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Investigator's perception of the facilitators and barriers to consent and recruitment in clinical trials involving pregnant women and neonates in an Irish Maternity Hospital

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Background

Medication use and lack of trials in pregnancy and neonates

Investigator-initiated clinical trials are crucial for improving quality of care for children and pregnant women as they are often excluded from industry-initiated trials and are therefore under-represented. (1)

Recruitment of pregnant women and neonates to clinical trials is challenging due to strict eligibility criteria in trial protocols excluding these two groups from participation for ethical reasons (1)

In 2014, a worldwide web-based study showed 81.2% of pregnant women reported use of at least one medication (prescribed or over-the-counter) (2) and more locally, an Irish study showed 46.8% of pregnancies were prescribed at least one medication. (3)

Despite the widespread use of medication in pregnancy, a PubMed review showed only about 1% of early phase clinical trials between 1960-2013 testing the safety, tolerance and activity of medicines in the body were carried out in pregnant women, (4) and a 2020 study found just 1.7% of COVID-19 research was pregnancy related. (5)

A 2017 review of NIH trials showed exclusion of pregnant women was 68% and 75.7% for children. (6)

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Background

- Recent EMA workshop concluded that the current approach of systematically excluding pregnant and breastfeeding women from clinical trials is too rigid and that a different approach is required for developing and approving new medicines for use in pregnant women and informing decision making around the treatment of this patient population. (7)

- Many medicines are being prescribed “off label” to treat neonates due to the lack of trials involving this patient population and subsequent lack of information available on the safety and efficacy of medications in the neonate (8,9) this results in increased risk of adverse drug reactions, medication errors and misuse (8,10)

Regulations

Pregnancy*	Neonates
International Conference on Harmonization S5 (R3) guideline on reproductive toxicology: Detection of Toxicity to Reproduction for Human Pharmaceuticals (11)	Regulation (EC) No 1901/2006 (the “Paediatric Regulation”) (15)
EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (12)	Guideline on the investigation of medicinal products in the term and preterm neonate (16)
EMA Guideline on good pharmacovigilance practices (GVP) product or population-specific considerations III: pregnant and breastfeeding women (13)	ICH E11 Clinical Investigation of Medicinal Products in the Paediatric Population CPMP/ICH/2711/99 (17)
EMA Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (14)	

**** No specific guidance published by the EMA for the use of medicinal products in pregnancy trials.***

New CTR may bring less stringent rules for “low-intervention clinical trials”

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Background

Overview of the facilitators and barriers to consenting pregnant women and neonates to clinical trials

- Inconvenience
- Altruism
- Perceived Impact on Pregnancy
- Trust & Communication
- Monetary or Collateral Benefit
- Third-party Influence

(18-28)

Facilitators & Barriers Identified in Pregnant Participants

- Distress, Trust & Communication
- Perceived Impact

(9, 30-34)

Facilitators & Barriers Identified in Parents of Neonates

- Recruiter's Judgement of trial acceptability
- Recruitment through the lens of a healthcare professional
- Recruitment Context

(23, 35-39)

Irish Context

- Perceived impact on pregnancy & future babies
- Trust and Relationship
- Support by Research Lead
- Workload
- Gatekeeping

(39)

Facilitators & Barriers Identified in Recruiters of pregnant women

- Consent & Recruitment Method
- Uncertainty
- Training Gap

(30, 34, 41-42)

Facilitators & Barriers Identified in Recruiters of neonates

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Aims of the Research

- To explore the most common facilitators and barriers to consent and recruitment of pregnant women and neonates to clinical trials from the perspective of clinical investigators working in a large Irish urban maternity hospital

- To illustrate improvements needed in the recruitment of pregnant women and neonates to clinical trials in an Irish maternity hospital setting.

Methodology

Study Design

Semi-structured interviews were conducted using a purposive (non-probability) sample of 8 clinical investigators working in one large urban Irish maternity hospital who had experience of recruiting pregnant women and/or neonates to clinical trials.

The semi-structured interviews were determined most appropriate for this research project as they consisted of open-ended questions that defined the area to be explored but allowed the interviewer or interviewee to diverge to pursue a perspective or view in more detail through follow-up questions and comments. (43)

Methodology

Ethics Approval

-Ethics approval was granted for the study by the School of Medicine Research Ethics Committee, Trinity College Dublin

-Interview schedule, participant information leaflet and consent form were approved by the Ethics Committee prior to distribution and use

-A gatekeeper was used to distribute the participant information leaflet

-All 8 participants gave full written informed consent following dissemination of verbal and written study information and before any interviews were booked with the researcher.

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Methodology

Inclusion Criteria

- Investigators working in an Irish Maternity Hospital.
- Experience of at least 2 clinical trials involving either pregnant women or neonates.

Exclusion Criteria

- Investigators not involved in pregnancy or neonatal clinical trials

Six of the 8 participants were registered medical doctors working in maternal medicine and 2 of the 8 participants were registered medical doctors working in neonatology.

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Methodology

Semi-structured Interviews & data collection

- Eight individual interviews with clinical investigators were carried out on Microsoft Teams and each interview was recorded to allow for transcription

- Each interview was downloaded from Microsoft Teams and transcribed for analysis with anonymisation.

- Transcribed data was analysed by thematic analysis using Braun & Clarke's framework. (44)
    - Firstly, the accuracy of the transcribed data was verified by reading each transcript twice while listening to the audio of the recorded interviews.

    - Each transcript was then re-read several times for data familiarisation and the transcripts were coded to generate an initial pool of codes.

    - A search for themes was performed and codes were collated into potential themes with continuous consideration of the research question.

    - Differentiation of themes enabled a hierarchical structure of overarching superordinate themes and sub-ordinate themes to emerge that were based on the interview transcripts

    - The most relevant illustrative quotations were extracted to reflect each theme identified

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Reflexivity and Quality Assurance

- Due to my professional role as a Quality and Regulatory Affairs Manager overseeing clinical trials in the areas of Obstetrics & Gynaecology as well as Neonatology for 5 years, I have witnessed the barriers reported by clinical investigators when recruiting for trials with pregnant women and neonates.

- Therefore, prior beliefs existed about the complexity and interdependency of factors which impact the recruitment of pregnant women and neonates to clinical trials.

- When considering how my own views and opinions of clinical trial recruitment in these patients may influence the interpretation of the findings, it was decided to employ a quality assurance step using an independent qualitative researcher who performed a review of all codes extracted during data analysis to reduce bias.

Results

Facilitators to recruitment of pregnant women and neonates to clinical trials

Superordinate Themes	Meaning	Subordinate Themes	Illustrative Quote
1. Perceived benefit	The belief of investigators that pregnant women and parents of neonates participate in trials due to some perceived benefit	(a) Benefit for future pregnant women/babies (b) Benefit for own pregnancy/baby	*"Parents of sick babies recognise the importance of high tech medicine and recognise the importance of pushing things forward and learning and developing and progress, so are more likely to participate" (Participant 2)*
2. Consent process	The belief of investigators that the consent process can positively affect participation in clinical trials	(a) Adequate time (b) Alternative consent methods	*"Ideally, if you're able to approach the parents before the baby is delivered and give them time to assimilate the information, but obviously just the nature of the field that we work in is often very acute, very spontaneous" (Participant 7)*
3. Communication and trust	The belief of investigators that the person and manner in which a trial is communicated to pregnant women and parents of neonates can positively affect participation	(a) Communication style/method (b) Trust between subject and recruiter	*"I do believe that mothers generally don't mind being enrolled if the risks versus benefits are well explained to them" (Participant 3)*
4. Informed population	The belief of investigators that interest and information motivates pregnant women to participate in clinical trials		*"I think that women of childbearing age tend to be super informed actually even and sometimes surprisingly so" (Participant 8)*

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Results

Barriers to recruitment of pregnant women and neonates to clinical trials

Superordinate Themes	Meaning	Subordinate Themes	Illustrative Quote
1. Trial Impact	The belief of investigators that pregnant women and parents of neonates participate decline participation in trials due to the perceived impact of the trial	(a) Pain/discomfort of intervention (b) Side effects of intervention (c) Experimental nature of intervention (d) Conservatism (e) Fear of the unknown	*"I think there is a baseline anxiety and nervousness about the health of the fetus that is commonly the first thing that's said. That is probably the overarching concern, a theoretic or potential that any intervention or treatment they might take, could it possibly affect the fetus" (Participant 2)*
2. Third party influence	The belief of investigators that pregnant women decline participation in trials due to the influence of third parties (family/partner/clinician)	(a) Influence of family/partner (b) Influence of clinician/recruiter	*"The role of the investigator or the recruiting person is I think the biggest barrier probably. Kind of equipoise or sort of apathy on the part of the recruiting person who might not feel as strongly as they should do about the importance of recruitment" (Participant 8)*
3. Routine exclusion of vulnerable subjects in clinical trials	The belief of investigators that the routine exclusion of pregnant women and neonates from clinical trials is a barrier to recruitment and hinders research in this area		*"A lot of studies actually exclude mothers who are pregnant from studies, which is, I think is the wrong thing to do. I think it's it stems from the fear of medical legal issues, kind of coming down the line, but I think we're disadvantaging those mothers and that they end up being excluded from the therapeutic interventions" (Participant 3)*

Summary of Results

It was evident from the results that the most commonly cited facilitator was perceived benefit, with all 8 participants mentioning this as a facilitator and the least common facilitator that was cited was pregnant women being an informed population who are particularly interested in research.

With regard to barriers to recruitment, the most commonly cited barrier to recruitment was trial impact with all 8 participants citing this as a motivator for pregnant women and parents of neonates to decline trial participation. The themes of third party influence and routine exclusion of vulnerable subjects were cited equally by participants.

Discussion

- New insights into the facilitators and barriers to recruitment of pregnant women and neonates to clinical trials suggested that altruism and personal benefit are strong on the facilitator side, while the barriers related to the themes of trial impact, third party influence and routine exclusion, with trial impact being the most commonly cited barrier.

- Since pregnant women and neonates are under-represented in clinical trials, it is not surprising that perceived benefit emerged as a prominent facilitator in this research project and that the altruism of pregnant women and parents of neonates for future generations is strong.

- The themes found in the results of this research study are comparable to the existing European and International literature from the perspective of pregnant women, parents of neonates, as well as trial recruiters.

- Investigators interviewed advocated for inclusion of pregnant women and neonates into clinical trials at the protocol design stage but the existing clinical trial directive creates difficulty with inclusion of these subjects (1)

- New EU clinical trial regulation that is planned for implementation in January 2022 adopts a wider understanding of vulnerable participants than the current clinical trial directive, (45) and offers less stringent rules for low-intervention clinical trials.

Discussion-Irish Context

- Unique themes emerged in an Irish context such as communication and trust being an important facilitator in Ireland perhaps due to the unique doctor-patient relationship (46, 47)

- This relationship also acted as a barrier to recruitment as many patients are heavily influenced by their clinicians who may be reluctant to encourage trial participation due to a protective sentiment or fear of litigation.

- The importance of the consent process itself was cited as a facilitator to recruitment, however, alternative consent methods suggested by participants of this research project and in supporting EEA literature would be challenging in Ireland due to the stringent interpretation of GDPR in the Health Research Regulations 2018 (48)

- When compared with other countries in the EEA, Ireland does not have the same flexibility to consider alternative consent approaches such as deferred consent in trials involving neonates and pregnant women but may consider antenatal approaches to consent, once explicit consent is obtained. (49)

Strengths & Limitations

Strengths

-Qualitative study in Ireland that explored solely the experience of medical doctors in consenting and recruiting pregnant women and neonates to clinical trials (limited research in this area)

-Purposive sampling ensured a knowledgeable sample of interviewees & high quality data set

Limitations

-Single site study meaning findings from this research project could not easily be generalised to a larger population of clinical investigators or other healthcare professionals involved in trial recruitment

-Did not include perspectives of midwives and neonatal nurses whose experience may have offered additional insights

-Sample was known to the researcher (may have enhanced communication)

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Conclusion and Recommendations

- Cognisance of the facilitators and barriers to recruitment of pregnant women and neonates to clinical trials will enable researchers to improve future recruitment strategies, improving recruitment rates and attrition.

- Further research in this area across multiple sites would be helpful to increase the scope and reliability of the research and to assess the impact of the new clinical trial regulation on recruitment in these patient populations.

References

1. Knaapen M, Corrette Ploem M, Kruijt M, Oudijk MA, Van der Graaf R, Bet PM et al. Low-risk trials for children and pregnant women threatened by unnecessary strict regulations, does the coming EU clinical trial regulation offer a solution? Eur. J. Pediatr. 2020;179: p. 1205–1211.
2. Lupattelli A, Spigset O, Twigg MJ, Zagorodnikova K, Mårdby AC, Moretti ME, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open. 2014;4(2): p.1-11.
3. Dillon P, O'Brien K, McDonnell R, Donnelly-Swift E, Galvin R, Roche A et al. Prevalence of prescribing in pregnancy using the Irish primary care research network: a pilot study. BMC Pregnancy Childbirth. 2015;15(1): p.1-9.
4. McCormack S, Best B. Obstetric Pharmacokinetic Dosing Studies are Urgently Needed. Front Pediatr. 2014;2: p. 1-9.
5. Smith DD, Pippen JL, Adesomo AA, Rood KM, Landon MB, Costantine MM. Exclusion of Pregnant Women from Clinical Trials during the Coronavirus Disease 2019 Pandemic: A Review of International Registries. AJP. 2020 Jun;37(8): p. 792–9.
6. Spong CY, Bianchi DW. Improving Public Health Requires Inclusion of Underrepresented Populations in Research. JAMA. 2018;319(4): p. 337–338.
7. European Medicines Agency. Report workshop on benefit-risk of medicines used during pregnancy and breastfeeding. 2020 Sep 22.
8. Gidey M, Gebretsadkan Y, Tsadik A, Welie A, Assefa B. Off-label and unlicensed drug use in Ayder comprehensive specialized hospital neonatal intensive care unit. Ital. J. Pediatr. 2020;46(1): p.1-7.
9. Neyro V, Elie V, Thiele N, Jacqz-Aigrain E. 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(6): p.1-19.
10. Conroy S, McIntyre J. The use of unlicensed and off-label medicines in the neonate. Semin Fetal Neonatal Med. 2005 Jan 1;10(2): p. 115–22.
11. International Conference on Harmonization S5 (R3) guideline on reproductive toxicology: Detection of Toxicity to Reproduction for Human Pharmaceuticals
12. European Medicines Agency Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data.
13. European Medicines Agency Guideline on good pharmacovigilance practices (GVP) product or population-specific considerations III: pregnant and breastfeeding women.
14. European Medicines Agency Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling
15. European Medicines Agency. Paediatric Regulation. [Internet]. [Accessed 02-May-2021] Available from: https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation
16. European Medicines Agency. Guideline on the investigation of medicinal products in the term and preterm neonate. [Internet]. [Accessed 05-May-2021] Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-medicinal-products-term-preterm-neonate-first-version_en.pdf
17. European Medicines Agency. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population. [Internet]. [Acessed 05-May-2021] Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-1.pdf
18. Gul RB, Ali PA. Clinical trials: The challenge of recruitment and retention of participants. J. Clin. Nurs. 2010 Jan;19(1–2): p. 227–33.
19. van der Zande ISE, van der Graaf R, Hooft L, van Delden JJM. Facilitators and barriers to pregnant women's participation in research: A systematic review. Wo
Birth. 2018 Oct 1;31(5): p. 350–61
20. Frew PM, Saint-Victor DS, Isaacs MB, Kim S, Swamy GK, Sheffield JS, et al. Recruitment and retention of pregnant women into clinical research trials: an
of challenges, facilitators, and best practices. Clin Infect Dis. 2014;59 Suppl 7: p. 400-7.
21. Strommer S, Lawrence W, Rose T, Vogel C, Watson D, Bottell JN, et al. Improving recruitment to clinical trials during pregnancy: A mixed methods i
Soc Sci Med. 2018;200: p. 73-82

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References

22. Strommer S, Lawrence W, Rose T, Vogel C, Watson D, Bottell JN, et al. Improving recruitment to clinical trials during pregnancy: A mixed methods investigation. Soc Sci Med. 2018;200: p. 73-82
23. Van der Zande ISE, van der Graaf R, Oudijk MA, van Vliet-Lachotzki EH, van Delden JJM. A qualitative study on stakeholders' views on the participation of pregnant women in the APOSTEL VI study: a low-risk obstetrical RCT. BMC Pregnancy Childbirth. 2019;19(1):65. p. 1-12.
24. Hollada J, Marfori W, Tognolini A, Speier W, Ristow L, Ruehm SG. Successful Patient Recruitment in CT Imaging Clinical Trials: What Factors Influence Patient Participation? Acad. Radiol. 2014 Jan 1;21(1): p. 52–7.
25. Sawyer A, Chhoa C, Ayers S, Pushpa-Rajah A, Duley L. Women's views and experiences of two alternative consent pathways for participation in a preterm intrapartum trial: a qualitative study. Trials. 2017;18(1): p. 1-9.
26. Hayes-Ryan D, Meaney S, Nolan C, O'Donoghue K. An exploration of women's experience of taking part in a randomized controlled trial of a diagnostic test during pregnancy: A qualitative study. Health Expect. 2020 Feb;23(1): p. 75-83.
27. Sheppard MK. Vulnerability, therapeutic misconception and informed consent: is there a need for special treatment of pregnant women in fetus-regarding clinical trials? J. Med. Ethics. 2016;42(2): p. 127-31.
28. Monteiro TM, Katz L, Bento SF, Amorim MM, Moriel PC, Pacagnella RC. Reasons given by pregnant women for participating in a clinical trial aimed at preventing premature delivery: a qualitative analysis. BMC Pregnancy Childbirth. 2019;19(1): p.1-9.
29. Frew PM, Zhang S, Saint-Victor DS, Schade AC, Benedict S, Banan M, Ren X, Omer SB. Influenza vaccination acceptance among diverse pregnant women and its impact on infant immunization. Hum Vaccin Immunother. 2013 Dec;9(12): p. 2591-602.
30. Wilman E, Megone C, Oliver S, Duley L, Gyte G, Wright J. 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(1): p. 1-13.
31. Dahan S. Trust and consent: a prospective study on parents' perspective during a neonatal trial. J Med Ethics 2020;0: p. 1–6.
32. Richards J, Rankin J, Juszczak E, Dorling J, McGuire W, Embleton ND. Parental experiences of being approached to join multiple neonatal clinical trials: qualitative study (PARENT). Arch Dis Child Fetal Neonatal Ed. 2021;106(1): p. 84-7.
33. O'Shea N, Doran K, Ryan CA, Dempsey E. Parental And Clinician Views Of Consent In Neonatal Research. Ir Med J. 2018 Mar 14;111(3): p.706.
34. McLeish J, Alderdice F, Robberts H, Cole C, Dorling J, Gale C. Challenges of a simplified opt-out consent process in a neonatal randomised controlled trial: qualitative study of parents' and health professionals' views and experiences. Arch Dis Child Fetal Neonatal Ed. 2021 May;106(3): p. 244–50.

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References

35. Hanrahan V, Gillies K, Biesty L. Recruiters' perspectives of recruiting women during pregnancy and childbirth to clinical trials: A qualitative evidence synthesis. PLoS One. 2020;**15**(6): p. 1-25.
36. Hallowell N, Snowdon C, Morrow S, Norman JE, Denison FC, Lawton J. The role of therapeutic optimism in recruitment to a clinical trial in a peripartum setting: balancing hope and uncertainty. Trials. 2016;17: p. 1–13
37. Lawton J, Snowdon C, Morrow S, Norman JE, Denison FC, Hallowell N. Recruiting and consenting into a peripartum trial in an emergency setting: a qualitative study of the experiences and views of women and healthcare professionals. Trials. 2016; 17(195): p. 1-14.
38. Stuart J, Barnes J, Spiby H, Elbourne D. Understanding barriers to involving community midwives in identifying research participants; experience of the first steps randomised controlled trial. Midwifery. 2015;31(8): p. 779-786.
39. Chhoa CY, Sawyer A, Ayers S, Pushpa-Rajah A, Duley L. Clinicians' views and experiences of offering two alternative consent pathways for participation in a preterm intrapartum trial: a qualitative study. Trials. 2017;18(1): p. 1-10.
40. Daly D, Hannon S, Brady V. Motivators and challenges to research recruitment – A qualitative study with midwives. Midwifery. 2019 Jul 1;74: p. 14–20.
41. Woolfall K, Frith L, Gamble C, Young B. How experience makes a difference: Practitioners' views on the use of deferred consent in paediatric and neonatal emergency care trials. BMC Med Ethics. 2013 Nov 6;14: p. 1-11.
42. Garcia J, Elbourne D, Snowdon C. Equipoise: a case study of the views of clinicians involved in two neonatal trials. Clinical trials. 2004;1(2): p. 170–8.
43. Britten, N. Qualitative Interviews In Medical Research. BMJ. 1995;311(6999): p. 251-253.
44. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2): p. 77-101
45. Gennet É, Andorno R, Elger B. Does the new EU Regulation on clinical trials adequately protect vulnerable research participants? Health Policy. 2015;119(7): p. 925-31.
46. Mulligan K, Egan S, Brennan D, Irish Society of Gynaecological oncology Public and patient involvement group members, O MY, O TS. Doctor-Patient Communication in an Outpatient Setting. Ir Med J. 2019 May 9;112(5): p. 1-10.
47. Conroy RM, Teehan M, Siriwardena R, Smyth O, McGee HM, Fernandes P. Attitudes to doctors and medicine: The effect of setting and doctor-patient relationship. Br. J. Health Psychol. 2002 Feb;7(1): p. 117-125.
48. Health Research Regulations 2018 [Internet]. Hrb.ie. 2021 [cited 23 August 2021]. Available from: https://www.hrb.ie/funding/gdpr-guidance-for-researchers/health-research-regulations-2018/
49. Clarke N, Vale G, Reeves EP, Kirwan M, Smith D, Farrell M, et al. GDPR: An impediment to research? Irish Journal of Medical Science (1971 -). 2019;188(4): p. 1129–35

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