Please see below for a link to the webinar recording for the Trials Methodology Research Partnership:

**Recruiting pregnant women to clinical trials: the ENCOUNTER study**

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14 April 2021

On behalf of the Health Research Board Trials Methodology Research Network

The slides are also available below.

For any queries, please contact uktmn@nottingham.ac.uk

[https://www.youtube.com/watch?v=plxkXVX5seg](https://www.youtube.com/watch?v=plxkXVX5seg)
ENounter Study
rEcruiter’s experieNce Of recrUiting pregNanT womEn to clinical tRials

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#trialmethodology
Outline

• Background

• Qualitative Evidence Synthesis

• Taking a Behavioural Approach
  • Specifying, Diagnosing and Treating the behaviour

• ENCOUNTERT preliminary findings

• What’s next?

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Identifying trial recruitment uncertainties using a James Lind Alliance Priority Setting Partnership – the PRioRiTy (Prioritising Recruitment in Randomised Trials) study

Patricia Healy, Sandra Galvin, Paula R. Williamson, Shaun Treweek, Caroline Whiting, Beccy Maeso, Christopher Bray, Peter Brocklehurst, Mary Clarke Moloney, Abdel Douin, Carrol Gamble, Heidi R. Gardner, Derick Mitchell, Derek Stewart, Joan Jordan, Martin O'Donnell, Mike Clarke, Sue H. Pavitt, Eleanor Woodford Guegan, Amanda Blatch-Jones, Valerie Smith, Hannah Reay, and Declan Devane.

Abstract

Background: Despite the problem of inadequate recruitment to randomised trials, there is limited guidance on how best to prioritise recruitment in future trials. The purpose of this study was to identify priority areas for improving recruitment to randomised trials in order to guide future research.

Question 5

What are the barriers and enablers for clinicians/healthcare professionals in helping conduct randomised trials?
Recruitment in pregnancy

What’s different about it?

• Dyad of mother & baby offers an extra layer of complexity to the challenge of recruitment

Why does it matter?

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Pregnant women aren’t typically included in clinical trials, but that’s changing with COVID

By SY Mukherjee
March 18, 2021 8:15 PM GMT

Involving Pregnant Individuals in Clinical Research on COVID-19 Vaccines

The ongoing global escalation of coronavirus disease 2019 (COVID-19) cases is of particular concern for pregnant, and lactating individuals. While many cases of COVID-19 are asymptomatic or relatively mild, recent evidence suggests that pregnant people are at increased risk of hospitalization and have a 3-fold increased relative risk of needing intensive care (2.9 vs 1.3/1000 cases) and mechanical ventilation (3.4 vs 1.3/1000 cases) compared with non-pregnant individuals. Pregnant people with hospitalization or critical COVID-19 disease have higher adjusted relative risks of maternal death (0.57 vs 0.39; CI, 1.90-15.38; p=.04), preterm birth (0.11 vs 0.03; CI, 1.28-1.44; p=0.003), and stillbirth (0.86 vs 0.58; CI, 0.14 vs 0.10; p=.001) than non-pregnant counterparts. Most of the risk has been provided for pregnant patients. Efforts by the Centers for Disease Control and Prevention to include V-safe registry as well as industry and the Food and Drug Administration will yield postmarket vaccine surveillance information from pregnant people, the vast evidence on the effects of the vaccine on pregnancy and infant outcomes. These data will be useful in the meantime, pregnant people and their healthcare providers make real-time decisions based on the evidence.

As noted in 2019, when a Task Force on Research Specific to Pregnant Women and Lactating Women (PPLAC) was established as part of the 21st Century Cures Act, there is a continuing need to address the data gaps in research related to the development, use, and safety of vaccines for pregnant women and infants. The JAMA, the Journal of the American Medical Association, has provided a platform for researchers and practitioners to share their findings and insights on the impact of vaccines on maternal and fetal health.

HOW DOES COVID AFFECT MOTHER AND BABY?

Pregnant women fare worse than others, although the risks to the baby are still not known. By Nidhi Subbaraman

The JAMA

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Inclusion of pregnant women in COVID-19 treatment trials: a review and global call to action


Inclusion of pregnant women in COVID-19 studies is critical to improve maternal health, pregnancy, and birth outcomes for pregnant women. We explored the inclusion of pregnant women in international clinical trial registries at two time points: biological drugs for the April 7–10, 2020 timeline and a same registry search for the July 10–15, 2020 timeline.

“Without an explicit and proactive effort to recruit and retain pregnant women in clinical trials, the understanding of treatment effects, dosing, side-effects, and potential benefits of COVID-19 treatment for pregnant women will be limited. Inclusion of pregnant women is a matter of equity as much as efficacy and safety…”

Health Policy: Inclusion of pregnant women in COVID-19 treatment trials: a review and global call to action

THE LANCET Global Health

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Include pregnant women in research—particularly COVID-19 research

Adapting interventions and changing attitudes will drive scientific progress

Manan Knight, R. Katie Morris, Jenny Furniss, Lucy C Chapple

The UK Confidential Enquiries into Maternal Deaths have repeatedly highlighted inequities in the medical treatment of pregnant and postpartum women, noting that women are denied investigations and life-preserving treatments simply because they are pregnant or breastfeeding.1,2 These inequities emphasise that the default position should be to investigate and treat pregnant and breastfeeding women in the same way as non-pregnant women, unless there are clear reasons not to.3 Clinical trials, particularly those of drug treatments, have typically automatically excluded pregnant or breastfeeding women, meaning data are unavailable on safety and effectiveness.4 These challenges were noted by the Task Force on Research Specific to Pregnant Women and Lactating Women,5 which issued 13 recommendations, centred around tackling the cultural assumptions that limit scientific progress into preventive and therapeutic interventions for pregnant women.

This disparity in trial inclusion has been exacerbated in the COVID-19 pandemic. A recent review reported that of 972 trials related to COVID-19, 52% explicitly excluded pregnancy, 46% did not mention pregnancy, and only 1.7% specifically included pregnant women, of which just three were interventional trials.1 The risks of untested interventions have been highlighted by others,2 and the moral imperative to include pregnant women in such trials is obvious,6 but the mechanisms to do so are less clear.

Dealing with safety concerns

The RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial showed that excluding pregnant and breastfeeding women does not be default option.7 Inclusion of these women in trials has challenges, and approaches developed for the RECOVERY trial provide a template for other studies.

or breastfeeding does not solve safety concerns to be alleviated for women, their families, and healthcare professionals. Even if regulatory barriers have been overcome or set to one side, there may be local ethics committees who take an overwhelming precautionary approach, overriding recognition of the potential benefits of including pregnant and breastfeeding women. This problem can be mitigated by networking of maternity researchers, familiarising ourselves with drug trials in pregnancy, who can) rapidly mobilised to help implement study adaptations.

The pressure on health services in the pandemic necessitates streamlined approaches to clinical research. The need to add data collection about pre-pandemic outcomes is perceived as a daunting inclusion of pregnant women. However, these data can contribute to the body of knowledge about the effects of interventions. The use of electronic patient records has facilitated rapid roll-out of observational studies of COVID-19 in those designed before the pandemic in those trials.

Changing the default

These examples show how some interventions—such as vaccinations—have been more widely studied in pregnant women. However, the challenges remain for other interventions. The principle of sharing data and knowledge is central to achieving equity in research.

Policy paper

Savings and improving lives: the future of UK clinical research delivery

Published 23 March 2021

Ministerial foreword

The last year has delivered unprecedented challenges for us all. But through these dark times, UK clinical research has provided a beacon of hope.

The tireless efforts of our healthcare professionals, researchers, participants, regulators, medical charities and industry have helped us to lead the world in COVID-19 research. From the rapid delivery of innovative platform trials, like RECOVERY, to our massive contribution to the global vaccine effort, our research ecosystem has pulled together across the UK to provide us with a route back to normality.

This is testament to our strengths. The UK has long been at the forefront
Qualitative Evidence Synthesis

RESEARCH ARTICLE
Recruiters' perspectives of recruiting women during pregnancy and childbirth to clinical trials: A qualitative evidence synthesis

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Abstract

Introduction
Research on research is key to enhancing efficacy in trial methodology. Clinical trials involving women during pregnancy and childbirth are limited, with a paucity of data guiding evidence-based practice. Following a prioritisation exercise that highlighted the top ten unanswered recruitment questions, this qualitative evidence synthesis was designed specifically to focus on the barriers and enablers for clinicians/healthcare professionals in helping conduct randomised trials within the context of recruitment during pregnancy and childbirth.

Methods
The synthesis was undertaken using Thomas and Harden’s three stage thematic synthesis.
Recruiter’s perspectives of recruiting women during pregnancy and childbirth to clinical trials

Recruitment through a clinician’s lens
- Clinical care is a priority
- Recruiter’s perception of pregnant women in clinical trials

Framing recruitment in context
- The situational context
- Research knowledge & understanding of the trial

Recruiter’s judgement of acceptability
- Acceptability of the trial
- Acceptability of the intervention

From protocol to recruiter’s lived experience
- Recruiters as gatekeepers
- Recruitment encounters

Hanrahan et al., (2020)

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Takeaway from the QES
Recruiter focused recruitment interventions

REVIEW

Limited evidence exists on the effectiveness of education and training interventions on trial recruitment; a systematic review of interventions on trial recruitment.

Abstract

Objective: The objective of this study was to examine the effectiveness of education and training interventions on recruitment to randomised and non-randomised trials.

Study Design and Setting: A systematic review of the effectiveness of education and training interventions for recruitment to trials. This review included randomised and non-randomised controlled trials of any type of intervention and recruitment for recruitment to trials within any health care field. The primary outcome was recruitment rate, and secondary outcomes were quality of reported information, number of potential trial participants approached, satisfaction with training, and retention rates.

Results: Of the 19 records reviewed at full text, six met the inclusion criteria for our review. Owing to heterogeneity of outcomes, the pooled analysis was not performed.

Background: Recruitment to randomised controlled trials (RCTs) is often difficult. Clinically related factors have been identified as important reasons for low rates of recruitment. Clinicians (doctors and other health professionals) can experience discomfort with some underlying principles of RCTs and experience difficulties in conveying them to potential trial participants. Recruiter training has been suggested to address identified problems but a training intervention for recruiters is needed.

Methods: Studies that evaluated training programmes for trial recruiters were included. Those that provided only an introduction or consultation were excluded. Data extraction and quality assessment were performed by two reviewers independently. This review was performed using the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement.

Results: Seventeen studies of 2015 potentially eligible titles and abstracts were included in the review. Three randomised controlled studies, two non-randomised controlled studies, nine uncontrolled pre-post studies, and one post-training questionnaire survey were conducted. Most studies were of moderate or weak quality. Additionally, recruitment was measured in terms of recruitment rates or recruitment outcomes. The review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Conclusion: There is a need to develop recruiter training programmes that can lead to improved recruitment and retention.
Behavioural approach

Specify + Diagnose + Treat
Applying behavioural theory

- **Behaviour Change Wheel**
  Michie et al., 2014

- **Theoretical Domains Framework (TDF)**
  Cane et al., 2012

- 33 psychological theories
- Arranged into 14 domains

Sources of behaviour

TDF Domains

- Soc - Social influences
- Env - Environmental Context and Resources
- Id - Social/Professional Role and Identity
- Bel Cap - Beliefs about Capabilities
- Opt - Optimism
- Int - Intentions
- Goals - Goals
- Bel Cons - Beliefs about Consequences
- Reinf - Reinforcement
- Em - Emotion
- Know - Knowledge
- Cog - Cognitive and interpersonal skills
- Mem - Memory, Attention and Decision Processes
- Beh Reg - Behavioural Regulation
- Phys - Physical skills
Previous application of the TDF in trial recruitment

Science in the Heartland: Exploring determinants of offering cancer clinical trials in rural-serving community urology practices

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Andrew Zganjar, M.D., a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z
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d Department of Family Medicine, University of Arizona, Tucson, AZ

Abstract

Objective: Engaging community urologists in referring patients to clinical trials could increase the reach of cancer trials and, ultimately, affect cancer disparities. We sought to identify determinants of referring patients to clinical trials among urology practices serving rural communities.

Methods: We conducted semi-structured qualitative interviews based on a Theoretical Domains Framework at nonmetropolitan academic urology practices located in communities offering urological cancer trials. Participants were asked to describe barriers and strategies that might impact practices located in communities offering urological cancer trials and referring them appropriately. Recorded interviews were transcribed and coded using template analysis.

Results: Most participants were not aware of available trials and had no experience with trial referral. Overall, participants held positive intentions to refer patients to clinical trials if they were willing to take the time to investigate eligibility criteria and were compensated for their effort.

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Specifying the behaviour

• **Action** - Behaviour that needs to change
• **Actor** - Person/people that do(es) or could do the action targeted
• **Context** - Setting in which the action is performed
• **Target** - To whom or for whom the action is performed
• **Time** - When the action is performed

Presseau et al., (2019)

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“Healthcare professional recruiters inviting all eligible pregnant women to participate in a trial”
Three Phased Recruitment Plan

ISLAGIATT principle

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Diagnosing the behaviour

• 22 Semi-structured online interviews

Broad range of clinical backgrounds

8 individual trials (covering 15 different sites) in Ireland & UK

• Inductive & deductive analysis

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Our findings

• This is still a work in progress… but preliminary findings suggest…

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Inductive Thematic analysis

- Incentives & rewards
- Precarity of employment
- Availability & accessibility of resources
- Benefit of experience
- Putting women’s clinical care & wellbeing first
- Planning & preparation
- Approach to recruiting
- The ‘right’ participant
- Recruitment targets
- Gatekeeping
- Being supported
- Acceptability of the intervention
- Commitment to the research
- Being visible
- Putting women’s clinical care & wellbeing first
## Deductive analysis
### Mapping inductive themes to the TDF

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Theoretical Domains Framework - salient domains

• Environmental context and resources

“So, it can be quite difficult sometimes to have confidential conversations, which really is essential. So, I often spend time wandering around the hospital trying to find an empty cupboard to try and have a conversation in. Which, I mean you manage it, but it’s not ideal.” 2RM
Theoretical Domains Framework - salient domains

• Social/Professional Role & Identity

“I feel like in the hospital, we’re not quite second-class citizens, but... you’d never take precedence explaining your study over a nurse coming in, or a midwife coming into the room to a patient, you know, giving them their medication or taking their temperature, you’d always step back.” 17RN
Beliefs about Consequences

“If you’re doing a trial, where they were having to attend for more visits, that might not suit someone, though some women like that, and it is a reason they might take part in a trial. But, you know, that could be a little bit of a burden on them, an extra burden.” 20CI/PI
Treating the behaviour

• Co-design an intervention through online workshop

• Testing the intervention

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• Applying learning from behavioural science provides a framework to rigorously specify, diagnose and treat behavioural problems in trials.

• It enables learning from one study to another to be maximised by application of a common set of principles.
Behavioural approach beyond recruitment

Using a behavioural approach to explore the factors that affect questionnaire return within a clinical trial: a qualitative study based on the theoretical domains framework

Louisa Lawrie, Eilidh M Duncan, Jennifer Dunsmore, Rumana Newlands, Katie Gillies

ABSTRACT

Objectives To identify barriers and enablers to participant retention in trials requiring questionnaire return using the theoretical domains framework (TDF).
Study design and setting We identified and subsequently invited participants who did not return at least one questionnaire during their participation in a clinical trial for one-to-one semi-structured telephone interviews. We used a behavioural framework (TDF) to explore whether any of the behavioural domains (e.g., beliefs about consequences, emotion) affected questionnaire return. Thereafter, we generated a series of belief statements which summarised the content of participants’ main responses and coded these under separate themes.
Participants We distributed questionnaires to two sites in Ireland and subsequently interviewed 7 participants who took part in the C-Gall trial. The C-Gall trial required

Strengths and limitations of this study

- We used an established theoretical framework to explore the factors that influence questionnaire non-response among clinical trial participants.
- It was difficult to engage trial non-responders and thus we recruited a small purposive sample (n=8).
- Findings, and the overall approach, will be useful for trials to consider and adapt according to their clinical context.

INTRODUCTION

Postal and electronic questionnaires are commonly used to obtain outcome data from participants within randomised controlled
Thank you

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#trialmethodology
References


3. Mukherjee (2021) Pregnant women aren’t typically included in clinical trials, but that’s changing with COVID. Fortune Magazine


7. Knight et al 2020 Include pregnant women in research—particularly covid-19 research Adapting interventions and changing attitudes will drive scientific progress BMJ 2020;370:m3305 http://dx.doi.org/10.1136/bmj.m3305


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