RESEARCH PROPOSAL

DEPARTMENT OF OBSTETRICS & GYNAECOLOGY
FACULTY OF MEDICINE
UNIVERSITY OF MALAYA

TITLE: ORAL REHYDRATION THERAPY VS INTRAVENOUS REHYDRATION THERAPY IN THE FIRST 12-HOUR FOLLOWING HOSPITALISATION FOR HYPEREMESIS GRAVIDARUM- A MULTICENTRE RANDOMISED TRIAL (ORIV trial)

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INTRODUCTION

Nausea and vomiting are common early pregnancy symptoms affecting about 85% of pregnant women, when all other portentous cause has been excluded. However, in about 0.3-1% women the symptoms are severe enough and termed hyperemesis gravidarum (HG) which warrant in patient care[1]. Hyperemesis gravidarum is the most common and recurring cause for hospital admission in pregnancy [2].

It is characterised by intractable nausea and vomiting that is not related to other cause leading to a sign of acute starvation indicated by presence of ketonuria, weight loss of 5% of prepregnancy weight, with presence of electrolyte imbalances. Hyponatremia and hypochloremia are common electrolytes imbalance seen in about 40% on hospital admission [3].

Affected women reported feeling distress from the unbearable symptoms of not just nausea and vomiting but also being limited in daily physical activity in addition to the psychological affliction that was caused by feeling ill for weeks to months at any time of the day with varying severity [4, 5] .

Aim of treatment in these women is to restore hydration, dietary and lifestyle modification, maintaining or correcting electrolyte imbalance [6], emotional support and psychosomatic care if needed. They should be attended to immediately and early form of intervention is needed to reduce disease severity.

Systematic review by McParlin et al highlighted that use of antiemetics is effective in treating HG [7]. Many antiemetics have been studied, metoclopramide has better adverse effect profile [8], thus was chose as antiemetics for the purpose of this study.

Hydration can be in the form of encouraging oral intake or intravenous fluid supplementation. Modification in the amount of food and meals taken throughout the day may improve symptoms, drinks that contain electrolytes and other supplements are advised [9], and women should be encouraged to drink at least 2L/ day. Traditionally, intravenous fluid therapy (IVT) has been used for treatment of HG and it is proven effective in correcting electrolytes imbalances and at the same restoring hydration [10]. However, risk of rapid infusion may cause complications such as central pontine myelinolysis, thus careful consideration is advised [7]. Other risk associated with IVD includes, pulmonary oedema, fluid overload, infection at branula site- thrombophlebitis, extravasation, pain and prolonged hospital stay[11].

Recent study conducted in this centre on delayed compared with early oral intake in initial management of hyperemesis gravidarum showed that patients prefer to eat early (65%) than being fasted (41%). Once vomiting is controlled with the use of antiemetic, women should be encouraged to take orally by drinking, and eating as much as they want, whatever they feel like eating whenever they want [12].

Day care management is proven to be beneficial and feasible for managing nausea and vomiting in pregnancy, this can avoid admissions and reduce maternal anxiety [13].

A study done by van Vliet et al on patient preferences of HG treatment showed that patients stressed on the need of early intervention, home care options and more support among all other [14]. Taking

into account patient concern and predilections, management of HG can be tailored accordingly and improve the course of HG.

Oral rehydration salts (ORT) therapy can be an alternative measure for rehydration. It constitutes sodium, potassium, chloride and glucose and is a primary means of treating dehydration in gastroenteritis. It uses sodium-glucose cotransport mechanism to passively absorb water across the intestinal mucosa thus increasing intravascular volume and correct dehydration. Consequently, ORT helps with correction of electrolyte imbalances. A meta-analysis by Bellemare et. al, 2004 stated that there were no clinically important differences between ORT and Intravenous fluid therapy in terms of efficacy and safety [15].

It is easily available and can be self-prepared and administered by patients/ their caregiver. Patients can take as early, as much, as often as they can tolerate. This will also empower women to practice self-care.

ORS is easily available as 'over-the-counter' medication, doesn't need prescription, treatment can be started early at home, where women are surrounded by their loved ones, with more psychological support and in more convenient environment [14]

So far there has been no study to compare oral vs intravenous rehydration in the management of acute HG at hospitalisation.

We seek to evaluate the response of oral rehydration therapy (ORT)- in terms of patient satisfaction, ability to restore hydration and improve ketonuria and can be used as an alternative to intravenous rehydration (IVT) as a basis to construct a substitute management plan for HG.

RESEARCH HYPOTHESIS:

Although IV rehydration is superior than oral rehydration therapy in improving ketonuria, ORT has greater patient satisfaction and also resulted in resolution of ketonuria in the initial management of HG.

OBJECTIVE:

1. To evaluate patient satisfaction with given rehydration regime (IVT vs ORT) in the initial hospital management of HG in term
2. To evaluate improvement of rehydration with use if IVT vs ORT
3. To evaluate if use of ORS would result in similar improvement of ketonuria as with IVT

PRIMARY OUTCOME / ENDPOINT

1. Patients satisfaction with allocated rehydration regime using VNRS scale (Visual Numerating Rating Score) from 0 to 10, with 0 being the worst score) at 12hours
2. Weight difference (in grams) after 12hours
3. Improvement of ketonuria after 12hours

SECONDARY OUTCOME

1. Hospital admission to discharge interval
2. Serial nausea score at 0,4,8,12 hours
3. Likert's scale on preference of treatment
4. Deviation from protocol
5. Hematocrit (Hct), electrolytes level after 12hours
6.

METHODS

STUDY DESIGN

This is a prospective randomised trial in which participants will be divided into a group of 2. One group will receive standard care of intravenous fluid rehydration (control group) and be asked to be fasting for 12hours and another arm will receive oral rehydration therapy (trial/ experimental) and encouraged to eat and drink normally. Prior to any interventions both groups will receive standard antiemetics

STUDY POPULATIONS

This is a multicentre trial. Trials will be conducted in University Malaya Medical Centre and at least another hospital under under MOH (Ministry of Health)

SAMPLE SIZE

p value of significance will be $p< 0.016$ to prove individual level of significance from the 3 primary outcomes. As this study is powered to 3 primary outcome, Bonferroni correction [16] implies that the adjusted threshold of $0.05/m$ is used of each outcome (Fisher 1935) thus the need to adjust the significant level (p value)

There was no previous trial comparing oral vs intravenous rehydration therapy in HG to guide sample size calculations.

Taking the patient satisfaction score at 12-hour, assuming a 1 point difference and it is a normally distributed data with a standard deviation of 2, alpha of 0.016 and power of 80%, a sample size of 78 is needed in each arm.

Assuming 50% improvement of ketonuria with IVT whilst 25% improvement in ORT group, power of 80% and alpha of 0.016, using an independent student T-test, 86 patients are needed each arm.

Presuming 500g weight improvement seen in IVT, and estimated 300gm changes in weight difference, of both groups, utilising power of 80%, alpha 0.016, (δ 300, σ 500),m1 (ratio 1:1), the sample required will be 86 for each arm.

By using Mann-Whitney U test in a non-normally distributed data, another 10% is added in to achieve a level of significance; also assuming there will be a 10% dropout, the sample size needed for each arm will be 106 patients.

Rounding up, we plan to recruit 110 in each arm.

INCLUSION CRITERIA

a. Age 18 and above
b. Confirmed pregnancy at least by UPT test and presence of intrauterine sac
c. Clinical diagnosis of Hyperemesis Gravidarum, with presence of ketonuria of at least 2+ on admission
d. Gestation age less than 14w
e. First hospital admission for HG- within 2hours of admission where rehydration therapy has not formally been commenced

EXCLUSION CRITERIA

a. Allergy to oral rehydration salts / its contents
b. Women with underlying medical disorder (Diabetes Melitus, Hypertension, Heart disease/ renal disease/ endocrine disorder- hyperthyroid disorder)
c. Multiple pregnancy
d. Proven non viable pregnancy

STUDY PROCEDURES

RECRUITMENT

a. Patients admitted to gynaecology ward, 10U, University Malaya Medical Centre or at least one other hospital under MOH for presumed diagnosis of HG will be approached within 2H of admission.
b. Those who fulfilled inclusion criteria will be invited to participate in the study. They will be given Patient Information Sheet and verbal and written consent taken.

RANDOMISATION

a. Patient will be randomised into 2 arms- ORT vs IVT arm.
b. ONE arm receiving oral rehydration therapy and ANOTHER arm will receive intravenous rehydration therapy and routine standard care. They are encourage to have normal diet.
c. Randomisation will be generated by a random sequence generator, provided by random.org. to avoid bias, and labelled on an envelope, which will be taken out from a designated box upon recruitment of the patient, which will determine which arms does the patient belongs to.
d. Each centre will perform their own randomisation with a sealed envelope.
e. No attempt of blinding is performed due to the nature of the intervention.

STUDY PROTOCOL

1. Patient personal information and characteristics including pre-pregnancy weight, vitals sign- Temp, Blood Pressure, Pulse Rate, weight on admission and baseline investigation (ketone, FBC, blood urea and serum electrolytes) on admission will be recorded in Trial Performa.
2. Weight- will be taken using personalised weighing scale, patient will be ask to empty their bladder, wearing single layer of hospital gown, remove their shoes and other accessories.
3. Patient will be given PUQE and nausea score scale using a VNRS to be fill in at recruitment (0h)
4. All patients will receive standard antiemetics (as per routine practice of the institution) e.g IV metoclopramide 10mg stat on admission, and 8 hourly.
5. Participants in IVT group will receive standard intravenous hydration therapy (1.5L of 0.9% saline/ or HM solution over 12hours, run at 125cc/hour).
6. After 1 hour of receiving antiemetic, participants in oral rehydration therapy (ORT) group will be given ORS plus salts (diluted in 250cc water)—((time to Peak of action of metoclopramide to takes place)), this will be given every 4 hours, extra sachet will also be provided to patient and they are encouraged to take as much as, as soon as and as often as they can. The patient is also encouraged to take a normal diet as tolerated and is asked to fill in input chart. The patient can ask to be started on IV hydration therapy if they deemed so and if the patients think that they cannot tolerate orally at all (this will clearly be informed and stated in PIS- Patient Information Sheet) and time started will be recorded in the case report form.
7. The patient is asked on their nausea scoring 4 hourly at 0, 4, 8 and 12-hour
8. Patients are also provided with a vomiting and input diary to keep track on their frequency of vomiting and oral/parenteral input.
9. Vital sign using modified obstetric early warning scoring system (MOEWS) chart is recorded at 0,4,8,12- hour.
10. At 12-Hour,
    - 10.1. Urine will be checked for ketonuria.
    - 10.2. Patient weight is measured, they will be asked to empty their bladder and weight is taken using the individualised digital weighing scale used during recruitment.
    - 10.3. Patients are asked to rate their nausea score.
    - 10.4. Patients are asked to score their satisfaction score of their rehydration regime using VNRS (where 0 being the worst possible)
        - 10.4.1. Those who deviate from protocol, will automatically be given the worst score (of 0), however they will also be asked to rate their own satisfaction score using VNRS
    - 10.5. Patients are asked if they would recommend their rehydration regime to a friend with similar circumstances using a Likert's score.
    - 10.6. FBC for hematocrit level, blood for urea and electrolytes are taken and recorded.

11. After 12-Hour, both groups are encouraged to eat as soon as, as much as and as often as tolerated. Any initiation of intravenous rehydration in ORT-group within 24hours of admission will be considered as violation of protocol to reduce risk of bias.

DEVIATION FROM PROTOCOL

1. When?
    a. When patient request for Intravenous rehydration therapy (those in ORT group)
    b. Any abnormality observed on vitals sign using modified MOEWS chart taken 4hourly, i.e HR >120bpm, BP <90/60mmHg, or Temp >38'C
    c. Or care provider ascertain that patient need to be put on IV rehydration
    d. If anyone from ORT group who subsequently need IV rehydration within 24-hour of recruitment

2. What will happen to the data?
    a. Data will be included in secondary outcome
    b. Patient satisfaction score is considered as 0

CONSENT

Informed and written consent will be taken from those who are willing to participate in this study. Those who agree to participate will be required to personally sign and date the informed consent form. Emphasize will be given on the voluntary nature of participation, patient will also be informed that if they wish to withdraw at any point of time, they are allowed to do so by just informing the attending personnel and that their subsequent care will not be affected.

DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS FROM STUDY

Each participant has the right to withdraw from the study at any time by informing the Investigators.

Upon withdrawal / discontinuation from this study, participants will be treated as any other patients with similar presentations but not participating in this study.

REPORTING OF ADVERSE EVENTS/ INTERCURRENT ILLNESS

As there are new drugs/ procedure being tested, a very low/ none adverse events are expected to occur. However, if unexpected adverse events do occur, it need to be informed to investigator as soon as possible and investigator need to report it to MREC immediately from the awareness of the investigator, followed by complete reporting to MREC. Name of investigators and their contact number is imprinted on patient information sheets.

Patient will be followed up until discharge and will begiven outpatient follow up dates until at least 2 consecutive normal review.

No compensation will be given.

DATA ANALYSIS AND INTERPRETATION

Data entry and analysis will be done using SPSS Statistics software. Analysis is by intention-to-treat basis. Normally distributed continuous data will be analyzed with the Student's t test or chi square. Mann-Whitney U test will be used for non-normally distributed continuous data or ordinal data.

DATA MANAGEMENT

ACCESS TO DATA

Access to data will be granted to investigators and representative from Sponsor(s) for monitoring and/or audit purposes only.

DATA COLLECTION AND RECORD KEEPING

Demographic, and clinical data will be derived from medical records. A case report form will be used for data collection and new ID will be given to the patient, no personal information will be available on patient CRF The data collection will be performed by investigators.

Data will be stored in locked cabinet in the investigator office where only the investigator will have the access to. It will be kept for duration of 7 years before it is being destroyed.

PROJECT MANAGEMENT

Data collection will be conducted between Nov 2020- May 2022

Data entry will be done concurrently.

Data analysis will be performed from October 2020 - November 2020

Report will be prepare from December 2020 - January 2021

GANTT CHART:

YEAR 1		YEAR 2
2020	2021	2022

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nov	dec	jan	feb	march	april	may	jun	july	august	sept	oct	nov	dec	jan	feb	march	april	may	june	july	sept
SAMPLE COLLECTION																					
	DATA ENTRY																				
																	DATA ANALYSIS				
																				REPORT	

ETHICAL AND REGULATORY CONSIDERATIONS

APPROVALS

This research will be registered with the National Medical Research Registry (NMMR). Ethical approval has been obtained from the Ethic Committee of University Malaya Medical Centre, NMRR-20-2223-54789 on 7-4-2020.

PARTICIPANTS CONFIDENTIALITY

All participants' anonymity is maintained. The participants will be given a unique Study ID upon recruitment into this study. This Study ID will be the only mean of identifying the participant on the Case Report Form (CRF) and electronic database. There will be a separate document (Participant Identification List) containing participant's name, identification card number, telephone number and address along with their Study ID. This document will only be accessible to Investigators and will be stored separately from the data documents.

The result of this study may be presented at medical conferences or published in medical journals. However, all data obtained will be reported with no reference to a specific individual. Hence, every participant's data will remain confidential.

EXPENSES

Participants are not paid any fee to participate in this study. They are not exempted from any hospital charges.

CONFLICT OF INTEREST STATEMENT

The Authors declare that there is no conflict of interest.

Appendix 1:

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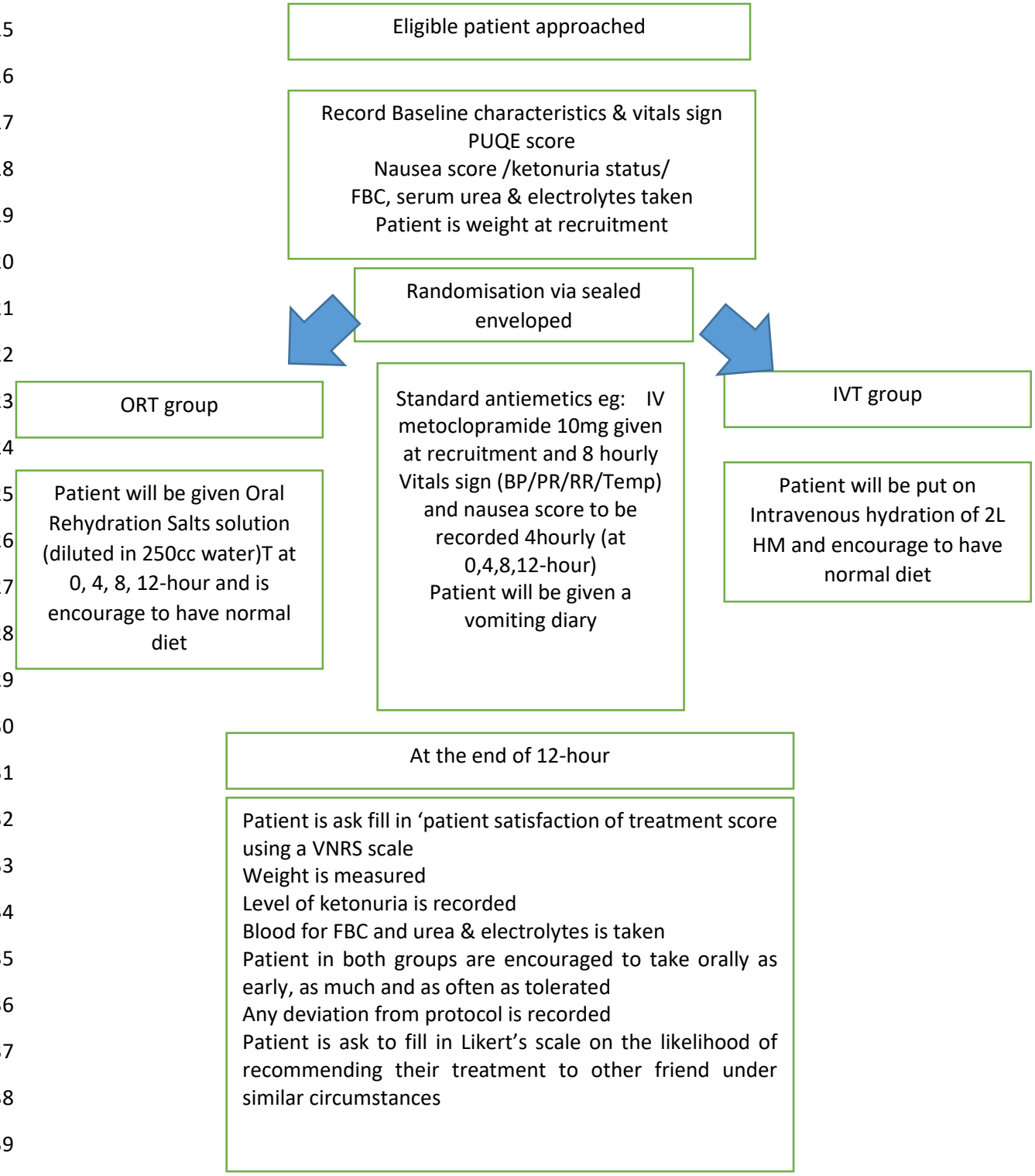
Research protocol flow chart



Appendix 2: PUQE score form

PUQE form will be distributed to patient to be answer upon recruitment.

Objective: To assess the severity of Nausea & Vomiting perceive by patient upon recruitment.

PUQE form:

Pregnancy-Unique Quantification of Emesis and nausea

Circle the answer that best suits your situation in the last 24 hours

1. On average in a day, for how long do you feel nauseated or sick to your stomach?

>6 hours 5 points	4–6 hours 4 points	2–3 hours 3 points	≤1 hour 2 points	Not at all 1 point

2. On average in a day, how many times do you vomit or throw up?

≥7 times 5 points	5–6 times 4 points	3–4 times 3 points	1–2 times 2 points	Not at all 1 point

3. On average in a day, how many times have you had retching or dry heaves without bringing anything up?

≥7 times 5 points	5–6 times 4 points	3–4 times 3 points	1–2 times 2 points	Not at all 1 point

Total score (sum of replies to 1, 2 and 3): mild NVP ≤6; moderate NVP, 7–12; severe NVP ≥13.

Quality of life question:

On a scale of 0 to 10, how would you rate your well-being? _____

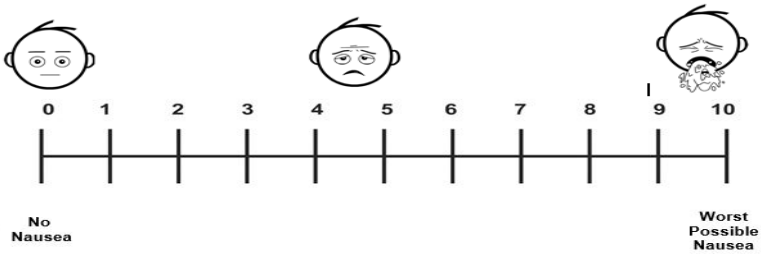
0 (worst possible) 10 (as good as you felt before pregnancy)

PATIENT STICKER

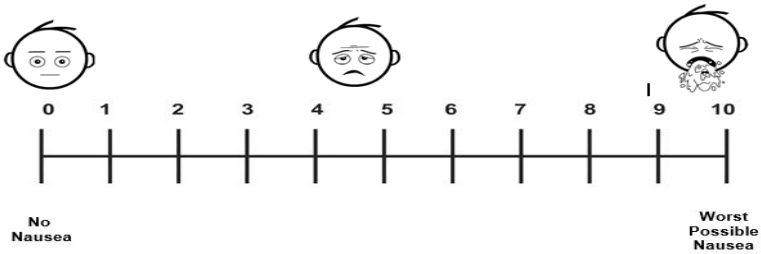
Appendix 3: Nausea score.

Please rate the nausea that you feel according to the visual scale below.
(with 10 being the worst possible nausea)

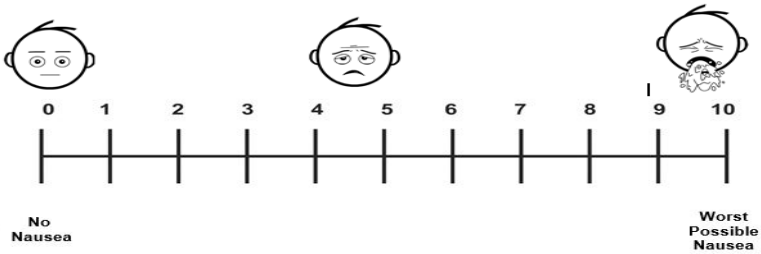
NAUSEA SCORE 0-H (upon recruitment)



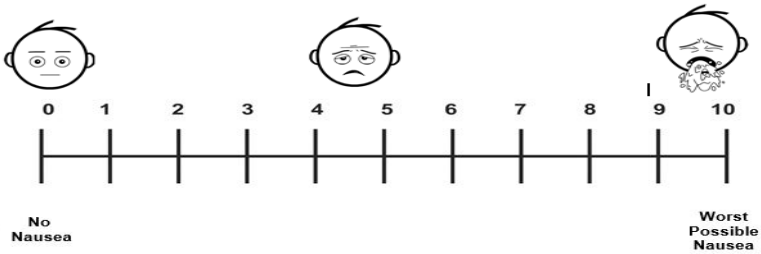
NAUSEA SCORE 4-HOUR



NAUSEA SCORE 8-HOUR



NAUSEA SCORE AT 12-HOUR



PATIENT STICKER

Appendix 4: Patient satisfaction score of regime received and Likert's scale

Please rate your level of satisfaction regarding the treatment regime that you received.
(With 0 being the worst score)

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Very satisfied

Will you recommend the type of treatment that you received today to your friend with similar circumstances?

- Strongly agree
- Strongly disagree
- Neither agrees/ disagrees

PATIENT STICKER

Appendix 5: vomiting and input chart

TITLE: ORAL REHYDRATION THERAPY VS INTRAVENOUS REHYDRATION THERAPY IN THE FIRST 12-HOUR FOLLOWING HOSPITALISATION FOR HYPEREMESIS GRAVIDARUM- A MULTICENTRE RANDOMISED CONTROLLED TRIAL (ORIV trial)

DATE :			
		INPUT	
TIME	**VOMITING FREQUENCY**	**ORAL**	**PARENTERAL**
0700H			
0800H			
0900H			
1000H			
1100H			
1200H			
1300H			
1400H			
1500H			
1600H			
1700H			
1800H			
1900H			
2000H			
2100H			
2200H			
2300H			
0000H			
0100H			
0200H			
0300H			
0400H			
0500H			
0600H			

PATIENT STICKER

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