Appendix. Trial Protocol

1. Trial title
Randomized controlled trial of day care versus inpatient management of nausea and vomiting of pregnancy.

Trial Acronym
D.I.M. trial (Day care versus Inpatient Management of nausea and vomiting of pregnancy)

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Trial Sponsor
The investigators have not sought sponsorship for this trial.

2. Abstract/ summary

• Objective
To compare the initial daycare management of nausea and vomiting of pregnancy (NVP) with the standard inpatient management of NVP on the number of inpatient days, duration of inpatient stay and patient satisfaction

• Design
Open label, single center, randomized controlled trial

• Setting
Cork University Maternity Hospital, a tertiary referral maternity hospital.

• Population
Pregnant women under 22 weeks gestation presenting to the emergency department of Cork University Maternity Hospital for the management of NVP.

• Methods

The authors provided this information as a supplement to their article.
Following initial presentation and assessment the women are randomized to either initial day care management of NVP or standard inpatient management of NVP.

- **Main outcome measures**
  The primary outcome will be the total number of inpatient nights spent in hospital.
  Secondary outcomes include a cost effective analysis, total hours spent in hospital, total amount of intravenous fluids administered, total amount of antiemetics administered, total doses of multivitamin complexes administered intravenously, patient satisfaction measured via CSQ-18B (see attached), number of sick days secondary to NVP, incidence of miscarriage, gestational age at delivery and infant birth weight.

- **Results**
  Patient data will be analyzed on an intention to treat basis. Continuous outcome measures will be analyzed using a t-test and the results will be reported as mean difference and 95% CI. If the assumptions of the t-test are violated a suitable normalizing transformation will be used. For the analysis of categorical variables a chi-squared test will be used and a p-value will be reported.

- **Funding sources**
  No funding was received for this study

- **Conclusions**
  Estimated date of completion: 1\textsuperscript{st} May 2009

- **Keywords**
  Hyperemesis gravidarum, nausea, vomiting, pregnancy, day care, inpatient management

3. Background
Upto 80% of all pregnant women experience some form of nausea and vomiting during their pregnancy. [1-3] The International Statistical Classification of Disease and Related Health Problems ICD-10 [4] defines hyperemesis gravidarum (HG) as persistent and excessive vomiting starting before the end of the 22nd week of gestation, and further subdivides the condition into mild and severe, severe being associated with metabolic disturbances such as carbohydrate depletion, dehydration or electrolyte imbalance. HG is a diagnosis of exclusion, characterized by prolonged and severe nausea and vomiting, dehydration, large ketonuria and > 5% bodyweight loss.[5, 6]
HG affects approximately 0.3- 2.0% of pregnancies and is the commonest indication for admission to hospital in the first half of pregnancy and second only to preterm labor as a cause of hospitalisation overall.[7, 8] According to


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the Hyperemesis Education and Research Foundation, conservative estimates indicate that HG can cost a minimum of $200 million annually in inhouse hospitalizations in the United states. [9] Taking into account other factors such as emergency room treatments, potential complications of severe HG and the fact that upto 35% of women with paid employment will lose time from work through nausea the actual cost of NVP to the economy is significantly higher.[3]

NVP can be extremely debilitating for the patient and if inadequately managed can cause significant morbidities including malnutrition and electrolyte imbalances, thrombosis, Wernicke’s encephalopathy, depressive illness and poor pregnancy outcomes such as prematurity and small for gestational age fetuses.[10-14]

Several randomised trials have been performed testing different treatments for the treatment and prevention of HG including oral ginger root extract, intravenous diazepam and acupuncture. Both ginger and acupuncture appear to improve nausea but no treatments were shown to be of benefit in HG.[15-18] The management of NVP is therefore based on correcting electrolyte imbalance and dehydration, prophylaxis against recognised complications and providing symptomatic relief. There is an understandable reluctance to prescribe anti-emetics for symptomatic relief but extensive data exists to show a lack of teratogenesis with dopamine antagonists, phenothiazines and histamine H1 receptor blockers. [19-21]

Day care has proven to be beneficial and safe mode of care for patients in other clinical settings.[22] Studies have demonstrated that day care management of patients with NVP appears acceptable and feasible [23] but no systematic reviews or randomized controlled trials have been performed which examine the effects of introducing day care on rates of hospital admission, duration of inpatient stay and patient satisfaction.

4. Study Hypothesis
We aim to conduct a prospective open label randomized controlled trial to test the hypothesis that the availability of day care services for the initial treatment of NVP reduces the mean duration of stay in hospital by 1 day (28.6%) and results in significantly greater patient satisfaction compared with standard inpatient management.

The null hypothesis states there is no difference in the amount of inpatient hospital days when women with NVP are treated initially in day care or by standard inpatient admission.

5. Interventions
All pregnant women under 22 weeks gestation, who have not already been treated for NVP in their current pregnancy, presenting with the diagnosis of NVP are eligible for inclusion in the trial. The treatment group will be day care treatment of NVP. The comparison group will be the inpatient treatment of NVP.
6. Randomization process

Randomization: Sequence generation
Subjects will be allocated to the study groups by simple randomization.

Randomization: Allocation concealment
A computer-generated randomization list will be drawn up by the study statistician (AK) and given to the recruiting physician.

Randomization implementation
Determination of whether a patient would be allocated to day care or inpatient treatment will be made by reference to a statistical series computer generated using simple randomization. The details of the series were unknown to the co-ordinator or recruiting physician and were contained in a set of sealed opaque envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the trial coordinator the appropriate numbered envelope will be opened by the recruiting physician. The card inside will state if the patient is to be allocated to day care or inpatient treatment and this information will then be given to the medical officer. A register will be kept in the emergency department of all envelopes and the names of the subjects.

7. Outcome measures

- Primary Outcome
The primary outcome will be the number of inpatient nights spent in hospital secondary to NVP from initial presentation until 22 weeks gestation. An inpatient night will be defined as requiring an inpatient bed between the hours of 20.00 and 08.00.

- Secondary Outcomes
Secondary outcomes are

1. Total number of hours spent in hospital secondary to NVP from initial presentation until 22 weeks gestation.
2. Total amount of intravenous fluids administered secondary to NVP from initial presentation until 22 weeks gestation.
3. Total amount of anti-emetics administered secondary to NVP from initial presentation until 22 weeks gestation.
4. Total Multivitamin complexes administered secondary to NVP from initial presentation until 22 weeks gestation.
5. Patient satisfaction recorded after the first day care/ inpatient treatment. Patient satisfaction will be measured by the Client Satisfaction Questionnaire (CSQ-18B) [24-26] (see attached). To avoid bias, this questionnaire will be recorded only once after the first day care/ inpatient treatment. If a participant receives
more than one treatment she will not be asked to fill in the questionnaire again. The first presentation for day care/ inpatient treatment may range from conception to 22 weeks gestation.

6. Incidence of miscarriage
7. Infant birth weight at delivery.
8. Gestational age at delivery.
9. Total days lost at work secondary to NVP from initial presentation until 22 weeks gestation. (Asked at 16 weeks gestation)
10. Cost effective analysis

8. Sample size
At the time of the study design the mean inpatient stay for women with NVP was 3.52 days with a standard deviation of 1.47. To have an 80% statistical power of detecting a one day reduction in mean inpatient stay at P<0.05 with a two tailed test we require 46 subjects in each arm of the study. We anticipate that 25% of the participants would drop out from the study therefore the final sample size needed under the same assumptions is 62 patients in each group. The calculations were performed in Stata Software. [27]

9. Study Participants/ Eligibility criteria
All pregnant women under 22 weeks gestation presenting to the emergency department of Cork University Maternity Hospital with nausea and vomiting of pregnancy are candidates for inclusion in the trial.

Inclusion Criteria. Women (no age limits) will be admitted to the study if they have two or more of the following criteria
- Ongoing viable intrauterine pregnancy/ pregnancies < 22 weeks gestation
- Persistent vomiting (>x3 episodes/ 24 hours) not attributable to other causes
- Severe nausea not attributable to other causes.
- Dehydration diagnosed by the presence of ketonuria.
- Electrolyte imbalance not attributable to other causes.

Exclusion Criteria: Women will not be admitted to the study if any of the following criteria are present.
- Women with a confirmed urinary tract infection (mid stream urine isolation of a single strain of uropathogen >10^5 bacteria/ml)
- Women with molar pregnancies
- Women with non viable pregnancies.
- Women who have already received treatment for NVP outside of this trial.


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• Pregnant women who present who will not be booking at CUMH for their pregnancy or are not resident in the South West of Ireland i.e. day care treatment is not an option.
• Women who do not have a good understanding of English.

10. Trial process
The study protocol was prepared in line with the CONSORT guidelines. [28, 29] and will be submitted to the Lancet for review before recruitment of women. The study is a randomized controlled one centre study at an Irish teaching maternity hospital. Cork University Maternity Hospital (CUMH) is a maternity hospital serving the South West of Ireland with over 8500 deliveries per annum. The study flow is planned as per Flow diagram 1. Our day care unit operates between 08.00 and 17.00 Monday to Friday. For patients recruited outside of these hours or patients representing outside of these hours, if they have been randomized to day care they will receive the same day care protocol in the emergency department. They will be referred to the day care unit for subsequent presentations.

• Recruitment
Patients will be recruited in the emergency department of CUMH on initial presentation following assessment as per CUMH guidelines (details under intervention section)

• Consent
Following initial assessment patients will be assessed by the recruiting physician (who will be 1 of 7 non consultant hospital doctors working in CUMH) regarding eligibility for the trial. If patients meet entry criteria for the trial they will be given written and oral information on the trial and alternatives to the trial. If willing to participate in the trial patients will be asked to sign a written consent form. (See form 4)

• Registration/ randomization
Following consent the recruiting physician will contact the trial coordinator (FMcC) or the chief recruiting physician (RKS) to confirm eligibility for the trial. Subjects will be allocated to the study groups by simple randomization with 124 sealed, opaque sequentially numbered envelopes. The details of the series will be unknown to any of the investigators or to the co-ordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the trial coordinator or chief recruiting physician the appropriate numbered envelope will be opened by recruiting physician. The card inside will state if the patient is to be allocated to day care or inpatient treatment and this information will then be given to the medical officer. A register will be kept in the emergency department of all envelopes and the names of the subjects.
• Treatment
Following randomization patients will be informed that they have been randomly assigned either to day care or inpatient management. Depending on their treatment arms patients will receive a pre-written drug kardex as per their treatment arm. (See forms 3a and 3b) The treatment regimens are described in detail later.

• Follow- up

Follow- up inpatient treatment arm
Patients will be discharged by the managing obstetric team. The criteria for discharge are one or more of the following

• <3 episodes of vomiting in a 24 hour period.
• When the patient can tolerate oral fluids +/- food.
• <2+ ketonuria on ward urine dipstick performed on the morning following admission.

They will then be instructed to re-present if symptoms which have led to the initial admission occur again. Patients will be treated until resolution of symptoms. On discharge following each presentation patients will be asked to fill out a Client Satisfaction Questionnaire (CSQ-18B- See form 5). For the purpose of analysis the first recorded CSQ-18B will be used.

Follow- up daycare treatment arm
The patient will be reviewed by the managing physician following day care treatment. On their first discharge patients will be asked to fill out a CSQ-18B. Patients will be instructed to present on a daily basis to the day care unit until resolution of symptoms. The patients will also be asked to fill out the CSQ-18B following attendance at each day care presentation. For the purpose of analysis the first recorded CSQ-18B will be used.

• Study period
Expected Start date: 23rd March 2009
Expected completion date: 30th Dec 2009
Expected reporting date 1st May 2009

• Registering and reporting of suspected adverse reactions
Any unexpected and serious reactions or outcomes will be immediately reported to either the trial co-ordinator (FmcC) or the principle investigator (JRH) as well as the Clinical Research Ethics Committee of the Cork teaching Hospitals and the trial steering committee.

11. Data Collection
• Pre- randomization data


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Patients will be reviewed on presentation to the emergency department of CUMH by a midwife and all necessary information recorded. The patient will then be reviewed by a doctor who will perform the following standard initial assessment as per CUMH guidelines as follows:

1. An 18G or 20G IV line should be inserted and a blood sample taken to test urea, electrolytes, liver function (LFTs).
2. Urinalysis and a mid-stream urine should be performed on each presentation.
3. With recurrent presentations a full blood count, thyroid function tests (TFT’s) calcium and glucose should also be performed.
4. An ultrasound examination should be performed once to confirm gestation and viability and outrule multiple pregnancies and molar pregnancy decide whether or not to refer the women to the study.

Following assessment and diagnosis of NVP patients will be counseled regarding the study and the study recruiting physician contacted.

All this data will be recorded in a study flow sheet (See form 1)

- **Post randomization data**
  On each admission/attendance at day care unit a flowsheet will be filled out by midwife in charge (See form 2)

- **Outcome data**
  The CSQ-18B will be completed by the patient following their first attendance at day care or following their first discharge from hospital. Studies have shown a response rate of approximately 45% with the CSQ-18B when patients are followed up via a postal and telephone survey. In order to avoid this poor response rate and to avoid bias the CSQ-18B will be filled out after first presentation and treatments.

**12. Interventions/ Treatment Regime**

**Daycare management of NVP**

- Initial assessment should be performed as outlined above.
- The patient should receive 2 liters of fluid (Normal Saline) intravenously over 5 hours.
- Anti-emetics should be considered when patients fail to respond to intravenous fluid administration.
- Anti-emetics are administered orally if tolerated or intramuscularly/ intravenously/ rectally if unable to tolerate oral medications.
- Anti-emetics will be administered on a prn basis in the following order [17, 30-34]

  a) Metoclopramide (Maxolon. Preg Cat B) 10 mg stat intravenously until able to tolerate oral.
b) Prochlorperazine (Stemetil. Preg Cat C) 12.5mg PO /IM/ prn/ tds or 25mg PR 12hrly

If symptoms persist or worsen despite maximum daily dose consider

a) Cyclizine (Preg Cat B) 50mg PO/ IM

OR

b) Domperidone (Preg Cat B) 10mg PO prn/ qid

If symptoms persist or worsen despite maximum daily dose consider

c) Ondansetron (Preg Cat B) 4mg bd IV/ PO.

- If prolonged NVP, one ampoule of Multivitamin complexes will be administered in 1 liter of normal Saline over 3 hours on a weekly basis.
- If vomiting persists consider admission of patient.

**Inpatient management**

- Initial assessment should be performed as outlined above.
- The initial liter of fluid (Normal Saline) can be given over 3 hours.
- The patient should then receive 1 liter of fluid (Normal Saline) intravenously every 6 hours until able to tolerate oral fluids.
- Anti-emetics should be considered when patients fail to respond to supportive management. Anti-emetics are administered orally if tolerated or intramuscularly/ intravenously/ rectally if unable to tolerate oral medications.
- Anti-emetics will be administered on a prn basis in the following order

a) Metoclopramide (Maxolon. Preg Cat B) 10 mg stat intravenously until able to tolerate oral.

OR

b) Prochlorperazine (Stemetil. Preg Cat C) 12.5mg PO /IM/ prn/ tds or 25mg PR 12hrly

If symptoms persist or worsen despite maximum daily dose consider

a) Cyclizine (Preg Cat B) 50mg PO/ IM

OR

b) Domperidone (Preg Cat B) 10mg PO prn/ qid

If symptoms persist or worsen despite maximum daily dose consider

a) Ondansetron 4mg bd IV/ PO (see 4.1.14)
• If prolonged NVP, one ampoule of Multivitamin complexes will be administered in 1 liter of normal Saline over 2 hours on a weekly basis.

13. Statistical analysis plan
All data analysis will be carried out according to a pre-established statistical analysis plan. Continuous outcome measures will be analyzed using a t-test and the results will be reported as mean difference and 95% CI. If the assumptions of the t-test are violated a suitable normalizing transformation will be used. For the analysis of categorical variables a chi-squared test will be used and a p-value will be reported.[35]

• Primary analysis
Patient data will be analyzed on an intention to treat basis.

• Interim analysis
Due to the small numbers required to achieve statistical significance and anticipated zero potential risk or adverse outcomes to patients no interim analysis will be performed.

• Stopping points/Data audit
An independent midwife will review compliance with treatment arms, patient recruitment, data recording and any adverse outcomes every 10 patients that are recruited to the trial. This independent midwife will report these results to the Trial steering committee. The Trial Steering Committee may terminate the trial if there are any unacceptable side effects or toxicities, if patient recruitment to the trial is so slow the trial is no longer sufficient or if poor execution of the trial compromises the ability of the trial to meet its objectives.

• Data and Safety Monitoring Board
The trial was determined to be “low risk” by our ethics committee a Data and Safety Monitoring Board was not established.

• Cost effective analysis
For the economic evaluation, costs and Quality Adjusted Life Years (QALYs) will be calculated. Costs of an Inpatient stay are available from the relevant Diagnostic Related Group, which are collected routinely for hospital records. Since costs for the Day Case arm are not collected routinely. Therefore microcosting techniques will be used, following well established economic principles.[36] Outcomes will be measured using Quality Adjusted Life Years (QALYs). All patients will be asked to respond to the EuroQoL questionnaire to measure their health-related quality of life during a day with and a day without NVP and report the number of days with NVP. Combining the two we will generate QALYs. Results will be presented as 'incremental cost per


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incremental QALY ratios and 'incremental cost per incremental day free of NVP' ratios.

14. Publication policy
The study protocol was reviewed by the Lancet editorial team prior to patient recruitment. The manuscript will be sent to the Lancet upon completion of the data analysis.

15. Data Monitoring and Ethics Committee
The study was approved by the Cork University Teaching Hospitals Clinical Research Ethics Committee on the 3rd September, 2008. (Reference for the ethical approval notification is ECM 5 (5) 02/09/09). The study protocol is available online at www.ClinicalTrials.gov (NCT00795561) and was reviewed by the Lancet editorial team prior to patient recruitment. The International Randomized Controlled Trial Number is ISRCTN05023126. Each participating woman in the study will sign an informed consent and will be insured through the Clinical Indemnity Scheme.

16. Trial Steering Committee
- Professor Deirdre Murphy, Professor of Obstetrics & Gynaecology, Consultant Obstetrician, Trinity College, University of Dublin & Coombe Women’s Hospital
- Dr Declan Keane, Consultant Obstetrics and Gynaecology, National Maternity Hospital Dublin.
- Dr Michael Geary, Consultant Obstetrician and Gynaecologist and Master of the Rotunda Hospital, Dublin.
- Professor Richard A Greene, Director National Perinatal Epidemiology Centre, Consultant Obstetrician and Gynecologist, Cork University Maternity Hospital, Cork.
- Dr Louise Kenny, Senior Lecturer, Department of Obstetrics and Gynecology, Anu Research Centre, University College Cork, Cork University Maternity Hospital, Cork.
- Professor C. Anthony Ryan, Associate Professor of Paediatrics and Neonatology, Department of Paediatrics and Child Health, University College Cork, Cork University Maternity Hospital, Cork

17. Centers
The study will be a one centered study performed at Cork University Maternity Hospital.

18. Funding
No funding has been received for this study.

19. References


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36. MF Drummond, M.S., GW Torrance, BJ O'Brien, GL Stoddart (2005), M.f.t.E.E.o.H.C.P.r Ed., and O. OUP.