and respect during consent discussions in neonatal clinical trials. Pediatrics. 2014 Jul;134(1):e1-3.
2. **Gill D.** Ethics Working Group of the Confederation of European Specialists in Paediatrics. Ethical principles and operational guidelines for good clinical practice in paediatric research. Recommendations of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). Eur J Pediatr. 2004 Feb;163(2):53-7.
3. **McCarthy M.** US researchers failed to disclose risks of newborn study, finds government office. BMJ. 2013 Apr 12;346:f2367.
4. **Watterberg, et al.** Barriers to enrollment in a randomized controlled trial of hydrocortisone for cardiovascular insufficiency in term and late preterm newborn infants. J Perinatol. 2017 Nov;37(11):1220-1223.
5. **Huang GD, et al.** Clinical trials recruitment planning: A proposed framework from the Clinical Trials Transformation Initiative. Contemp Clin Trials. 2018 Mar;66:74-79.
6. **Franck LS et al.** Parental concern and distress about infant pain. Arch Dis Child Fetal Neonatal Ed. 2004 Jan;89(1):F71-5.
7. **European Commission.** Ethical considerations for clinical trials on medicinal products conducted with minors. Revision 1, 18 September 2017. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_09_18_ethical_consid_ct_with_minors.pdf
8. **Allmark, et al.** Improving the quality of consent to randomised controlled trials by using continuous consent and clinician training in the consent process. J Med Ethics. 2006 Aug;32(8):439-43.
9. **Jansen-van der Weide MC,** et al. Clinical Trial Decisions in Difficult Circumstances: Parental Consent Under Time Pressure. Pediatrics. 2015 Oct;136(4):e983-92.
10. **Shah AR, et al.** Informed consent for a neonatal clinical trial: parental experiences and perspectives. J Perinatol. 2018 Jul;38(7):865-872.
11. **Wang LW, et al.** Assessing readability formula differences with written health information materials: application, results, and recommendations. Res Social Adm Pharm. 2013;9(5), 503–516.
12. **Ridpath JR, et al.** PRISM Readability Toolkit. 3rd ed. Seattle: Kaiser Permanente Washington Health Research Institute; 2007. URL: https://www.kpwashingtonresearch.org/application/files/6415/5500/0956/PRISM_readability_toolkit.pdf
13. **Neyro V, et al.** Clinical trials in neonates: How to optimise informed consent and decision making? A European Delphi survey of parent representatives and clinicians. PLoS One. 2018 Jun 13;13(6):e0198097.
14. **European Commission (EC).** Ethical considerations for clinical trials on medicinal products conducted with minors - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, Revision 1, 18 September 2017. URL: https://ec.europa.eu/health/sites/health/files/files/ eudralex/vol-10/2017_09_18_ethical_consid_ct_with_minors.pdf




PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

**Table 2. PedCRIN Tool : Examples of parent/ patient organisations**

| Organisation | Website |
|---|---|
| BLISS<br>for babies born to soon or sick | http://www.bliss.org.uk/ |
| ECHDO<br>European Congenital Heart Disease Organisation | http://www.echdo.eu/ |
| ECO<br>European Cleft Association | http://europeancleft.org/ |
| EFCNI<br>European Foundation for the care of newborn infants | http://www.efcni.org/ |
| EPF<br>European Patients Forum | http://www.eu-patient.eu/ |
| IF<br>International Federation for Spina Bifida and Hydrocephalus | https://www.ifglobal.org/ |
| IPOPI<br>International Patient Organisation for Primary Immunodeficiencies | https://ipopi.org/ |
| EURORDIS<br>European Organisation for Rare Diseases | https://www.eurordis.org/ |



PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046