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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
BACKGROUND 2
Figure 1. 3
OBJECTIVES 4
METHODS 4
ACKNOWLEDGEMENTS 14
REFERENCES 15
APPENDICES 20
WHAT'S NEW 25
HISTORY 26
CONTRIBUTIONS OF AUTHORS 26
DECLARATIONS OF INTEREST 26
SOURCES OF SUPPORT 26
NOTES 26

[Intervention Protocol]

Preconception care for women with epilepsy: a mixed methods review

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the evidence of the effectiveness of preconception care interventions to improve pregnancy outcomes for women with epilepsy (WWE). The objectives include:

- A synthesis of quantitative data on the effectiveness of differing preconception interventions for improving pregnancy planning and fitness for pregnancy.
- A synthesis of qualitative data on participants' experiences, opinions and preferences regarding preconception care/counselling.
- A convergent synthesis integrating the results of quantitative and qualitative synthesis to address the overall review question (a results-based convergent synthesis), to enhance and extend understanding of how preconception care/counselling interventions may work and how context impacts on the implementation.

BACKGROUND

Description of the condition

Epilepsy is a common neurological disorder affecting up to 1% of the population (Hauser 1990). The incidence of the condition is linked to social deprivation (Pickrell 2015), and it is estimated that 75% of people with epilepsy reside in low- and middle-income countries (LMIC) (Espinosa-Jovel 2018). Active point prevalence of epilepsy in women is estimated to be 6.85 cases per 1000; reported incidence rates are thought to be lower in women, due to concealment of the diagnosis, in counties where women with epilepsy (WWE) are perceived to be unmarriageable and are socially marginalised (Fiest 2017).

Antiepileptic drugs are the mainstay of treatment for the majority of individuals with epilepsy, of whom approximately one-third of those receiving antiepileptic drugs (AEDs) are women of reproductive age (Yerby 1994). It is estimated that 0.3% to 0.7% of all births are to women with epilepsy, most of whom require continuation of AEDs during pregnancy due to the risks of uncontrolled seizures to the mother and fetus (Joint Epilepsy Council 2011; Lunardi 2011; Tomson 2011). The estimate of in utero exposure to AEDs or uncontrolled seizures (or both) is likely to be higher for WWE in Low-to-Middle Income Countries (LMIC), owing to the impact of the treatment gap and disease-related stigma on the care of WWE (von Gaudecker 2017).

Whilst the outcome of pregnancy for the majority of WWE is normal, the risk of adverse pregnancy outcomes — such as maternal mortality and morbidity, together with fetal risks of death, major congenital malformations, dysmorphism (anatomical malformation) and long-term cognitive delay — is two to three times higher (Bromley 2017; Weston 2016). The magnitude of fetal risk is influenced not only by the type of AED (e.g. Increased risk is associated with the use of the drug, valproate; there is international consensus that its use should be avoided in pregnancy when possible (MHRA 2019.)) but also, AED dosage and other variables (e.g. maternal age and parental history of major congenital malformation), all of which need to be taken into account in the management of epilepsy in women of childbearing potential (Tomson 2011). Geographical variations for epilepsy care provision have been shown to increase the risk of pregnancy complications, including risks of sudden unexpected death in epilepsy (SUDEP) and poorer pregnancy outcomes for WWE in LMIC and resource-poor settings (Allotey 2017; Edey 2014; Galappatthy 2018).

Description of the intervention

Preconception care is defined by the World Health Organization as a series of promotive, preventive and curative health interventions able to benefit a wide range of stakeholder needs to maximise the gains for maternal and child healthcare (WHO 2013). Preconception interventions include those interventions with the intention of improving maternal and child health prior to conception in a woman of childbearing potential. This includes the stages of preparation for a first pregnancy and peri-conception interventions to improve future outcomes by intervening in between pregnancies (PHE 2018a). Preconception interventions involve single or multiple health risk assessments, education and counselling (delivered as a single session or an intense programme involving multiple sessions over several weeks) (Hussein 2016). The effectiveness of preconception care interventions relies on the identification of and reduction in (modifiable) risk factors before conception in order to improve obstetric outcomes (Steegers 2005).

Preconception interventions employ both individual and population perspectives to improve health before pregnancy (by planning for pregnancy, e.g. use of contraception to avoid pregnancy until the right time) and improve fitness for pregnancy (e.g. risk assessment/health promotion/health behavioural interventions), with the benefit of improved outcomes for mothers and babies (PHE 2018a). The settings for preconception intervention delivery include primary and secondary healthcare; social care, education, religion and community providers including public health initiatives (e.g. family planning); and the voluntary sectors (PHE 2018a; WHO 2013).

The International League Against Epilepsy Women and Pregnancy Task Force have recommended management strategies/discussion topics, blood tests, and communication between professionals and the patient (Tomson 2019b). Preconception management for WWE includes the following: risk assessment, health education and promotion, and targeted advice concerning epilepsy.

Risk assessment

Risk assessment involves the identification and quantification of modifiable health risks associated with antiepileptic medication and seizures prior to pregnancy. All older AEDs and the majority of the newer AEDs are classed as teratogenic agents with the potential to influence structural congenital anomalies, growth disturbance, and functional deficits such as behavioural and cognitive abnormalities, that may not be apparent until some time after birth (Friedman 2013). Valproate should be avoided whenever possible; and where possible monotherapy or AED withdrawal should be considered, whilst balancing the risk of seizure against the risks associated with AED use (Tomson 2019b). A risk assessment will involve identification of WWE at risk of poor adherence to AED treatment, and those at risk of abrupt withdrawal of AEDs on the discovery of pregnancy. The identification of risk will support targeted advice concerning epilepsy, for example warning against abrupt AED withdrawal on the discovery of pregnancy as a contributing factor to uncontrolled epilepsy during pregnancy and risk of sudden unexpected death in epilepsy (SUDEP). Guidelines recommend communication of risk information that emphasises the importance of optimising and maintaining AEDs during pregnancy (McCall 2018; RCOG 2016).

Health education and promotion

Health education and health promotion interventions target behaviours to improve fitness for pregnancy, including promoting knowledge of (and initiation of) vitamin D and folic acid, immunisation, reducing alcohol, giving up smoking, contraception and family spacing, and sexual health (PHE 2018b; Whitworth 2009). Health promotion activities aim to improve health knowledge and awareness in advance of sexual activity, and focus on pregnancy planning to avoid pregnancy until the time of optimal health (Hanson 2015); this also includes pre-pregnancy seizure control (Tomson 2019b). Contraceptive advice for WWE promotes the selection, and use, of appropriate contraception and promoting awareness of the clinically significant interactions between AEDs and contraceptive drugs (De Weerd 2002; Pack 2009; SIGN 2019).

Promoting preconception healthcare in adolescence, at a life stage when many behaviour patterns become established, is a

key recommendation made by the UK Chief Medical Officer (PHE 2018b). This is a further challenge for adolescents with epilepsy since WWE experience earlier sexual debut compared to their non-epilepsy population controls (Lossius 2016).

Targeted advice concerning epilepsy

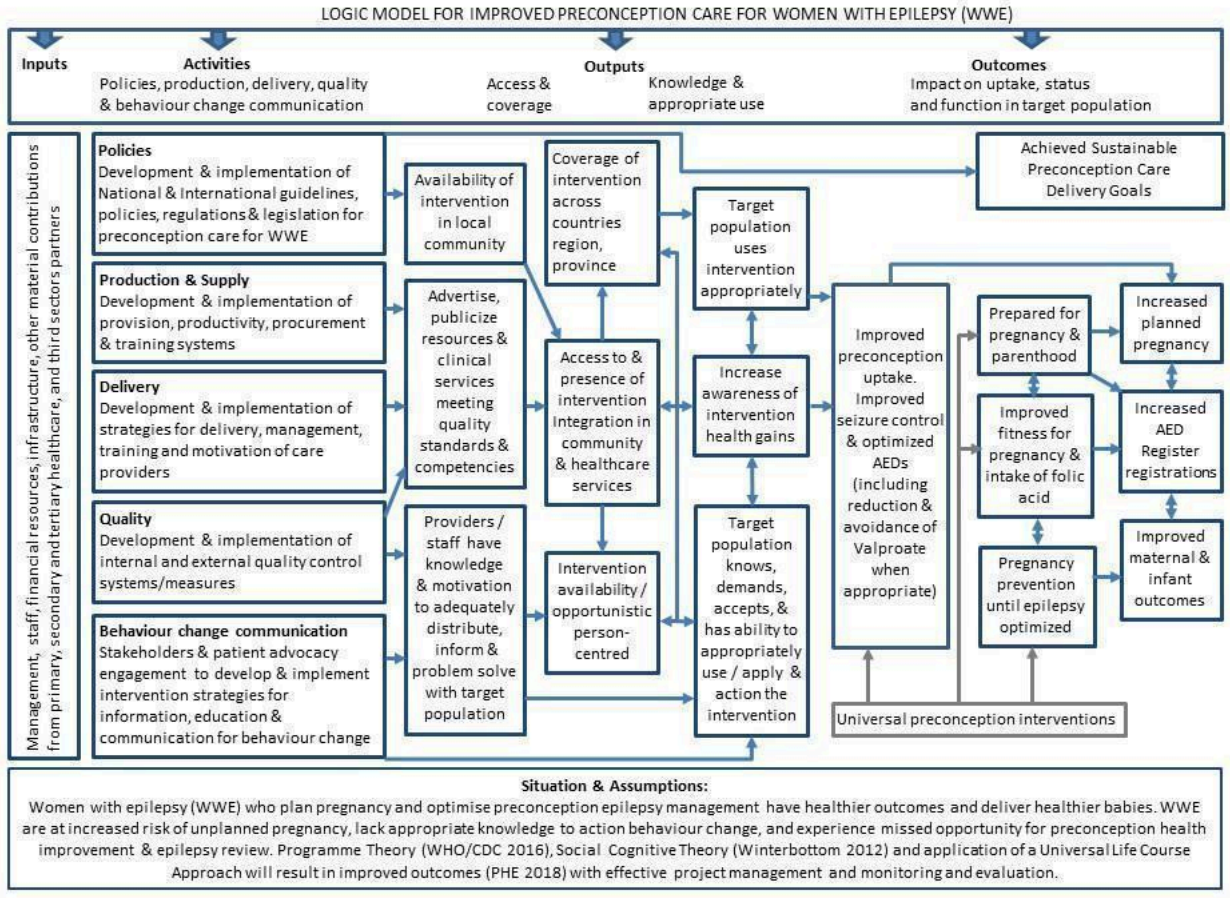
Women and girls with epilepsy require information and counselling to be tailored to their personal needs, on topics including: contraception, conception, pregnancy, caring for children and breastfeeding. This information/counselling needs to be provided in advance of sexual activity and pregnancy (NICE 2012; SIGN 2019). Due to the risk of unplanned pregnancy, women taking AEDs are recommended to take a high-dose folic acid supplement (5 mg/day) (NICE 2012; RCOG 2016; Tomson 2019b).

Due to the chronic nature of epilepsy, targeted preconception care requires an ongoing process of preparation and review of epilepsy management, to ensure the WWE conceives with a minimum of risk factors, is fully aware of any risks and benefits of treatment, and is able to make informed decisions about future pregnancies (Crawford 2005).

How the intervention might work

Preconception care interventions bring together an interventional process involving assessment, planning, treatment, education, decision support and counselling, resulting in a wide range of potential health outcomes before, during and after pregnancy for both the woman and her future offspring (NICE 2019). Preconception care is conceptualised through a life course approach and takes account of intervening to improve fitness for pregnancy by focusing on the "four Ps": pregnancy planning, pregnancy prevention, pregnancy preparation and preparing for parenthood (Hanson 2015; PHE 2018b). Programme theory and the influence of behaviour change communication has been proposed to support changes in micronutrient interventions for population health outcomes (Centeno Tablante 2019; WHO 2016). Social cognitive theory has been proposed to support the development and maintenance of reproductive/preconception health behaviours (Winterbottom 2012). See Figure 1.

Figure 1. AED: antiepileptic drug
WWE: women with epilepsy
Logic model adapted with reference to WHO/CDC (2016), Tablante (2019), PHE (2018) and Winterbottom (2012).



Improving rates of a planned pregnancy for WWE will result in more women having preconception epilepsy reviews and appropriate changes in prescribing (Leach 2017). Making changes from treatment with high-risk AEDs has the potential to prevent

31 children each year born to mothers with epilepsy being affected by major congenital malformation, with an estimated cost saving of GBP 1,746,000 (in 2011) by avoiding valproate alone, and reducing the economic burden by preventing five cases of spina bifida per year (Kinney 2011). The European Epilepsy and Pregnancy register have reported a 27% reduction in rates of AED-related major congenital malformations since 2000 due to changes in prescribing (reducing use of valproate and carbamazepine), without significant changes to rates of tonic-clonic seizures in pregnancy over the same time period (Tomson 2019a). Additional strategies to reduce valproate exposure have been implemented, including mandatory risk acknowledgement and pregnancy prevention, further demonstrating the importance of planning pregnancy and having epilepsy reviews to optimise AEDs and seizure control before conception (EMA 2018; MHRA 2019).

Pre-pregnancy commencement of folic acid supplementation has been proposed to influence the neurodevelopmental outcomes of children born to mothers with epilepsy (Meador 2011). Improving the provision of risk information ahead of pregnancy is proposed to reduce the risk of adverse pregnancy outcomes, by supporting the completion of AED changes prior to pregnancy, thereby reducing the rates of abrupt withdrawal of AED or termination of an otherwise wanted pregnancy (Betts 1999; Rapcencu 2012). The changes to prescribing patterns observed in the European Epilepsy and Pregnancy register (EURAP) revealed a significant 27% decrease in the prevalence of major congenital malformations (Tomson 2019a).

Why it is important to do this review

This review will address the increased focus on the benefits of preconception care (WHO 2013), as a complex intervention to improve reproductive health (PHE 2018b). The need for this updated review was confirmed in an online patient and public involvement survey managed by one UK voluntary organization, Epilepsy Action, which highlighted the need to include core outcomes of relevance to WWE and their key supporters. This review will seek to increase understanding of the importance of pre-pregnancy interventions to improve maternal neurological outcomes prior to pregnancy, and the potential to influence obstetric and offspring outcomes (Al Watter 2017).

This updated review protocol will extend the scope of the original review (Winterbottom 2008), to evaluate quantitative and qualitative research to improve understanding, and strengthen and extend the evidence of the effectiveness of preconception interventions for WWE. It will also take into account all of the key stakeholder perspectives.

The rationale for this review is in response to the following key recommendations.

- To reduce preventable maternal death among pregnant and postpartum WWE (Kelso 2017; Knight 2014).
- To improve risk assessment and communication about high-risk AEDs, including valproate, for women of childbearing age (EMA 2018; Kmietowicz 2016; MHRA 2019).
- To improve maternal and child health outcomes by intervening to improve preconception health (PHE 2018a).

OBJECTIVES

To assess the evidence of the effectiveness of preconception care interventions to improve pregnancy outcomes for women with epilepsy (WWE). The objectives include:

- A synthesis of quantitative data on the effectiveness of differing preconception interventions for improving pregnancy planning and fitness for pregnancy.
- A synthesis of qualitative data on participants' experiences, opinions and preferences regarding preconception care/counselling.
- A convergent synthesis integrating the results of quantitative and qualitative synthesis to address the overall review question (a results-based convergent synthesis), to enhance and extend understanding of how preconception care/counselling interventions may work and how context impacts on the implementation.

METHODS

Criteria for considering studies for this review

Types of studies

Quantitative studies

- Randomised controlled trials. These studies will be considered if individual or cluster-randomised allocation were used.
- Quasi-randomised trials (with the exclusion of cross-over trials as this design is not feasible for the intervention).
- Non-randomised studies. These studies will be considered for inclusion if they used study design descriptors as suggested within the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2019). Justification for inclusion of non-randomised studies is based on the results of the original review and as an update extending to include mixed-methods; the protocol authors recognise the potential difficulty in conducting randomised studies in this topic as prospective participants will likely have a strong reason for the preference for the intervention and restriction/delay of the intervention delivery would be unethical (Reeves 2019).

Qualitative studies

Qualitative studies will be considered for inclusion if they used qualitative methods for data collection (e.g. focus group interviews, individual interviews, observation, document analysis, experiential and interpretative studies) and also qualitative methods for data analysis (e.g. grounded theory, interpretative phenomenological analysis, discourse analysis, thematic analysis). This criterion has been successfully used as a basic quality threshold for considering studies for inclusion, thereby excluding studies where qualitative methods were used to gather data that were then analysed using descriptive statistics (Ames 2017).

Qualitative studies reporting the views and opinions of participants of preconception care programmes will be considered if they used qualitative methods of data collection and data analysis reporting people's perspectives, beliefs, feelings, understanding, experiences or behaviour that were presented as data (e.g. direct quotes from participants or description of findings). There will be no limits on location, however, the language will be limited to English due to the cost requirements of detailed and specialist language translation.

Types of participants

Quantitative studies

Participants of interest are women of childbearing potential aged 12 to 50 years, with a confirmed diagnosis of epilepsy, who are on or off treatment. Due to ethical concerns of withholding interventions, controlled trials will be considered with a comparison between differing interventional components, delivery methods or healthcare settings.

Participants of interest in cluster-RCTs will be "those on whom the investigators seek to measure the outcome of interest" (Higgins 2019c). How individual participants are identified and recruited within clusters will be noted.

In addition, studies will be considered taking account of women and their spouse/partners, carers, other family members, or members of the health and social care team, and the voluntary sector.

Qualitative studies

We will include women of childbearing potential aged 12 to 50 years, with a confirmed diagnosis of epilepsy, who have experienced preconception care or who have expressed an interest in preparing for pregnancy. WWE who have experience of unplanned pregnancy, who failed to attend preconception care, may also be included. Participants may also be extended to include people with epilepsy, partners, carers or other family members of a person with epilepsy, members of the health and social care team, and the voluntary sector.

Types of interventions

Preconception care interventions include any educational, health promotion, or counselling interventions (or a combination of these) targeting WWE, with the intention of improving preconception health outcomes. These interventions are delivered in hospitals or the community. Programmes could vary in content (e.g. changes of AED; provision of risk information; commencement of folic acid) and their delivery mode (individual (hospital or community clinic) or group (hospital or community)), length, frequency or intensity (see Subgroup analysis and investigation of heterogeneity). Interventions, such as valproate risk acknowledgement/pregnancy prevention programmes (required annually in the UK) may be offered before the decision to have a baby, and acknowledge the return for an earlier review if there are changes in plans for pregnancy (MHRA 2019).

We will include pre-pregnancy and between-pregnancy interventions involving assessment of lifestyle, health and fitness by a healthcare professional (NICE 2019). Preconception care interventions will also be considered for inclusion if the interventions include any of the following: epilepsy review with the intention of reducing the number or dose of AEDs or reducing seizure-related risk; improving the chances of healthy pregnancy outcome through health improvement and health education including risk information; improving knowledge of the importance of planned pregnancy; avoiding unplanned pregnancy and increasing uptake of contraception; knowledge of contraception and potential AED-related interactions; interventions focused on improving preconception care uptake and adherence).

Control groups (if present in the study design) might include a comparison of different intervention components or delivery methods.

Studies will be considered for inclusion if they explore preconception care (including the delivery of care) from the perspective of the WWE, their partner, family, members of the health and social care team, and voluntary sector (see Types of participants; Types of outcome measures).

Types of outcome measures

As a mixed-methods review, the outcomes of interest are the improvement in maternal health, including seizure control and epilepsy management (AED use) prior to pregnancy.

Short/mid-term outcomes, will include the planned pregnancy, or pregnancy avoidance during the interventional stages to improve seizure control and epilepsy management.

Long-term outcomes will include improvement in obstetric and child health outcomes (see Figure 1).

Primary outcomes

Quantitative outcomes

Preconception outcomes

- Overall clinical improvement in seizure management prior to pregnancy
  - The proportion of women who are seizure-free at the completion of the intervention compared to baseline
  - The proportion of women with a reduced seizure frequency compared to baseline
  - The proportion of women who are on monotherapy/polytherapy (compared pre- and post-intervention)
  - The proportion taking valproate monotherapy/polytherapy (compared pre-and post-intervention)
- Measures of self-efficacy and self-management, using validated scales
- Intention to plan pregnancy, measured by use of validated scales such as the London Measure of Unplanned Pregnancy (Hall 2017; PHE 2018b); questionnaires of self-rated pregnancy intention; use of long-acting reversible contraception (self-reported, case note review); recorded attendance at preconception review
- Commencement of folic acid (self-reported, case note review)
- Knowledge of preconception care and epilepsy in pregnancy issues, measured by questionnaire pre- and post-intervention; and/or, measured by validated epilepsy in pregnancy knowledge scale; epilepsy knowledge scale; preconception health/reproductive health scale
- Serious adverse events (mortality, SUDEP, seizure-related injury, pregnancy exposed to valproate)
- Adverse events relating to the intervention, measured as the proportion of individuals experiencing any of the following adverse effects: anxiety (measured by a validated scale, e.g. the Hospital Anxiety and Depression Scale (HADS), pre- post-intervention); unplanned pregnancy; accidental pregnancy (as defined by study authors, measured yes/no); the proportion of unplanned pregnancy associated with AED polytherapy

Pregnancy outcomes

Whilst pregnancy outcomes are important primary outcomes, it is recognised that pregnancy might not be an appropriate outcome of all recipients of preconception care interventions, especially where the primary outcome of the intervention is pregnancy prevention for WWE taking a high-risk AED(s), and pregnancy prevention recommended during the planned switch of AED(s). Medium/long-term preconception care intervention outcomes are seen as the primary prevention of adverse pregnancy outcomes.

The following outcomes will be reviewed, if available when considering studies for inclusion.

- The proportion of women who maintain pre-pregnancy seizure control in pregnancy.
- Obstetric outcomes, measured by booking early into antenatal/prenatal review (i.e. weeks of gestation at booking); obstetric complications (Al Watter 2017); live birth; miscarriage; stillbirth; preterm birth; mode of delivery; breastfeeding (yes/no; measured by the number of weeks/months).
- Congenital malformations, measured by rates and frequency of classified abnormality.
- Neurodevelopmental outcomes, measured by a validated scale of infant development e.g. Bayley Scales of Infant and Toddler Development (Bromley 2017).
- Registration with the Epilepsy in Pregnancy Register (yes/no).
- Infant/maternal mortality and morbidity.

The qualitative phenomenon of interest

The phenomenon of interest for qualitative studies will include the perceptions and experiences of WWE, their partners, friends, family, healthcare providers and other key stakeholders. Qualitative studies will be considered for inclusion if reporting opinions and experiences of preconception care/counselling from any stakeholder perspective (e.g. views and beliefs about the utility of pregnancy planning to improve preconception health for WWE; barriers to adherence to preconception care interventions; observations and experiential accounts).

Secondary outcomes

Quantitative outcomes

- Adherence to the intervention (i.e. retention rate, characteristics of non-responders)
- Knowledge of AED-related contraceptive interactions, and alternative effective contraceptive methods, measured by questionnaire/self-report (pre- and post-intervention)
- Adherence to AEDs (AED adherence, measured by self-report, hair analysis, AED blood level monitoring, or use of adherence technology; validated drug-adherence measure)
- Pre-conception health improvement: smoking/alcohol cessation, weight management; measured by validated rating scales, questionnaire, self-report (pre- and post-intervention) (Whitworth 2009)
- Measures of quality of life, using validated scales for people with epilepsy
- Satisfaction with care, including involvement in shared decision-making, measured by a validated rating scale, or as defined by the study authors
- Breastfeeding (yes/no)
- Infant and child injury secondary to maternal seizures (self-reported, questionnaire)

Outcomes will be considered in selecting studies for inclusion; however, it is acknowledged that studies are unlikely to report on all outcomes of interest. We intend to include studies reporting on at least one or more outcomes of interest, with time frames of measurement of outcomes considered for inclusion pre-specified as 'short-term' or 'medium/long term', as referred within the logic model (see Figure 1).

Search methods for identification of studies

The search methods for this mixed-methods protocol have been updated and extended to include additional criteria, with the goal of retrieving both non-randomised studies and qualitative studies, as suggested in *Cochrane Handbook* (Higgins 2019a; Noyes 2019a). The search methods for qualitative research were informed by running and re-running selected search terms in a simulated review in order to address the challenges of identifying studies by title and to counter inadequate indexing and other factors as barriers (Booth 2016a). The challenge of searching for both quantitative and qualitative research in this mixed methods review will be acknowledged and documented in sufficient detail to allow full reporting in the complete review (search terms used, additional sources of evidence retrieval used, number of hits). For quantitative research, a systematic and thorough search of all available evidence is required and will be presented. The retrieval of qualitative research using the same strategies as quantitative research has been reported as difficult and ineffective (Booth 2016a). Locating qualitative research requires an iterative process searching for data able to reflect the review objectives; this will include contacting authors of quantitative research to ask for details of qualitative add-on studies or stand-alone studies. Full details of the search strategy/processes for the identification of qualitative studies will be reported.

Electronic searches

We will search the following databases.

- The Cochrane Epilepsy Group's Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies (CRS Web), using the search strategy set out in Appendix 1.
- MEDLINE (Ovid) 1946 to present, using the search strategy set out in Appendix 2.
- SCOPUS 1823 to present, using the search strategy set out in Appendix 3.
- CINAHL Plus (EBSCOhost) 1937 to present, using the search strategy set out in Appendix 4.
- PsycINFO (EBSCOhost) 1887 to present, using the search strategy set out in Appendix 5.
- ClinicalTrials.gov, to present, using the search terms: Preconception counselling OR Preconception care | Epilepsy.
- WHO International Clinical Trials Registry Platform ICTRP, to present, using the search terms: Preconception counselling AND epilepsy OR Preconception care AND Epilepsy.

No restrictions will be placed on the date of publication. The language will be restricted for qualitative studies due to the costs associated with detailed and specialist translation.

Searching other resources

We will search conference abstracts for the last five years (2015 to 2020) from conferences including: International Epilepsy Congress, European Congress on Epileptology and American Epilepsy Society Meeting.

Reference lists of original research and review articles will be cross-matched to the studies generated from the electronic searches. Reference lists of recent review articles will be searched and lead corresponding authors in the area will be contacted for any relevant unpublished material. Citation searching and contact with experts in the area will be used to overcome problems with indexing of qualitative studies (Booth 2016a).

Data collection and analysis

We will apply inclusion and exclusion criteria and report any deviation from the protocol. We will firstly complete analysis of included quantitative studies, then complete the second analysis of included qualitative studies. We will then complete a final mixed method analysis combining both quantitative and qualitative data.

Selection of studies

Two review authors (JW and AM) will independently apply inclusion and exclusion criteria successively to titles, abstracts and full reports. Full details of possibly relevant studies will be obtained and assessed independently for inclusion in the review. Multiple reports of the same study will be linked together. If necessary, authors will be contacted to clarify study eligibility. If a disagreement occurs, the review authors will attempt to reach a consensus by discussion or involvement of a third author (CTS to resolve disagreement for the selection of quantitative studies; AN to resolve disagreement for the selection of qualitative studies; and AGM for any disagreement concerning eligibility).

We will list all studies excluded after full-text assessment and the reasons for exclusion in the 'Characteristics of excluded studies' section. We will document the study selection process in a flow chart, as recommended in the PRISMA statement (Moher 2009), and will show the total numbers of retrieved references and the numbers of included and excluded studies (and reasons why they were excluded).

Studies that do not meet the inclusion criteria will be excluded and their bibliographic details listed, with reasons for exclusion. For studies published in abstract form only, we will include the study if it is clearly eligible; if this is unclear then we will contact the study authors for further information and place the study in the 'Studies awaiting classification' section of the review until a reply is received (in an appropriate time frame).

Selecting quantitative studies for inclusion

If both randomised and non-randomised trials are defined eligible for an intervention addressing a specific outcome, then we will follow the guidance provided in the *Cochrane Handbook* for including non-randomised studies on intervention effects (Reeves 2019). We plan to present and analyse the results from randomised and non-randomised trials separately (Reeves 2019).

Qualitative study sampling

When selecting qualitative studies, we will consider the relevance of an included study to address the review question and meet the inclusion criteria. We will make an assessment of the relevance of the included study sample, as this may require the inclusion of studies that only partially address the context of the review question, or only cover a subgroup of the population or the subtype of the intervention stage (Noyes 2018a; Noyes 2019b). The potential for collecting a large sample of relevant studies will be addressed by using a sampling frame, with the aim of generating a variation of concepts rather than an exhaustive sample (Booth 2016a). A sampling frame will help manage the potential for inclusion of large numbers of studies and reduce the risk of impairing the quality of the analysis; we will purposively sample from studies meeting the review inclusion criteria.

We will use the sampling frame to select qualitative studies based on closeness to the following criteria:

- Focus on preconception care/counselling.
- The closeness of study data to review objectives.
- The richness of data to address the above criteria.
- Diverse settings.

Judgements on the relevance of the studies selected for inclusion will be assessed within the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) approach to determine the extent to which the review findings are a reasonable representation of the phenomenon of interest (Noyes 2019b). We will list all qualitative studies not included in the purposive sample, and the reasons for their exclusion, in the 'Characteristics of excluded studies' section.

Data extraction and management

Use of the PROGRESS (place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital) framework will ensure that all data extraction maintains an explicit equity focus (O'Neill 2014). Two review authors (JW, CTS) will extract quantitative data; and two review authors (JW, AM) will extract qualitative data, using a predefined data extraction form. For quantitative studies, we will use the Excel spreadsheet tool available from the website of version 2 of the Cochrane 'Risk of bias' tool for randomised trials (RoB 2) (RoB2 tools). Any disagreements will be resolved by discussion with a third review author (AGM for quantitative studies; and AN for qualitative studies). Data extraction forms will be piloted by one review author (JW) on at least one quantitative and one qualitative study. The data extracted will be reviewed for completeness of required data retrieval (any modifications will be fully reported in the complete review). Covidence software will be used for importing and de-duplicating citations; screening of titles, abstracts and full-text reports; and extracting data into excel format (Covidence). When necessary data are unavailable from the study report, we will correspond with the study authors.

Quantitative studies

The quantitative data extraction forms will comply with criteria provided in the *Cochrane Handbook* (Higgins 2019b) and with reference to the Cochrane Effective Practice and Organisation of Care (EPOC) group (EPOC 2017b) and RoB 2 website (RoB2 tools).

The additional requirements for data extraction of non-randomised study designs will be included (Reeves 2019).

Two review authors (JW, CTS) will obtain the following information for each included quantitative study, where possible.

Methodology/trial design

1. General information: author, year of publication, journal, country, and language
2. The number of eligible participants, number randomised if an RCT, and reasons why patients were not included in the study
3. The number of participants evaluated at follow-up(s) and what the follow-up time points were
4. Study design features, for example, whether it is an RCT on masking, whether a parallel design was used, features of randomisation, and sample size calculation
5. Description of the content of preconception intervention, including dosage, duration and method of delivery, number of sessions/intensity
6. Comparison intervention, including duration and mode
7. Outcome data at all time points, including how they were measured, and the mean or categorical scores of the primary and secondary outcomes
8. Notes: funding for the trial, notable conflicts of interest of trial authors, ethical approval

Participant demographics

1. Age (overall and by treatment group)
2. Gender (preconception care is increasingly targeting women and their partners)
3. Epilepsy/seizure type
4. Epilepsy duration and aetiology
5. Existing antiepileptic drug regimen (including dose, overall and by treatment group)
6. Baseline seizure frequency (overall and by treatment group)
7. Co-morbidity, including pregnancy history
8. Type of health care or community setting,
9. Stage of pregnancy intention and/or patient factors determining the selection of the type of intervention considered, and reasons given for the selection of preconception care intervention

Outcome data

We will extract from each included study the number of participants who met the following criteria:

1. Number of women included in the analysis of each outcome by the intervention group.
2. Outcome summary of data for each intervention (see Types of outcome measures).

For all serious adverse events, and adverse event reporting, we will extract data on both intervention and control/comparison arms. We will record any intervention withdrawal (e.g. withdrawal after the first visit), the number of serious adverse events, and the adverse events per intervention arm/period.

For continuous outcomes, we will extract the means and standard deviation of the comparison groups, where possible.

We will extract the study authors' definitions of the duration of seizure freedom; planned pregnancy and preconception folic acid intake, and important outcomes included in the review. We will extract the measure used in included studies to measure the reported outcome. We will extract arm-level data were possible, and if not available we will extract effect size. We will extract data at the authors' defined time points.

Data on potential effect modifiers

We will extract data on the following potential effect modifiers from each included study:

- Population: seizure frequency at baseline; the number of AEDs at baseline; and the number taking valproate at baseline.
- Study design: follow-up duration.
- Intervention: intensity, for example, single visit; the number of intervention visits; the time between visits.

Specifically for non-randomised studies, we will follow the guidance in the *Cochrane Handbook* (Reeves 2019). Where possible, we will also extract the following.

- Data on confounding factors considered and methods used to control for confounding. We will use the ROBINS-I tool as a template for this information (Sterne 2019a).
- Comparability of groups on confounding factors considered.
- Data about multiple effect estimates (both unadjusted and adjusted estimates, if available).
- Outcome data; including the type of outcome, how measured, and time point for primary and secondary outcomes.
- Study design characteristics: for example, whether there was a comparison, participant/cluster allocation, which parts of the study were prospective, which variables were assessed for comparability between groups.

Qualitative studies

We will enter data into QSR NVivo 11 qualitative electronic analysis software to support analysis (NVIVO11). We will use data extraction methods to preserve the context of the primary study data, to extract detailed contextual and methodological information on each study, and to report this information in a table of 'Characteristics of included studies' (Noyes 2019a).

The following information will be extracted for each qualitative study, independently by two review authors (JW, AM).

- Methodology/study design
  - Qualitative methodology (e.g. grounded theory, ethnography, etc.)
  - Study location and settings
  - Study aims
  - Method of collecting data (e.g. observation/focus groups/ interviews, etc.)
  - Method of analysis (e.g. thematic/discourse analysis, etc.)
  - Method of sampling (e.g. stratified, purposeful, etc.)
  - Source of funding
  - Quality assessment (Critical Appraisal Skills Programme (CASP) tool; Appendix 6)
  - Source of funding

- Participants/demographics
  * Number of participants
  * Age and gender of participants
  * Seizure type/classification
  * Seizure frequency
  * Treatment status
- Findings (the findings of interest can be located anywhere in a qualitative paper, and can be presented in a variety of formats, including text quotes, themes, conceptual framework and typologies, theories, charts, models and diagrams, photos and images, and also as supplementary online data). In order to take these factors into consideration, the data extraction form will be flexible, including the following.
  * Quotes, pictures, photographs, images.
  * Themes, conceptual frameworks or theories, diagrams, charts, typologies.
  * Views and interpretation relating to the delivery, communication, and/or perceived effectiveness of the preconception intervention.
  * Evidence of interest in any format, or reported within any section of the included paper, and/or additional online-only files.

Assessment of risk of bias in included studies

Assessment of risk of bias will be conducted for all studies meeting the inclusion criteria, using accepted methods for included study designs (randomised, non-randomised, and qualitative) (Sterne 2014; Sterne 2019a; Sterne 2019b; Noyes 2019a).

Quantitative studies

Assessment of risk of bias for included randomised controlled trials

Two review authors (JW and CTS) will independently assess the risk of bias for each included study using the RoB 2 tools as outlined in the *Cochrane Handbook* (Higgins 2019b). We will follow the interim guidance from the RoB 2 team for assessment of cluster-RCTs (Sterne 2019b, RoB2 tools). If there is disagreement in assessment, a third review author (AGM) will be consulted and a consensus judgement recorded.

We will use the RoB 2 tool to assess the following domains (for cluster-RCTs, additional signalling questions will be used for Domain 1b, in accordance with the interim guidance from the RoB 2 team).

- Domain 1: risk of bias arising from the randomisation process.
- Domain 1b: risk of bias arising from the timing of identification and recruitment of participants (for cluster-RCTs).
- Domain 2: risk of bias due to deviations from the intended interventions (effect of assignment to intervention).
- Domain 3: risk of bias due to missing outcome data.
- Domain 4: risk of bias in the measurement of the outcome.
- Domain 5: risk of bias in the selection of the reported results.

A judgement will be made for each domain, in response to a series of signalling questions. We will determine the overall risk of bias of each included outcome; this will be judged as 'low' if the risk of bias is low for all domains. The risk of bias will be judged as 'some concerns' if at least one domain is 'low', but not at high risk for any domain. The risk of bias will be judged 'high' if there is a high risk of bias in at least one domain or some concerns for multiple domains in a way that substantially lowers confidence in the result (Higgins 2019b). Justification of the responses will be included in the free text box, and the option to predict (and explain) the likely direction of bias will be applied as appropriate (Higgins 2019b).

The overall risk of bias will be assessed to form a judgement of predicted direction of bias for the outcome (either: 'not applicable', 'favours experimental', 'favours comparator', 'towards null', 'away from null' or 'unpredictable'). The overall RoB 2 judgement for each result will be used to contribute to the GRADE assessment for each result.

We will focus on the review outcomes and on the nature of the effect of intention-to-treat, to support final judgements and assist in drawing conclusions about preconception care for WWE. We intend to review results by means of the type of outcome, how the outcome was measured, and at which time points results were reported.

Assessment of risk of bias for included non-randomised studies of interventions

For non-randomised studies of interventions (NRSI), we will use the ROBINS-I tool for evaluating the risk of bias in estimates of the comparative effectiveness (harm or benefit) of interventions from studies that did not use randomisation to allocate units (individuals or clusters of individuals) to comparison groups (Sterne 2019a). Two review authors (CTS, JW) will independently follow the ROBINS-I methods to assess the risks of bias covering seven domains; pre-intervention, at intervention, and post-intervention (Sterne 2016a).

- Pre-intervention
  * Domain 1: Bias due to confounding
  * Domain 2: Bias in the selection of participants into the study
- At intervention
  * Domain 3: Bias in the classification of interventions
- Post-intervention
  * Domain 4: Bias due to deviations from intended interventions
  * Domain 5: Bias due to missing data
  * Domain 6: Bias in the measurement of outcomes
  * Domain 7: Bias in the selection of the reported result

The assessment of the risk of bias for each domain will be based on answers to the ROBINS-I signalling questions. If answering no to the signalling questions for a domain having potential problems, then the risk of bias for the domain can be judged to be low (Sterne 2016a). The categories for risk of bias judgements are “Low risk”, “Moderate risk”, “Serious risk” and “Critical risk” of bias. The results will be used to formulate an overall judgement on the risk of bias for the outcome and result being assessed. We will follow the full guidance documentation for ROBINS-I and comply with the latest variants for different included study designs (ROBINS-I). The ROBINS-I assessment requires consideration of the problems that might arise in the context of the research question, and when making a causal assessment of the effect of the intervention(s) of interest on the basis of NRSI (Sterne 2016a). In line with ROBINS-I methods, at the protocol stage, consideration of potential confounding domains and co-interventions was addressed. (Sterne 2019a).

Confounding domains

- Seizure severity
- Presence of co-morbidity (e.g. diabetes, mental disorders)
- Healthcare use (e.g. patient in receipt of specialist epilepsy care versus primary care; or no healthcare use versus healthcare use in the preceding 12 months)
- Physician prescribing practice (e.g. patient is prescribed valproate)
- Socioeconomic status

Potential co-interventions

- Contraception
- Folic acid
- Decision support
- Counselling
- Disease-specific information

Hypothetical target trial

Evaluations of the risk of bias in an NRSI is conceptualised as the attempt to emulate a pragmatic randomised trial, referred to as the target trial. The first part of a ROBINS-I assessment for a particular study is to specify a target trial. The target trial is a hypothetical randomised trial to produce results to be the same as those from the NRSI under consideration, in the absence of bias. The key characteristics are the types of participant (including exclusion/inclusion criteria) and a description of the experimental and comparator interventions. For each included NRSI, we will specify a target trail (Sterne 2016b).

We will present a 'Risk of bias' table for all results for all review primary outcomes, and all outcomes reported in the 'Summary of findings' table.

Assessing methodological strengths and limitations of qualitative studies

We will use the CASP checklist (CASP 2018) to assess the risk of bias of qualitative views' studies. Two review authors (JW and AM) will independently apply the CASP tool to determine the rigour of qualitative methods of included studies. Disagreements will be resolved by seeking a third review author's view (AN). The CASP tool will be used to examine the quality of a study in relation to 10 questions about research aims, appropriateness of methodology and design, recruitment strategy, data collection, the relationship of the researcher, consideration of ethical issues, data analysis, statement of finding and the value of the research (Noyes 2019b) (see also Appendix 6). We will include a further criterion to assess methodological rigour to supplement the CASP checklist by questioning 'usefulness', i.e. how well the intervention processes were described and whether or not the process data could illuminate why or how the interventions worked or did not work (Noyes 2019a).

We will report our assessment of methodological limitations for each study in the 'Characteristics of included studies' tables. We will assess the risk of bias after the identification of relevant data when making judgements about the relative strength of messages in the included research. We will present a 'Risk of bias' table for all studies.

Storage and presentation of data

It is anticipated a large volume of data will be generated from the completion of RoB 2, ROBINS-I and the qualitative analysis. We plan to make data available in an online format and provide detailed appendices.

Measures of treatment effect

When considering treatment effects, we will take into account the risks of bias and methodological limitations for the studies that contribute to that outcome.

Quantitative studies

When at least two studies are available for comparison with the same outcomes, we plan to present dichotomous data as a risk ratio (RR) with 95% confidence intervals (CIs) (e.g. for the outcomes preconception commencement of folic acid, pregnancy, and registration into the UK Epilepsy and Pregnancy Register). We will adjust for baseline differences, in line with EPOC and Cochrane methodology (EPOC 2017a; Higgins 2019a).

For continuous data, we plan to present the overall effect estimates as mean differences or standardised mean differences (SMDs) depending on the nature of the measures being used. For continuous outcomes measured on the same scale (e.g. the Liverpool Seizure Severity Scale or London Measure of Unplanned Pregnancy) we will estimate the treatment effect using mean differences and 95% CIs. For continuous outcomes that measure the same underlying concepts (e.g. preconception knowledge, attitudes, behaviour change) but use different measurement scales, we will calculate the SMD. We plan to express time-to-event data as hazards ratio (HR) with 95% CIs. We will present conceptually distinct outcomes in separate forest plots.

If it is possible to combine continuous outcomes (such as cognitive effects and quality of life) in a meta-analysis, we plan to report the mean difference. However, since we expect to identify significant variability, we plan to report the SMD. In the event that there is significant clinical heterogeneity (determined as variability in the participants, interventions and outcomes studied) of outcome measures, and meta-analysis is deemed to be inappropriate, we plan to report the results of these outcomes narratively.

Specific issues for non-randomised studies of interventions

We will take into account EPOC methodology when analysing results from interrupted time series (ITS) study designs (EPOC 2017a). We will use the preferred methods to analyse ITS studies, where possible, to make statistical comparisons of time trends before and after the intervention. We will also consider techniques of regression analysis with time trends before and after the intervention, with adjustment for autocorrelation and any periodic changes, or time series analysis using autoregressive integrated moving average (ARIMA) models.

As there are a number of statistical techniques that can be used depending on the characteristics of the data, decisions for the methods used will be documented in the completed review, with reference to the number of data points available and whether autocorrelation is present. We will present the results for the outcomes as changes along two dimensions: change in level and change in slope (EPOC 2017a).

Unit of analysis issues

Quantitative studies

We anticipate that studies will allocate individuals to one of two intervention groups and a single measurement will be made for each participant for each outcome. We do not expect to find cross-over trials or studies that use repeated measures. If a unit-of-analysis error is identified in the analysis of an included study, we will assess if sufficient information is available to re-analyse the results. We will contact study authors to obtain necessary data.

We will follow EPOC methods to perform analysis at the same level as the allocation to avoid unit-of-analysis errors. If cluster-randomised trials are identified, we will adjust the standard errors or sample sizes using methods described by the EPOC analytic methods group and the *Cochrane Handbook* (EPOC 2017a; Higgins 2019a). Based on methods described in the *Cochrane Handbook* we plan to adjust cluster-randomised data by inflating standard errors using a design effect calculated with an intra-cluster correlation coefficient. If analogous studies are not available, we will use a series of plausible values in a sensitivity analysis (see Sensitivity analysis).

For NRSI, we plan to perform analysis at the same level as the allocation to avoid unit-of-analysis errors. For cluster-randomised trials, we plan to perform analysis adjusting for clustering to avoid unit-of-analysis errors. We will review extracted results for cluster trials to confirm analysis has been adjusted for clustering, a reanalysis of the results will be performed (we will contact the authors of such studies for the required data).

Dealing with missing data

Quantitative studies and qualitative studies

We plan to contact study authors to retrieve any missing information. As part of Domain 3 of RoB 2, we will assess the risk of missing data to define judgements of risk of bias. If study authors are unable to provide missing information, this will be entered into the tool as 'no information' to contribute to the algorithm to propose the judgement. The degree of 'missingness of outcome data' will require inference of the true value, and will be applied with reference to the *Cochrane Handbook*, review of how the trial author has reported missing data, the proportion of missing data, and how this was managed (e.g. through sensitivity analysis) (Higgins 2019b).

Assessment of heterogeneity

Quantitative studies

We intend to assess clinical heterogeneity by examining differences in study characteristics in order to inform decisions regarding the combination of study data. Heterogeneity will be defined as clinical (variability in the participants, interventions and outcomes studied); methodological (variability in study design and risk of bias) and statistical (variability in the intervention effects being evaluated). The identification of clinical or methodological heterogeneity, or both, among the studies will be used to describe the intervention effects being more different from each other than one would expect due to random error (chance) alone.

We will identify sources of clinical heterogeneity by constructing tables to summarise studies in terms of participants, setting, type of intervention, intervention delivery (e.g. group or individual, number of visits/appointments) and outcomes examined. Where studies are similar, we will conduct further investigations, initially by visually reviewing the consistency of the results across studies using graphical representations, e.g. forest plots (Deeks 2019). To initially identify the heterogeneity/inconsistency of study results we will use the Q statistic, separating the studies based on design.

We will assess statistical heterogeneity with the Chi^2 test, to provide evidence of variation in effects, disregarding the effect of chance. As the Chi^2 test is ineffective for analysing heterogeneity in studies with only a small number of participants or trials, we plan to set the P value at 0.10, and assess heterogeneity using the I^2 statistic, which will calculate the percentage of variability due to heterogeneity outside of the effect of chance (Deeks 2019).

We assume that some statistical heterogeneity is inevitable, and hence, we will evaluate heterogeneity using the I^2 statistic, using the following thresholds of interpretation (Deeks 2019).

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity*.
- 50% to 90%: may represent substantial heterogeneity*.
- 75% to 100%: considerable heterogeneity*.

*The importance of the observed value of I^2 depends on: 1) the magnitude and direction of effects, and 2) the strength of evidence for heterogeneity (Deeks 2019). We will take into consideration the size and direction of effects, and the strength of evidence for heterogeneity using the Chi^2 test and the 95% CI for I^2.

Where there is evidence for statistical heterogeneity, we will use the strategies outlined in chapter 10 of the *Cochrane Handbook* (Deeks 2019), to identify potential sources of heterogeneity among the results of the studies. In particular, we will explore differences in the characteristics of the studies or other factors as possible explanations for heterogeneity in the results. We will summarise any differences identified in the narrative summary. We will investigate heterogeneity by using subgroup analyses to explore whether the intervention effects vary between populations and intervention characteristics (see Subgroup analysis and investigation of heterogeneity).

Non-randomised studies

It is anticipated that non-randomised studies will introduce greater heterogeneity due to their methodological diversity, risks of bias and extent of residual confounding (and the methods used to control for confounding) (Reeves 2019). We plan to display any variation in results with forest plots. Forests plots will be used to display estimates of standard errors for each included study, where possible using consistent effect measures (if not available, or calculable, then additional tables will be used to systematically present results) (Reeves 2019).

Qualitative studies

For qualitative data, we intend to assess heterogeneity by examining study differences (including methods of analysis and types of participants) to allow appropriate synthesis/meta-synthesis of data.

Assessment of reporting biases

Quantitative studies

We plan to investigate outcome reporting bias using the ORBIT matrix system (Kirkham 2010). We plan to assess publication bias by identifying unpublished data, by carrying out a comprehensive search of multiple sources and requesting any unpublished data from study authors. If we are able to combine a sufficient number of studies for analysis, we will assess funnel plots and look for small-study effects to establish the likelihood of publication bias (Higgins 2019b).

Qualitative studies

Dissemination bias is not included within the overall assessment of GRADE-CERQual (Booth 2018a). Dissemination bias is presented as a future component of the CERQual approach awaiting methodological development, and is conceptualised as the "systematic distortion of the phenomenon of interest due to selective dissemination of qualitative studies or the findings of qualitative studies" (Booth 2018a). We will report any changes to protocol methods to take account of any methodological developments published in the time taken to complete the current review.

Data synthesis

Quantitative studies

We plan to perform data synthesis using Review Manager Web (RevMan Web 2020). We plan to make comparisons between separate comparisons for interventions and controls if data are available. However, as previously noted, the use of the control group might be a challenge; therefore, we plan to complete a separate analysis for each intervention, e.g. intervention 1 versus intervention 2.

If we do not identify substantial heterogeneity among the included studies, we intend to use a fixed-effect model to perform the meta-analysis. If the statistical heterogeneity among the included studies is substantial (indicated by an I^2 value of more than 75%), we intend to use a random-effects model. If it is not possible to pool data, we will provide clear reasons for this and report results narratively.

Qualitative studies

We plan to perform qualitative syntheses to help understand how participation in preconception care interventions might (or might not) improve perception/experience of maternal and future infant health for WWE preparing for pregnancy and to better understand the interventions' acceptability, usefulness and barriers to uptake in a range of healthcare settings. The RETREAT framework will be used to identify the most appropriate synthesis method (Booth 2016b; Booth 2018b). The RETREAT framework is a conceptualisation of the important factors to be considered in the selection of a method of qualitative evidence synthesis. The framework considers seven domains and within each domain includes questions concerning: research question, epistemology, time frame, resources, expertise, audience, and purpose and type of data (Booth 2016b; Booth 2018b). The final selection of qualitative synthesis method will be deferred until the data extraction is complete, and decision rationale documented with review methods (Booth 2016b; Flemming 2019; Noyes 2018b).

The type of data retrieved within the review findings will be further categorised, in terms of quality/quantity (quantity will be managed by application of a sampling frame, see Selection of studies); context (thick/thin); theory (rich/poor); and the units of analysis (Booth 2018b; Flemming 2019). The available time frame, resources and review authors' expertise will be considered, as well as the need for a pragmatic approach. Final consideration of the purpose of this mixed-methods review to produce syntheses that can subsequently be integrated within an intervention review will take into account the recommendations of appropriate methods including thematic synthesis, framework synthesis and meta-ethnography (Flemming 2019; Noyes 2019a).

Mixed methods synthesis: combining quantitative and qualitative data

We will use methods of synthesis to combine qualitative and quantitative data as described in chapter 21 of the *Cochrane Handbook* (Noyes 2019a), as well as the recommendations outlined by the Cochrane Qualitative and Implementation Methods Group (Harden 2018).

There are two main approaches to integrating qualitative and quantitative data: sequential and convergent. The convergent approach involves qualitative and quantitative research being collected and analysed at the same time in parallel, with the integration occurring at three different time points dependent on the review objectives (Noyes 2018b; Noyes 2019b). We plan to use a results-based convergent synthesis to support the origins of this review update.

The choice of methods for this final synthesis will be dependent on the number of studies and extracted evidence available, and the quality of description within included studies (e.g. intervention content, context, and study findings). The final synthesis method will be selected from methods including; for example, narrative, tables, matrices or reanalysing evidence, to help to identify gaps in the evidence (Noyes 2019b). If sufficient data are available we plan to use juxtaposing synthesis methods to present findings in a matrix with quantitative studies grouped according to preconception interventions along one side of the matrix, with the themes from qualitative evidence synthesis relating to the acceptability and feasibility of the intervention components plotted along the other side of the matrix to allow comparison (of match or mismatch) (Harden 2018). A juxtaposing synthesis using a matrix will importantly help determine if the presence of acceptable/feasible intervention components has an impact on the outcomes. This approach can help us to understand why heterogeneity that we may find in the quantitative analyses exists (Harden 2018).

We plan to use the results of this mixed-methods synthesis to explore the convergence and divergence of results and we aim to provide a narrative explanation of intervention effectiveness. Decisions made in the selection of mixed methods synthesis and the application of the chosen methods will be fully documented within the complete review.

Subgroup analysis and investigation of heterogeneity

Quantitative studies

Randomised studies

Where there are sufficient data, we will carry out subgroup analyses based on the following factors that may cause the effect of the

preconception care intervention to vary. We will complete the subgroup analysis on all primary outcomes.

- Location of intervention delivery (hospital or the community).
- Intervention content (e.g. changes of AED; provision of risk information; commencement of folic acid).
- Delivery mode (individual (hospital or community clinic) or group (hospital or community)).
- Length, frequency or intensity of intervention delivery.
- Delivery methods/personnel (e.g. multidisciplinary, individual discipline).
- Participant ethnicity /Economic status (low-to-middle income, or high-income countries)(as defined in the included studies).
- Country or location of study (Europe versus North America versus Asia versus others).
- Study design

We will explore heterogeneity within these subgroups using the Chi^2 test and visual inspection of forest plots generated within Review Manager Web (RevMan Web 2020). We will develop a narrative summary for these subgroups and this will be supported by harvest plots to help graphically illustrate the results. Risk of bias will be presented as a traffic light plot on meta-analysis at the results level.

Non-randomised studies

In addition to the above analyses, it is recognised that greater heterogeneity is observed in NRSI; and where there are sufficient data on intervention effect estimates available, we will undertake meta-regression analyses to identify important determinants of heterogeneity (Reeves 2019).

Sensitivity analysis

Quantitative studies

We will base our primary analyses on available data from all included studies/results relevant to the comparison of interest. However, in order to examine any effects of methodological decisions on the overall outcome, we will perform sensitivity analyses provided there are sufficient numbers of studies. These sensitivity analyses may include the following.

- Reanalysis of the data, excluding studies with results at high risk of bias.
- Reanalysis of data, excluding studies judged to have some concerns of risk of bias for at least one domain of RoB 2.
- Reanalysis of the data, excluding studies with missing outcome data.

Additional sensitivity analyses may be required if particular issues related to the studies under review arise.

Qualitative studies

We will complete a qualitative 'sensitivity analysis', by exploring the robustness of the synthesis and its vulnerability to methodologically limited studies (Carroll 2013). This will involve a reanalysis of the data following the exclusion of inadequately reported studies. The reanalysis will question the impact of exclusions upon the following.

- Themes generated within the initial synthesis.
- Richness ('thickness') of data within the synthesis.

These sensitivity analyses will be reported within the overall confidence in synthesis findings.

Summary of findings and assessment of the certainty of the evidence

Quantitative studies

We will create a 'Summary of findings' table for each comparison, using GRADEpro GDT (GRADEpro GDT 2015). In these tables, we will report the outcomes at post-intervention (Schünemann 2019a). We will include all the primary preconception care outcomes in the 'Summary of findings' tables.

The GRADE approach will be used to assess the certainty of the evidence for each outcome, considering the risk of bias, indirectness, inconsistency, imprecision of effect estimates, and risk of publication bias. For evidence from non-randomised studies (and, rarely, randomised studies), assessments may be upgraded through consideration of three further domains: effect size; the presence of plausible confounding that will change the effect; and dose-response gradient.

Two review authors (JW, CTS) will independently assess the certainty of the evidence for each outcome, and assign ratings of high, moderate, low or very low certainty, according to the presence of the five criteria listed above and in line with methods described in the *Cochrane Handbook* (Schünemann 2019a). We will take account of the review objectives, and the recommendations in chapters 14 and 25 of the *Cochrane Handbook* (Schünemann 2019a; Sterne 2019a) when assessing the within-study risk of bias using GRADE and ROBINS-I. We will use the Excel tool on the RoB 2 website to record and manage the RoB 2 assessments that contribute into GRADE, displaying traffic light plots for each result. We will describe any patterns of bias seen across results and offer our reasoned interpretation.

We will report judgements in selecting the most appropriate methods for presenting findings and will follow GRADE guidance regarding presenting evidence from randomised trials and evidence from non-randomised studies (Schünemann 2019b). In keeping with Schünemann and colleagues (2019b), one 'Summary of findings' table will be presented if the higher-certainty evidence is from RCTs. If certainty ratings are the same between study designs then separate 'Summary of findings' tables will be presented for results from randomised trials and those from non-randomised studies. If the results are consistent, then the overall certainty assessment is that of the two bodies of evidence (typically, findings from non-randomised studies are of lower certainty). If the results are inconsistent, we will consider the bodies of evidence from each study design and will downgrade further for this inconsistency, and the final rating will be one category lower (typically, non-randomised designs are graded as very-low certainty), with all decisions reported within the final review (Schünemann 2019b).

We plan to report the grading of the certainty of evidence in the review results section for each outcome for which an assessment is performed. We will justify and document all assessments of the certainty of the body of evidence and provide the rationale for downgrading or upgrading the evidence, with reference to the 'Summary of findings' table as applicable.

Qualitative studies

We will use the GRADE-CERQual approach to make a transparent assessment of the degree of confidence in findings from the synthesis of qualitative evidence (Noyes 2018b). The GRADE-CERQual approach will be used to determine the confidence of the evidence as an assessment of the extent to which the review findings are a reasonable representation of the phenomenon of interest, i.e. preconception interventions for WWE (Lewin 2018b; Noyes 2019a). Confidence will be assessed for each review finding, independently by two review authors (JW, AM). The assessment of the confidence of the evidence will be based on the assessment of four CERQual components/domains.

- Methodological limitations: the extent to which there are problems in the design or conduct of the primary studies that contributed evidence to a review finding.
- Coherence: the extent to which the review finding is well-grounded in data from the contributing primary studies and provides a convincing explanation for the patterns found in these data.
- Adequacy of data: an overall determination of the degree of richness and quantity of data supporting a review finding.
- Relevance: the extent to which the body of evidence from the primary studies supporting a review finding is applicable to the context (perspective or population, the phenomenon of interest, setting) specified in the review question.

We will manage the results from qualitative synthesis, taking account of the minimum criteria for fidelity to the GRADE-CERQual approach (Lewin 2018a). We will record the transparency of quality assessment and data synthesis using NVIVO 10 qualitative analysis software to create a CERQual Summary of Qualitative Findings table to display a structured summary of each study contributing data to each finding (Lewin 2018b). The summary table will also provide an assessment of confidence in the evidence as well as an explanation of this assessment, based on the GRADE-CERQual approach (Lewin 2018a).

Two review authors (JW; AM) will assign a level of confidence for each component, as detailed below. By default, they will start with 'high confidence' and downgrade if there are concerns regarding any of the CERQual components; they will provide a description of the concerns influencing the decision (Lewin 2018b).

- High confidence: no or very minor concerns that are unlikely to reduce confidence in the review finding as a reasonable representation of the phenomenon of interest.
- Minor concerns: that may reduce confidence in the review finding.
- Moderate concerns: that will probably reduce confidence in the review finding.
- Serious concerns: that are very likely to reduce confidence in the review finding.

Reflexivity

Reflexivity refers to the researchers' acknowledgement of potential influence upon the findings, in relation to all aspects of the research process including analysis and interpretation. Whilst seen as an essential component of qualitative research quality, it has an important role to play in quantitative research as a source of bias. Within this mixed-methods review, it will be our intention to incorporate reflexivity throughout, acknowledging the review authors' prior standpoints, professional backgrounds and beliefs, and the potential for these to influence judgements, review findings and interpretations.

Involvement of patients and public

The review update and increased scope of the mixed methods review protocol was the result of a wider consultation with patients and public engagement. Members of Epilepsy Action, a UK voluntary organisation, were surveyed concerning their experience of preconception counselling for WWE in the UK. The protocol and review will receive feedback from at least one consumer referee in addition to a health professional as part of the Cochrane Epilepsy editorial process.

Assessment of bias in conducting the review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

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APPENDICES

Appendix 1. CRS Web search strategy

1. MESH DESCRIPTOR Preconception Care EXPLODE ALL AND INSEGMENT

2. MESH DESCRIPTOR Pregnancy EXPLODE ALL AND INSEGMENT

3. MESH DESCRIPTOR Pregnant Women EXPLODE ALL AND INSEGMENT

4. pregnan* AND INSEGMENT

5. #2 OR #3 OR #4 AND INSEGMENT

6. MESH DESCRIPTOR Personal Narratives as Topic EXPLODE ALL AND INSEGMENT

7. (personal narratives):PT AND INSEGMENT

8. (narrativ* or biograph*) not "narrative review" AND INSEGMENT

9. #6 OR #7 OR #8 AND INSEGMENT

10. #5 AND #9 AND INSEGMENT

11. prepregnancy or "pre-pregnancy" or "pre pregnancy" AND INSEGMENT

12. (plan* NEAR3 pregnan*) OR (pregnan* NEAR3 plan*) AND INSEGMENT

13. (plan* NEAR3 conceive) OR (conceive NEAR3 plan*) AND INSEGMENT

14. (plan* NEAR3 conception) OR (conception NEAR3 plan*) AND INSEGMENT

15. preconception* or "pre-conception*" or "pre conception*" or periconception* or "peri-conception*" or "peri conception*" AND INSEGMENT

16. reproductive health AND INSEGMENT

17. MeSH DESCRIPTOR Reproductive Health Explode All AND INSEGMENT

18. MeSH DESCRIPTOR Family Planning Services Explode All AND INSEGMENT

19. (plan* NEAR3 family) OR (family NEAR3 plan*) OR "planned parenthood" AND INSEGMENT

20. folic acid AND INSEGMENT

21. MeSH DESCRIPTOR Folic Acid Explode All AND INSEGMENT

22. #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 AND INSEGMENT

23. MeSH DESCRIPTOR Counseling Explode All OR MESH DESCRIPTOR Health Promotion EXPLODE ALL OR MESH DESCRIPTOR Risk Reduction Behavior EXPLODE ALL AND INSEGMENT

24. counsel* or educat* or inform* or advice or advise AND INSEGMENT

25. #23 OR #24 AND INSEGMENT

26. #22 AND #25 AND INSEGMENT

27. #1 OR #10 OR #26 AND INSEGMENT

28. MESH DESCRIPTOR Preconception Care EXPLODE ALL AND CENTRAL:TARGET

29. MESH DESCRIPTOR Pregnancy EXPLODE ALL AND CENTRAL:TARGET

30. MESH DESCRIPTOR Pregnant Women EXPLODE ALL AND CENTRAL:TARGET

31. pregnan* AND CENTRAL:TARGET

32. #29 OR #30 OR #31 AND CENTRAL:TARGET

33. MESH DESCRIPTOR Personal Narratives as Topic EXPLODE ALL AND CENTRAL:TARGET

34. (personal narratives):PT AND CENTRAL:TARGET

35. (narrativ* or biograph*) not "narrative review" AND CENTRAL:TARGET

36. #33 OR #34 OR #35 AND CENTRAL:TARGET

37. #32 AND #36 AND CENTRAL:TARGET

38. prepregnancy or "pre-pregnancy" or "pre pregnancy" AND CENTRAL:TARGET

39. (plan* NEAR3 pregnan*) OR (pregnan* NEAR3 plan*) AND CENTRAL:TARGET

40. (plan* NEAR3 conceive) OR (conceive NEAR3 plan*) AND CENTRAL:TARGET

41. (plan* NEAR3 conception) OR (conception NEAR3 plan*) AND CENTRAL:TARGET

42. preconception* or "pre-conception*" or "pre conception*" or periconception* or "peri-conception*" or "peri conception*" AND CENTRAL:TARGET

43. reproductive health AND CENTRAL:TARGET

44. MeSH DESCRIPTOR Reproductive Health Explode All AND CENTRAL:TARGET

45. MeSH DESCRIPTOR Family Planning Services Explode All AND CENTRAL:TARGET

46. (plan* NEAR3 family) OR (family NEAR3 plan*) OR "planned parenthood" AND CENTRAL:TARGET

47. folic acid AND CENTRAL:TARGET

48. MeSH DESCRIPTOR Folic Acid Explode All AND CENTRAL:TARGET

49. #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 AND CENTRAL:TARGET

50. MeSH DESCRIPTOR Counseling Explode All OR MESH DESCRIPTOR Health Promotion EXPLODE ALL OR MESH DESCRIPTOR Risk Reduction Behavior EXPLODE ALL AND CENTRAL:TARGET

51. counsel* or educat* or inform* or advice or advise AND CENTRAL:TARGET

52. #50 OR #51 AND CENTRAL:TARGET

53. #49 AND #52 AND CENTRAL:TARGET

54. #28 OR #37 OR #53 AND CENTRAL:TARGET

55. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET

56. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET

57. epilep* OR seizure* OR convuls* AND CENTRAL:TARGET

58. #55 OR #56 OR #57 AND CENTRAL:TARGET

59. #54 AND #58 AND CENTRAL:TARGET

60. #27 OR #59

Appendix 2. MEDLINE search strategy

1. exp Preconception Care/

2. exp Pregnancy/

3. exp Pregnant Women/

4. pregnan$.tw.

5. 2 or 3 or 4

6. exp personal narratives as topic/

7. personal narratives.pt.

8. ((narrativ$ or biograph$) not "narrative review").tw.

9. 6 or 7 or 8

10. 5 and 9

11. (prepregnancy or "pre-pregnancy" or "pre pregnancy").tw.

12. (plan$ adj3 pregnan$).ti,ab.

13. (plan$ adj3 conceive).ti,ab.

14. (plan$ adj3 conception).ti,ab.

15. (preconception$ or "pre-conception$" or "pre conception$" or periconception$ or "peri-conception$" or "peri conception$").tw.

16. reproductive health.mp. or exp Reproductive Health/

17. exp Family Planning Services/

18. ((family adj3 plan$) or "planned parenthood").ti,ab.

19. folic acid.mp. or exp Folic Acid/

20. or/11-19

21. exp Counseling/ or exp Health Promotion/ or exp Risk Reduction Behavior/

22. (counsel$ or educat$ or inform$ or advice or advise).tw.

23. 21 or 22

24. 20 and 23

25. exp Epilepsy/

26. exp Seizures/

27. (epilep$ or seizure$ or convuls$).tw.

28. 25 or 26 or 27

29. exp *Pre-Eclampsia/ or exp *Eclampsia/

30. 28 not 29

31. 1 or 10 or 24

32. 30 and 31

33. remove duplicates from 32

Appendix 3. SCOPUS search strategy

((TITLE-ABS(pregnan* AND (narrativ* or biograph*) AND NOT "narrative review")) OR (((TITLE-ABS-KEY(prepregnancy OR "pre-pregnancy" OR "pre pregnancy" OR preconception* OR "pre-conception*" OR "pre conception*" OR periconception* OR "peri-conception*" OR "peri conception*")) OR (TITLE-ABS-KEY("family planning" OR "reproductive health" OR "planned parenthood" OR "folic acid"))) AND (TITLE-ABS-KEY(counsel* OR educat* OR inform* OR advise OR advice)))) AND ((TITLE-ABS-KEY(epilep* OR "infantile spasm" OR "ring chromosome 20" OR "R20" OR "myoclonic encephalopathy" OR "pyridoxine dependency") OR (TITLE-ABS-KEY(syndrome) W/2 (aicardi OR angelman OR doose OR dravet OR janz OR jeavons OR "landau kleffner" OR "lennox gastaut" OR ohtahara OR panayiotopoulos OR rasmussen OR rett OR "sturge weber" OR tassinari OR "unverricht lundborg" OR west)) OR TITLE(seizure OR convuls*) OR (TITLE-ABS-KEY(lafora*) W/4 (disease OR epilep*) AND NOT (TITLE(dog OR canine) OR INDEXTERMS(dog OR canine)))) AND NOT (TITLE(*eclampsia) OR INDEXTERMS(*eclampsia))) AND NOT INDEX(medline)

Plus forward citation searches for:

(AUTHOR-NAME(Weckesser) AND TITLE("Re-working biographies")) OR (AUTHOR-NAME(Weckesser) AND TITLE("women living with epilepsy")) OR (AUTHOR-NAME(Pashley) AND TITLE("The safety of anti-epileptic drug regimens")) OR (AUTHOR-NAME(Thompson) AND TITLE("Chronic illness, reproductive health and moral work")) OR (AUTHOR-NAME(Wallace) AND TITLE("Quality of epilepsy treatment and services"))

Appendix 4. CINAHL Plus search strategy

S13 S9 AND S12

S12 S10 OR S11

S11 MM ("Epilepsy+") OR (MM "Seizures")

S10 epilep* OR seizure*

S9 S1 OR S2 OR S8

S8 S6 AND S7

S7 counsel* OR educat* OR inform* OR advise OR advice

S6 S3 OR S4 OR S5

S5 prepregnancy OR "pre-pregnancy" OR "pre pregnancy" OR preconception* OR "pre-conception*" OR "pre conception*" OR periconception* OR "peri-conception*" OR "peri conception*"

S4 family planning OR reproductive health OR planned parenthood OR folic acid

S3 (MM "Family Planning") OR (MM "Reproductive Health") OR (MM "Folic Acid")

S2 MM "Prepregnancy Care"

S1 pregnan* AND ((narrativ* or biograph*)) NOT "narrative review"

Appendix 5. PsycINFO Search strategy

S13 S9 AND S12

S12 S10 OR S11

S11 MM ("Epilepsy+") OR (MM "Seizures")

S10 epilep* OR seizure*

S9 S1 OR S2 OR S8

S8 S6 AND S7

S7 counsel* OR educat* OR inform* OR advise OR advice

S6 S3 OR S4 OR S5

S5 prepregnancy OR "pre-pregnancy" OR "pre pregnancy" OR preconception* OR "pre-conception*" OR "pre conception*" OR periconception* OR "peri-conception*" OR "peri conception*"

S4 family planning OR reproductive health OR planned parenthood OR folic acid

S3 (MM "Family Planning") OR (MM "Reproductive Health") OR (MM "Folic Acid")

S2 MM "Prepregnancy Care"

S1 pregnan* AND ((narrativ* or biograph*)) NOT "narrative review"

Appendix 6. CASP 2013

©Critical Appraisal Skills Programme (CASP) Qualitative Research Checklist 31.05.13 (CASP 2018)

We will assess the methodological limitations for each included qualitative study using an the Critical Appraisal Skills Programme (CASP) quality assessment tool and record results of the following ten questions.

1. Was there a clear statement of the aims of the research? #Yes #Can't tell #No

Consider:

- What is the goal of the research?
- Why is it important?
- Its relevance

2. Is a qualitative methodology appropriate? #Yes #Can't tell #No

Consider:

- If the research seeks to interpret or illuminate the actions and/or subjective experiences of research participants
- Is qualitative research the right methodology for addressing the research goal?

3. Was the research design appropriate to address the aims of the research? #Yes #Can't tell #No

Consider:

- If the researcher has justified the research design (e.g. have they discussed how they decided which method to use?)

4. Was the recruitment strategy appropriate to the aims of the research? #Yes #Can't tell #No

Consider:

- If the researcher has explained how the participants were selected
- If they explained why the participants they selected were the most appropriate to provide access to the type of knowledge sought by the study
- If there are any discussions around recruitment (e.g. why some people chose not to take part)

5. Were the data collected in a way that addressed the research issue? #Yes #Can't tell #No

Consider:

- If the setting for data collection was justified
- If it is clear how data were collected (e.g. focus group, semi-structured interview, etc.)
- If the researcher has justified the methods chosen
- If the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews were conducted, or did they use a topic guide?)
- If methods were modified during the study. If so, has the researcher explained how and why?
- If the form of data is clear (e.g. tape recordings, video material, notes, etc.)
- If the researcher has discussed saturation of data

6. Has the relationship between researcher and participants been adequately considered? #Yes #Can't tell #No

Consider:

- If the researcher critically examined their own role, potential bias and influence during:
  - Formulation of the research questions
  - Data collection, including sample recruitment and choice of location
- How the researcher responded to events during the study and whether they considered the implications of any changes in the research design

7. Have ethical issues been taken into consideration? #Yes #Can't tell #No

Consider:

- If there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained
- If the researcher has discussed issues raised by the study (e.g. issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study)
- If approval has been sought from the ethics committee

8. Was the data analysis sufficiently rigorous? #Yes #Can't tell #No

Consider:

- If there is an in-depth description of the analysis process
- If thematic analysis is used. If so, is it clear how the categories/themes were derived from the data?
- Whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process
- If sufficient data are presented to support the findings
- To what extent contradictory data are taken into account
- Whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation

9. Is there a clear statement of findings? #Yes #Can't tell #No

Consider:

- If the findings are explicit
- If there is adequate discussion of the evidence both for and against the researcher's arguments
- If the researcher has discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst)
- If the findings are discussed in relation to the original research question

10. How valuable is the research?

Consider:

- If the researcher discusses the contribution the study makes to existing knowledge or understanding e.g. do they consider the findings in relation to current practice or policy, or relevant research-based literature?
- If they identify new areas where research is necessary
- If the researchers have discussed whether or how the findings can be transferred to other populations or considered other ways the research may be used

WHAT'S NEW

Date	Event	Description
3 December 2020	New citation required and major changes	Since the previous protocol published in 2014 (Winterbottom 2014b), the review team have updated the methodology to adhere to the guidelines for a Cochrane mixed methods review.

HISTORY

Protocol first published: Issue 3, 2014

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the writing of this protocol. AGM provided supervision throughout the development of the protocol and provided comments on drafts. AN and AGM contributed to updating the protocol, and reviewed the updates to the background and methods.

DECLARATIONS OF INTEREST

JW has been awarded an NIHR grant to complete a mixed methods Delphi to develop a preconception care pathway and identify patient-reported outcomes for preconception care for women with epilepsy in the UK.

AGM: is part funded by the National Institute for Health Research Applied Research Collaboration North West Coast (NIHR ARC NWC). A consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to University of Liverpool.

AN: none known.

CTS: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

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NOTES

Janine Winterbottom is the principal author of the Cochrane Review "Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome" (Winterbottom 2008). This review has now been withdrawn from publication as this protocol supersedes the review.