


Informed consent for neonatal trials: practical points to consider and a check list

Beate Aurich ,¹ Eric Vermeulen,² Valéry Elie,¹ Mariette H E Driessens,² Christine Kubiak,³ Donato Bonifazi,^{4,5} Evelyne Jacqz-Aigrain^{6,7}

To cite: Aurich B, Vermeulen E, Elie V, *et al*. Informed consent for neonatal trials: practical points to consider and a check list. *BMJ Paediatrics Open* 2020;**4**:e000847. doi:10.1136/bmjpo-2020-000847

► Additional material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjpo-2020-000847>).

Received 20 August 2020
Revised 23 November 2020
Accepted 29 November 2020

ABSTRACT

Obtaining informed consent from parents of critically ill neonates can be challenging. The parental decision-making process is influenced by the severity of the child's condition, the benefit–risk balance, their emotional state and the quality of the relationship with the clinical team. Independent of local legislation, parents may prefer that consent is sought from both. Misconceptions about the absence of risks or unrealistic expectations about benefits should be openly addressed to avoid misunderstandings which may harm the relationship with the clinical team. Continuous consent can be sought where it is unclear whether the free choice of parental consent has been compromised. Obtaining informed consent is a dynamic process building on trusting relationships. It should include open and honest discussions about benefits and risks. Investigators may benefit from training in effective communication. Finally, involving parents in neonatal research including the development of the informed consent form and the process of obtaining consent should be considered standard practice.

BACKGROUND

Children, including neonates, have long been excluded from clinical research due to ethical and practical challenges.¹ This has led to a situation where up to 90% of newborn babies admitted to neonatal intensive care units (NICUs) are treated at least once with off-label or unlicensed medicines.^{2–4} This is associated with a higher risk of lack of efficacy, serious adverse drug reactions and medication errors.^{5–7}

In 2007, the European Paediatric Regulation governing the development and authorisation of medicines for children, came into force.^{8,9} In addition, the European Commission is financing various European projects for the development of a paediatric research infrastructure.¹⁰ In this context, the Paediatric Clinical Research Infrastructure Network (PedCRIN), a 4-year project, was initiated in January 2017.¹¹ During the PedCRIN project the expertise of the European Clinical Research Infrastructure Network and the European Paediatric Clinical Trial Research

Key messages

- Key factors influencing parental consent decisions are summarised.
- A checklist of points to consider when talking to parents about the possible inclusion of a neonate into a clinical trial has been built.
- The checklist may help researchers to optimise the setting for seeking parental consent.

Infrastructure was combined with the aim of developing points to consider documents (so-called ‘Tools’) for researchers to support the setup and management of non-commercial clinical trials in children.¹¹

The aim of this article is to summarise the key points researchers may want to consider when preparing for the informed consent discussion for a neonatal trial.

SURVEY

At the beginning of the PedCRIN project, in 2017, an online survey was conducted (4 April to 15 May 2017) among 663 researchers involved in European and international paediatric research networks (eg, ESDPPP, GRiP, INC, ENCePP).¹² The objective was to understand what the needs of the research community are with regards to clinical trials in children. The response rate was 22.2%. Using a Likert scale of 0 (not needed) to 4 (extremely needed) the survey grouped topics previously identified into six large themes and researchers had the possibility to add a free-text comment.^{12,13} Based on the results of this survey, a series of neonatal topics were developed with the aim of responding to these questions and developing a set of practical tools for researchers.¹⁴ The survey questions are provided in online supplemental table 1 and the results are summarised in online supplemental material figure S1.¹²



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Beate Aurich; beate.aurich@gmx.fr

**Table 1** Check list of points to consider when talking to parents about the possible inclusion of a neonate into a clinical trial

Points to consider during informed consent process	Done	Delayed	Not applicable	Comments
Informed consent setting				
Consider approaching parents prior to delivery. ³³	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Both parents should be present. ¹⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Both parents should be asked for consent. ¹⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Offer the possibility to have the responsible nurse and/or doctor, trusted friend and/or family member or a parent from an NICU association joining the conversation. ⁴⁹	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Introduce the investigator/HCP who will be seeking consent during routine contacts with the parents. ^{45 46}	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Ensure parents are comfortable and trust the investigator/HCP seeking consent. ⁴⁹	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
In multinational trials local beliefs, customs and traditions should be taken into consideration. ⁵⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Consent information				
Information needs to be clear and well structured. ^{58 59}	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Information should be provided in the parent's native language. ¹⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pause for questions—do not rush. ²⁸	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Provide written information where parents can find additional, independent information and NICU parent organisations. ⁴⁸	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Reassure that their decision to participate or not will not change the level of care. ⁵²	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Clarify that parents can always change their mind and that this does not have any consequences for the routine treatment of their child. ⁵²	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Be prepared to re-explain and re-consent. ^{49 66}	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Adapt communication to what the parents can take in at the time. ^{23 67}	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If parents are struggling with the decision-making process, acknowledge that it is difficult. ^{49 52}	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If parents are anxious provide more support and ask how you can help them, reassure them that they should take their time to decide. ^{49 52}	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Benefits of study treatment				
Do not exaggerate benefits. ⁴⁹	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Explain how the study will benefit the child. ⁵²	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Explain how the study will benefit neonates with the same condition. ⁵²	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Risks of study treatment				
Be upfront about potential risks of the study treatment and the comparator. ^{48 49}	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Explain how study related risks will be minimised. ⁵²	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Address concerns about pain and discomfort proactively. ⁶⁸	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Study procedures				
Explain whether and how the study will interfere with routine clinical care. ⁵²	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Be clear about additional procedures and follow-up—other than what is normally done. ⁶³	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Explain how additional follow-up (other than routine) will be organised and address any questions about reimbursement of costs for transport and additional child care. ⁶³	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

HCP, healthcare professional; NICU, neonatal intensive care unit.

One of the topics highlighted by the survey concerned the informed consent process and one of the free-text comments suggested the development of 'Strategies to improve the enrolment in clinical trial'.¹² The challenges surrounding neonatal consent have previously been

highlighted by a Delphi survey.¹⁵ Neyro *et al* reported that parents and healthcare professionals agreed on 58 items to be included in the informed consent information.¹⁵

In February 2019 a narrative review of the literature was conducted in PubMed and of regulatory guidance

documents issued by the European Medicines Agency. Reviewing the literature, no single publication was identified providing a check list for investigators on the practical points to consider when preparing for the informed consent discussion with parents.

Team discussions including representatives from a patient organisation (EV and MHED), a neonatologist and paediatric pharmacologist (EJA), a paediatrician (BA) and a project leader of paediatric clinical research (VE) were held and the following question was formulated for the development of a neonatal tool:

- ▶ What are some of the practical points to consider during informed consent discussions with parents of neonates to be included into a clinical trial?

The rationale for this question was that the consent discussion with parents does not easily fit into established processes of informed consent. It is often obtained in circumstances which may make taking a valid decision challenging.^{16–18} The understanding and process of parental consent in such extreme circumstances is informed by ethics guidelines, trial procedures driven by regulations, behavioural science, the needs of parents and feedback from health care professionals (HCPs). For the purpose of developing a tool that can be used by investigators these very varied topics had to be included into one single tool.

Patient and public involvement

The involvement of parents and patient representatives is an integral part of the PedCRIN project with a dedicated team reflecting on processes to improve their involvement in the design, conduct and reporting of paediatric clinical trials.¹⁹ The results of the survey were discussed with representatives of a patient organisation involved in PedCRIN. The tool was then codeveloped with them. The representatives of the patient organisation suggested to publish the tool. The article was written in collaboration with the aim of distributing the tool.

POINTS TO CONSIDER

Obtaining informed consent for a clinical study from parents of critically ill neonates can be challenging.^{16 20–22} In this context, it may be helpful to remember that parents would have expected to have a healthy baby.²³ Witnessing the severity of their child's condition is extremely stressful for parents and the NICU setting can be intimidating.^{23–25}

Parents may feel overwhelmed by the large amount of information they receive, time pressure and their emotions.^{23 26–29} Taking voluntary decisions under such circumstances can be very difficult.^{23 28 30} The parent's decision-making process is influenced by the severity of the child's condition, the perceived benefit-risk balance of trial participation, their emotional state, timing of the request and the quality of the relationship with the clinical team, among others.^{28 31} However, most parents will

respond positively to requests for inclusion into a well-designed clinical trial.^{27 32}

Informed consent setting

Routine antenatal visits are a unique opportunity to provide general information to all future parents about neonatal research currently being conducted at the hospital.³³ For certain neonatal and maternal conditions, these visits can also be an opportunity to provide more specific information and discuss with parents the potential inclusion of their child into a study.³⁴ This may provide parents with more time to discuss compared with providing this information only at the time of inclusion.^{23 28 30 35} The timing of detailed discussions will depend on when the diagnosis of the neonatal condition has been confirmed, the delivery date and the individual circumstances of the women and their family.^{36 37} Parental decision making in favour of trial participation is facilitated by parents having sufficient time to consider their decision.^{38–40} Antenatal discussions may also provide an opportunity to introduce the investigator to the family. Deferred consent may be used for the recruitment into studies of life-threatening neonatal conditions.⁴¹ However, multicentre studies may need to consider differences in local practices and the acceptability of deferred consent.⁴¹ Depending on local legislation, informed consent needs to be provided either by one or both parents/legal guardians.⁴² However, independent of the legislation, parents may prefer that consent is sought from both.¹⁵

Clinical trial regulations and regulatory documents provide guidance on the informed consent process.^{43 44} If informed consent is sought by an investigator, who is not the treating physician, parents may have difficulties establishing a trusting relationship and this should be addressed proactively by the study team.^{45 46} On the other hand, if informed consent is requested by the treating physician parents may find it difficult to decline the request and may create conflicts of interest for the physician.⁴⁷ One way of addressing these challenges is to introduce the investigator to the parents during standard clinical practice, for example at a routine visit to the clinic or on ward rounds.^{45 46}

The decision-making process of families during consent is dynamic and will be facilitated by building trusting relationships through the provision of transparent and clear information on the benefit–risk of available treatment options and ensuring the needs of families are addressed proactively.^{44 48–52} Attention should be paid to the possible misconceptions parents may have about the absence of any risk and unrealistic expectations about the benefits of the clinical trial, as this may lead to misunderstandings and harm the trust parents have placed in the clinical team.²³

Consent information

Awareness of the difficulties some parents may experience may help to ensure that trial procedures and communication are optimised to meet their needs.⁵³

Cultural differences should be taken into account and information should be provided in the parent's native language.^{15 54 55}

Parental decisions are strongly influenced by how the information is provided, timing and content.²⁸ While, from a legal perspective, the written informed consent form is important, many parents feel that the conversation and verbal information provided is more important.⁵⁶ Having a script or check list which can be gone through together with the parents may help ensuring all relevant information is not only provided but also understood by the parents/legal guardians. Written informed consent documents can be difficult to read and parents may feel that they are lengthy.^{57–59} Understanding the perspective of parents on the conduct of neonatal clinical trials is important for successful recruitment. Requesting input from parent organisations has been shown to increase recruitment numbers and improve the quality of trial protocols and consent forms.^{42 43 60–64} Involving parent organisations should follow a structured process such as described by Babies Born premature or Sick (BLISS), for example.⁶⁵

A variety of techniques are available to improve the understanding of the information provided during the informed consent process.^{38 51} Spending more time with parents appears to be the most effective measure in obtaining parental consent, while time pressure may lead to difficulties in having their agreement.^{38–40} Jansen-van der Weide *et al* have proposed to adapt the consent process to the time constraints depending on the urgency for treatment.⁴⁰ However, it is important to remember that parental decision making in extremely stressful situations may be difficult and their ability to provide voluntary consent may be temporarily impaired.⁶⁶ Miller *et al* have developed a tool to assess the degree of the voluntariness of a parent's decision.⁶⁶ Furthermore, continuous consent can be sought in trials where it is unclear whether the free choice of parental consent has been compromised.^{17 18} Continuous consent provides the opportunity to initially seek parental assent, followed by full consent once parents had the opportunity to make a valid informed consent decision.¹⁶ An example would be assent for trial inclusion in an emergency situation, followed by full consent once the neonate is stabilised.

Finally, it can be challenging to ensure that the informed consent conversation provides all the relevant information and that the language used is understandable.⁵⁷ Sponsors may consider training investigators on effective communication and what kind of information needs to be included.⁵⁷

To support researchers preparing for the informed consent process of a neonatal trial a checklist of points to consider was developed, which summarises key information from this article (table 1).

CONCLUSIONS

Obtaining informed consent for neonatal research is challenging. This was confirmed in a survey of paediatric researchers in the context of the PedCRIN project. Therefore, a tool was developed which is described in this paper. The tool is providing background information on specific aspects of consent for neonatal trials. A check list of points to consider was developed which may be used by researchers preparing for informed consent. Future research may examine how this tool performs and how it can be improved. Finally, involving parents at all stages of neonatal research including the development of the informed consent form and the process of obtaining consent should be considered standard practice.

Author affiliations

¹Department of Paediatric Clinical Pharmacology and Pharmacogenetics, Robert Debré Hospital, 48 Boulevard Sérurier, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France

²Dutch patient association for rare and genetic diseases (VSOP), Soest, The Netherlands

³The European Clinical Research Infrastructure Network (ECRIN), 5-7 Rue Watt, Paris, France

⁴Consorzio per le Valutazioni Biologiche e Farmacologiche, Via Nicolo Putignani, Bari, Italy

⁵TEDDY European Network of Excellence for Paediatric Research, Via Luigi Porta 14, Pavia, Italy

⁶Department of Paediatric Clinical Pharmacology and Pharmacogenetics, Robert Debré Hospital, APHP, 48 Boulevard Sérurier, Paris, France

⁷Paris University, Paris, France

Acknowledgements We thank Professor Jacques Demontes, Director General of ECRIN and coordinator of the Paediatric Clinical Research Infrastructure Network (PedCRIN), and his team as well as the PedCRIN work package leaders for the support provided for this article.

Contributors CK led the PedCRIN project. DB conducted the survey. BA and VE reviewed the literature. EV, MHED, BA, VE and EJ-A developed the question. EV and BA wrote the article. All authors reviewed the manuscript and contributed with comments.

Funding The work for this article was funded by the European Commission Grant Agreement 731 046.

Disclaimer The views expressed are those of the authors and not necessarily those of the organisations for which the authors work.

Competing interests 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.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. No additional data are available for this article.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is

properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID ID

Beate Aurich <http://orcid.org/0000-0002-8830-023X>

REFERENCES

- Mulugeta YL, Zajicek A, Barrett J, *et al*. Development of drug therapies for newborns and children: the scientific and regulatory imperatives. *Pediatr Clin North Am* 2017;64:1185–96.
- Jobe AH. Off-Label drugs in neonatology: analyses using large data bases. *J Pediatr* 2019;208:9–11.
- Yackey K, Stukus K, Cohen D, *et al*. Off-label medication prescribing patterns in pediatrics: an update. *Hosp Pediatr* 2019;9:186–93.
- Nir-Neuman H, Abu-Kishk I, Toledano M, *et al*. Unlicensed and off-label medication use in pediatric and neonatal intensive care units: no change over a decade. *Adv Ther* 2018;35:1122–32.
- Knight M. Adverse drug reactions in neonates. *J Clin Pharmacol* 1994;34:128–35.
- Conroy S. Association between licence status and medication errors. *Arch Dis Child* 2011;96:305–6.
- Bellis JR, Kirkham JJ, Thiesen S, *et al*. Adverse drug reactions and off-label and unlicensed medicines in children: a nested case-control study of inpatients in a pediatric hospital. *BMC Med* 2013;11:238.
- European Commission (EC). Regulation (EC) NO 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending regulation (EEC) NO 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and regulation (EC) NO 726/2004. official Journal of the European Union, 27.12.2006; L 378/1. Available: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf [Accessed 17 Sept 2019].
- European Commission (EC). Regulation (EC) NO 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending regulation 1901/2006 on medicinal products for paediatric use. official Journal of the European Union, 27.12.2006; L 378/20. Available: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol1/reg_2006_1902/reg_2006_1902_en.pdf [Accessed 17 Sept 2019].
- European Commission (EC). Medicines for children. Available: https://ec.europa.eu/health/human-use/paediatric-medicines_en [Accessed 3 Jun 2020].
- ECRIN. Paediatric clinical research infrastructure network (PedCRIN) overview. Available: <https://www.ecrin.org/projects/pedcrin> [Accessed 29 May 2020].
- Ruggieri L, Bartoloni F, Ceci A. Deliverable 3.1: Survey on infrastructure and service needs for paediatric and neonatal trials. *PedCRIN*, 2019. Available: https://ecrin.org/sites/default/files/PedCRIN/PedCRIN%20Deliverables/WP3%20D3.1_%20Survey%20Report%20on%20infrastructure%20and%20service%20needs%20for%20paediatric%20and%20neonatal%20trials%20FV_28082017.pdf. [Accessed 15 Oct 2020].
- Legrand F, Boukheid R, Elie V, *et al*. A Delphi process to optimize quality and performance of drug evaluation in neonates. *PLoS One* 2014;9:e104976.
- Aurich B, Elie V, Evelyne Jacqz-Aigrain E, *et al*. Deliverable D3.5: Procedures for setup of neonatal trials. *PedCRIN*, 2017. Available: https://ecrin.org/sites/default/files/PedCRIN/PedCRIN%20Deliverables/WP3%20D3.5_Procedures%20for%20the%20set%20up%20of%20neonatal%20clinical%20trials_FV_28022019.pdf [Accessed 15 Oct 2020].
- Neyro V, Elie V, Thiele N, *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;13:e0198097.
- Megone C, Wilman E, Oliver S, *et al*. The ethical issues regarding consent to clinical trials with pre-term or sick neonates: a systematic review (framework synthesis) of the analytical (theoretical/philosophical) research. *Trials* 2016;17:443.
- Allmark P, Mason S. Improving the quality of consent to randomised controlled trials by using continuous consent and clinician training in the consent process. *J Med Ethics* 2006;32:439–43.
- Gupta UC. Informed consent in clinical research: revisiting few concepts and areas. *Perspect Clin Res* 2013;4:26–32.
- Vermeulen E, Jansen-van der Weide M, Karsenberg K, *et al*. Deliverable D5.13 Report on patient engagement and perspective integration. *PedCRIN*, 2017. Available: <https://ecrin.org/sites/default/files/PedCRIN/PedCRIN%20Deliverables/WP5%20D5.13%20Patient%20engagement%20and%20perspective%20integration%20.pdf> [Accessed 15 Oct 2020].
- Wilman E, Megone C, Oliver S, *et al*. The ethical issues regarding consent to clinical trials with pre-term or sick neonates: a systematic review (framework synthesis) of the empirical research. *Trials* 2015;16:502.
- Meinich Petersen S, Zoffmann V, Kjærgaard J, *et al*. Disappointment and adherence among parents of newborns allocated to the control group: a qualitative study of a randomized clinical trial. *Trials* 2014;15:126.
- Lawton J, Hallowell N, Snowdon C, *et al*. Written versus verbal consent: a qualitative study of stakeholder views of consent procedures used at the time of recruitment into a Peripartum trial conducted in an emergency setting. *BMC Med Ethics* 2017;18:36.
- Jollye S. An exploratory study to determine how parents decide whether to enrol their infants into neonatal clinical trials. *J Neonatal* 2009;15:18–24.
- Vecchi Brumatti L, Montico M, Russian S, *et al*. Analysis of motivations that lead women to participate (or not) in a newborn cohort study. *BMC Pediatr* 2013;13:53.
- Pritchard VE, Montgomery-Hönger A. A comparison of parent and staff perceptions of setting-specific and everyday stressors encountered by parents with very preterm infants experiencing neonatal intensive care. *Early Hum Dev* 2014;90:549–55.
- Latour JM, Duivenvoorden HJ, Hazelzet JA, *et al*. Development and validation of a neonatal intensive care parent satisfaction instrument. *Pediatr Crit Care Med* 2012;13:554–9.
- Cartwright K, Mahoney L, Ayers S, *et al*. Parents' perceptions of their infants' participation in randomized controlled trials. *J Obstet Gynecol Neonatal Nurs* 2011;40:555–65.
- Snowdon C, Elbourne D, Garcia J. "It was a snap decision": parental and professional perspectives on the speed of decisions about participation in perinatal randomised controlled trials. *Soc Sci Med* 2006;62:2279–90.
- Ward FR, Chaos WFR. Chaos, vulnerability and control: parental beliefs about neonatal clinical trials. *J Perinatol* 2009;29:156–62.
- Manning DJ. Presumed consent in emergency neonatal research. *J Med Ethics* 2000;26:249–53.
- Thomas M, Menon K. Consenting to pediatric critical care research: understanding the perspective of parents. *Dynamics* 2013;24:18–24.
- Morley CJ, Lau R, Davis PG, *et al*. What do parents think about enrolling their premature babies in several research studies? *Arch Dis Child Fetal Neonatal Ed* 2005;90:F225–8.
- McCarthy KN, Ryan NC, O'Shea DT, *et al*. Parental opinion of consent in neonatal research. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F409–14.
- Ayers S, Sawyer A, Düring C, *et al*. Parents report positive experiences about enrolling babies in a cord-related clinical trial before birth. *Acta Paediatr* 2015;104:e164–70.
- Kenyon S, Dixon-Woods M, Jackson CJ, *et al*. Participating in a trial in a critical situation: a qualitative study in pregnancy. *Qual Saf Health Care* 2006;15:98–101.
- Nieuwenhuijze MJ, Korstjens I, de Jonge A, *et al*. On speaking terms: a Delphi study on shared decision-making in maternity care. *BMC Pregnancy Childbirth* 2014;14:223.
- Goldberg H. Informed decision making in maternity care. *J Perinat Educ* 2009;18:32–40.
- Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. *JAMA* 2004;292:1593–601.
- Clinical Trials Transformation Initiative (CTTI). CTTI recommendations: informed consent, 2015. Available: <https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/CTTI-InformedConsent-Recs.pdf> [Accessed 17 Sept 2019].
- Jansen-van der Weide MC, Caldwell PHY, Young B, *et al*. Clinical trial decisions in difficult circumstances: parental consent under time pressure. *Pediatrics* 2015;136:e983–92.
- den Boer MC, Houtlosser M, Foglia EE, *et al*. Deferred consent for the enrolment of neonates in delivery room studies: strengthening the approach. *Arch Dis Child Fetal Neonatal Ed* 2019;104:fetalneonatal-2018-316461–F352.
- Lepola P, Needham A, Mendum J, *et al*. Informed consent for paediatric clinical trials in Europe. *Arch Dis Child* 2016;101:1017–25.
- Medical Research Council (MRC). Consent and participant information guidance, 2019. Available: <http://www.hrdecisiontools.org.uk/consent/links.html> [Accessed 17 Sept 2019].
- Marc-Aurele KL, Steinman SL, Ransom KM, *et al*. Evaluation of the content and process of informed consent discussions for neonatal research. *J Empir Res Hum Res Ethics* 2012;7:78–83.
- Dekking SAS, van der Graaf R, van Delden JJM. Strengths and weaknesses of guideline approaches to safeguard voluntary



- informed consent of patients within a dependent relationship. *BMC Med* 2014;12:52.
- 46 Dekking SAS, van der Graaf R, Kars MC, *et al*. Balancing research interests and patient interests: a qualitative study into the intertwining of care and research in paediatric oncology. *Pediatr Blood Cancer* 2015;62:816–22.
- 47 Black L, Batist G, Avarid D, *et al*. Physician recruitment of patients to non-therapeutic oncology clinical trials: ethics revisited. *Front Pharmacol* 2013;4:25.
- 48 McCarthy M. Us researchers failed to disclose risks of newborn study, finds government office. *BMJ* 2013;346:f2367.
- 49 DeMauro SB, Cairnie J, D'Illario J, *et al*. Honesty, trust, and respect during consent discussions in neonatal clinical trials. *Pediatrics* 2014;134:e1–3.
- 50 Mundy CA. Assessment of family needs in neonatal intensive care units. *Am J Crit Care* 2010;19:156–63.
- 51 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, 2017. Available: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_09_18_ethical_considerations_with_minors.pdf [Accessed 17 Sept 2019].
- 52 Hoberman A, Shaikh N, Bhatnagar S, *et al*. Factors that influence parental decisions to participate in clinical research: consenters vs nonconsenters. *JAMA Pediatr* 2013;167:561–6.
- 53 Eiser C, Eiser JR, Mayhew AG, *et al*. Parenting the premature infant: balancing vulnerability and quality of life. *J Child Psychol Psychiatry* 2005;46:1169–77.
- 54 Simon CM, Kodish ED. Step into my zapatos, doc: understanding and reducing communication disparities in the multicultural informed consent setting. *Perspect Biol Med* 2005;48:123–38.
- 55 Natale JE, Lebet R, Joseph JG, *et al*. Racial and ethnic disparities in parental refusal of consent in a large, multisite pediatric critical care clinical trial. *J Pediatr* 2017;184:204–8.
- 56 Lentz J, Kennett M, Perlmutter J, *et al*. Paving the way to a more effective informed consent process: recommendations from the clinical trials transformation initiative. *Contemp Clin Trials* 2016;49:65–9.
- 57 Koyfman SA, Reddy CA, Hizlan S, *et al*. Informed consent conversations and documents: a quantitative comparison. *Cancer* 2016;122:464–9.
- 58 Simonds VW, Garroutte EM, Buchwald D. Health literacy and informed consent materials: designed for documentation, not comprehension of health research. *J Health Commun* 2017;22:682–91.
- 59 Wang L-W, Miller MJ, Schmitt MR, *et al*. Assessing readability formula differences with written health information materials: application, results, and recommendations. *Res Social Adm Pharm* 2013;9:503–16.
- 60 Boote J, Julious S, Horspool M, *et al*. 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;17:536–48.
- 61 Bate J, Ranasinghe N, Ling R, *et al*. Public and patient involvement in paediatric research. *Arch Dis Child Educ Pract Ed* 2016;101:158–61.
- 62 Bakhbakhi D, Siassakos D, Storey C, *et al*. Parents 2 study protocol: pilot of parents' active role and engagement in the review of their Stillbirth/perinatal death. *BMJ Open* 2018;8:e020164.
- 63 Harvey M, Nongena P, Edwards D, *et al*. 'We knew it was a totally at random thing': parents' experiences of being part of a neonatal trial. *Trials* 2017;18:361.
- 64 European Commission (EC). Ethical considerations for clinical trials on medicinal products conducted with the paediatric population - Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use, 2008. Available: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/ethical_considerations_en.pdf [Accessed 17 Sept 2019].
- 65 Babies born premature or sick (BLISS). Research investigator guidelines - public involvement role description template. Available: <https://www.bliss.org.uk/research-campaigns/research/involving-parents-in-research> [Accessed 15 Oct 2020].
- 66 Miller VA, Ittenbach RF, Harris D, *et al*. The decision making control instrument to assess voluntary consent. *Med Decis Making* 2011;31:730–41.
- 67 Freer Y, McIntosh N, Teunisse S, *et al*. More information, less understanding: a randomized study on consent issues in neonatal research. *Pediatrics* 2009;123:1301–5.
- 68 Franck LS, Cox S, Allen A, *et al*. Parental concern and distress about infant pain. *Arch Dis Child Fetal Neonatal Ed* 2004;89:71F–5.