Postoperative nausea and vomiting (PONV) is one of the most common complications affecting patients after surgery and causes significant morbidity and increased length of hospital stay. The pathophysiology of PONV is multifactorial, but it is accepted that patients undergoing gastrointestinal surgery are at a higher risk.

In the current era of minimally invasive surgery combined with enhanced recovery after surgery (ERAS) pathways, reducing the incidence and severity of PONV is particularly important. The cost implications related to prolonged hospital stay and of further complications affect both open and laparoscopic surgery.

In practice, dexamethasone is widely, but not universally used. It is known to improve appetite and gastric emptying, reduce vomiting and aid early recovery. However, dexamethasone has possible side effects such as increased risk of wound infection and anastomotic leak and could therefore adversely affect recovery.

DREAMS is a phase IV, double blind multicentre randomised controlled trial with the primary objective of determining whether preoperative dexamethasone reduces postoperative vomiting in patients undergoing major elective gastrointestinal surgery.

Patients undergoing laparoscopic or open resections for malignant or benign pathology are randomised to 8mg IV dexamethasone or control (no dexamethasone)es. All patients are given one additional anti-emetic at the time of induction, however, this must not be dexamethasone. Both the patient and their surgeon are blinded to the randomised allocation.

Secondary objectives of the DREAMS trial are to determine whether there are other measurable benefits during recovery from surgery with the use of dexamethasone, including quicker return to oral diet and reduced length of stay. Health related quality of life, fatigue and infection rates will be investigated. Patients will also be stratified for gender, smoking status, open or laparoscopic surgery, patient controlled analgesia (PCA) or epidural/spinal analgesia, ASA grade and use of an ERAS pathway.

DREAMS is designed in two stages. The initial pilot study showed that patient identification, recruitment and follow-up were feasible. The full phase IV DREAMS trial aims to randomise 1320 patients over 2 years, which would provide 90% power to detect a 24% proportional reduction in the proportion of patients experiencing vomiting within 24 hours post-surgery in the dexamethasone group (the primary outcome)

Protocol Version 4.0 20th January 2015

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1. BACKGROUND AND LITERATURE REVIEW
Postoperative nausea and vomiting (PONV) is one of the most common complications affecting patients after surgery. The pathophysiology of PONV is multifactorial, but as patients undergoing colorectal surgery are exposed to various causative agents in addition to physical factors predisposing to ileus, they are at a relatively higher risk of developing this problem. Following surgical intervention, patients view PONV as a very undesirable outcome, even more unpleasant than pain. It can cause significant morbidity, and increased length of stay, and given that over 60,000 colorectal operations are performed in the UK annually, PONV is important because of its medical and cost implications.

Pathophysiology of PONV
The pathophysiology of nausea and vomiting is complex. The vomiting centre in the medulla receives stimulation from the chemoreceptor trigger zone (CTZ), vagal nerve afferents from the gut, the vestibular apparatus and the cerebral cortex. The mechanisms underlying PONV are multifactorial and include stimulation of dopamine and 5HT3 receptors in the CTZ by noxious substances such as opiates and anaesthetic agents, and the stimulation of gut chemoreceptors and stretch receptors. Despite advances in antiemetic agents, anaesthetic agents and minimally invasive surgical techniques, PONV remains a significant and persistent problem. Other risk factors that increase the likelihood of PONV are female gender, non-smoking status, history of motion sickness, childhood and young adulthood and increasing length of surgery (1). Intra-abdominal and laparoscopic surgery have been implicated as having an increased risk of PONV (2) with intra-abdominal surgery having a relative risk of 1.23 and laparoscopic cholecystectomy having a relative risk of 2.85.

Clinical Relevance of PONV
In patients undergoing surgery, the incidence of PONV is 30% overall and up to 70% in high risk patients (1). In a study investigating the ten most undesirable post-operative outcomes, vomiting ranked first, gagging on the ET tube second, and postoperative pain third (3). Nausea was ranked fourth. Although mortality rates are rarely affected, PONV can cause significant morbidity including dehydration, electrolyte disturbance, delayed return to diet and aspiration pneumonia. Delayed recovery in the hospital setting predisposes to serious and life threatening complications such as hospital acquired pneumonia and
thromboembolic events (deep venous thrombosis and pulmonary embolism). The delay in patients resuming an oral diet affects nutrition and subsequent general well being, predisposing to tissue breakdown, pressure sores, wound infection, fatigue, weakness and delay in mobilisation.

In the current era of minimally invasive colorectal surgery combined with enhanced recovery protocols in order to optimise recovery and reduce the length of patient hospital stay, reducing the incidence and severity of PONV is particularly important. The cost implications related to prolonged hospital stay and the additional costs of further complications affect both open and laparoscopic surgery.

**Dexamethasone for PONV**

In practice, dexamethasone is widely, but not universally used by anaesthetists for post-operative nausea and vomiting in colorectal patients. Single dose dexamethasone on induction of anaesthesia is reported to reduce PONV and perioperative fatigue. Its use is advocated in enhanced recovery after surgery (ERAS) programmes to improve recovery after major colorectal surgery (4) (5) (6). Its precise mechanism of action is unknown but it has been proposed that the anti-emetic properties arise due to activation of glucocorticoid receptors in the medulla (7), or by inhibiting central production of prostaglandins or inhibiting the release of endogenous opioids (8). It is known to improve appetite (9), and in combination with reduced nausea and vomiting, aids early recovery. Glucocorticoids can also reduce pain by suppression of bradykinin and neuropeptides from nerve endings (8). Dexamethasone does have potential theoretical side effects such as increased risks of wound infections and anastomotic leaks that could adversely affect recovery, but a systematic review of 51 studies using a single (high) dose of methylprednisolone in cardiac, general and trauma surgical patients found no significant increase in adverse events (10).

**Dexamethasone Use in Abdominal Surgery**

In 2008, a systematic review and meta-analysis of 17 randomised clinical trials looking at pre-operative dexamethasone in patients undergoing laparoscopic cholecystectomy (LC) was published (11). This review suggested that regardless of co-intervention (the administration of other anti-emetics in the control arm), dexamethasone reduced the incidence of nausea and vomiting. Small studies investigating use of dexamethasone to
reduce PONV in many other fields of surgery have been undertaken (table 1). However, there are only two single centre colorectal trials, totalling 100 patients that have assessed this guidance (12) (13). Interestingly, one of these trials (13) measured cytokine levels in peritoneal drain fluid following colorectal surgery and found significantly reduced levels of IL-6, a potent pro-inflammatory cytokine produced by T-cells and macrophages. There was also a significant reduction in IL-13 (a cytokine involved in type 2 T-helper (Th2) cell responses) which is a stimulator of inflammation and tissue remodelling at sites of Th2 inflammation. There was also a reduction in plasma levels of IL-6 and IL-8, another major stimulator of the inflammatory response. These changes in cytokine levels correlated with improved fatigue scores. Dexamethasone is thought to perhaps prevent PONV probably by reducing surgery-induced inflammation (14, 22).

The well-conducted Apfel et al study randomised over 4000 patients and assessed sixty-four different combinations of anaesthetic measures (14); they concluded that dexamethasone was effective in preventing PONV. However, only 11% of patients in this study underwent general surgical procedures and only a fraction of these underwent major colorectal surgery (14). Colorectal patients comprise a high risk population for PONV who may gain considerable benefit from dexamethasone. As yet, there is little evidence to support its use in gastrointestinal surgery.

Apfel et al also demonstrated that the type of volatile anaesthetic used had no effect on the incidence of nausea and vomiting. The additional anti-emetic given at induction will not be standardised in the trial, this will ensure that all patient groups will benefit from the trial findings and that the results will be more generalisable and relevant to current clinical practice. Factors such as patient controlled analgesia (PCA) and epidural/spinal which is thought to effect nausea and vomiting will be considered in the sub-group analysis.

In the absence of good evidence, dexamethasone is variably used in patients undergoing colorectal surgery. We have surveyed six major colorectal units in the West Midlands region and found that only 25% of colorectal patients currently receive dexamethasone. DREAMS seeks to determine the effectiveness of dexamethasone for colorectal patients.
The need for DREAMS – a large, multi-centre, randomised trial.

DREAMS is designed as a two-stage trial; a pilot study and the main phase IV RCT. The pilot study informed the processes to be used in the full phase IV trial. Three main areas were addressed: the strategies used for the identification of eligible patients; the patient pathway and the case report forms (CRFs). The pilot trial successfully showed that patients could be identified and randomised and high CRF return rates obtained.

Randomised controlled trials have shown a reduction in postoperative nausea and vomiting amongst patients undergoing various types of surgery who are given dexamethasone. No multicentre trial has been undertaken to further investigate this and only two underpowered studies investigated colorectal patients. The aim of DREAMS is to evaluate the potential benefits of a single dose of dexamethasone for patients undergoing gastrointestinal surgery. The findings from DREAMS may also give an indication of its appropriate use inside and outside of ERAS programmes, although this would require further confirmatory research.
## Literature Review

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n=</th>
<th>Type of surgery</th>
<th>Findings</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apfel</td>
<td>2004</td>
<td>5199</td>
<td>Gynae, Trauma Abdominal, ENT,</td>
<td>Ondansetron, dexamethasone, and droperidol each reduced the risk of PONV by 26%</td>
<td>(14)</td>
</tr>
<tr>
<td>Wallenborn</td>
<td>2006</td>
<td>3140</td>
<td>Gynae, Trauma Abdominal, ENT,</td>
<td>Metoclopramide plus dexamethasone is an effective, safe, and cheap way to prevent PONV</td>
<td>(15)</td>
</tr>
<tr>
<td>Zagar-Shostari</td>
<td>2009</td>
<td>60</td>
<td>Colorectal</td>
<td>Dexamethasone in an enhanced recovery protocol, gives a significant reduction in early post-operative fatigue, and an attenuated peritoneal cytokine response</td>
<td>(13)</td>
</tr>
<tr>
<td>Kirdak</td>
<td>2008</td>
<td>30</td>
<td>Colorectal</td>
<td>Dexamethasone has no significant effect on reducing postoperative pain, inflammatory response or PONV</td>
<td>(12)</td>
</tr>
<tr>
<td>Weren</td>
<td>2008</td>
<td>118</td>
<td>Abdominal and Gynae</td>
<td>Steroids are mostly effective in the prevention of late PONV, (rather than early).</td>
<td>(16)</td>
</tr>
<tr>
<td>Hans</td>
<td>2006</td>
<td>32</td>
<td>Abdominal</td>
<td>After dexamethasone, blood glucose levels increase in non-diabetic and type 2 diabetic patients undergoing abdominal surgery.</td>
<td>(17)</td>
</tr>
<tr>
<td>Coloma</td>
<td>2001</td>
<td>80</td>
<td>Anorectal</td>
<td>Reduction in time to 'home readiness' in ambulatory surgery</td>
<td>(18)</td>
</tr>
<tr>
<td>Gautam</td>
<td>2008</td>
<td>150</td>
<td>Lap chole</td>
<td>Combination of Ondansetron and Dexamethasone is better than each drug alone.</td>
<td>(19)</td>
</tr>
<tr>
<td>Tiippana</td>
<td>2008</td>
<td>160</td>
<td>Lap chole</td>
<td>Dexamethasone decreased the need for opiates.</td>
<td>(20)</td>
</tr>
<tr>
<td>Bianchin</td>
<td>2007</td>
<td>80</td>
<td>Lap chole</td>
<td>Reduced PONV. No change in pain or time to discharge.</td>
<td>(21)</td>
</tr>
<tr>
<td>Wang</td>
<td>1999</td>
<td>90</td>
<td>Lap chole</td>
<td>Dexamethasone significantly decreased the incidence of PONV</td>
<td>(22)</td>
</tr>
<tr>
<td>Sanchez-Rodriguez</td>
<td>2010</td>
<td>210</td>
<td>Lap chole</td>
<td>Dexamethasone significantly reduced PONV at 0, 6, 12 hours and reduced post-op pain and fatigue.</td>
<td>(23)</td>
</tr>
<tr>
<td>Mathiesen</td>
<td>2009</td>
<td>116</td>
<td>Gynae</td>
<td>Reduced PONV. Combinations of paracetamol, pregabalin and dexamethasone did not reduce morphine consumption.</td>
<td>(24)</td>
</tr>
<tr>
<td>Biswas</td>
<td>2003</td>
<td>160</td>
<td>Gynae</td>
<td>Ondansetron plus dexamethasone is most effective in preventing PONV. Results comparable for single agents.</td>
<td>(25)</td>
</tr>
<tr>
<td>Yursek</td>
<td>2003</td>
<td>60</td>
<td>Gynae</td>
<td>Ondansetron, but not dexamethasone, prevented PONV by 3h postop.</td>
<td>(26)</td>
</tr>
<tr>
<td>Wang</td>
<td>2000</td>
<td>90</td>
<td>Gynae</td>
<td>Dexamethasone significantly decreases the incidence of PONV</td>
<td>(27)</td>
</tr>
<tr>
<td>McKean</td>
<td>2006</td>
<td>72</td>
<td>ENT</td>
<td>Significant decrease in PONV and pain scores.</td>
<td>(28)</td>
</tr>
<tr>
<td>Mathew</td>
<td>2004</td>
<td>210</td>
<td>Paediatrics</td>
<td>Dexamethasone is effective for the prevention of PONV after strabismus repair in children.</td>
<td>(29)</td>
</tr>
</tbody>
</table>

Table 1: List of recent and relevant articles to show the use of dexamethasone for PONV in surgical specialties
2. TRIAL DESIGN

The DREAMS trial is a two stage trial: i) a pilot study and ii) a phase IV randomised controlled trial. The pilot study assessed recruitment rates, the randomisation process, patient pathway and piloted the CRFs. The aim of the pilot study was to inform the processes used in the main trial.

The pilot trial completed successfully and the main trial has followed on directly. It is a large, phase IV, double-blind multi-centre randomised controlled trial comparing the effects of a single dose of 8mg IV dexamethasone on patient recovery after major gastrointestinal surgery.

The patient, responsible surgeon and the assessor will be blinded to the randomisation allocation.

**Randomised Comparison**

Patients undergoing laparoscopic or open gastrointestinal resections for malignant or benign pathology will be randomised, in a 1:1 ratio, between 8mg IV dexamethasone and control.

All patients must be given one additional anti-emetic at the time of induction, however, this must not be dexamethasone. Thus, the two treatment arms are:

Group A - 8 mg IV dexamethasone (plus one other anti-emetic of the anaesthetist’s choice) following induction of anaesthesia but prior to commencement of surgery.

Group B - No dexamethasone (but one anti-emetic of the anaesthetist’s choice)
Objectives

The DREAMS study is a two stage trial - the objective of the pilot was to assess the feasibility of running the phase IV study. The pilot study was to develop effective strategies for patient identification, recruitment and follow-up in the substantive phase of the trial. Patients were successfully identified and the pilot recruited ahead of schedule.

PRIMARY OBJECTIVE

The primary objective of the main phase of DREAMS is to determine whether pre-operative dexamethasone reduces post-operative vomiting in patients undergoing elective gastrointestinal surgery.

SECONDARY OBJECTIVES

To determine whether preoperative dexamethasone results in other measurable benefits during recovery from surgery. Benefits investigated will include quicker return to oral diet and reduced length of stay.

Outcome Measures

The outcome measures of the full, phase IV trial are:

PRIMARY OUTCOME:

1. Proportion of patients experiencing vomiting, within 24 hours post-surgery. Patients who have vomiting episodes recorded by either themselves or by staff will be counted as having experienced vomiting.

SECONDARY OUTCOMES:

1. Number of episodes of vomiting post-surgery until discharge. A single episode of vomiting is defined as having an interval of 5 minutes between episodes.
2. Nausea and vomiting measured objectively by the frequency of use of PRN post-operative anti-emetics.
3. Nausea measured subjectively by the validated PONV Intensity Scale.
4. Fatigue measured using a validated assessment score (FACIT – F questionnaire).
5. Time to tolerating oral diet.
7. Health-related quality of life (as measured by the Euroqol EQ-5D)
8. Incremental cost-effectiveness of dexamethasone compared to standard care.
9. Infection rates and healing complications within 30 days of surgery (wound infections/dehiscence, anastomotic leaks, intraabdominal collections, urinary/chest infections and new onset diabetes).

3. PATIENT ENTRY & ELIGIBILITY

Centre Eligibility
Centres in the UK undertaking major elective gastrointestinal surgery are eligible to take part in the trial.

Patient Eligibility and Recruitment
The DREAMS trial will recruit patients admitted for laparoscopic or open elective gastrointestinal surgery. It is likely that suitable patients will be identified in either the outpatient clinic, the preoperative assessment clinic or by obtaining planned theatre lists for those consultants who agree to take part in the trial.

Patients will be seen by a member of the trial team (the Principle Investigator, Research Investigator or a Colorectal Nurse Specialist), who will discuss the trial with the patient and provide the Patient Information Sheet (Appendix B) and consent form (Appendix C). The patient will be able to take these forms home with them to consider taking part in the trial.

Eligibility criteria

Inclusion Criteria:
All patients undergoing elective open and laparoscopic gastrointestinal surgery for malignant or benign pathology. This includes small and large bowel resections, defunctioning stomas and closures of stomas.

Exclusion Criteria:
1. Obstructed patients.
2. Pregnant patients.
3. Known adverse reaction to dexamethasone.
4. Patients currently taking any form of steroid medication except steroid inhalers, suppositories, pessaries, eye-drops, one-off local injections to a joint, and topical preparations. Patients previously taking regular oral or intravenous steroid medication must have discontinued the steroid medication at least 3 months prior to trial entry.
5. Diabetic (including diet controlled)/ hyperglycaemic patients (blood glucose level >10mmol/l)
6. Active gastric ulceration confirmed endoscopically.
7. Glaucoma.
8. Patients under the age of 18.
9. Patients unable or unwilling to give written informed consent for the study.

4. CONSENT AND RANDOMISATION

Informed Consent

It is anticipated that patients will be identified from one of 3 settings:

1. At the first outpatient clinic, for patients with benign pathology. The trial can be discussed with the patient and the patient given the Patient Information Sheet.
2. At the preoperative assessment clinic visit for patients with benign or malignant pathology.
3. From planned theatre lists, for those patients previously missed at preoperative assessment. These patients would be approached for entry into the trial at the time of admission for surgery.

Once eligibility is confirmed, the patient can be consented for participation in DREAMS. The Principal Investigator or Research Investigator will obtain written informed consent. Written informed consent may not be taken by a Research Nurse. Suitable patients will be approached for entry into DREAMS, the rationale for the study and information regarding drug side effects explained and a Patient Information Sheet provided. In each of the scenarios, patients will be seen by the Local Principal Investigator, a Research Investigator or Specialist Nurse. In scenario 1 above, the patient can either consent at their preoperative
assessment visit or on admission for surgery. For scenarios 2 and 3 the patient can consent on admission for surgery. Patients will have the opportunity to further discuss the study at their preoperative assessment or on their day of admission with the Principal Investigator or Research Investigator at each hospital.

The original copy of the consent form (Appendix C) should be kept in the DREAMS study site file, one given to the patient, one in the patient’s notes and one sent to the DREAMS study office. When consent has been obtained, patients can be randomised into the trial (see below).

**Randomisation (Telephone and online randomisation)**

The randomisation notepad should be completed by the research nurse or DREAMS investigator on or before the morning of surgery. Randomisation should only take place on the morning of surgery. The randomised allocation will only be given to the anaesthetist, or a member of their team, following induction and after the administration of the one other anti-emetic of the anaesthetist’s choice but not dexamethasone. This is to maintain the double-blinding in the trial and to avoid bias in the anaesthetic regime.

Randomisation can be either by internet on the website [https://www.trials.bham.ac.uk/DREAMS](https://www.trials.bham.ac.uk/DREAMS) or by a telephone call to the randomisation service (0121 415 9105). Telephone randomisation is available Monday-Friday 0900-1700 UK time. Secure internet-based central randomisation is available 24 hours a day and will ensure concealment of treatment allocation. Each centre and each randomiser will be provided with a unique log-in and password to enable them to access the online randomisation service. Randomisation notepads (Appendix E) are provided in the DREAMS study folder and should be used to collate the necessary information prior to randomisation.

After all the necessary details have been provided, the patient will be assigned a unique trial identification number to be used on all trial related material for the patient. The randomised treatment allocation will only be given to the anaesthetist (or a member of their team).

This randomisation allocation will not be entered on the anaesthetic chart, operation record or patient notes. Dexamethasone must not be prescribed nor its administration recorded.
on the anaesthetic or drug chart, instead, stickers are provided in the DREAMS site file which should be added to the patient notes to explain that the patient is in a blinded trial.

The trial randomisation number will be entered onto the operation note and the anaesthetic chart.

The patient's GP should be notified that they are in the DREAMS trial and a specimen "Letter to GP" is provided for this purpose (Appendix D). The patient’s GP will not be told of the randomised allocation.

**Randomisation method and stratification variables**

Participants will be randomised into the DREAMS trial in a 1:1 ratio of 8mg IV dexamethasone to control (no dexamethasone). A ‘minimisation’ procedure using a computer-based algorithm will be used to avoid chance imbalances in important stratification variables.

The stratification variables are:

1. Gender.
2. Smoking status.
3. Open and laparoscopic surgical cases.
4. Intended postoperative analgesia: Intravenous PCA, epidural/spinal (infusion or PCA), other or unknown.
5. ASA grade.
6. Patients within and outside of the ERAS pathway.

For trial purposes, ERAS is defined as any recovery process that is expedient over traditional patient care to include but not exclusive to earlier feeding and mobilisation. The definition of ERAS is specifically left broad to recognise differences in implementation of this system across the various units.

The primary components of ERAS are:

- Communication - patients educated about early exercise, mobility and breathing
- Minimal invasive procedures where possible (laparoscopic)
- Eating and drinking immediately after surgery & targeted fluid replacement
• Symptom control of PONV only

The scenario below is an example of an ERAS pathway:

Day 1 – IV down, mobilisation, sit out, walk and eat

Day 2 – Epidural/spinal out, catheter out and walk

Day 3 – Walk, shower, dress

Day 4 – Shower, dress and home.

5. TREATMENT & FOLLOW-UP

On admission, patients will have blood glucose levels checked to exclude undiagnosed hyperglycaemia. On the day of admission and following consent for the trial, patients should be asked to complete the EuroQoL EQ-5D Quality of Life Questionnaire (Appendix L) and the FACIT-F fatigue questionnaire (Appendix M).

All patients will be submitted to general anaesthesia. This is not standardised in the trial. Prior to the operation, patients will be randomised into one of two groups. Group A (intervention arm) will receive 8mg IV dexamethasone once anaesthetised and prior to the commencement of surgery. Group B (control arm) will receive standard care without dexamethasone.

The anaesthetist will use their routine choice of anti-emetic intra-operatively in addition to any dexamethasone given. The anaesthetists will only be informed of the randomisation after induction of anaesthesia and administration of their choice of anti-emetic. This is to avoid bias in the choice of anaesthetic technique or additional anti-emetic administered. The anaesthetist will not write details of the randomised allocation on the anaesthetic chart. Both the ‘other’ antiemetic and the randomised allocation must be administered before knife to skin and then no further antiemetics are to be administered during the operation then only prn when the patient is in recovery as described below.

Use of Dexamethasone Post-Surgery

Following surgery, patients will be given anti-emetics as required. The choice of anti-emetic will be as per local policy. After 24 hours post-operation, dexamethasone can be prescribed
for the patient, however this must be on a PRN basis only. Dexamethasone MUST not be prescribed to a patient within the first 24 hours post-operatively.

**Assessment Schedule and Follow-Up**

Trial data will be recorded by hospital research staff on the CRFs and submitted to the DREAMS Study Office at the Birmingham Clinical Trials Unit (BCTU). Only the patient’s trial number and hospital number will be recorded on the CRFs to ensure data collection is anonymous.

At the time of patient entry into the trial, baseline data will be captured on the Randomisation Notepad (Appendix E). This will include information on the following:

- Demographics
- If surgery will be laparoscopic or open.
- Smoking status – for the purposes of the trial, an ex-smoker is defined as not having smoked within at least the previous 3 months.
- Whether the patient is being treated within an ERAS programme. For DREAMS, ERAS is defined as any post-operative treatment pathway that is expedited in comparison to the traditional patient care in relation to feeding, mobilisation and discharge form hospital.
- If the intended postoperative analgesia will be intravenous PCA, epidural/spinal (infusion or PCA), other or unknown.

Anaesthetic will be administered as described in Section 5 above. Operative and anaesthetic data, including post-operative analgesia will be recorded (Appendix F).

Follow-up data will include a nausea and vomiting review completed post-operatively at days 1, 3 and 5 (or day of discharge) (Appendix G, H and I) This will include episodes of nausea and vomiting captured from patients’ care charts and antiemetic use captured from drug charts. Patients will also be requested to complete the validated Post Operative Nausea and Vomiting Intensity Scale at these timepoints (Appendix J).

Quality of Life forms including the FACIT-F Fatigue questionnaire (Appendix L, and M) should be completed prior to surgery and then at 5 and 30 days post-operatively. If the patient is
discharged prior to Day 5, the EQ-5D and FACIT-F should be completed at the time of discharge.

An assessment of wound and chest infection as well as other complications during the postoperative period will be done at an out-patient appointment at 30-days post-surgery. The 30-day follow-up may be by telephone in exceptional circumstances if it is not possible for a follow-up visit at an out-patient appointment.

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a. Quality of Life forms to be completed at each timepoint are the EuroQoL EQ-5D and the FACIT-Fatigue QoL.

b. Forms due at this timepoint, i.e. both QoL forms and the Nausea and Vomiting review, should be completed at Day 5 post-op or when the patient is fit for discharge.

c. Patients also to complete the PONV Intensity Scale questionnaire at Day 1, 3 and 5 (Appendix J).

Upon trial closure and post-analysis, patients will be given the option of knowing which study treatment they received. All data will be collated by the dedicated trials team at BCTU.

**Dexamethasone Sodium Phosphate**

The active compound of dexamethasone is Dexamethasone Sodium Phosphate. Dexamethasone administered within the trial will be from standard NHS hospital stock.

There are two dexamethasone preparations available for parenteral use in the UK. In line with MHRA-guidance, changes to the labelling were made in 2010 so that both preparations
are labelled to reflect the amount of dexamethasone base per volume; the two products remain different concentrations.

It is now recommended that parenteral dexamethasone is prescribed as dexamethasone base, for trial purposes 8mg dexamethasone base should be given. As dexamethasone comes in two forms of 4mg/ml and 3.3mg/ml, the anaesthetist/research investigator administering the drug will draw up the accurate volume to make up 8mg (2ml from the 4mg/ml vial and 2.4ml from the 3.3mg/ml vial).

**Unblinding**

Participants, research investigators (excluding the anaesthetist) and research nurses will remain blind to the trial drug allocation until after the study has closed and the results analysed.

Should a serious adverse event occur, management of the patient should be initiated as though the patient had received dexamethasone. Cases that are considered serious, unexpected and possibly, probably or definitely related (i.e. possible SUSARs, see Section 6) should be unblinded only at the DREAMS Study Office by the DREAMS Trial Coordinator. The local PI will not be made aware of the randomised allocation unless required for the medical management of particular patients.

**Compatibility With Other Studies**

Patients who are already in other colorectal cancer trials should only be approached to enter DREAMS after discussion with the Trial Management Group. Recruitment of patients into both DREAMS and the neo-adjuvant colorectal cancer trial, FOxTROT, is not encouraged; inclusion of patients in both studies should be discussed with the Trial Management Group prior to trial entry.
6. SAFETY MONITORING PROCEDURES

General definitions:

Investigational Medicinal Products (IMPs)
Within the DREAMS trial only dexamethasone is defined as an Investigational Medicinal Product (IMP). The IMP is defined by its active substance only; dexamethasone sodium phosphate.

Adverse event (AE)
An AE is:
- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests

The following are not AEs:
- A pre-existing condition (unless it worsens significantly during treatment).
- Diagnostic and therapeutic procedures, such as surgery (although the medical condition for which the procedure was performed must be reported if new)

Serious adverse event (SAE)
An SAE is an untoward event which:
- is fatal or immediately life threatening
- requires or prolongs hospitalisation
- is significantly or permanently disabling or incapacitating
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

Events NOT considered to be SAEs are hospitalisations for:
- admission to a hospital or other institution for general care, not associated with any deterioration in condition
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

Serious adverse reaction (SAR)
All adverse events judged as having a possible causal relationship to a product, qualify as serious adverse reactions.
Suspected unexpected serious adverse reaction (SUSAR)
A SUSAR is an SAE suspected to be related to a product, which is of a type or severity which is NOT consistent with the up-to-date product information (i.e. SmPC for dexamethasone).

Expected SAEs for specific drugs
Expected SAEs are those listed in the current Summary of Product Characteristics (SPC) for dexamethasone. These events do not meet the criteria of SUSAR unless for reason of their unexpected severity. Up-to-date SPCs of dexamethasone as used in DREAMS is available at http://emc.medicines.org.uk/.

For the purposes of this study, adverse events include, but are not limited to:
- Peptic ulceration or GI disturbances
- Complicated hyperglycaemia
- Bacterial / viral or fungal disease
- Psychiatric disturbances
- Anaphylactoid / Anaphylactic reactions
- Wound infections / dehiscence
- Anastomotic leaks
- Intra-abdominal collections

Reporting SAEs
SAEs will be collected for all patients in the study from the first trial treatment to 30 days after the last trial treatment. All SAEs must be recorded on the SAE Form (Appendix N) and faxed to the BCTU on +44 (0) 121 415 8871 within 24 hours of the research staff becoming aware of the event. Please ensure that the local Principal Investigator has assigned causality to the SAE before reporting.

For each SAE, the following information will be collected:
- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome
- causality, in the opinion of the investigator*

*Assessment of causality must be made by a doctor. If a doctor is unavailable, initial reports without a causality assessment should be submitted to the BCTU by a healthcare
professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter. An SAE which is assessed as possibly, probably or definitely related to study treatment is classified as a Serious Adverse Reaction (SAR)

The local investigator and others responsible for patient care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors and provide further follow-up information as soon as available. If a patient dies, any post-mortem findings including histopathology must be provided to the BCTU. The BCTU will report any fatal SAEs to the Data Monitoring and Ethics Committee (DMEC) for continuous safety review.

SAEs still present at the end of the study must be followed up at least until the final outcome is determined, even if it implies that the follow-up continues after the patient finishes the study treatment and, when appropriate, until the end of the planned period of follow-up.

All adverse drug reactions suspected to be related to other licensed drugs used in standard care should be reported by the local investigator using the yellow card system.

**Reporting SUSARs**

SAEs categorised by the local investigator as both suspected to be related to the trial drugs and unexpected are SUSARs, and are subject to expedited reporting. The Chief Investigator (CI) or nominated individual will undertake urgent review of SUSARs within 24 hours of reporting and may request further information immediately from the patient’s clinical team. The CI will not overrule the causality, expectedness or seriousness assessment given by the local investigator but may comment on these.

The BCTU will report all SUSARs to the MHRA, DMEC and the main REC. If the SUSAR resulted in death or was life-threatening this will be done within 7 days of the initial report being received, or within 15 days for any other SUSAR.

If information is incomplete at the time of initial reporting, or the event is ongoing, the BCTU will request follow-up information, including information for categorisation of causality, from the local investigator and will send the follow-up information to the MHRA.
and main REC within an additional 8 days for fatal or life-threatening SUSARs and as soon as possible for any other events.

Pharmacovigilance responsibilities

Local Principal Investigator (or nominated individual in PI’s absence):
- Medical judgement in assigning seriousness, expectedness and causality to AEs.
- To fax SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
- To report SAEs to local committees if required, in line with local arrangements.
- To sign an Investigator’s Agreement accepting these responsibilities.

Chief Investigator (or nominated individual in CI’s absence):
- To assign causality and expected nature of SAEs where it has not been possible to obtain local assessment.
- To review all events assessed as SAEs in the opinion of the local investigator.
- To review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and Chief Investigator with regards to SUSAR status, local assessment will not be over-ruled, but the Chief Investigator may add comments prior to reporting to MHRA.

Birmingham Clinical Trials Unit:
- To report SUSARs, blinded to treatment, to MHRA and main REC within required timelines.
- To prepare annual safety reports, blinded to treatment, to MHRA, main REC and Trial Steering Committee (TSC).
- To prepare SAE safety reports for the DMEC at 3-monthly intervals.
- To notify Investigators of SUSARs which compromise patient safety.

Trial Steering Committee:
- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies.
- To review blinded data and liaise with the DMEC regarding any safety issues.
- To receive and consider any recommendations from the DMEC on protocol modifications.

Data Monitoring & Ethics Committee:
- To review unblinded data to identify safety issues which may not be apparent on an individual case basis.
• To review interim analyses of unblinded safety data annually.
• To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or be halted.

**End of trial**
The end of trial is defined as the date of final data capture, i.e. once all data required to answer the research question has been collected, which will be no later than 1 year from the date of the last visit of the last patient undergoing the trial.

### 7. SIZE, STATISTICS & DATA MONITORING

**Projected Accrual**
The primary aim of the pilot study was to assess recruitment. Recruitment was shown to be feasible and the recruitment target was attained ahead of time. We will be aiming to recruit patients from at least 20 units across the United Kingdom. Each centre will aim to recruit an average of 50 patients per year.

**Statistical Considerations**
With 1320 patients randomised, DREAMS would have 90% power to detect a 24% proportional reduction (37% to 28%) in the proportion of patients experiencing post-operative vomiting in patients taking Dexamethasone after undergoing gastrointestinal surgery. This sample size includes an additional 10% for crossover and dropout to ensure that sufficient data is obtained to answer the question. Subgroup analyses will be undertaken, appropriately cautiously, for variables for which the randomisation is stratified (e.g. enhanced vs. non-enhanced recovery pathway, PCA vs. epidural/spinal) using standard tests for interactions. Additional exploratory analyses will also be undertaken e.g. to investigate any correlation between operative length and risk of nausea and vomiting. Analysis of the study will be on an Intention-To-Treat basis.

**Data Monitoring and Ethics Committee**
During the period of intake in the study, interim analyses of safety and outcome data will be supplied, in strict confidence, to an independent DMEC along with any other analyses that the committee may request.
The DMEC will meet annually, or more frequently if considered appropriate, and will advise the chair of the trial’s steering committee if, in their view, the randomised comparison in DREAMS has provided both (a) “proof beyond reasonable doubt” that for all, or for some types of patient, one treatment with dexamethasone is clearly indicated or clearly contraindicated in terms of a net difference in the main outcome measures, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results.

The steering committee can then decide whether to modify the study protocol. Unless this happens, however, the steering committee, the collaborators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain ignorant of the interim results.

If the clinical coordinators are unable to resolve any concern satisfactorily, collaborators, and all others associated with the study, may write through the DREAMS trial office to the chairman of the data monitoring committee, drawing attention to any worries they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

8. ORGANISATION

To ensure the smooth running of DREAMS and to minimise the overall procedural workload, it is proposed that each centre should designate individuals who would be chiefly responsible for local coordination of the surgical and administrative aspects of DREAMS. The DREAMS Trial Office will provide as much assistance as they can to local co-ordinators and investigators in obtaining Trust approval in each centre and helping resolve any local problems that may be encountered.

Principal Investigator

Each Centre should nominate a Consultant Colorectal Surgeon or Consultant Anaesthetist to act as the local Principal Investigator and bear responsibility for the conduct of research at their centre. Close collaboration between all clinical teams is particularly important in order that patients for whom the DREAMS Trial is an option can be identified sufficiently
early for entry. The responsibilities of the local Principal Investigator will be to ensure that all medical and nursing staff involved in the care of potential patients are well informed about the trial and trained in trial procedures, including obtaining informed consent. The local PI should liaise with the Trial Coordinator on logistic and administrative matters connected with the trial.

Central Coordination
The Trial Office at the BCTU is responsible for providing the following trial materials:

- The Site File, containing all documentation required under the Medicines for Human Use (clinical Trials) Regulations 2004 to define the involvement of the centre in the trial.
- An Investigators folder containing printed materials, such as participant information sheets, consent forms and algorithms.
- An online randomisation system, including individual log-in and passwords and guidance.

These will be supplied to each collaborating centre, after relevant authorisations have been obtained. Additional supplies of printed material can be obtained on request, all CRFs are also downloadable from the DREAMS website. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data (including managing any reports of serious adverse events thought to be due to trial treatment), for reporting of serious and unexpected adverse events to the sponsor and regulatory authorities on behalf of the Chief Investigator and for analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

Clinical Queries
During office hours, the clinical co-ordinators (see inside front cover for contact details) provide an on-call service for any clinical queries about the trial.

Funding and Cost Implications
The research costs of the trial are funded by a grant from the National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) programme. The DREAMS trial team can offer no financial support to the collaborating hospitals, however, the DREAMS trial should not involve any extra costs for participating centres as no additional follow-up visits or
investigations are needed other than those that would normally be required for standard patient care. Support can be sought from the CLRN as this is a portfolio trial.

Publication
A meeting will be held after the end of the trial to allow discussion of the main results among the collaborators prior to publication. The success of the trial depends entirely on the wholehearted collaboration of a large number of doctors, nurses and researchers. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the trial. A writing committee will be convened to produce publications on behalf of the DREAMS Collaborating Group. Centres will not be permitted to publish data obtained from participants in the DREAMS Trial that use trial outcome measures without discussion with the Chief Investigator and the TSC.

9. RESEARCH GOVERNANCE
The conduct of the trial will be in accordance with the EU Directive on Clinical Trials (2001/20EC), the UK Medicines for Human Use (Clinical Trials) Regulations 2004 and the principles of the International Committee on Harmonisation of Good Clinical Practice Guidelines (E6) and any subsequent amendments.

Sponsor
National sponsorship will be provided by the University of Birmingham upon signing of the Clinical Study Site Agreement with each trial site.

Clinical Trials Unit
Data from this trial will be handled by the Birmingham Clinical Trials Unit, a full-time research facility dedicated to, and with substantial experience in, the design and conduct of randomised clinical trials. The Birmingham Clinical Trials Unit recognises the responsibilities of a data management centre with respect to the ethical practice of research and the adequate protection of human subjects.

Confidentiality of Personal Data
The trial will collect personal data about participants, and medical records will be reviewed for all patients and routine physical examinations will be performed. Participants will be
informed that their trial data and information will be securely stored at the trial office at the Birmingham Clinical Trials Unit, and will be asked to consent to this. The Birmingham Clinical Trials Unit abides by the UK law Data Protection Act 1998. The data will be stored on a secure computer database, and all personal information obtained for the study will be held securely and treated as strictly confidential. Any data processed outside of the Birmingham Clinical Trials Unit will be anonymised.

**Long-Term Storage of Data**

In line with Good Clinical Practice guidelines, all essential documentation and data will be retained for at least 15 years.

**Indemnity**

DREAMS was developed by the West Midlands Research Collaborative and is funded by the Bowel Disease Research Foundation and the NIHR Research for Patient Benefit programme. The University of Birmingham is the trial ‘sponsor’. As it is not an industry-sponsored trial, the Association of the British Pharmaceutical Industry (ABPI) guidelines on indemnity do not apply and there are no special arrangements for compensation for any non-negligent harm suffered by patients as a result of participating in the study. The normal NHS indemnity liability arrangements for clinician initiated research will, therefore, operate – see NHS Executive Health Service Guidelines HSG (96) 48, 8th November 1996. It should be noted, however, that negligent liability remains the responsibility of the hospital, whether or not a patient is part of a clinical trial, because of the duty of care that the hospital has for their patients.
10.  PATIENT PATHWAY

**DREAMS PATIENT JOURNEY**

- Outpatient appointment
- Pre op clinic
- Admission
- Anaesthetic
- Operation
- Day 1 & 3 post-op
- Day 5 post-op (or discharge)
- Day 30 post-op

**DREAMS TRIAL PROCESSES**

- Patient identified
- Receive Patient Information Sheet (PIS)
- Obtain consent (if benign pathology)
- Check blood glucose for eligibility
- Obtain consent (benign or malignant pathology) and inform trials unit
- Baseline QoL forms (EuroQoL EQ-5D and FACIT-F QoL)
- Separate research investigator (with no other involvement in trial) to contact trials unit for randomisation
- Dexamethasone 8mg IV
- No dexamethasone
- Intraoperative form
- Nausea and vomiting proforma
- Nausea and vomiting proforma
- QoL forms (EuroQoL EQ-5D and FACIT-F QoL)
- Patient completed review (by telephone)
  QoL forms (EuroQoL EQ-5D and FACIT-F QoL)
REFERENCES


