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Protocol for a systematic review and economic modelling of the relative clinical- and cost-effectiveness of interventions for hyperemesis gravidarum

DATE OF PROJECT

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NAME OF TEAM AND PROJECT 'LEAD'

Newcastle Evidence Synthesis Group

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SUMMARY

Design: The study will involve four components. (i) systematic review of randomised controlled trials and nonrandomised controlled studies for clinical effectiveness, and population-based case series for adverse events, fetal outcomes and outcomes following assisted feeding (e.g. those receiving total parenteral nutrition); (ii) narrative synthesis, meta-analysis of clinical effectiveness outcomes; (iii) economic modelling of the effectiveness, adverse events and cost-effectiveness comparing non-pharmacological and pharmacological treatments for hyperemesis gravidarum; and (iv) future research needs informed by value of information analysis.

Setting: Community, primary care, hospital outpatients and hospital inpatients.

Target population: Women experiencing severe nausea, vomiting and/or retching in pregnancy where recruitment to a trial took place up to 20 weeks gestation for relative effectiveness.

Health technologies to be considered: All pharmacological and non-pharmacological interventions relevant to the National Health Service (NHS) in the community and in hospital (inpatient or outpatient treatment). These interventions will include: dietary/lifestyle interventions; vitamins such as vitamin B6 and vitamin B12; ginger; acupressure/acupuncture; hypnosis; antiemetic drugs such as antihistamines; dopamine antagonists; 5-hydroxytryptamine (HT)-receptor antagonists; corticosteroids; intravenous fluids; enteral feeding and total parenteral nutrition.

Outcome measures: The primary outcome is the reduction of nausea and vomiting measured by the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score, the Rhodes Index of Nausea, Vomiting and Retching, the McGill Nausea Questionnaire, the Nausea and Vomiting of Pregnancy Instrument and Visual Analogue scales. Secondary outcomes include health-related quality of life, healthcare utilisation including admission to hospital, fetal outcomes, patient satisfaction, costs and cost-effectiveness of interventions. For the economic model the primary outcome is incremental cost per QALY from the perspective of the NHS and personal social services (PSS) and QALYs to the woman.

Search strategy: Based upon a comprehensive search of MEDLINE, CINAHL, EMBASE, PsycInfo, Allied and Complementary Medicine Database (AMED), British Nursing Index, Cochrane CENTRAL, NHS Economic Evaluation Database (NHS EED), Health Economics Evaluation Database (HEED), Scopus and Web of Science along with sources of grey literature. Further focused searches will be conducted to identify cost and utility data required for the economic evaluation.

Measurement of costs and outcomes: (a) Systematic review and meta-analysis: Identified titles and abstracts will be examined and full text papers of studies that potentially meet the inclusion criteria will be sought. These will be assessed for inclusion by two independent researchers. Any disagreements at this stage will be resolved by discussion either by the two researchers or in consultation with another team member. Data on effectiveness, fetal outcomes and adverse events will be tabulated and described in a narrative review. A meta-analysis is planned, carried out using fixed- or random-effect models as appropriate. The team will investigate the validity of performing mixed treatment (indirect) comparisons, using appropriate methods to compare interventions that have not been compared directly with each other. Heterogeneity will be explored through consideration of study populations, methods and interventions, by visualisation of results and, in statistical terms, by the chi-squared test for homogeneity and the I2 statistic. Evidence of publication bias will be examined by funnel plots.

(b) Economic evaluation: Data from the systematic review and meta-analysis will be combined in a micro-simulation cost-effectiveness economic model. The structure of the model will be based upon care pathways that represent a range of plausible pathways describing the key events in women's care, outcomes and areas of resource use. An existing data set will be used to help derive relevant utilities. Where necessary (to estimate treatment cost) study specific costs will be derived. Point estimates of costs, QALYs and incremental cost per QALY will be estimated. Cost-effectiveness acceptability curves will be used to represent the imprecision surrounding estimates of cost-effectiveness. The economic model will be used to conduct a value of information analysis to inform future research.

BACKGROUND

Description of the underlying health problem

Nausea and vomiting (NVP) is one of the commonest symptoms of pregnancy affecting 50-85% of all pregnant women during the first half of pregnancy (1). Symptoms usually commence between 6-8 weeks gestation, rise to a peak before the end of the first trimester and in the majority of women, resolve by 20 weeks (2). In 65-70% of cases, women self-manage their symptoms with avoidance of dietary triggers and oral hydration (2). However, in the remainder symptoms are more severe/protracted and lead to physical and psychosocial sequelae with reduced quality of life, lost work time and negative effects on relationships with family and friends (3). The most severe form of nausea and vomiting in pregnancy is referred to as hyperemesis gravidarum (HG) and is reported to affect 0.3-1% of pregnant women (1). It is characterised by intractable vomiting, dehydration, ketosis, electrolyte imbalance, nutritional deficiencies and weight loss (usually defined as more than 5% of pre-pregnancy weight). However, there is no widely accepted point at which NVP becomes HG; likewise the distinction between studies of women with NVP and HG is impossible as the degree of dehydration and weight loss prior to the intervention are rarely reported. Further, while some studies report baseline symptom severity using a validated scale, this is insufficient to make a diagnosis of HG. For this reason study populations are rarely described as having HG, and are more frequently defined in terms of severity of NVP. Therefore for the purposes of this protocol and the subsequent review both NVP and HG will be included.

The aetiology of NVP/HG remains unclear and the underlying pathophysiology is poorly understood but is thought to involve a combination of genetic, endocrine, gastrointestinal, environmental and psychosocial factors (4, 5). The diagnosis of NVP/HG is made after excluding differential diagnoses including gastrointestinal disorders, urinary tract infection, metabolic and endocrine disorders, drugs, psychological disorders (such as eating disorders) and other pregnancy associated conditions (such as molar pregnancy). In the absence of a definitive cause, management of hyperemesis tends to focus on the alleviation of symptoms and prevention of serious morbidity. Typically, women are admitted to hospital, prescribed

intravenous (IV) fluid therapy and antiemetic medication, but there is little time spent dealing with their psychological, social and emotional needs or providing information and guidance about the condition. The result is that women can feel unsupported, dissatisfied with care and experience negative interpersonal interactions with health care providers (6).

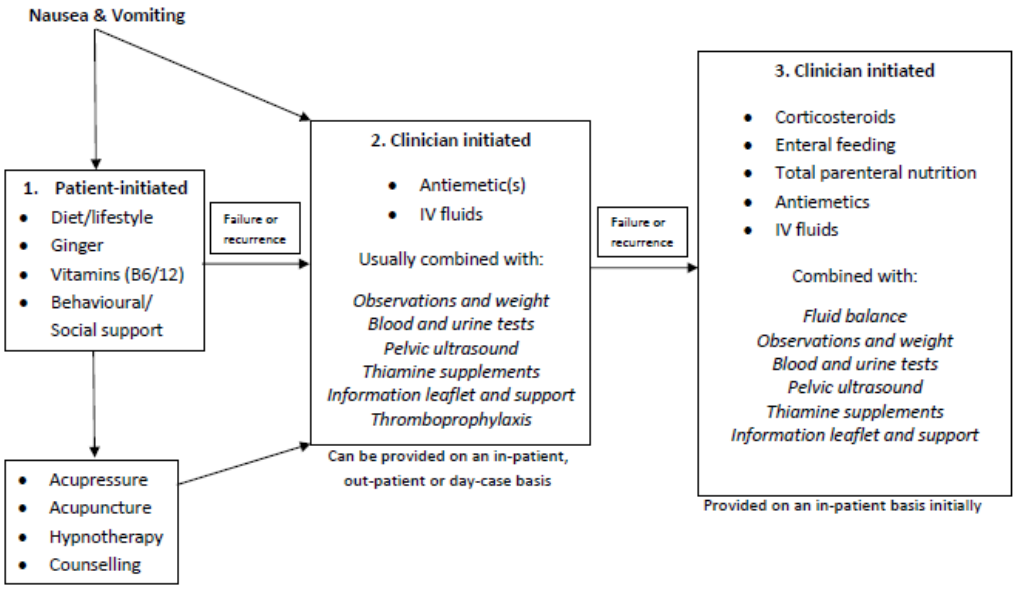
Women also report feeling isolated, depressed and lonely, unable to cope with routine daily interactions, tasks or childcare. As a result women make greater use of health care resources. Based on Hospital Episode Statistics data for England, there were nearly 26,000 admissions to hospital in 2010-11 with an average length of stay of 2 days related to NVP/HG (7). While this is undoubtedly a cost to the NHS, the costs of hospitalisation are likely to underestimate the full costs as women may purchase a variety of products over the counter, pay for alternative therapies, receive treatment in primary care settings or as a hospital outpatient and may incur extra childcare and living costs. It has been shown that women with NVP/HG are at increased risk of cognitive, behavioural and emotional dysfunction in pregnancy (5), which may prompt the use of further services.

Furthermore, severe NVP/HG has implications for offspring; a recent systematic review and meta-analysis reported that women with HG were more likely to deliver preterm (OR 1.32 [95% CI 1.04-1.68]) and to have a baby that was small-for-gestational age (OR 1.28 [95% CI 1.02-1.60]), although there was no evidence of an association with congenital anomalies or perinatal death (8).

Description of the interventions

For the purposes of this summary, interventions have been considered in three groups (Figure 1). First line interventions are usually initiated by women before seeking medical care and hence tend to be used in less severe NVP. Second line therapies are typically prescribed when a women presents to medical care. As a result they tend to be used for more severe symptoms on an in-patient, out-patient or day-case basis. Third line in-patient interventions are reserved for women with persistent or recurrent symptoms despite second line therapies. Where second or third line interventions fail, some women opt for termination of pregnancy.

Figure 1: Treatments for Nausea and vomiting in pregnancy



Patient-initiated first-line interventions

A number of dietary and lifestyle interventions are available to women without the need for medical prescription. These include a range of supplements that are available 'over the counter' (OTC). Many women try one or more of these before seeking medical advice.

Dietary / lifestyle interventions

Women report using a range of dietary/lifestyle interventions to alleviate symptoms, many of which are advised in information leaflets on NVP or on the internet e.g. increasing oral fluid intake, eating small frequent meals, eating bland foods/protein-predominant meals and avoiding spicy, odorous and fatty foods and stopping iron-containing multivitamins (2, 4). We were unable to identify any trials investigating the effectiveness of dietary/lifestyle interventions or self-help measures in NVP.

Vitamins

Vitamins are vital nutrients. They are available OTC as single vitamin or multivitamin preparations.

Vitamin B6 (pyridoxine). A Cochrane review of interventions for nausea and vomiting in early pregnancy identified two studies (n=416) comparing vitamin B6 (10-25 mg 6h) with placebo. Results favoured B6 for reduction in nausea after 3 days (mean difference 0.92 95% confidence interval (CI) 0.40 to 1.44) but provided no evidence that B6 reduced vomiting (9). Pooling of results from 3 trials (n=949), 2 randomised controlled trials (RCTs) of pyridoxine alone and one in combination with doxylamine, indicated that treatment failure did not differ between groups (pooled OR 0.97 [95%CI 0.78-1.20]) although pyridoxine was shown to reduce nausea score (pooled weighted mean difference for change in nausea score 0.918

[95% CI 0.441-1.395]) (9). Vitamin B6 has been shown to be safe in combination with doxylamine; one retrospective case-control study (n=458 cases) found no increased risk of major malformations with vitamin B6 monotherapy (RR 1.05 [95% CI 0.60-1.84])(10).

Vitamin B12 (cyanocobalamin). Pooled data from 2 RCTs comparing vitamin B12 and multivitamins (including vitamin B12) with placebo (n=1018) show homogeneity and a reduction of nausea and vomiting (pooled RR 0.49 [95% CI 0.28,0.86]) (10). Based on data from multivitamin preparations, vitamin B12 is thought to be safe although Mazzotta and Magee found no controlled trials to determine the teratogenicity of vitamin B12 (10).

Ginger

Ginger is considered a food supplement (not a drug) and is available in several preparations. The Cochrane review identified four studies (n=283) comparing ginger (250 mg capsules 4 h) with placebo (9). Of the three studies that provided useable data on symptomatic relief, all used different outcome measures and none used a validated symptom score. Two showed some evidence of benefit in terms of stopping vomiting and reducing nausea intensity. The authors concluded that use of ginger products may be helpful to women but the evidence of effectiveness was limited and not consistent. One further trial of ginger (0.5 g) biscuit not included in the Cochrane review (n=65) reported a reduction in nausea over 4 days (based on visual analogue scale) but no change in vomiting episodes (11). Based on available RCTs and one large observational cohort study (n=862), Borrelli et al. concluded that ginger was not associated with adverse effects (12).

The Cochrane review identified four trials comparing vitamin B6 with ginger (n=624). For two measures of symptom improvement it was possible to pool data from two studies but neither showed statistically significant differences (9). One further trial was identified comparing ginger, metoclopramide and placebo (n=102); symptom severity, as determined by Rhodes Score over 5 days, was reduced by both treatments but no differences were found between ginger and metoclopramide (13).

Acupressure/Acupuncture

Acupressure involves the application of physical pressure to specific acupuncture points; with respect to NVP this involves the P6 point near the wrist. The Cochrane review identified 4 studies of P6 acupressure wrist bands (n=408) but none showed evidence of improvement in symptoms compared with placebo (9). A lack of effect was also shown in one study of auricular acupressure (n=91). In contrast, one study of nerve stimulation (acustimulation) at P6 point reported an improvement in 'time averaged' Rhodes Index over the three week study period compared with placebo. An additional single-blind RCT of P6 acupressure in 80 women admitted with NVP reported no reduction in antiemetic use or length of stay with active bands compared to sham bands (14). The Cochrane review identified one trial comparing P6 acupressure and vitamin B6 (n=66) which found no difference between the interventions for improvement of nausea on day three.

Acupuncture involves the manipulation of thin needles inserted into acupuncture points in the skin. The Cochrane review identified two trials of acupuncture (n=648) (9); one found no differences in symptom relief between traditional, P6 and sham acupuncture while the data from the other study were not in a form that could be entered into RevMan (although the authors reported no differences between control and intervention groups for symptom relief). We identified one further randomised single blind crossover study of active (deep) P6 acupuncture versus placebo (superficial) acupuncture (n=33). Baseline nausea visual analogue scores differed between the groups and hence the authors could not directly compare visual analogue scores. Change in nausea visual analogue scores at day 4 was greater in the active group and fewer of this group women were vomiting by day 3 (15).

Hypnotherapy

Hypnotherapy employs direct suggestion of symptom removal with the subject under hypnosis. McCormack reviewed 45 studies describing hypnotherapy in the treatment of NVP. No RCTs were found and it was concluded the evidence was insufficient to establish if the intervention is effective (16).

Clinician-prescribed second-line interventions

Second-line interventions tend to be used for more severe symptoms either instead of or, less frequently, in addition to, first-line interventions. These may be initiated either in primary care by the GP or in a secondary care hospital setting.

Antiemetic drugs

Antiemetic drugs include antagonists to histamine, acetylcholine, dopamine and 5-hydroxytryptamine (5-HT) receptors in the chemoreceptor trigger zone, vestibular apparatus and visceral afferents.

Antihistamines (H1 receptor blockers) are probably the most widely used antiemetics and include doxylamine, meclizine, diphenhydramine, hydroxyzine, dimenhydrinate and cyclizine (25-50 mg 4-6h). Drugs are available in oral, parenteral and suppository forms. A summary of 7 controlled trials of various antihistamines (n=1190) indicated that these drugs were effective in reducing vomiting (RR 0.34 [95% CI 0.27, 0.43]) but the studies were not homogeneous and neither study design nor outcome definitions explained the heterogeneity (10). Pooling of data from 4 controlled trials of doxylamine/vitamin B6 (n=812) also indicated a reduction in nausea and vomiting (RR 0.53 [95% CI 0.41,0.68]) (10). The Cochrane review included 3 trials of antihistamines (2 with doxylamine in combination with vitamin B6) (9); the results for nausea relief favoured the intervention groups in all 3 trials but outcome measures varied and meta-analysis was not possible. An additional recent randomised placebo controlled trial was identified (n=256); doxylamine / vitamin B6 was associated with greater improvement in symptoms of NVP/HG compared to placebo based on both PUQE and quality of life measures (17). A recent case-control observational study involving 58 pregnant women which compared twice daily pyridoxine, (50mg twice

daily) and doxylamine (25-50 mg) with metoclopramide found that the combined treatment was safe and had a comparable treatment effect to metoclopramide. It was suggested that this combined therapy could be used as a treatment option in countries where Diclectin was not available (18).

Antihistamines are safe; a meta-analysis of 24 controlled trials involving more than 200,000 first trimester exposures revealed a reduced risk of major/minor malformations (pooled OR 0.76 [95% CI 0.60, 0.94]) (19). Based on these data, both the American and Canadian Colleges of Obstetrics and Gynaecology recommend doxylamine/vitamin B6 as first line treatment for NVP/HG.

Dopamine antagonists Several phenothiazines including promethazine (25 mg 4-6 h) and prochlorperazine (5-10 mg 4-6 h) have been used to treat NVP/HG. A summary of 3 controlled trials (n=398) indicated these drugs were effective in reducing vomiting (RR 0.31 [95% CI 0.24-0.42]) but again trial results were inconsistent (10). These drugs are also regarded as safe; a meta-analysis of 8 studies (n=2948) failed to demonstrate an increased risk of major malformations (pooled RR 1.03 [95% CI 0.888, 1.22]). Other drugs in this class used to treat NVP/HG include domperidone, droperidol , trimethobenzamide and metoclopramide. No RCTs of these drugs as the sole therapy for NVP/HG were identified in the Cochrane review (9) while Mazzotta and Magee (10) identified one RCT (n=394) of trimethobenzamide in which the drug, alone or in combination with vitamin B6, improved symptoms of NVP compared with placebo (RR 0.11 [95% CI 0.08, 0.18]. A recent RCT comparing metoclopramide with promethazine (n=149) reported no differences in frequency of vomiting and well-being numerical rating scale scores but side effects (drowsiness and dystonia) were more common with metoclopramide (20). A further recent double blind RCT compared metoclopramide, ginger and placebo (13). Both active treatments were more effective than placebo, as assessed by Rhodes score, but there was no difference between metoclopramide and ginger. Limited evidence suggests that trimethobenzamide is safe while a recent large study of metoclopramide use during the first trimester of pregnancy (n=3458) found no increased risk of major malformations (OR 1.04 [95% CI 0.89, 1.14]) or adverse obstetric outcome (21).

5-HT receptor antagonists One small RCT (n=30) of intravenous ondansetron (4mg 6h) versus promethazine for women with very mild NVP reported similar efficacy with respect to severity of nausea and treatment failure although ondansetron was associated with less sedation (22). 5-HT antagonists may be safe in pregnancy but experience is limited; one recent case-control study reported an increased risk of cleft palate (adjusted OR 2.37 [95% CI 1.18, 4.76]) (23); however, another study involving over 600,000 pregnancies in Denmark found no association with any adverse fetal outcomes (24).

Intravenous fluids

Women who are severely dehydrated and ketotic need hospital admission and intravenous fluid and electrolyte replacement. Day-case 'rapid rehydration' (2-3 L intravenous (IV) fluid over 4-6 hours) has been reported; one small pilot RCT (n=53) reported no change in PUQE score or quality of life 7 days after randomisation. All women were also given intravenous cyclizine (25).

Clinician-prescribed third line interventions

Third line interventions are reserved for women who have severe and persisting symptoms and associated with weight loss and dehydration (although latter may have been corrected). Although commenced while the women are in hospital, some of these interventions may be continued on an out-patient basis.

Corticosteroids

Steroids are being increasingly used in refractory cases of NVP/HG (IV hydrocortisone 100 mg twice daily. followed by oral prednisolone 40-50 mg, reducing to a maintenance dose). The Cochrane review did not include any trials of corticosteroids. Pooling of 2 trials using corticotrophin or corticosteroids (n=71) failed to show a difference in treatment failure rates (RR 1.22 [95% CI 0.35, 4.17]) (10). A subsequent RCT of IV methylprednisolone/oral prednisolone (n=110) found no difference in readmission rates compared to placebo-treated controls (26); both arms also received promethazine and metoclopramide. One further trial compared IV hydrocortisone with IV metoclopramide in women on intensive care because of intractable NVP/HG; compared to metoclopramide, steroids were associated with a reduction in mean vomiting episodes within the first 3 days (27). Concerns remain about the safety of corticosteroids. In one meta-analysis, the pooled RR for cohort and case-control studies combined revealed no increased risk of major malformations associated with first trimester exposure to corticosteroids (RR 1.24 [95% CI 0.97-1.60]) but a sub-analysis of case-control studies revealed an increase in the risk of the fetus developing an oral cleft palate (RR 7.08 [95% CI 3.00, 16.68]) and the results were homogeneous between studies (28). However, other studies do not show this association with cleft palate formation (29, 30).

Enteral feeding and total parenteral nutrition (TPN)

A review of case series of enteral feeding in severe NVP/HG suggests this intervention may be of some benefit (31) but no RCTs were identified. For women who cannot tolerate enteral nutrition, the use of TPN has been reported in case series but use is associated with significant maternal morbidity (32).

Assessing the effectiveness of interventions for NVP/HG

Previous reviews of NVP & HG intervention effectiveness have been challenging to conduct because of the heterogeneity between studies in terms of stage of pregnancy, severity of symptoms, variations in interventions and comparator studies and differences in outcome

measures. In the most recent Cochrane Review of interventions for NVP (as opposed to HG) published in 2010, the authors felt unable to pool findings from studies for most review outcomes (and the reviewers specifically excluded studies of treatments for HG) (9). Further, symptoms improve over time with advancing gestation, most NVP resolves by 12 weeks of pregnancy (4), underscoring the necessity of a control group when interpreting the effect of interventions on treatment success/failure. Also, as described previously, the distinction between HG and severe NVP often remains unclear. For the purposes of this review, studies involving women with reported or diagnosed NVP or HG will be considered for inclusion.

As symptom relief (reduction in nausea, vomiting and retching) is the main aim of treatment of NVP/HG, most research studies have focused on symptom relief as the primary outcome. There is no commonly accepted way to measure severity of symptoms or subsequently measure a change in reported severity. The following tools (Table 1) are most commonly used and therefore will be used as primary outcome measures in this review.

Table 1: Tools used to measure the severity of nausea and vomiting in pregnancy

Tool	Description
Pregnancy Unique Quantification of Emesis and Nausea (PUQE score)	Contains 3 questions regarding nausea, vomiting and retching over the preceding 12 hours, each answered on a 5 point Likert scale, giving a total score out of 15. (0= no symptoms – 15 = worst possible.) Scores over 13 indicate severe symptoms. (33-35)
The Rhodes Index of Nausea, Vomiting and Retching (RINVR).	Contains total of 8 items about duration/amount, frequency and distress caused by symptoms. 3 questions regarding nausea, 3 regarding vomiting, 2 regarding retching each on a 5 point Likert scale giving a total out of 40. (0= no symptoms – 40 = worst possible). Scores greater than 33 indicated severe symptoms. (36-38)
McGill Nausea Questionnaire (measures nausea only)	Comprised of a nausea rating index, (9 sets of words which describe sensory, affective, evaluative and miscellaneous afferent feelings related to nausea that patients rank), an overall nausea index on a scale of 0-5, where 0 = no symptoms – 5= excruciating symptoms, and a visual analogue scale 10cm long, 0cm= no nausea, 10cm= extreme nausea. (39, 40)
Nausea and vomiting of pregnancy Instrument (NVPI)	Contains 3 questions relating to nausea, retching and vomiting over the past 7 days, each scored on a 6 point Likert scale, 0= not at all – 5= all the time, maximum score 15. A score of 8 or above indicates severe symptoms (41, 42)
Visual analogue scale (VAS)	Patients rate their symptoms on a scale of 0-10, where 0= no symptoms – 10= extreme symptoms.

**This is not an exhaustive list and other measures may be added during the review process*

Whilst symptom relief is the main aim for women and practitioners and the primary outcome for most research studies, other wider outcomes are also relevant when assessing the effectiveness of interventions. Secondary outcomes measured in studies have included (Table 2):

Table 2: Secondary outcome measures for the review

Maternal-physical	Maternal-psychosocial	Fetal/Neonatal
• Admission/readmission rate	• Quality of life (eg. Via SF-12 or SF-36 score)	• Congenital abnormality
• Length of hospital stay	• General Health Questionnaire	• Low birth weight (<2.5kg)
• Antiemetic / other medication use	• Pregnancy specific quality of life instrument	• Small for gestational age (<10th centile)[1]
• Amount/duration IV fluid administration	• NVP specific questionnaire	• Pre-term birth (before 37 weeks gestation)
• Enteral/total Parenteral nutrition	• Satisfaction with care	• 5 minute APGAR
• Side effects	• Direct costs to woman/family	• Stillbirth/Intra uterine death
• Economic costs (hospital/medical care)	• Time lost from work	• neonatal death
• Adverse pregnancy outcomes	• Edinburgh post natal depression score	• Spontaneous miscarriage
• Weight loss		• Admission to special care baby unit
• Therapeutic termination of pregnancy		• Long term infant development outcomes

Summary of economic data

An initial search yielded five cost analyses or economic evaluations, none of which took a UK NHS perspective, illustrating the need for a formal economic evaluation (43-47). Ramzan et al 2012 in their cost analysis found that in the US inpatient setting, the cost of treating NVP/HG increased by 50% from $167 million in 2000 to $250 million in 2009 (44); illustrating the increasing economic burden of the condition as NVP/HG is the second most common complication of pregnancy resulting in Emergency Department visits.

Three of the five papers looked at pharmaceutical interventions to treat NVP/HG (43, 45, 46). Reichmann and Kirkbride 2008 provided a brief overview on the efficacy and costs of 11 pharmaceutical treatments for NVP/HG (according to the study authors, NVP can range from morning sickness to moderate NVP to HG). The paper argued that continuous subcutaneous ondansetron and metoclopramide are not cost-effective and called for more research into the efficacy and cost effectiveness of the medical treatments considered (45). This study had a number of methodological weaknesses, notably the methods used to estimate costs were not reported. Cost results were presented as *Mean cost per patient for*

[1] Small for gestational age to include measurement at birth and at later dates.

management of nausea and emesis of pregnancy compared with hospitalisation and home care treatment options. The intervention and cost data for the comparators came from two different studies (48, 49) respectively but the study failed to adjust for the different price years that the cost data related to. This is of concern given that Lombardi et al. 2004 (48) and Neaf et al 1995 (49) were conducted almost a decade apart. Reichmann and Kirkbride (2012) (46) was a review of updated evidence; though the data are not related to the cost data presented and the cost data themselves were identical to those presented in the 2008 paper (45). The final paper looking at pharmaceutical treatment options identified concluded the use of droperidol and diphenhydramine to be cost-effective treatment compared with 7 other pharmaceutical treatments for NVP/HG (43). This was based on an assessment that shorter hospital stays and fewer readmissions compensated for the higher drug costs. Data used to make this judgement were not contemporaneous (comparator group data related to 1990-1992 while the intervention group data related to 1992-1994) and the authors stated that the length of hospitalisations in general were falling over this time period.

Another RCT looked at clinical, psychosocial, and economic effects of antenatal day care for complications of pregnancy (47). This study was not specifically looking at NVP/HG as one of the complications though the authors suggest this trial may be generalisable to other complications including NVP/HG. The intervention was shown to decrease the total cost of care per mother as well as reduce the length of antenatal stay in hospital wards. The cost analysis was the most robust of the papers reviewed, as it stated the price year for the average total cost and length of stay in 1999/2000 Aus$.

Overall, this evidence base shows that few published economic data exist and that what data do exist have not been based upon the best available estimates and may not be applicable to the UK NHS.

Rationale for the study

There are a multitude of treatment choices available for practitioners and for women who are suffering from NVP/HG. Much of the key evidence on the effectiveness of these interventions has been summarised elsewhere (1, 2, 9, 10, 12, 16, 31, 45, 46, 50-54) (the most recently published was a Cochrane review on interventions for NVP in early pregnancy (9)), and suggests that many of the interventions look promising. However, there is still considerable need for guidance and advice on the relative merits of each intervention, both from a clinical effectiveness perspective, and in terms of interventions that best meet the need of NVP/HG patients themselves.

Scope of our review

Previous reviews have either not distinguished between NVP and HG, or focussed exclusively on a specific condition. For example, the recent Cochrane review explicitly excluded treatments for HG despite this condition being difficult to differentiate in practice from severe NVP. A further Cochrane review is in progress which focuses solely on HG (55).

Other recent reviews (9, 46), while not necessarily systematic, have been vague in their search strategies (i.e. limited databases, selective interventions); make no mention of search strategy (2, 46); or have focussed on a single intervention (12, 16, 45, 46, 51, 53). In addition, both Cochrane reviews have restricted their study inclusion to RCTs, thus excluding a number of potentially useful non-randomised controlled studies. Furthermore, the focus on RCT evidence - especially if those trials are relatively small - may fail to identify robust data on rare fetal or adverse event outcomes, which while rare may be hugely important to women and their families. In addition, because of the restrictive inclusion criteria, the Cochrane reviews *de facto* exclude some interventions (e.g. Vitamin B12, hypnosis, IV fluids, enteral feeding and TPN). Finally, we are also aware that the Royal College of Obstetricians and Gynaecologists is currently conducting a (non-systematic) literature review to inform the development of their Green-top Guidelines in this area. We anticipate that our findings will inform this process and / or future versions of the Guidelines.

Analysis strategy

The Cochrane review (9) identified 27 eligible trials but noted difficulties in pooling data due to heterogeneity of participants, interventions, comparison groups and outcomes reported. While heterogeneity does exist, in terms of outcomes it may be possible to translate outcomes on to a common scale or measure, or in terms of success/failure of treatment to control symptoms as used by Mazzotta and Magee (2000) (10) in their review of treatments for NVP/HG. Furthermore, the existing trial evidence base has only been reviewed in a series of pairwise comparisons. Given the plethora of interventions this makes such systematic reviews difficult to interpret. Alternative methods of meta-analysis such as mixed treatment comparisons offer the opportunity to compare several interventions at the same time. The provision of such evidence would, when translated into suitable materials and suitably disseminated, provide additional guidance to women and practitioners (56, 57) (refer to section on Dissemination of findings and engagement with service users and practitioners for more details). A statistical analysis plan will be drawn up as a working document as part of the research project.

Economic modelling

Despite the number of interventions that exist, there is very little 'economic' evidence to guide those in priority setting about which treatment options should be provided. The few data available are methodologically weak, in that it fails to adequately capture the relevant costs and benefits or in some case even to describe the methods used to derive the data that were presented. Furthermore, none of the data identified to date is relevant to the UK. All the high quality data that are available could be used to inform a cost-effectiveness analysis where interventions relevant to the NHS are compared. Such an analysis would enable guidance to be developed. Even if the available evidence is systematically reviewed and incorporated into a cost-effectiveness model, there will undoubtedly be areas where further research is needed. There is a need to systematically determine where these evidence gaps are and to prioritise them as areas for future research.

In response to the evidence gaps identified above, this study will systematically review studies of treatments for NVP and HG (note comments above about difficulties in distinguishing between these two conditions), use advanced methods of meta-analysis to combine data (taking into account both the severity and duration of symptoms prior to treatment) and then incorporate these data into an economic model, which will be specifically designed to inform decision-making in the UK NHS.

AIMS AND OBJECTIVES

The study aims to systematically review and meta-analyse evidence for clinical effectiveness and model the efficiency of treatments for interventions for NVP and HG within the context of the UK NHS. The specific objectives of the study are to:

1. Systematically summarise evidence of the clinical effectiveness and adverse events of each treatment for NVP/HG. Consideration will be given to how evidence varies according to severity and duration of symptoms before treatment; and place of treatment.
2. Determine, using economic evaluation modelling methods, which therapies or sequence of therapies are most likely to be cost-effective for which groups for the UK NHS.
3. Identify priorities for practitioners and service users arising out of the review.
4. Disseminate findings through engagement with service users and practitioners from the inception of the project.
5. Identify future research needs.

RESEARCH METHODS

To address the objectives outlined above the research will have the following components which will be developed and completed iteratively and in parallel:

1. A systematic review and meta-analyses.
2. An economic model comparing the relative cost-effectiveness for different patient groups of alternative managements, including usual care for NVP/HG.
3. Dissemination of findings through engagement with service users and practitioners from the inception of the project.

Systematic review of the adverse events and relative effectiveness of treatments for hyperemesis gravidarum

The review will use systematic methods to search, screen, and describe existing literature on interventions for NVP/HG. The design of the review will employ the approach suggested by the EPPI-Centre at the Institute of Education, London which is consistent with Cochrane methodology. The review is registered with PROSPERO, the International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/prospero/). By providing a lasting

record of the review protocol, and any changes to this, prospective registration reduces the possibility of selective reporting and associated biases.

Inclusion criteria

Types of studies: Randomised controlled trials (RCT), non-randomised comparative studies and population based case series, the latter primarily for estimates of rare adverse events and fetal outcomes and for treatments reserved for the most severe cases such as TPN. This is similar to the approach used to assemble evidence to inform judgements on safety in the NICE Interventional Procedures Programme. We have elected to focus on these study designs so that the NHS is presented with the best available evidence for each treatment and so that we can inform the subsequent economic model (which will explicitly incorporate uncertainty surrounding estimates into the modelling process).

Population: Women experiencing severe nausea, vomiting and/or retching in pregnancy where recruitment to a trial took place up to 20 weeks gestation. As HG is difficult to differentiate from severe or intractable NVP, we will use two approaches to identify relevant populations of women: (i) studies selected where their study samples are reported as suffering severe symptoms using published scales and cut-points for severity e.g. PUQE ≥ 13, Rhodes ≥ 33. These cut-off points are well correlated (33). For studies of mixed levels of severity the study will be included if greater than 80% exceed these cut-offs; (ii) studies will be selected if, using the authors' definition, women in the study sample are defined as having severe symptoms. Similarly, studies will be included if greater than 80% of the sample meet this definition. Details of the method used by authors to define severity will be recorded.

Intervention and comparators: All pharmacological and non-pharmacological interventions relevant to the NHS in the community and in hospital either as an inpatient or an outpatient. These interventions will include: Dietary/lifestyle interventions; vitamins such as vitamin B6 and vitamin B12; ginger; acupressure/acupuncture; hypnosis; antiemetic drugs (such as antihistamines; dopamine antagonists 5-hydroxytryptamine (HT)-receptor antagonists); corticosteroids; and intravenous fluids; enteral feeding and total parenteral nutrition. We will include studies that have a comparative group for assessment of relative effectiveness. This may be a no treatment group, a treatment as usual group or an alternative intervention group. For the treatment as usual group we will endeavour to clearly define what this is. For rare fetal or adverse events outcomes and for studies investigating treatments for women with the most severe symptoms (e.g. TPN) no comparator group is defined as the target studies are population based series.

Primary outcomes: Severity of symptoms (such as Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) (33); The Rhodes Index of Nausea, Vomiting and Retching (36); McGill Nausea Questionnaire (39); Nausea and Vomiting of Pregnancy Instrument (42); Visual Analogue scales (58-60)) (see Table 1).

Secondary outcomes: Duration of symptoms (reported period of symptoms, date of symptom relief); study specific measures of NVP; health-related quality of life; healthcare utilisation (including: admission and length of stay of the woman; readmission to hospital of the women; admission and length of stay on special care baby units); patient satisfaction; mothers weight; fetal outcomes (fetal or neonatal death, congenital abnormalities; low birth weight (< 2.5kg), preterm birth (before 37 weeks gestation) or small for gestational age (<10th centile); adverse events e.g. pregnancy complications (as reported in the study) but including haemorrhage, hypertension; pre-eclampsia; proteinuria; costs (as defined by the study authors); cost-effectiveness (as defined by the study authors) (see Table 2).

Search strategy for identification of published reports of studies

In order to identify relevant papers, a search strategy will be designed by an information specialist in conjunction with the rest of the research team. The search strategy will combine the two main conditions of pregnancy and nausea/vomiting with a wide variety of interventions and quality of life outcomes. Terms will be coupled with relevant MeSH/thesaurus terms and terms will be truncated as appropriate, and variant spellings will be used. In order to reduce the number of studies returned, search filters for the relevant study types will be applied where possible e.g. 'economic' and 'trials' (to ensure that we capture all relevant RCTs). No time or language limit will be set within the search strategy. We will also check the references of articles included in the review to search for additional relevant studies. The full list of search terms is presented in Appendix 1.

Databases to be searched are: MEDLINE, CINAHL, EMBASE, PsycInfo, Allied and Complementary Medicine Database (AMED), British Nursing Index, Cochrane CENTRAL, Scopus and Web of Science.

A separate search will be conducted for health-economic related papers in the NHS Economic Evaluation Database (NHS EED) and Health Economics Evaluation Database (HEED). The same terms as used for the main review will be used with the addition of health economic related terms (also included in Appendix 1).

Identification of other relevant information, including unpublished data

Other sources of information will be investigated using a hand search; including bibliographies of related review papers, reference lists of key papers, conference proceedings and the output of key journals in the field (American Journal of Obstetrics and Gynecology, Journal of Psychosomatic Obstetrics and Gynecology, Obstetric Medicine). Recent reviews (2, 9, 46, 54) make no mention of the inclusion of grey literature. We will search the websites of relevant organisations (e.g. Pregnancy Sickness Support, Hyperemesis Education and Research, Motherisk, UK Teratology Information Service) to identify any grey literature. Furthermore, trials registers will be searched and authors will be contacted to locate any unpublished reports.

Data extraction

Search results (minus duplicates) will be imported into an Endnote file which will be available to all Newcastle University review team staff.

Phase 1: Using the inclusion criteria, titles and abstracts of potentially relevant references will be examined by two independent researchers to exclude any that do not meet the inclusion criteria. In case of doubt papers will go through to the next stage.

Phase 2: Copies of the full text of papers that meet the criteria in phase 1 will be obtained and assessed by two independent researchers to identify those that definitely do not meet the inclusion criteria. Any disagreements at this stage will be resolved by discussion either by the 2 researchers or in consultation with another team member. Tables of excluded studies at this stage will be prepared detailing reasons for exclusion.

Phase 3: A structured data abstraction form will guide the extraction of information about: (i) key study characteristics (including bibliographic details, setting, intervention type, study population including definition of severity, etc); (ii) methodology and reporting; and (iii) summary of quantitative findings and conclusions. Data extraction will be carried out by one researcher and checked by another. Where publications lack details required for quality assessment or full data extraction, authors will be contacted to request further information.

The data extraction form for clinical effectiveness is presented as Appendix 2, with Appendix 3 demonstrating the approach to economic data abstraction

Quality assessment

The quality of the included studies will be evaluated in accordance with the comprehensive approach advised by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (61). The risk of bias of included RCTs will be assessed independently by two reviewers using the Cochrane Collaboration's tool (62), see Appendix 4 for full details. Disputes will be resolved by discussion with another member of the team. This will include assessment of: sequence generation; allocation concealment; blinding; selective reporting of outcomes; incomplete outcome data; and other possible sources of bias. The risk of bias in non-randomised studies will be assessed in accordance with four additional criteria, based on a modified version of the Ottawa-Newcastle system reported in a systematic review published in the Lancet (63). This will include assessment of cohort selection and the comparability of treatment groups**.** The risk of bias tool will be applied independently by two review authors and differences will be resolved by discussion. In addition, both reviewers will independently assess all included studies for the potential for imprecision, inconsistency and indirectness of results, using GRADE guidelines (64-68).

For any economic evaluations conducted alongside included studies we will follow the methods set out by the Campbell and Cochrane Economic Methods Group for the systematic review of economic evidence as part of a Cochrane intervention review (69, 70).

Data analysis and statistical methods

We will begin by describing the range of interventions, populations, and outcomes that have been studied. The direction and size of the reported effects from effectiveness studies will be presented overall, as well as grouped according to population, intervention type, outcome and study design. Results will be summarised in tables. As definitions of severity are likely to differ between studies, we will identify groups of studies using similar definitions. These grouping will be based upon the data extracted and expert opinion. Specifically, one of the systematic reviewers will assess the definitions used and develop a coding frame for the different definitions used. This will then be checked by the second systematic reviewer. Two of the clinical specialists, who are members of the research team, will then attempt to group the studies into the coding frame. The grouping produced will be compared and any discrepancies, including definitions that do not fit into the coding frame, will be resolved by discussion, which may involve refining the coding frame.

We will prepare a 'summary of findings' table as described in the Cochrane Handbook (62). Data on effectiveness, fetal outcomes and adverse events will be tabulated and described in a narrative review including variation in the form, setting, study population and delivery of the interventions. The findings of the narrative review on comparative effectiveness will be used to decide whether meta-analysis is feasible and appropriate to estimate summary effect measures for relevant outcomes. We do not anticipate that any form of meta-analysis of rare adverse events or fetal outcome data identified from case series will be possible (likewise if only data from case series are available for interventions like TPN we do not anticipate any meta-analysis of that data). Heterogeneity will be explored through consideration of study populations, definitions of outcomes, methods and interventions, by visualisation of results and, where relevant in statistical terms, by the chi-squared test for homogeneity and the I^2 statistic. Meta-analysis will be carried out using fixed-or random-effect models as appropriate. If judged to be appropriate, findings from studies using different scales to measure the same outcome (e.g. change in level of nausea and vomiting) will be combined using standardised mean differences. We will also explore whether data from different studies can be transformed on to a common scale, e.g. symptom severity might be recoded into number no longer experiencing severe symptoms. Such an approach is likely to require a degree of imputation. For example, the number of women from a sample for a given point estimate of severity and measure of variance that would be expected to fall below a given threshold. Any such analysis would be subject to sensitivity analysis and methods and assumptions explicitly detailed.

If any included studies had multiple treatment groups, the 'shared' comparison group will be divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons. Evidence of publication bias will be examined by funnel plots. If sufficient data are available, subgroup analysis will be conducted to explore the variation with pre-determined factors (e.g. the setting in which the intervention was applied and the severity and duration of

symptoms at baseline). In addition to that identified above, sensitivity analysis will be used to explore the impact of study design, including variation in definitions of outcomes, on measures of effectiveness. Initial analysis will combine data from interventions regardless of whether they have been given after treatment failures but will explore in sensitivity analysis the impact on relative effectiveness of interventions given as primary treatments and as secondary treatments. The team will investigate the validity of performing mixed treatment (indirect) comparisons, using appropriate methods to compare interventions that have not been compared directly with each other (56, 57). All direct and indirect comparisons depend upon the availability of good-quality data and the assessment of whether any assumptions necessary for the analysis are met.

Economic evaluation

The scoping review identified little cost-effectiveness data, none of which took a UK perspective. Given the paucity of evidence we propose to conduct a cost-utility analysis, with results presented in terms of incremental costs per quality adjusted life year (QALY). This analysis will be based upon an economic evaluation model as described below.

Model structure

We propose to develop a discrete event simulation model to estimate the costs, long-term effects and relative cost-effectiveness of the alternative interventions for NVP & HG from the perspective of the UK NHS and PSS. The model will describe the pathways of individuals who have different severities of symptoms and have treatment initiated in different sectors of the health service (primary care, hospital outpatients, and hospital inpatients). It will cover the period of initial intervention and the costs and consequences of any subsequent outcomes including further interventions. The processes modelled will be simulated probabilistically, drawing random deviates from known distributions of events. Events will be explicitly mapped through care pathways, and will be linked by logical and mathematical relationships.

Many of the effects of NVP and HG may be short-term; however, there may be some persisting impacts on the mother and longer term effects on the child. We will therefore estimate cumulative costs and QALYs for the mother and longer terms effect on the child (reported either in natural units or, if data allow, QALYs) over a longer time horizon (up to the expected lifetime of child if that is deemed necessary and data allow). The discrete event simulation model derives its probabilities from the systematic review and meta-analyses proposed in this study and - as described below - additional focused searches and new data collection. All uncertainty surrounding estimates of input parameters will be informed by appropriate distributions calculated from meta-analysis (e.g. surrounding event rate) or from expert opinion (e.g. resources required to provide specific intervention). As described below, we will employ probabilistic sensitivity analysis to investigate the impact of uncertainty in model parameters using Monte Carlo simulation. This will highlight gaps in our knowledge and help identify priorities for future research.

Modelling will conform with recommendations for best practice including those developed for economic evaluation models (71). The economic perspective will be that of the UK NHS and PSS and discounting in the base case will be at 3.5% (72).

Derivation of cost data

Information on the precise description of the resources required for each intervention is unlikely to be obtained from identified studies. The most appropriate sources for these data will be centres currently providing the target interventions. With the help of relevant members of the expert group and a further search of the literature, we will seek information on the resources required to provide each intervention. This will be supplemented by advice from the systematic review, e.g. on length of stay, and hospital admission/readmission rate. Unit costs will be taken from appropriate routine sources, e.g. NHS reference costs, British National Formulary for drugs, etc. Data on the costs of managing persisting complications for the mother will be derived from the literature and will depend upon the nature of the event. Similarly, we will seek UK relevant data from the literature of managing long-term consequence of fetal outcomes.

Derivation of utilities

For the cost utility analysis effects/benefits will be estimated in QALYs. For each health state a health state utility will be defined. The data will come from the included studies in the systematic review and an additional focused search to identify utility data, including a search on the CEA Registry (https://research.tufts-nemc.org/cear/default.aspx). The estimates used within the model will be based upon the best available data, ideally derived using EQ-5D or SF-6D. One anticipated problem will be linking of clinical levels of severity such as those provided by the PUQE to measures of health state utilities. We will use our existing data set that has collected data using both this score and the SF-36 to explore the relationship between the PUQE score and SF-6D utility scores derived from the SF-36. We currently have access to a small trial containing 53 participants, who completed the PUQE and SF-36v2 at recruitment and seven days after intervention (25). PUQE was also completed daily for the 7 days after intervention. Health state utilities for long-term consequences of some maternal and fetal outcomes will be obtained from similar searches, with the precise data sought dependent upon the outcomes modelled (see Section 3.1).

Epidemiological and relative effectiveness data

The main source of evidence to inform the probabilities required for the model will be the systematic reviews and meta-analyses. It is unlikely that sufficient data to inform all probabilities (e.g. the longer term consequences of any outcomes for the child and mother) will be derived from these sources. Additional focused searches will be conducted as necessary to identify the best available evidence relevant to the UK NHS for such probabilities.

Estimation of relative efficiency

The results of the economic model will be presented as a cost-utility analysis (CUA). In the CUA, mean costs, mean QALYs, incremental costs and QALYs, which capture mother's preferences for changes in health outcomes, and the incremental cost per QALY gained will be reported. We will also consider whether and how to capture the effects on the child. It is possible that these may be modelled in terms of QALYs and cost as well, should data allow. However, as a minimum the effects on the child will be presented in natural or clinical measures presented alongside the cost and QALY data for the mother. Likewise, although the stated perspective for costs is NHS and PSS where data exist, we will consider the wider costs falling on the women and child. This is especially pertinent as some interventions may be accessed directly by women but their use in the future may be influenced by advice from the NHS. Costs falling on women and children will be presented alongside NHS & PSS costs and QALY and further explored in sensitivity analyses.

Uncertainty

Deterministic sensitivity analyses will be carried out to test for the effect of assumptions and variability (73). Examples of such sensitivity analyses might be exploration of changed in discount rates or perspective such as including the QALY effects on the child or the costs falling on mother and child. A probabilistic sensitivity analysis will also be undertaken for both the base case analysis and, where sensible, all deterministic sensitivity analyses allowing presentation of results in a series of cost-effectiveness acceptability curves (CEAC). Estimates of costs and QALYs will be calculated as the expectation over the joint distribution of the parameters. Relevant distributions will be informed by the systematic reviews and meta-analyses, other literature or expert opinion according to best practice (74).

Dissemination of findings and engagement with service users and practitioners

Dissemination activities

Publications

We will publish a full account of our research in the journal *Health Technology Assessment*. In addition, we anticipate that this research will result in three peer-reviewed journal articles. Target journals include BMJ for the main results of the review of clinical effectiveness and European Journal of Health Economics for the economic evaluation. We anticipate that a further paper reporting further systematic review results will also be published in a specialist clinical journal. We will also present our research at meetings of appropriate learned societies including British Maternal & Fetal Medicine Society (BMFMS); International Society of Obstetric Medicine (ISOM); Society for Maternal and Fetal Medicine (SMFM); European network of Teratology Information Services (ENTIS); Teratology Society. We will work with press officers at Newcastle University to publicise the results of our work to local and national news media.

Internet and social media

A Newcastle University webpage for the project will be developed in collaboration with the Pregnancy Sickness Support Forum (www.pregnancysicknesssupport.org.uk). We will also engage NVP & HG sufferers in both the website development and to explore appropriate ways of using social media (Facebook, blogs, podcasts, twitter [#pregnancy; #sicknessinpregancy]) to disseminate information about the project both during and after completion. The UK Teratology Information Service is currently preparing information leaflets for patients. These will be openly accessible on their website (www.uktis.org). We will work with them to further disseminate our findings to the public.

Local and national networking activities

The research team comprises several associate members of Fuse – The Centre for Translational Research in Public Health (www.fuse.ac.uk). Fuse is a UK Clinician Research Collaboration funded Centre of Public Health Research Excellence which includes members and partners from across public health research, policy and practice communities in the North East of England. We will use established Fuse initiatives including the Quarterly Research Meetings (with around 100 participants) to disseminate our findings to the wider public health community. A summary of this meeting, and podcasts of presentations, will be posted on the Fuse website with links to The Pregnancy Sickness Support Forum.

Patient and Public Involvement

Key to the study is the role played by practitioner and service user members of the research team. We will consult with them and a wider group of doctors, nurses, midwives and women who have suffered from NVP & HG at the start of the study, informing them about the activity and inviting their comments on how the project can be improved. In so doing we will be encouraging those involved to engage with the project so that they will more readily contribute to meetings in the latter stages of the project where we will be asking for their input to help the research team generate ideas for dissemination. By locating these meeting with practitioners and services users across the country we hope to widen interest in the review. Finally, we have allocated funds for a member of the research team to attend one international and one national conference to disseminate findings to a wider practitioner/research community. We anticipate that the former will be to the Society for Maternal and Fetal Medicine (SMFM) and the latter will be the British Maternal and Fetal Medicine Society (BMFMS).

ETHICAL ARRANGEMENTS

It is envisaged that only secondary data sources will be used in the systematic review and meta-analysis and ethical approval is not required. It is proposed to use a previously collected dataset to explore the relationship between symptom scores and health state utilities in order to inform the economic model. Permission has been given by the guardian of the data, who is also one of the applicants, Professor Robson, and the relevant Ethics

Committee will be informed to confirm that the data can be used for research purposes. Newcastle University will conform to recognised high standards of research governance and abide by the Data Protection Act 1998.

MANAGEMENT OF THE PROJECT

The core research team is a multi-disciplinary partnership based in the Institutes of Health & Society and Cellular Medicine at Newcastle University. Given the UK wide and international significance, the team also includes specialist practitioner expertise drawn from the NHS. The study will also draw on the experience and expertise of an expert advisory panel comprising of: three women who have suffered from hyperemesis gravidarum; Director of The Motherisk Program at the Hospital for Sick Children at the University of Toronto and Professor of Medicine, Pediatrics and Physiology/Pharmacology and the Ivey Chair in Molecular Toxicology at the University of Western Ontario; a senior midwife at the Royal Victoria Infirmary Maternity Assessment Unit, Newcastle upon Tyne; and a Trustee of the Pregnancy Support Website. Members of the team will meet on the following basis.

Study Working Group

The core research team (the PIs and Newcastle based researchers) will meet on a weekly basis to identify and address concerns and discuss progress.

Project Management Group

A project management group (comprising all co-applicants and researchers) will be responsible for strategic leadership and for ensuring the project is delivering in a timely manner. The project management group will teleconference or meet on a monthly basis.

Project Steering Group

A project steering group will be convened at the start and towards the end of the project to discuss the proposed clinical pathways, results of the economic modelling and to identify relevant data sources. In addition to the co-applicants and researchers working on the study, members of the steering group will also include the expert advisory panel.

PROJECT TIMETABLE AND MILESTONES

The protocol, including the development of all review tools, will be completed by the end of month 3. The first meeting of the Project Steering Group will be convened by the end of month 3. The systematic review will then be completed over the remainder of the first year along with preliminary meta-analysis and economic modelling. The results from this work will be discussed at the second project steering group meeting held in month 13. The focus of this meeting will be to suggest refinements to the analyses and discuss the implications of the findings to key stakeholders (women with or potentially at risk of HG; practitioners and the NHS). This will inform the development of the final report which will be completed in the final two months of the study.

Figure 2: HG interventions systematic review and economic evaluation

	Study month														
	Sept-13	**Oct-13**	**Nov-13**	**Dec-13**	**Jan-14**	**Feb-14**	**Mar-14**	**Apr-14**	**May-14**	**Jun-14**	**Jul-14**	**Aug-14**	**Sep-14**	**Oct-14**	**Nov-14**
Key research activities															
Develop review protocol			◆												
Conduct reviews												◆			
Statistical analysis													◆		
Economic modelling															◆
Final report															◆
Research management															
Project Management Group		◈			◈	◈	◈	◈	◈	◈	◈	◈		◈	◈
Project Steering Group				◈									◈		

◆ = project milestone / deliverable
◈= study meeting

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Appendix 1: Search terms and study types. (MeSH/thesaurus terms will be used as appropriate)

Restrictions: *None (all languages and all dates)*

Databases to be searched are:

MEDLINE
CINAHL
EMBASE
PsycInfo
Allied and Complementary Medicine Database (AMED)
British Nursing Index
Cochrane CENTRAL
Scopus
Web of Science
NHS Economic Evaluation Database (NHS EED)
Health Economics Evaluation Database (HEED)

Study type

RCTs
Comparative non-randomised studies
Economic evaluations
Case series

Outcomes

Fetal outcomes
Healthcare utilisation
Health-related quality of life
Neonatal outcomes
Pregnancy outcomes
Pregnancy complications
Preterm delivery/prematurity
Pregnancy-Unique Quantification of Emesis and Nausea/PUQE scoring system
Quality of life
Rhodes' score
Safety/adverse events
Teratogenicity
Modified-PUQE score
Reduction in NVP
Fetal abnormality, Congenital anomalies / anomaly, birth defect
PUQE
Hyperemesis Beliefs Scale
McGill nausea questionnaire
Nausea and Vomiting in Pregnancy Instrument (NVPI)

Condition 1

Pregnancy
Pregnant

Condition 2

nausea
retching
vomiting
emesis
dry heaving
hyperemesis gravidarum
morning sickness
NVP/nausea and vomiting in pregnancy
Pregnancy sickness
Ptyalism
spitting

Interventions*

Acupressure
Acupuncture
Acustimulation
alternative therapies
Antacids
Antiemetics
Antihistamine/anti a histamine;
Anti-nausea
Avomine
Benadryl
Benedectin
Bonine
Calcium carbonate
Carbohydrates
Cetirizine
Chamomile/camomile
Cinnarizine
Compazine
complementary and alternative medicine/CAM
Corticosteroids
Cyclizine
Debendox
Diclegis
Diclectin;
Dicycloverine
diet modification/dietary modification
Dimenhydrinate
Diphenhydramine
Dopamine antagonists
Doxylamine
Doxylamine succinate-pyridoxine hydrochloride
Dramamine
Droperidol
Electrolytes
Enteral feeding
Fructose
Gabapentin
Ginger
Glucose
H1 antagonists;
H2 blockers
5 HT3 antagonists *(hydroxytryptamine receptor antagonists)*
Herbal remedies
Hydration
Hydroxyzine
Hydrocortisone
Hypnosis
Intravenous fluids/IV fluids
Intravenous hydration/IV hydration
Intravenous rehydration/IV rehydration
Lenotan
lifestyle change
Losec
Low fat diet
Maternal diet
Meal
frequency/frequency of meals
meal size
Meclizine
Meditation
Merbentyl
Methylprednisolone
Metoclopramide
Non-pharmacological
Nutrition
Omeprazole
Ondansetron
Peppermint
Pharmacological;
Phenergan
Phenothiazines
phosphoric acid
Prednisolone
Prednisone
Prochlorperazine
Prokinetics
Promethazine
Proton pump inhibiters
Psychosocial
Psychotherapy
Pyridoxine
Reglan
Ranitidine
Rehydration
Relaxation
Serotonin antagonists
Stemetil

Steroids
Stress reduction
Stugeron
Thiamine
Tigan
Total Parenteral Nutrition;
Trimethobenzamide
Valoid
Vitamin B1
Vitamin B12 (cyanocobalamin)
Vitamin B6
Vitamins
Zofran

Health economic outcomes**
Burden of disease
Burden of illness
Cost analysis
Cost effectiveness
Costs

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* Pharmacologic terms can be used as exclusion terms to identify studies where this is the only intervention and remove them from the set of studies of interest

** Only relevant databases (NHS Economic Evaluation Database (NHS EED), Health Economics Evaluation Database (HEED)) will be used to search for health economics outcomes

Appendix 2: Data extraction form: clinical effectiveness

Reviewer ID: Data extraction date:

GENERAL INFORMATION	
Report title:	
First author / contact details	
Publication year	
Publication status:	Full-text paper ☐ Conference abstract ☐ Personal communication ☐ Other unpublished reports ☐
Journal yy:vol(issue):pp	
Language (if non-English):	
Study IDs of any linked reports:	
Study funding sources *(including role of funders)*	
Possible conflicts of interest *(for study authors)*	

STUDY ELIGIBILITY

Type of study:

RCT ☐ Non-randomised comparative study ☐ Case series ☐

Type of intervention:

Dietary / lifestyle:

Vitamin B6 ☐ Vitamin B12 ☐ Ginger ☐
Acupuncture ☐ Acupressure ☐ Hypnosis ☐

Antiemetic drugs:

Antihistamines ☐ Dopamine antagonists ☐ 5-HT receptor antagonists ☐
Corticisteriods ☐ Doxylamine-Pyridoxine (combination therapy) ☐ Other (provide details below) ☐
_____

Intravenous fluids: ☐

Enteral and total parenteral nutrition

Enteral feeding ☐ Total parenteral nutrition ☐

Other Intervention ☐ _____

Comparator:

No treatment ☐ Treatment as usual (details below) ☐ Alternative intervention (details below) ☐

_____ _____

Comparator not applicable:

Women with severe symptoms ☐

Participants:

Gestational age ≤20 weeks ☐

Symptom severity:

PUQE score ≥ 13 ☐ Rhodes score ≥ 33 ☐ Author defined scale (provide details below) ☐

Percentage experiencing symptoms >80% ☐ _____

Primary outcomes:

Severity of symptoms:

PUQE ☐ Rhodes Index ☐ McGill Nausea Questionnaire ☐

Visual Analogue scales ☐ Nausea and Vomiting of Pregnancy Instrument ☐

Secondary outcomes:

Maternal-physical:

Admission/readmission rate	☐	Length of hospital stay	☐
Antiemetic / other medication use	☐	Amount/duration IV fluid administration	☐
Enteral/total Parenteral nutrition	☐	Adverse events	☐
Economic costs (hospital/medical care)	☐	Adverse pregnancy outcomes	☐
Weight loss	☐	Therapeutic termination of pregnancy	☐
Other author defined NVP scale	☐		

Maternal –psychosocial:

Quality of life (eg. Via SF-12/SF-36 score	☐	General Health Questionnaire	☐
Pregnancy specific quality of life instrument	☐	NVP specific questionnaire	☐
Satisfaction with care	☐	Direct costs to woman/family	☐
Time lost from work	☐	Edinburgh post natal depression score	☐

Fetal/Neonatal:

Congenital abnormality	☐	Low birth weight (<2.5kg)	☐
Small for gestational age (<10th centile)	☐	Pre-term birth (<37 weeks gestation)	☐
5 minute APGAR	☐	Stillbirth/IUD	☐
Neonatal death	☐	Spontaneous miscarriage	☐
Admission to special care baby unit	☐	Long term infant outcomes	☐

INCLUDE ☐ **EXCLUDE** ☐

Reasons for exclusion:

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

ADDITIONAL STUDY INFORMATION			
Population and setting			
	Intervention	**Comparator**	**Location in text**
Population description			
Setting (including country / location / social context etc)			
Inclusion exclusion criteria			
Method/s of recruitment			
Informed consent obtained	Yes ☐ No ☐ Unclear ☐	Yes ☐ No ☐ Unclear ☐	
Notes:			

Methods		
	Descriptions as stated in report / paper	**Location in text**
Aim of study		
Design (no of arms)		
Unit of allocation (by individuals, cluster / groups)		
Start date		
End date		
Total study duration		
Ethical approval needed / obtained for study	Yes ☐ No ☐ Unclear ☐	
Notes:		

Participant characteristics			
	Intervention	**Comparator**	**Location in text**
Number of patients enrolled:			
- Randomised (RCTs only), n (%)			
- Included (RCTs only), n (%)			
- Completed, n (%)			
- Available for follow-up, n (%)			
- Withdrew/lost to follow-up, with reasons, n (%)			

- Number analysed, n (%)			
Age (mean/median, SD/range)			
Ethnicity, n (%)			
Smoking status (give n (%) of smokers)			
BMI at baseline, (mean/median, SD/range)			
Weight at baseline (mean/median, SD range)			
Singleton pregnancy only (if no, give n (%))			
Gestational age at onset (week: mean/median, SD/range)			
Gestational age at primary admission (week: mean/median, SD/range)			
Gestational age at study entry / randomisation (week: mean/median, SD/range)			
Primiparas only (if no, give %)			
Obstetric history (previous NVP)			
Pre-existing medical conditions (please specify)			
NVP / HG Severity:			
- PUQE (Mean/median, SD/range)			
- Rhodes Index (Mean/median, SD/range)			
- McGill Nausea Questionnaire (Mean/median, SD/range)			
- Nausea and Vomiting of Pregnancy Instrument (Mean/median, SD/range)			
- Other scale (details)			
Other baseline characteristics (please specify):			
INTERVENTION GROUPS *(copy and paste table for each intervention group and comparator)*			
Intervention Group 1			
	Description in text		**Location in text**

Group name		
No. randomised to group		
Theoretical basis (include key references		
Description of intervention (include sufficient detail for replication eg content, dose, components)		
Duration of treatment period		
Timing of treatment (eg frequency, duration of each episode)		
Delivery (eg mechanism, medium, intensity, fidelity)		
Providers (eg number, profession, training, gender / ethnicity / age if relevant)		
Co-interventions		
Economic variables (eg intervention cost, changes in other others as result of intervention)		
Notes:		

OUTCOMES *(copy and paste table for each outcome)*		
Outcome 1		
	Description as stated in report / paper	**Location in text**
Outcome name		
Time points measured		
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		
Personal measuring/ reporting		
Unit of measurement (if relevant)		
Scales: upper and lower limits (indicate whether high or low score is good)		
Is outcome/tool validated?	Yes ☐ No ☐ Unclear ☐	
Imputations of missing data (eg assumptions made for ITT analysis)		
Assumed risk estimate (eg baseline or population risk note in background)		

Power		
Notes:		

RESULTS					
Dichotomous outcomes					
	Description as stated in report/paper				**Location in text**
Comparison					
Outcome					
Subgroup					
Timepoint (specify whether from start or end of intervention)					
Results	Intervention		Comparison		
	No. events	No. participants	No. events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis (by individuals, cluster/groups or body parts)					
Statistical methods used					
Notes:					

Continuous outcome		
	Description as stated in report/paper	**Location in text**
Comparison		
Outcome		
Subgroup		

Timepoint (specify whether from start or end of intervention)							
Post-intervention or change from baseline?							
Results	Intervention			Comparison			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							
Any other results reported							
Unit of analysis (individuals, cluster/ groups or body parts)							
Statistical methods used							
Notes:							

Other outcome				
	Description as stated in report/paper			**Location in text**
Comparison				
Outcome				
Subgroup				
Timepoint (specify whether from start or end of intervention)				
Results	Intervention result	SD (or other variance)	Control result	SD (or other variance)
	Overall results		SE (or other variance)	
No. participants	Intervention		Control	
No. missing participants and reasons				

No. participants moved from other group and reasons			
Any other results reported			
Unit of analysis (by individuals, cluster/groups or body parts)			
Statistical methods used			
Notes:			
Conclusion as reported by the authors of the study			
Additional information and comments			

Appendix 3: Data extraction form: health economics

Based on NHS CRD structured abstract form for economic evaluations as recommended by the Campbell and Cochrane Economic Methods Group

Summary	
Type of economic evaluation	
Study objective	
Interventions	
Location/setting	
Methods	
Analytical approach:	
Effectiveness data:	
Monetary benefit and utility valuations:	
Measure of benefit:	
Cost data:	
Analysis of uncertainty:	
Results	
Authors' conclusions	
CRD commentary	
Interventions:	
Effectiveness/benefits:	
Costs:	
Analysis and results:	
Concluding remarks:	
Funding	

Appendix 4: The Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Possible approach for *summary assessments* outcome (across domains) within and across studies

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias.
High risk of bias	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results.

Criteria for judging risk of bias in the 'Risk of bias' assessment tool

SEQUENCE GENERATION **Was the allocation sequence adequately generated? [Short form: *Adequate sequence generation*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The investigators describe a random component in the sequence generation process such as: Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: Sequence generated by odd or even date of birth; Sequence generated by some rule based on date (or day) of admission; Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: Allocation by judgement of the clinician; Allocation by preference of the participant; Allocation based on the results of a laboratory test or a series of tests; Allocation by availability of the intervention.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.
ALLOCATION CONCEALMENT **Was allocation adequately concealed? [Short form: *Allocation concealment*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: Central allocation (including telephone, web-based, and pharmacy-controlled, randomization); Sequentially numbered drug containers of identical appearance; Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: Using an open random allocation schedule (e.g. a list of random numbers); Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); Alternation or rotation; Date of birth; Case record number; Any other explicitly unconcealed procedure.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS **Was knowledge of the allocated interventions adequately prevented during the study? [Short form: *Blinding*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: Insufficient information to permit judgement of 'Yes' or 'No'; The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Were incomplete outcome data adequately addressed? [Short form: *Incomplete outcome data addressed*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods.

Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided); The study did not address this outcome.
SELECTIVE OUTCOME REPORTING **Are reports of the study free of suggestion of selective outcome reporting? [Short form: *Free of selective reporting*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any of the following: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.
OTHER POTENTIAL THREATS TO VALIDITY **Was the study apparently free of other problems that could put it at a risk of bias? [Short form: *Free of other bias*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The study appears to be free of other sources of bias.

Criteria for the judgement of 'NO' (i.e. high risk of bias).	There is at least one important risk of bias. For example, the study: Had a potential source of bias related to the specific study design used; or Stopped early due to some data-dependent process (including a formal-stopping rule); or Had extreme baseline imbalance; or Has been claimed to have been fraudulent; or Had some other problem.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	There may be a risk of bias, but there is either: Insufficient information to assess whether an important risk of bias exists; or Insufficient rationale or evidence that an identified problem will introduce bias.