EMPOWER: EMesis in Pregnancy - Ondansetron With mEtoclopRamide

Prepared By

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1- Summary of the EMPOWER study

Background: Nausea and vomiting in pregnancy (NVP) affects up to 85% of women in the first half of pregnancy.(1) Symptoms usually start at 6-8 weeks, peak by 9 weeks and for many women, subside by 20 weeks gestation.(2) Symptoms are often mild but 30% of sufferers experience more severe symptoms(2) requiring medical intervention. The most severe form, hyperemesis gravidarum (HG), affects 0.3-3% of women(1) and is characterised by intractable vomiting, dehydration, ketonuria and weight loss. HG can result in prolonged hospitalisation, multiple treatments and, where interventions fail, termination of pregnancy. NVP is associated with emotional and psychological distress and has a profound impact on quality of life affecting all aspects of a woman's life.(3) Women often feel unsupported, suffer higher rates of depression, anxiety and stress(4) and often feel dissatisfied with care.(5) Women with HG are also more likely to deliver preterm and to have small for gestational age infants although there is no association with congenital anomalies or perinatal death.(6)

The aetiology remains unclear and there is no cure for NVP - treatment focuses on relieving symptoms and preventing morbidity. Many women with mild symptoms are able to self-manage the condition using lifestyle modifications. Some also access other patient-initiated interventions (e.g. ginger, vitamins). Most women with moderate or severe disease require clinician-initiated interventions in the form of intravenous (IV) fluids and antiemetic drugs, primarily antihistamines (e.g. cyclizine), dopamine antagonists (e.g. metoclopramide) and 5-HT3 antagonists (e.g. ondansetron).

Summary of Trial Design and population: The original trial design consisted of a multi-centre, double dummy, double blinded controlled factorial trial and has been previously described in protocol version v5.0 19.03209 (EudraCT Number 2017-001651-31). An internal pilot phase was planned involving 8 sites, followed by a main phase including an additional 12-16 sites. Participants included women 18 years and older attending hospital with severe NVP, at 166/7 weeks of pregnancy or less, who had had little or no improvement whilst taking first line anti-sickness medication. 59 participants needed to be recruited at the pilot stage to then progress to full trial, however low recruitment has led to the study to close and not progress to the main trial stage. This decision was taken by NIHR HTA following a trial progress review on 24th July 2019.

Intervention Duration: 10 days

Follow Up Duration: Follow up will take place at 48 hours post first dose of Investigational

Medicinal Product (IMD), then at 5 days and the final follow up questionnaires at 10 days. Participants will then be followed up post birth via chart review.

Intervention: The intervention will be delivered as follows:

Group 1: metoclopramide 10mg IV three times a day + placebo ondansetron.

Group 2: ondansetron 4mg IV three times a day + placebo metoclopramide.

Group 3: ondansetron 4mg IV three times a day + metoclopramide 10mg IV three times a day.

Group 4: Double placebo IV three times a day.

Study drug will initially be given intravenously for up to 4 days. Once the women are able to tolerate fluids, the same drugs will be given by tablet for up to ten days. Treatment will be a maximum of ten days.

Primary Outcome: Proportion of participants experiencing treatment failure between 12 hours and 10 days from the start of trial treatment.

2- Outline of the economic analysis

The objective of this economic analysis plan is to outline the economic analysis that will be conducted as part of the EMPOWER study. Although a main trial had been planned following a pilot phase, low recruitment has led to the study to close and not progress to the main trial stage. Since the original proposed analysis is no longer appropriate given the achieved sample size, the economic analysis now has two primary components:

(i) Presentation of health service resource use data in the form of summary statistics
(ii) Presentation of willingness to pay data in the form of summary statistics.

The analysis will follow the intention to treat principle including all randomised participants with data available for analysis regardless of whether they were later found to be ineligible, a protocol violator or were never treated. Information will be presented per participant and per randomised group.

The design, conduct and analysis will follow guidelines for best practice as appropriate.(7) The analysis will take the perspective of the UK National Health Service (NHS) and personal and social (PSS) care services.

2.1- Intervention

The resources used for the delivery of each intervention will be summarised for each trial participant. This requires to ascertain the type of IMP, mode of administration and duration of treatment and hospital stay during the 10 day intervention period (Table 1). This information will be captured via electronic research forms (eCRFs) and the resources used will be estimated for each trial participant. Should any participants require, hospital stay and/or third line treatment within the 10 day framework considered for the analysis, this will be included accordingly and will be added to the resources required for the delivery of the intervention.

Table 1 – summary of intervention resources per patient per trial arm					
Resource use	**Mean usage (SD)/Median (IQR)**				**Primary source**
	Active metoclopramide and placebo ondansetron (n=)	**Active ondansetron and placebo metoclopramide (n=)**	**Active metoclopramide and active ondansetron (n=)**	**Placebo metoclopramide and placebo ondansetron (n=)**	
IMDs/Hospital stay/third line treatment					

Metoclopramide IV ampoules					eCRF
Metoclopramide PO tables					eCRF
Ondasetron IV ampoules					eCRF
Ondasentron PO tables					eCRF
IV administration (hospital setting)					eCRF
Hospital stay					eCRF
Third line treatment – High dose Ondansteron					eCRF
Third line treatment – Corticosteroids					eCRF

2.2- NHS Resource and social care resource use

Information on healthcare resource use will be collected via eCRFs (for concomitant medication) and participant completed questionnaires (accident and emergency (A&E) attendance, receipt of primary care and other NHS/PSS care services) at 10 days post baseline. Each of these categories are described in more detailed in sections 2.2.1 to 2.2.3.

Information on resource use will be presented descriptively using mean and standard deviation (SD) and/or median and interquartile range (IQR) as appropriate. We will initially report the completion rates for the health service utilisation (HSU) questionnaire (Table 2).

Table 2 - Summary of the health service utilisation questionnaire completeness at 10 days in the 4 trial arms		
Group 1: active metoclopramide and placebo ondansetron (n=)		
Missing (n)	Partial (n)	Complete (n)
Group 2: active ondansetron and placebo metoclopramide (n-)		
Missing (n)	Partial (n)	Complete (n)
Group 3: active metoclopramide and active ondansetron (n=)		
Missing (n)	Partial (n)	Complete (n)

Group 4: placebo metoclopramide and placebo ondansetron (n=)		
Missing (n)	Partial (n)	Complete (n)

The use of healthcare resources by the participants in the 4 trial arms at 10 days will be presented using means, SDs, medians and IQRs (Table 3).

2.2.1 Medications

Concomitant medication prescribed to participants during the 10 day intervention period will also be captured for each trial arm. Trial participants may be prescribed medications as inpatients, outpatients or from their GP at any point during the trial. The eCRF will collect data on the drug name, dosage, mode of intake frequency, start and end date of medication prescribed to each participants at 48 hours, 5 days and 10 days follow-up.

The mean number of units consumed for each patient per trial arm, as taken from the eCRF will be presented (Table 3). If dose, mode of intake or frequency is missing or incorrect, it will be assumed that the British National Formulary (BNF)(8) standard recommendation for the patient group was prescribed. Information from prescription cost analysis data(9) will be used in those cases where it was impossible to ascertain the intake duration.

2.2.2 Secondary care

The HSU questionnaire will gather data on the number of A&E visits for each participant in the 10 days since baseline.

For all trial arms, a point estimate and range for the mean number of A&E visits will be reported. Participants were also asked about consultations with “other health professionals” and this may also need to be classified as secondary care.

2.2.3 Primary care and other NHS/PSS care services

The number of visits to primary care services and other NHS/PSS care services will be obtained from the HSU questionnaire. Participants will be asked whether the consultation took place at the GP practice, at home or over the telephone.

Table 3 – Average healthcare resource use per patient per trial arm		
Resource use	**Mean usage (SD)/Median (IQR)**	**Primary source**

	Active metoclopramide and placebo ondansetron (n=)	**Active ondansetron and placebo metoclopramide (n=)**	**Active metoclopramide and active ondansetron (n=)**	**Placebo metoclopramide and placebo ondansetron (n=)**	
Medications					
Drug A					eCRF/BNF/Prescription cost analysis
Drug B					eCRF/BNF/Prescription cost analysis
Drug C					eCRF/BNF/Prescription cost analysis
Secondary care					
A&E / casualty attendance					Health service utilisation questionnaire q1 & q1b
Other					Health utilisation questionnaire q4
Primary care and other NHS/PSS care					
GP consultation at practice					Health service utilisation questionnaire q2b
Nurse consultation at practice					Health service utilisation questionnaire q2b
Other consultation at practice					Health service utilisation questionnaire q2b
GP consultation at home					Health service utilisation questionnaire q3c
Nurse consultation at home					Health service utilisation questionnaire q3c

Other consultation at home					Health service utilisation questionnaire q3c
GP telephone consultation					Health service utilisation questionnaire q4c
Nurse telephone consultation					Health service utilisation questionnaire q4c
Other telephone consultation					Health service utilisation questionnaire q4c
Consultation with other health care professional					Health service utilisation questionnaire q4c

2.3 - Patient borne costs

Patient borne costs will be obtained from the HSU questionnaire. These will include the purchase of private health care or personal care. Details relating to their employment status and the main activities that participants would otherwise be doing will also be collected (Table 4).

Table 4 – Patient borne costs

Type of cost	**Mean usage (SD)/Median (IQR)**				**Primary Source**
	Active metoclopramide and placebo ondansetron (n=)	**Active ondansetron and placebo metoclopramide (n=)**	**Active metoclopramide and active ondansetron (n=)**	**Placebo metoclopramide and placebo ondansetron (n=)**	
Private health care episodes					Health service utilisation questionnaire q5
Employment status: 1) Full employment 2) Part-time employment 3) Long term sickness (FT employment)					Health service utilisation questionnaire q6

4) Long term sickness (PT employment) 5) Student 6) Carer 7) Unemployed (seeking work) 8) Unemployed (not seeking work) 9) Other 10) House work					
Time off work/usual activities last 10 days					Health service utilisation questionnaire q7

2.4- Willingness to pay analysis

Participants will be asked to directly express their willingness to pay for a good or service using a Willingness To Pay (WTP) Questionnaire. In order to ascertain their preferences they will be presented with hypothetical scenarios and asked how much they would be willing to pay for to improve symptom severity for a 10 week period. The hypothetical scenarios will be fully informed by input from women with experience of NVP, the literature and other experts. For a given level of income, a higher WTP value indicates that individuals would derive greater benefit from the programme under consideration. This contingent valuation method will enable us to place a monetary value on health outcomes.(10)

We will report the completion rates for the WTP questionnaire (Table 5). WTP data will then be summarised descriptively and presented as a mean willingness to pay for improved symptom severity over a 10 week period (Table 6). Participants will also be asked about the factors influencing their stated maximum WTP amount. In those cases where participants refused to pay a sum of money for improved symptom severity, they will be asked to state the reasons for this decision. These answers will be presented as frequency and percentages in Tables 7 and 8 respectively.

Table 5 - Summary of the WTP questionnaire completeness at 10 days in the 4 trial arms		
Group 1: active metoclopramide and placebo ondansetron (n=)		
Missing (n)	Partial (n)	Complete (n)

Group 2: active ondansetron and placebo metoclopramide (n-)		
Missing (n)	Partial (n)	Complete (n)
Group 3: active metoclopramide and active ondansetron (n=)		
Missing (n)	Partial (n)	Complete (n)
Group 4: placebo metoclopramide and placebo ondansetron (n=)		
Missing (n)	Partial (n)	Complete (n)

Table 6 – Maximum WTP to improve symptom severity for a 10 week period					
Resource use (mean costs per patient)	**Active metoclopramide and placebo ondansetron (n=)**	**Active ondansetron and placebo metoclopramide (n=)**	**Active metoclopramide and active ondansetron (n=)**	**Placebo metoclopramide and placebo ondansetron (n=)**	**Overall (n=)**
Mean (SD)					
Median (IQR)					
Maximum WTP value					
Minimum WTP value					

Table 7 – Factors influencing maximum WTP amount to improve symptom severity at 10 weeks per trial arm					
Reason	**Active metoclopramide and placebo**	**Active ondansetron and placebo**	**Active metoclopramide and active**	**Placebo metoclopramide and placebo**	**Overall (n=)**

	ondansetron (n=)	metoclopramide (n=)	ondansetron (n=)	ondansetron (n=)	
Personal income/savings (n / %)					
Other financial commitments (n / %)					
Unpleasantness of symptoms (n / %)					
Impact of symptoms on family life (n / %)					
Other factor (n / %)					

Table 8 – Reasons for not providing a WTP amount to improve symptom severity at 10 weeks per trial arm					
Reason	**Active metoclopramide and placebo ondansetron (n=)**	**Active ondansetron and placebo metoclopramide (n=)**	**Active metoclopramide and active ondansetron (n=)**	**Placebo metoclopramide and placebo ondansetron (n=)**	**Overall (n=)**
I do not place any value on improved symptom severity over a 10 week duration (n / %)					
I believe that healthcare should be free (n / %)					
Lack of budget (n / %)					
Other reason (n / %)					

2.5 – Missing data

The level of missing data will be reported overall by trial arm. Since no formal economic evaluation is being conducted, no imputation methods will be applied.

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