towards woman-centred research

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Short title: Reducing research waste in obstetrics

The problem of research waste in obstetrics

Once awarded Archie Cochrane's infamous 'wooden spoon' for the limited application of randomised controlled trial evidence to questions of clinical practice, obstetricians were inspired to action and ultimately became leaders in the development of evidence based medicine.(1) Although the importance of randomised controlled trials and the systematic synthesis of their results to clinical practice is now undisputed, concern has moved to the quality of the design and conduct of primary trials and observational studies, completeness of reporting and the relevance of the research to clinical practice.

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It has been estimated that around 85% of all research funding is actually wasted, a staggering figure thought to be over USD $80 billion,(2) but the impact of research waste goes beyond misuse of finite financial resources. Incomplete reporting, duplicated work, poorly conducted trials, and delayed synthesis of existing evidence have led to substantial barriers in the identification of both beneficial new therapies and severe adverse effects associated with existing treatments, leading directly to patient harm.(3) As we seek to further integrate research within clinical settings, we must face the ethical implications of unaddressed research waste and commit to improving the quality of research in the same way that we strive to improve the quality of direct clinical care.

In a landmark series in *The Lancet* , 17 recommendations for the reduction of research waste across five stages of research production, dissemination, and implementation were proposed in 2014.(4–8) It is not our intention to revisit the comprehensive assessment and rationale of these recommendations, rather to consider how in the intervening years the field of obstetrics has responded to their challenges, identify those issues peculiar to our speciality in seeking to change the process of research production, dissemination, and implementation for the better and explore avenues for future development (Figure 1).

The ethical imperative for high value research in obstetrics

Women are under-represented in clinical trials generally, and pregnant women especially so.(9) This does not stop women from developing health conditions during pregnancy that require treatment, and most medications administered in pregnancy, both over the counter and by prescription, are off-label and unlicensed for use in pregnancy.(10) The clinical use of drugs

untested in pregnant women shifts the risk from monitored small populations in research contexts to uncounted and highly variable use in clinical practice. It is exactly this lacuna that contributed to the scale of the thalidomide disaster and yet pregnant women are still rarely included in drug trials. This issue was recently brought to the fore again when during the Ebola crisis pharmaceutical companies, governments and humanitarian organisations collaborated with remarkable speed to bring Ebola vaccines into clinical trials – and yet, despite the fact that pregnant women were particularly vulnerable to Ebola and that perinatal mortality in Ebola has been near total, pregnant women were initially excluded from the trials of the vaccine.(11) This situation was remedied, and forcibly illustrated the case made in the ethical guidelines prepared by the Council for International Organizations of Medical Sciences (CIOMS) which state that "research designed to obtain knowledge relevant to the health needs of the pregnant woman must be promoted". The STRIDER trials aimed to evaluate sildenafil as a treatment for fetal growth restriction – a treatment already creeping into common practice with the backing of observational data and physiological plausibility. Stopping the trial in the Netherlands early when evidence emerged that sildenafil was actually associated with increased fetal risks has changed clinical practice and demonstrates clearly how the responsible conduct of randomised controlled trials has protected women and children around the world.(12,13) The blanket exclusion of women from studies that offer them and future families important clinical benefits arises from a paternalistic determination that women are unable to assess risk for themselves and fails to take into account the fact that acceptable risk is contextual and individual, as in the Ebola vaccine trials for example. For obstetricians, there is an ethical imperative to advocate for the inclusion of pregnant women in clinical research and lead the way in developing responsible ethical frameworks to allow women to to make their own informed choices and access the benefits of research participation.

Fortunately, most mothers experience uncomplicated pregnancies and even relatively common obstetric disorders are rare in comparison to conditions such as diabetes, hypertension, and chronic renal disease within the general population. Fetal growth restriction secondary to placental insufficiency may be one of the most common conditions presenting to fetal medicine specialists, but on a population level it is rare enough to have been awarded orphan drug status by the European Medicines Agency (EMA).(14) (Orphan drug status is only available where a disease is classified as 'rare', affecting fewer than 5 in 10,000 Europeans) In a field where targeted conditions will be rare, the importance of ensuring all research performed is usable is paramount.

In obstetrics we deal with a human imperative stronger than the will to survive – the will to reproduce and to protect our offspring. Patient priorities in obstetrics, where the interests of the fetus and mother are not always in harmony, are often radically different than in other disciplines.(15) Personal and cultural perspectives play a strong role in the interpretation and choices of women and their families in challenging clinical scenarios. How can an obstetrician determine the relative importance of the risk of a procedural complication for the mother against the risk of harm to the fetus from non-intervention? Might the lived experience of making those decisions not provide a more valuable form of evidence than the clinicians perspective of observing patients pass through these experiences?(16) Where challenging and value laden decisions about care are required, as so frequently occurs in high risk obstetrics, we are obliged to provide the best possible evidence in the fullest sense of the word, addressing all the concerns of the patients, and research work that does not answer this purpose is wasted indeed.

Patient involvement in research: collaborative priority setting partnerships and patient involvement in research design

A traditional paradigm for shared decision making describes taking the best available evidence and integrating it with the personal and cultural perspectives of the patient in order to make decisions about care. This framing inherently assumes that the evidence itself is unaffected by cultural and personal biases, even those of researchers and clinicians who have chosen what and how to research. When we acknowledge that this cannot be the case, we must also accept that high-quality evidence is not something that researchers generate and present to patients, it is evidence produced with and for the people who will be using it.

Consciously opening the process of choosing research directions to as diverse a field of stakeholders as possible generates ideas that would not always have been identified as priorities for researchers.(17) The James Lind Alliance formally brings together patients and healthcare professionals to prioritise the most pressing research uncertainties for this reason. The results of priority setting exercises for infertility, preterm birth, and stillbirth generated questions covering not only new treatments and technologies, but also addressing topics ranging from empowering women to discuss their concerns with care providers to the holistic care of families after experiencing adverse outcomes.(18,19) Priority setting exercises across obstetrics and gynaecology including hypertension in pregnancy and multiple pregnancies are underway. The aim of these partnerships is not to restrict researchers from pursuing genuinely novel treatments and technologies, nor to generate questions that could each be addressed in discrete trials, but to formalise the core principle that research should serve our patients. By establishing as a norm the need to be collaborative in agreeing priority research questions, our speciality can ensure that the use and applicability of novel therapies and technologies are considered from the very earliest stages of investigation and development. Negative or non-

productive findings shared openly are not research waste – unreported, poorly analysed, unnecessarily duplicated or inaccessible research is. Changing the systemic incentives in terms of funding, publications and career development that prioritise the publication of statistically significant work over important null findings is key to reducing research waste. We should not fear to investigate questions where the answer may be 'no', but we should avoid questions where the answer would not matter either way.

The involvement of patients and stakeholders should not end with identifying important research questions; their involvement should be central to study design, patient recruitment, and participant retention.(15) Involving people with personal experience of the condition to be investigated in this way has objectively been shown to improve trial recruitment and retention, but is likely to improve the experience of trial participation and utility of the research output in ways more difficult to quantify. (20) We know that the patient agenda is not fully explored in most clinical encounters and yet has a major impact on patients choosing to continue or modify treatment – research designs that incorporate qualitative exploration of patient experience and priorities are more likely to generate information with utility in the real world of multiple concerns and priorities.(16) Changing the research design paradigm is not only beneficial for improving the quality of research and reducing research waste, it is ethically imperative on the grounds of justice, autonomy, and beneficence.

Prospective registration and incomplete reporting

A great wealth of patient data as yet unused or with unrealised potential still exists in unpublished or incompletely reported randomised controlled trials, and is the subject of the All Trials campaign.(21) Around half of all trials are estimated to remain unreported, with academic

sponsors performing particularly poorly.(22) With this level of performance, it is legitimate to wonder if it is ethical to approach women to participate in research at all. Prospective registration of trials can ensure more complete reporting of the data, particularly adverse events, than in journal publication alone and also allows sponsors and researchers to be held accountable for trials started but not reported. (23) Prospective registration and protocol sharing for trials is welcome, but when over 90% of published research is observational,(24) to address trial registration and reporting alone is to ignore the majority of our evidence base. This is particularly true in obstetrics, since the historical exclusion of pregnant women from controlled trials leads to an even greater dependence on observational data. Prospective registration is recommended in the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (25) and is feasible in a number of online registries but is not yet common practice. It might not be reasonable to expect that all observational studies undertake formal registration. There are reasonable concerns that the heterogeneity of methods and purpose of observational research makes it impractical to apply a single standard for prospective registration to all observational studies and might actually limit exploration of new ideas.(26) Major journals have, however, made it clear that they expect large, hypothesis driven observational studies to provide protocols and prospective registration in the same way as randomised trials.(27)

If the primary evidence base benefits from prospective registration, prospective registration of systematic reviews is also important to reduce selective reporting in evidence syntheses. The PROSPERO registry of systematic reviews exists to provide accountability and reduce the incidence of unnecessarily duplicated reviews.(28) Unfortunately, as demonstrated by the recent publication of four systematic reviews on the use of chewing gum after caesarean section, all showing a benefit and none yet having a noticeable impact on clinical practice, the

availability of prospective review protocol registration does not yet preclude research waste in this area.(29–33)

Perhaps in addition to requiring that all systematic reviews demonstrate a prospectively agreed protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we should also require study authors to demonstrate a search prior to commencing their review for similar ongoing projects and provide evidence for the novelty or relevance of their work? (34) Even before systematic reviews, triallists have an obligation to consider not only what research priorities exist, but also what is currently known and how their work might advance that in the process of developing new studies. Given that informal literature reviews are frequently found to be selective and avoid contradictory works, the gold standard for this process should be a formal systematic review prior to embarking on a new trial. (3) Of three new trials of therapeutic interventions in obstetrics published in this journal last year, all made reference to prior work in their field but only one referred to a systematic review of the literature on the topic. (35–37) In this one case, the systematic review referred to was published after trial recruitment was ended, so clearly was not able to inform trial design – why not perform a systematic review during the development of the trial?

Evidence synthesis in obstetrics

While our speciality is drowning in numerous studies of little to no clinical significance and the difficulty in comprehensively assessing the breadth of the evidence on any particular question is substantial. (38) Research is only of use, no matter how well registered, conducted, and reported, if it is accessible to the end user and implemented into clinical practice.(39) The gold standard of evidence synthesis is by systematic review and meta-analysis, but limitations in the primary studies, both trials and observational reports, the statistical methods of summarising

findings, and the accessibility of review findings to clinicians and the public can limit their impact on clinical practice. (40,41) A number of new approaches are being developed to address the limitations of traditional meta-analysis, including the development of core outcome sets, use of individual participant data (IPD), umbrella reviews, prospective and network meta-analyses.

Core outcome sets

A particular challenge in evidence synthesis is heterogeneity in case definitions and outcome reporting between studies.(42–45) Consensus definitions ensure that the populations in each trial are comparable (46–48) and minimum reporting sets ensure that key population information is available in primary reports.(49) Clearly and consistently defining the population investigated is key to determining the clinical applicability of trial results and summarising results across studies. Recent attention to consensus on the selection, collection, and reporting of outcomes in randomised controlled trials has set the stage for new work that will use core outcome sets in order to increase transparency, accessibility, and ease of evidence synthesis.

The Core Outcomes in Women's and Newborn Health (CROWN) initiative is a collaboration of over 80 speciality journals, including *Ultrasound in Obstetrics and Gynecology*, that has established the importance of core outcome sets and have committed to supporting their development, dissemination, and implementation. (38,50) The Core Outcome Measures in Effectiveness Trials (COMET) initiative allows prospective registration of core outcome sets development, and 98 projects are registered within obstetrics and gynaecology, just under 10% of the entire registry. Core outcome sets have been developed for a range of conditions relevant to obstetrics, including pre-eclampsia, preterm birth, and twin-to-twin transfusion syndrome.(51–56) In core outcome set development healthcare professionals, researchers, patients, and others come together to agree the outcomes that will be most useful. It is important these core outcome sets are developed using robust consensus science methods to ensure they do reflect

the perspectives of key stakeholders.(57) Embedding this perspective should prevent the practice of p-hacking, which is the selective reporting of outcomes or analyses based upon statistical significance,(58) and inadequate reporting of harms.(59,60) Such issues have been identified across a broad range of conditions relevant to obstetrics and maternity care.(61–63)

Individual participant data meta-analysis

Data reported in international trial registries not only promotes accountability and complete reporting, but allows researchers to avoid the limitations of heterogenous study quality, case definitions, and outcome reporting in primary study reports by returning to the raw data originally collected for evidence synthesis.(64) The use of individual participant data (IPD) in evidence synthesis allows increasing sample size, investigation of the interaction of individual patient factors with treatment response and the consideration of outcomes not necessarily included in the primary study reports. IPD meta-analysis (IPD-MA) has been described as the 'gold standard' for evidence synthesis because it enables full use of all collected data and standardisation of variables across studies, but the analysis can be costly and time consuming to undertake.

Although there are resource and training requirements for IPD-MA, in practice the most significant barriers are limitations on access to primary data.(65) Most researchers support responsible data sharing but the response to real requests for data is rather less enthusiastic.(64) In one analysis focusing on prediction of pre-eclampsia, 176 eligible studies were identified through a systematic literature search, but only 30 datasets were ultimately made available for analysis, with only 46% of authors contacted responding and many of those ultimately not sharing their data or finding the data unusable.(66) In two cases, institutional data custodians actually blocked data sharing.

Research funding bodies and journals are leading change with respect to supporting trial registration and data sharing – from 2013 the BMJ has only published new trials where a commitment to reasonable data sharing is present and the International Committee of Medical Journal Editors (ICMJE) has formally endorsed the position that sharing anonymised individual data is ethically mandated and is moving to change culture in their journals in support of more collaborative working. (67)(68) In obstetrics, where the benefits of shared data are so significant and the ethical imperative so strong, we should be leaders in the development of innovative models for collaboration that both harness the power of unused data and recognise the work of the researchers who designed and collected the original data. A useful example is the International Prediction of Pregnancy Complications (IPPIC) Network, bringing together more than 70 researchers from 21 countries who have contributed data from over 2 million pregnancies to be investigated using IPD-MA.(69) With journals and funders increasingly unified on this issue, the challenge is for individual researchers to embrace the opportunities of data sharing.

New horizons for systematic reviews and meta-analyses

An integral part of the IPPIC initiative has been the publication of a comprehensive review of all the published systematic reviews on screening for preeclampsia, which highlighted the ongoing unnecessary repetition of small studies with heterogenous case definitions and outcomes hindering further development in this field.(70) This form of 'umbrella review' provides a broad overview of the evidence and if rigorously performed should incorporate an assessment of the degree of confidence in findings of individual reviews that can usefully inform the decision making of individual patients.

Network meta-analysis allows indirect as well as direct comparison of existing treatments, enabling reviewers to compare a wider range of treatments. Recent examples include a large Cochrane review of uterotonics for post-partum haemorrhage (PPH)(71) and a network meta-analysis of labour induction methods.(72) In both these areas trials and observational studies abound, but rarely compare more than two or three interventions. The network meta-analysis permits a broader overview of the field and comparison of interventions than a traditional meta-analysis would permit, but requires relatively complex statistical input to achieve.

A key problem for meta-analysis is that commonly only published trials are available to be included, and the results of the trials are known prior to the initiation of evidence synthesis. A prospective meta-analysis attempts to address this, using the increasing fact of prospective trial registration to facilitate searching for and identifying eligible trials prior to completion and planning the meta-analysis, including any sub-group analysis, prospectively.

Data sharing for evidence synthesis

Open data does not only apply to trials but given that data storage is typically of higher quality in trials than in observational studies, access to high quality trial data is the right place to start. The next ambition should be to stop throwing away valuable data on outcomes on rare conditions in pregnancy by leaving routinely collected pregnancy data buried in mismatching hospital electronic records or small single centre cohort studies reporting varying outcomes with varying lengths of follow up. When rare conditions are investigated, single centres rarely have enough cases to identify uncommon outcomes or the interaction of treatment choices with patient factors and the effect on clinical outcomes. National or regional registries for rare diseases, including the Twin and Multiple Birth Association (TAMBA) funded national registry for complicated twin pregnancies or those designed for the capture of rare outcomes(73) could increase the number of cases available for analysis. With prospective registration and rigorous

follow up they offer the potential for exploring factors modifying treatment effects, rare harms from treatment and valuable avenues for future trials. (74) (75)

A call to action

Obstetricians are rightly proud of the work being done to reduce research waste in our field. We can point to examples including the CROWN initiative and numerous priority setting projects leading the way in promoting collaborative working, prioritising productive research, and ultimately improving the information and care we can provide to mothers and babies. Still, there is much work to do and many systemic barriers to dismantle to achieve the goal of 'less research, better research, done for the right reasons' (Figure 2).(76)

We need to consider cultural change across the board from funders, institutions and researchers to dismantle the system features that promote poorly conducted, incompletely reported, and ultimately wasted research. Increasing transparency, from the initiation and design of studies right through to the peer review of final reports is likely to be a key component of this culture change. The use of prospective registration of trials and systematic reviews, a collaborative approach to data sharing, innovative methods of evidence synthesis, and promotion of complete and accessible study reporting are all important priorities. The critical change we all need to make however, is placing mothers and babies at the centre of every process in research design, production, dissemination, and implementation. We have begun to realise the vision of woman centred care in clinical obstetrics: woman centred research should be the rule in developing the evidence base to support this care.

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Figure legends

Figure 1. Reducing waste and increasing value in obstetrics research

Figure 2. Reducing research waste in obstetrics.

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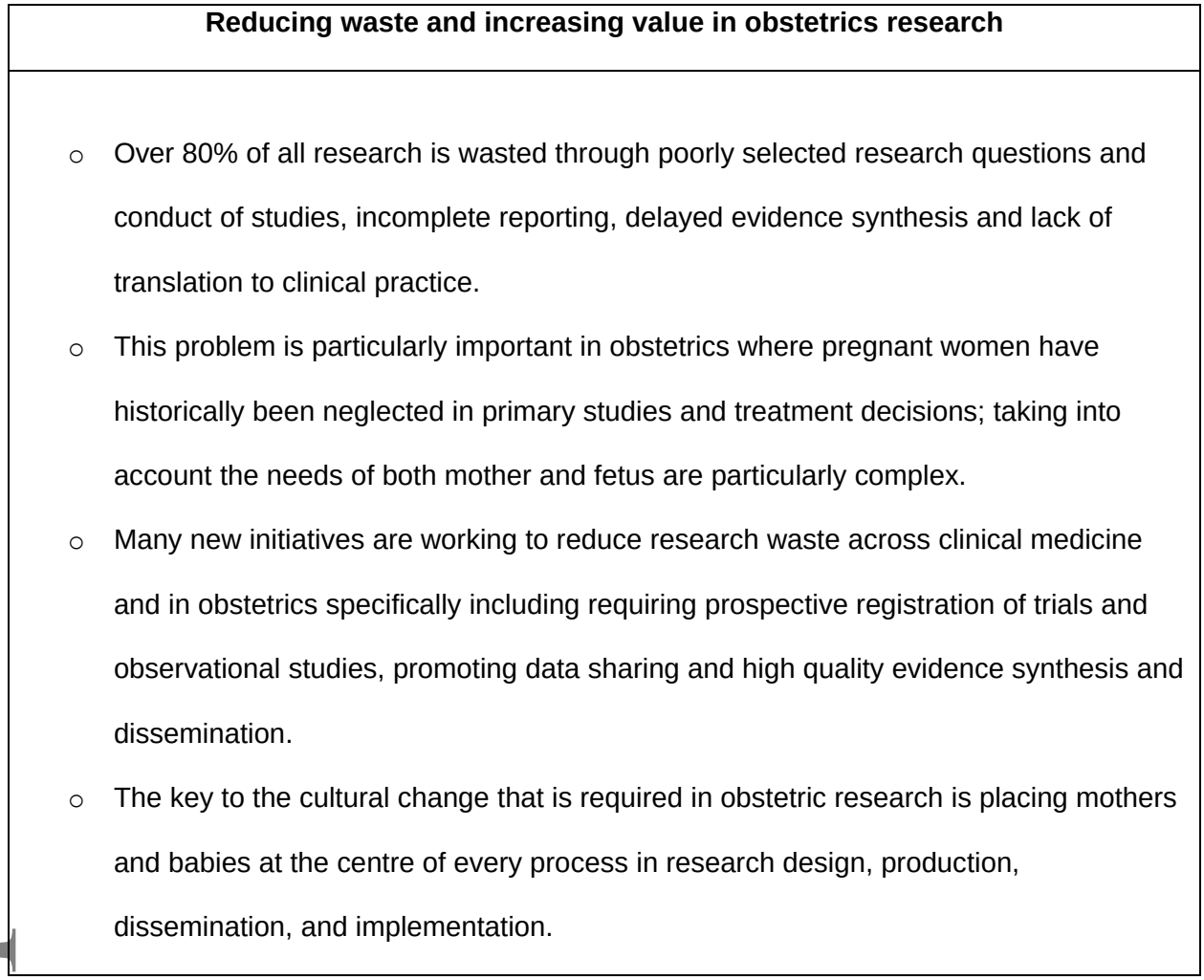

Figure 2. Reducing research waste in obstetrics.

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