PRISM Trial - Summary of Protocol Changes (version 1.5, dated 01 March 2016)

This document contains a summary of the minor updates to the PRISM trial protocol between the documents named PRISM Protocol dated 18 August 2015 (version 1.4) to the current final document version PRISM Protocol dated 01 March 2016 (version 1.5).

Section:	**Title Page (pg 1) and Chief Investigator Agreement (pg 4)**
Formerly read:	Version 1.4 Date: 18 August 2015 **Principal Investigator** *[Insert local PI details]*
Amended to:	Version 1.5 Date: 1 March 2016 ~~**Principal Investigator** *[Insert local PI details]*~~
Section:	**4. INTRODUCTION (pg 6-7)**
Formerly read:	Approximately 230 million surgical procedures are carried out worldwide each year. Whilst the results of these trials suggest that postoperative CPAP is efficacious, there has yet to be a large multi-centre trial to evaluate clinical effectiveness.
Amended to:	Approximately 310 million surgical procedures are carried out worldwide each year. Whilst the results of these trials suggest that postoperative CPAP is efficacious, there has yet to be a large multi-centre trial to evaluate the clinical effectiveness of this treatment.
Section:	**5.4 Secondary outcome measures (pg 8)**
Formerly read:	• Pneumonia within 30 days of randomisation • Endotracheal re-intubation within 30 days of randomisation • Death within 30 days of randomisation

	• Postoperative infection within 30 days of randomisation • Mechanical ventilation (invasive or non-invasive) within 30 days of randomisation • All-cause mortality at one year after randomisation • Quality adjusted life years (QALY) at one year after randomisation
Amended to:	• Pneumonia within 30 days of randomisation • Endotracheal re-intubation within 30 days of randomisation • Death within 30 days of randomisation • Postoperative infection within 30 days of randomisation • Mechanical ventilation (invasive or non-invasive) within 30 days of randomisation • All-cause mortality at one year after randomisation • Quality adjusted life years (QALY) at one year after randomisation In addition, we will use the following process measures (i.e. non-patient centred outcome measures), to facilitate comparison with other research: • 30-day re-admission • Days in critical care • Duration of hospital stay *Moved from later section*
Section:	**5.5 Safety objectives**
Formerly read:	5.5 Tertiary objectives
Amended to:	5.5 Safety objectives
Section:	**5.6 Safety outcome measures (pg 9)**
Formerly read:	5.6 Tertiary outcome measures Tertiary outcomes will quantify harm associated with CPAP (appendix). The following pre-defined adverse events will be measured within 24 hours of the

	end of surgery: • Interface intolerance due to excessive air leaks • Pain • Cutaneous pressure sore or pressure area • Claustrophobia • Oro-nasal dryness • Hypercapnia • Haemodynamic instability • Vomiting • Other harm assessed as probably or definitely related to CPAP In addition, we will use the following process measures: • 30-day re-admission • Days in critical care • Duration of hospital stay A full list of definitions is available in the appendix.
Amended to:	5.6 Safety outcome measures Safety outcomes will quantify harm associated with CPAP (appendix). The following pre-defined adverse events will be measured within 24 hours of the end of surgery in patients in the intervention group only: • Interface intolerance due to excessive air leaks • Pain • Cutaneous pressure sore or pressure area • Claustrophobia • Oro-nasal dryness • Hypercapnia • Haemodynamic instability • Vomiting • Aspiration of gastric contents • Other harm assessed as probably or definitely related to CPAP

	A full list of definitions is available in the appendix.
Section:	**6.2 Inclusion criteria**
Formerly read:	Patients aged 50 years or over undergoing major intra-peritoneal surgery using an open surgical technique.
Amended to:	Patients aged 50 years or over undergoing **elective** major intra-peritoneal surgery using an open surgical technique.
Section:	**7.1 Recruitment and screening**
Formerly read:	Potential participants will be screened by research staff at the site having been identified from pre-admission clinic lists, operating theatre lists and by communication with the relevant nursing and medical staff……
Amended to:	This is an international randomised controlled trial in several European countries. Potential participants will be screened by research staff at the site having been identified from pre-admission clinic lists, operating theatre lists and by communication with the relevant nursing and medical staff……
Section:	**7.3 Randomisation**
Formerly read:	Randomisation will occur after the participant has provided informed consent but before the surgical procedure is due to start. Participants will be centrally allocated to treatment groups (1:1) by a computer generated dynamic procedure (minimisation) with a random component. Minimisation variables will be country, surgical procedure category and planned use of epidural anaesthesia. The surgical procedure categories are: resection of colon, rectum or small bowel; resection of liver, pancreas or gall bladder; resection of stomach (non-obesity surgery); obesity surgery; vascular procedure; or other intra-peritoneal procedure. Each participant will be allocated with 80%

	probability to the group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability. To enter a patient into the PRISM trial, research staff at the site will log on to a secure web-based randomisation and data entry platform hosted by Queen Mary University of London and complete the patient's details to obtain a unique patient identification number and allocation to a treatment group.
Amended to:	Randomisation will occur after the participant has provided informed consent and up to four hours after the end of surgery. Participants will be centrally allocated to treatment groups (1:1) by a computer generated dynamic procedure (minimisation) with a random component. Minimisation variables will be country, surgical procedure category and planned use of epidural anaesthesia. The surgical procedure categories are: resection of colon, rectum or small bowel; resection of liver, pancreas or gall bladder; resection of stomach (non-obesity surgery); obesity surgery; vascular procedure; or other intra-peritoneal procedure. Each participant will be allocated with 80% probability to the group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability. To enter a patient into the PRISM trial, research staff at the site will log on to a secure web-based randomisation and data entry platform and complete the patient's details to obtain a unique patient identification number and allocation to a treatment group. Investigators will declare the intended postoperative care destination before randomisation. This will measure changes in postoperative care that could be attributed to the delivery of the intervention.
Section:	**7.4 Trial intervention**
Formerly read:	The trial intervention period will commence immediately after the completion of surgery and continue for at least four hours. After four hours, CPAP will be continued or discontinued at the clinician's discretion.

	Intervention group The trial intervention is defined as CPAP for at least four hours, with minimal interruption, started immediately after the patient has left the operating room after surgery. Administration of CPAP will only take place under the direct supervision of appropriately trained staff in an adequately equipped clinical area. The monitoring of patients receiving CPAP will be in accordance with local hospital policy or guidelines. Alterations to the administered dose will be recorded along with the reason for this change. Clinicians may only use commercially available CPAP equipment to deliver the intervention. The starting airway pressure should be 5cmH_2O and the maximal permissible airway pressure is 10cmH_2O. Nasal high flow oxygen is not considered CPAP. It is foreseeable that some patients in the intervention group will not receive CPAP or fail to complete the minimum four hours of CPAP, e.g. due to unplanned invasive or non-invasive ventilation after surgery or because the patient is unable to tolerate the CPAP mask. These situations will be managed as protocol deviations and follow-up data will still be collected. Please see section 7.9 for further details. *Usual care group* Patients in the *usual care group* will be managed by clinical staff according to local policy and guidelines. It is considered good practice for postoperative patients to receive oxygen via a facemask or nasal cannulae. However, this may vary according to local policy. It is foreseeable that some patients in the usual care group could receive CPAP as part of usual care. This will be managed as a protocol deviation and follow-up data will still be collected. Please see section 7.9 for further details.
Amended to:	The trial intervention will commence immediately after the completion of surgery and continue for at least four hours. This will allow widespread implementation of the treatment in post-anaesthetic recovery units, without the need for critical care admission, or other major changes in the perioperative

	care pathway. After four hours, CPAP will be continued or discontinued at the clinician's discretion. *Intervention group* The trial intervention is defined as CPAP for at least four hours, with minimal interruption, started immediately after (within four hours after) the end of surgery. Administration of CPAP will only take place under the direct supervision of appropriately trained staff in an adequately equipped clinical area. Delivery of the trial intervention and monitoring of patients receiving CPAP will be in accordance with local hospital policy or guidelines. Alterations to the administered dose will be recorded along with the reason for this change. Clinicians may only use commercially available CPAP equipment to deliver the intervention. The starting airway pressure should be 5cmH_2O and the maximal permissible airway pressure is 10cmH_2O. The airway pressure may be adjusted within this range at the discretion of the responsible physician. For example it may be deemed beneficial to increase the airway pressure above 5 cmH_2O for patients with obesity or low chest wall compliance. Since this is a pragmatic clinical effectiveness trial additional training or standardisation of the intervention will not be provided. Nasal high flow oxygen is not considered CPAP. It is foreseeable that some patients in the intervention group will not receive CPAP or fail to complete the minimum four hours of CPAP, e.g. due to unplanned invasive or non-invasive ventilation after surgery or because the patient is unable to tolerate the CPAP mask. These situations will be managed as protocol deviations and follow-up data will still be collected. Please see section 7.8 for further details. *Usual care group* Patients in the usual care group will be managed by clinical staff according to

	local policy and guidelines. The trial findings will therefore reflect the fact that usual care may differ between participating centres, and indeed this is one of the purposes of large clinical effectiveness trials. It is considered good practice for postoperative patients to receive oxygen via a facemask or nasal cannulae. However, this may vary according to local policy. The use of mechanical ventilation, recruitment manoeuvres or high flow nasal oxygen during the intervention period will be recorded on the case report form. It is foreseeable that some patients in the usual care group could receive CPAP as part of usual care. This will be managed as a protocol deviation and follow-up data will still be collected. Please see section 7.8 for further details.
Section:	**7.7 Data collection**
Formerly read:	The following data will be collected from all sites before and after the trial intervention. *Randomisation data* • Checklist to ensure the patient meets the eligibility criteria • Surgical procedure category • Centre ID *Baseline data* • Full name • Gender • Age/DOB • ASA grade • Planned surgical procedure • Diagnosis of chronic lung disease (COPD, Asthma, ILD) • Diagnosis of ischaemic heart disease • Diagnosis of diabetes • Diagnosis of stroke

	• Diagnosis of heart failure
	• Diagnosis of cirrhosis
	• Preoperative haemoglobin
	• Preoperative creatinine
	• Quality of life according to EQ-5D
	• Height
	• Weight
	• NHS number or corresponding patient identifier for database follow-up
	• Residential postcode or corresponding patient identifier for database follow-up
	
	Intraoperative period
	• Surgical procedure category
	• Open technique used
	• Anaesthetic technique (general, spinal, regional)
	• Mechanical ventilation (Y/N)
	  ○ Duration
	  ○ Maximum PEEP
	  ○ Maximum Vt
	• Extubated at the end of surgery (Y/N)
	
	24 hours postoperative
	• Patient received CPAP within four hours of surgery? (Y/N)
	  ○ Total duration of CPAP within 12 hours of surgery
	  ○ Delivery method (mask, nasal, helmet)
	  ○ Maximum airway pressure
	• Additional research staff present to help deliver CPAP (Y/N)
	• Were tools used to monitor CPAP and inspiratory oxygen fraction? (Y/N)
	• Did the patient have a nasogastric tube *in situ* during CPAP? (Y/N)

	• Adverse events during CPAP (tertiary outcomes)
	  ○ Interface intolerance due to excessive air leaks (Y/N)
	  ○ Pain (Y/N)
	  ○ *Cutaneous pressure sore or pressure area* (Y/N)
	  ○ Claustrophobia (Y/N)
	  ○ Oro-nasal dryness (Y/N)
	  ○ Hypercapnia (Y/N and peak $PaCO_2$)
	  ○ Haemodynamic instability (Y/N)
	  ○ Vomiting (Y/N)
	
	Clinical outcomes within 30 days of randomisation
	• Pneumonia (Y/N)
	• Re-intubation (Y/N)
	• Death (date)
	• Mechanical ventilation (Y/N)
	• Quality of life according to EQ5D
	
	Health economic outcomes
	• Duration of primary hospital stay (not including re-admission)
	• Days in critical care during the first 30 days after index surgical procedure
	
	Clinical outcomes within one year of randomisation
	• Death (date)
	• Quality of life according to EQ5D

Amended to:	The following data will be collected from all sites before and after the trial intervention. Component data will be collected to calculate the ARISCAT score.[14] *Randomisation data*

	• Checklist to ensure the patient meets the eligibility criteria • Surgical procedure category • Centre ID • Planned use of epidural anaesthesia *Baseline data* • Full name • Gender • Age/DOB • ASA grade • Planned surgical procedure • Diagnosis of chronic lung disease (COPD, Asthma, Interstitial lung disease) • Respiratory infection within the previous month • Diagnosis of ischaemic heart disease • Diagnosis of diabetes • Diagnosis of stroke • Diagnosis of heart failure • Diagnosis of cirrhosis • Diagnosis of active cancer • Preoperative haemoglobin • Preoperative creatinine • Quality of life according to EQ-5D • Height • Weight • NHS number or corresponding patient identifier for database follow-up • Residential postcode or corresponding patient identifier for database follow-up *Intraoperative period*

	• Surgical procedure category
	• Open technique used
	• Anaesthetic technique (general, spinal, regional)
	• Mechanical ventilation (Y/N)
	  ○ Duration
	  ○ Maximum PEEP
	  ○ Maximum Vt
	  ○ Maximum FiO_2 (excluding pre-oxygenation during induction of anaesthesia)
	  ○ Total IV fluid input (sum of crystalloid and colloid)
	  ○ Total blood product input (sum of all blood products)
	• Extubated at the end of surgery (Y/N)
	• Intraoperative recruitment manoeuvre (Y/N)
	
	24 hours postoperative
	• Patient received CPAP within four hours of surgery? (Y/N)
	  ○ Total duration of CPAP within 12 hours of surgery
	  ○ Delivery method (mask, nasal, helmet)
	  ○ Maximum airway pressure
	• Additional research staff present to help deliver CPAP (Y/N)
	• Were tools used to monitor CPAP and inspiratory oxygen fraction? (Y/N)
	• Did the patient have a nasogastric tube *in situ* during CPAP? (Y/N)
	• Did the patient receive high flow nasal oxygen? (Y/N)
	• Adverse events during CPAP (tertiary outcomes)
	  ○ Interface intolerance due to excessive air leaks (Y/N)
	  ○ Pain (Y/N)
	  ○ Cutaneous pressure sore or pressure area (Y/N)
	  ○ Claustrophobia (Y/N)
	  ○ Oro-nasal dryness (Y/N)
	  ○ Hypercapnia (Y/N and peak $PaCO_2$)

	○ Haemodynamic instability (Y/N) ○ Vomiting (Y/N) ○ Aspiration of gastric contents (Y/N) *Clinical outcomes within 30 days of randomisation* • Pneumonia (Y/N) • Re-intubation (Y/N) • Death (date) • Mechanical ventilation (Y/N) • Quality of life according to EQ5D *Health economic outcomes* • Duration of primary hospital stay • Days in critical care during the first 30 days after index surgical procedure *Clinical outcomes within one year of randomisation* • Death (date) • Quality of life according to EQ5D
Section:	**7.8 Predefined protocol deviations**
Formerly read:	• Failure to administer CPAP to patients in the intervention group. This includes patients that unexpectedly remain intubated after surgery • Starting CPAP at a dose other than 5cmH_2O • Administration of CPAP to a patient in usual care group. • Administration of CPAP for less than 4 hours or with significant interruption for a patient in the intervention group. Brief interruptions to CPAP to adjust mask, for oral care or routine nursing care are considered part of the intervention. However, if the interruption is prolonged this should be considered a protocol deviation.
Amended to:	• Failure to administer CPAP to patients in the intervention group. This includes patients that unexpectedly remain intubated after surgery or where CPAP is started more than four hours after the end of surgery

	• Starting CPAP at a dose other than 5cmH_2O • Administration of CPAP to a patient in usual care group. If this occurs within 12 hours of the end of surgery, investigators should consider this a protocol deviation. • Administration of CPAP for less than 4 hours or with significant interruption for a patient in the intervention group. Brief interruptions to CPAP to adjust mask, for oral care or routine nursing care are considered part of the intervention. However, if the interruption is prolonged this should be considered a protocol deviation. Investigators will make a judgement about whether the interruption is prolonged and encouraged to record the duration of any interruption on a protocol deviation form. As a guide, a continuous interruption of more than 15 minutes would usually be considered prolonged.
Section:	**7.9 Follow-up procedures**
Formerly read:	To minimise bias, follow-up data will be collected by an investigator who is unaware of the study group allocation. Investigators will review a participant's medical record (paper or electronic) and contact participants on the telephone to conduct brief interviews at 30 days and one year after surgery. To facilitate the health economic analysis, in terms of hospital episode data, and in cases where the participant is un-contactable during the follow-up period, we will request hospital episode statistics and mortality data from the HSCIC for UK participants or equivalent national database for other participating countries. Prospective consent for ONS/HES data linkage will be sought before enrolment into the trial.
Amended to:	To minimise bias, follow-up data will be collected by an investigator who is unaware of the study group allocation. Investigators will review a participant's medical record (paper or electronic) and contact participants on the telephone to conduct brief interviews at 30 days and one year after surgery. The health economic analysis will be restricted to data derived from UK centres. To facilitate this, we will request hospital episode statistics and mortality data from the HSCIC for UK participants. Prospective consent for ONS/HES data linkage will be sought before enrolment into the trial.

Section:	**7.11 Self-assessment of blinding by research staff**
Formerly read:	Research staff will complete a self-assessment to allow us to report the effectiveness of blinding procedures during the trial. They will grade themselves as one of the following options: • Suitably blinded • May have known study group allocation • Definitely knew study group allocation
Amended to:	The primary outcome will be assessed by an investigator that is blinded to the study group allocation. However, during the course of the primary outcome assessment, the investigator may become un-blinded, for example if the patient reveals information suggesting they received CPAP. To quantify the degree of un-blinding, the investigator will complete a self-assessment of blinding with respect to the treatment group allocation, at the time of assessing the primary outcome. This will allow a measure of the effectiveness of blinding procedures to be reported. Investigators will grade themselves as one of the following: • Suitably blinded • May have known study group allocation • Definitely knew study group allocation
Section:	**7.13 Schedule of assessment**
Formerly read:	EQ5D questionnaire
Amended to:	EQ5D questionnaire (UK only)
Section:	**8.2 Statistical analysis**
Formerly read:	All analyses will be conducted according to intention-to-treat principles, meaning that all patients with a recorded outcome will be included in the analysis, and will be analysed according to the treatment group to which they were randomised. The primary outcome (pneumonia, endotracheal re-intubation, or death within 30 days of randomisation) will be analysed using a

	mixed-effect logistic regression model……..
Amended to:	All analyses will be conducted according to intention-to-treat principles, meaning that all patients with a recorded outcome will be included in the analysis, and will be analysed according to the treatment group to which they were randomised. Baseline patient characteristics will be presented, stratified according to treatment allocation. The primary outcome (pneumonia, endotracheal re-intubation, or death within 30 days of randomisation) will be analysed using a mixed-effect logistic regression model…….
Section:	**8.3 Health economic analysis**
Formerly read:	The health economics analysis will assess whether routine postoperative CPAP is likely to be cost-effective on average. The intervention may have effects that impact on quality and duration of life beyond the trial follow-up period……
Amended to:	The health economics analysis will be restricted to data derived from UK centres, due to the different payment models operated in participating countries. The analysis will assess whether routine postoperative CPAP is likely to be cost-effective on average. The intervention may have effects that impact on quality and duration of life beyond the trial follow-up period……..
Section:	**9. RESEARCH ETHICS**
Formerly read:	The PI will ensure that this trial is conducted in accordance with the Principles of the Declaration of Helsinki as amended in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington DC (2002), Tokyo (2004), Seoul (2008) and Fortaleza (2013) as described at the following internet site: http://www.wma.net/en/30publications/10policies/b3/index.html. The trial will fully adhere to the principles outlined in the Guidelines for Good Clinical Practice ICH Tripartite Guideline (January 1997). The study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory

	requirements. At sites, all accompanying material given to a potential participant will have undergone an independent Research Ethics Committee review within that country. Full approval by the Research Ethics Committee will be obtained prior to starting the trial and fully documented by letter to the Chief Investigator naming the trial site, local PI (who may also be the Chief Investigator) and the date on which the ethics committee deemed the trial as permissible at that site. All members of the trial steering committee will declare conflicts of interest before joining the study group. These will be listed on any publications arising from the trial.
Amended to:	The PI will ensure that this trial is conducted in accordance with the Principles of the Declaration of Helsinki as amended in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington DC (2002), Tokyo (2004), Seoul (2008) and Fortaleza (2013) as described at the following internet site: http://www.wma.net/en/30publications/10policies/b3/index.html. The trial will fully adhere to the principles outlined in the Guidelines for Good Clinical Practice ICH Tripartite Guideline (January 1997). The study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements. Research ethics and regulatory approvals will be sought before starting the trial at each site, in accordance with national research legislation/guidelines for that country. This will usually require the translation of the trial protocol and patient facing documents. Where a document is translated it will be back translated into English to check for consistency with the original. Other trial documents will be translated at the discretion of the national lead investigator. At sites, all accompanying material given to a potential participant will have undergone an independent Research Ethics Committee review within that country. Full approval by the Research Ethics Committee will be obtained prior to starting the trial and fully documented by letter to the Chief Investigator naming the trial site, local PI (who may also be the Chief Investigator) and the date on which the ethics committee deemed the trial as permissible at that site. All members of the trial steering committee will

	declare conflicts of interest before joining the study group. These will be listed on any publications arising from the trial.
Section:	**12. SAFETY REPORTING**
	12.1 Adverse Events (AE) An AE is any untoward medical occurrence in a subject who has received CPAP initiated as part of the PRISM trial. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the trial intervention. Adverse events must be related to CPAP; the Principle Investigator (or nominated deputy) is responsible for confirming this. **12.2 Notification and reporting Adverse Events or reactions** We will record all AEs in the CRF (supplementary form) and in the patient notes (where appropriate). SAEs will be reported to the national co-ordinating centre within 72 hours. **12.3 Serious Adverse Event (SAE)** A serious adverse event (SAE) is defined as an untoward occurrence that: (a) results in death; (b) is life-threatening; (c) requires hospitalisation or prolongation of existing hospitalisation; (d) results in persistent or significant disability or incapacity; An SAE occurring to a research participant should be reported to the sponsor where in the opinion of the Chief Investigator the event was: • Related – that is, it probably or definitely arose as a result of the trial intervention, and • Unexpected – that is, the type of event is not listed in the protocol as

an expected occurrence.

The PRISM trial is an investigation of a perioperative intervention. It is expected that patients undergoing major abdominal surgery will suffer medical complications, up to and including death. Only complications *related* to the use of CPAP in the intervention group should be reported as SAEs.

Some complications of CPAP are expected. The following expected occurrences should be reported as AEs but not SAEs:

- Interface intolerance due to excessive air leaks
- Pain
- Cutaneous pressure sore or pressure area
- Claustrophobia
- Oro-nasal dryness
- Hypercapnia
- Haemodynamic instability
- Vomiting

12.4 Notification and reporting of Serious Adverse Events

Serious Adverse Event (SAEs) that are considered to be 'related' and 'unexpected' are to be reported to the sponsor and the sponsor's representative for that country within 72 hours of learning of the event.

12.5 Reporting an Adverse Event or Serious Adverse Event

Individual sites will notify the co-ordinating centre in that country of an SAE by emailing a scanned copy of the supplementary AE report form to the national co-ordinator. AEs will be reported by the eCRF. SAEs will be reported within 72 hours and will be forwarded to the sponsor via the UK co-ordinating centre.

12.5 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of trial participants from any immediate hazard to their health and safety. The

	measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Research Ethics Committee of this event within three days. The sponsor must be sent a copy of the correspondence with regards to this matter. **12.6 Annual safety reporting** The CI will send the annual progress report to the REC and to the sponsor. **12.7 Overview of the safety reporting responsibilities** The CI/PI has the overall oversight responsibility. The CI/PI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.
Amended to:	**12.1 Adverse Events (AE)** An AE is an untoward medical occurrence in a **PRISM trial participant**. This may be any unfavourable and unintended sign, symptom or disease**. It is expected that patients undergoing major abdominal surgery may often suffer medical complications, up to and including death. It follows that a large number of PRISM trial participants will experience complications of surgery, which are completely unrelated to the trial intervention. In the PRISM trial, only AEs clearly related to the use of CPAP will be reported. It is anticipated that almost all of these will fall under one of the following predefined categories:** • Interface intolerance due to excessive air leaks • Pain • Cutaneous pressure sore or pressure area • Claustrophobia • Oro-nasal dryness • Hypercapnia • Haemodynamic instability • Vomiting

	• **Aspiration of gastric contents** **The Principal Investigator (or suitably qualified nominee) is responsible for confirming the relatedness of any AE to the trial intervention. If an AE occurs the clinician responsible for the patient should decide whether it is safe to continue CPAP, with or without modification, or whether CPAP should be discontinued.** **12.2 Notification and reporting Adverse Events or reactions** Individual sites will record all adverse events in the CRF (supplementary form) and **submit this information via the online database. Paper copies should be kept locally.** ***12.3 Serious Adverse Event (SAE)*** **Whilst unlikely, it is recognised that an AE related to CPAP may become a SAE. Prompt reporting of SAEs is required to ensure any factors which affect the safety of other trial participants can be identified and acted upon. The Principal Investigator (or suitably qualified nominee) must assess the SAE as probably or definitely related to CPAP and meet one of the following criteria:** (a) Results in death; (b) Is life threatening; (c) Clearly prolongs the hospital stay; (d) Causes significant disability or incapacity. **12.4 Reporting a Serious Adverse Event** **Potential SAEs should be reported to the PRISM trial co-ordinating centre within 24 hours. For details of how to report a potential SAE please see the adverse event reporting SOP.** **12.5 Notification and reporting of Serious Adverse Events** **The chief investigator will determine whether an adverse event meets the**

	criteria for an SAE and consider what further action should be taken, if any, to protect current and future trial participants. This may involve discussion within the Principal Investigator, and if necessary, the independent chairs of the TSC and DMEC. Confirmed SAEs will be reported by the trial management group to the sponsor and/or ethics committee as required by national research regulations for the country in question. **12.6 Urgent safety measures** The CI may take urgent safety measures to ensure the safety and protection of trial participants from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Research Ethics Committee of this event within three days. The sponsor must be sent a copy of the correspondence with regards to this matter. **12.7 Annual safety reporting** The CI will send the annual progress report to the REC and to the sponsor. **12.8 Overview of the safety reporting responsibilities** The CI/PI has the overall oversight responsibility. The CI/PI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.
Section:	**13.1 Training of investigators**
Formerly read:	**13.1 Monitoring the safety and well-being of trial participants**
Amended to:	**13.1 Training of investigators** All investigators will complete training consistent with their national regulations

	for clinical research, as well as those in the country of the trial sponsor (UK). A representative of the national coordinating centre for that country will conduct a site initiation visit at each site before patient recruitment commences. This visit will include an induction to the trial protocol and procedures, the standardised assessment of outcome measures, and the trial database. Where new investigators join the research team at a particular site during the course of the trial, the responsibility for induction training will fall to the local principal investigator. **13.2 Monitoring the safety and wellbeing of trial participants**
Section:	**13.3 Monitoring the safety of investigators.**
Formerly read:	**13.2 Monitoring the safety of investigators** Each site has health and safety policies for employees. All personnel should ensure that they adhere to health and safety regulations relating to their area of work. The PI will ensure that all personnel have been trained appropriately to undertake their specific tasks. The trial team will complete GCP and consent training prior to start up
Amended to:	**13.3 Monitoring the safety of investigators** Each site has health and safety policies for employees. All personnel should ensure that they adhere to health and safety regulations relating to their area of work. The PI will ensure that all personnel have been trained appropriately to undertake their specific tasks. The trial team will complete GCP training, or equivalent, and consent training prior to start up.
Section:	**14.2 Trial steering committee**
Formerly read:	The Trial Steering Committee will oversee the trial and will consist of:

	• several independent clinicians and trialists • lay representation • co-investigators • an independent Chair
Amended to:	The Trial Steering Committee will oversee the trial and will consist of: • several independent clinicians and trialists • lay/**patient** representation • co-investigators (including a representative of each participating nation) • an independent Chair
Section:	**14.3 Data monitoring and ethics committee**
Formerly read:	The Data Monitoring and Ethics Committee (DMEC) is independent of the trial team and comprises of two clinicians with experience in undertaking clinical trials and a statistician. The committee will agree conduct and remit, which will include the early termination process. During the period of recruitment into the trial the DMEC will perform a single interim analysis as it sees fit. The trial will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile. The DMEC functions primarily as a check for safety by reviewing adverse events.
Amended to:	The Data Monitoring and Ethics Committee (DMEC) is independent of the trial team and comprises of two clinicians with experience in undertaking clinical trials and a statistician. The committee will agree conduct and remit, which will include the early termination process. The principle responsibility of the DMEC will be to safeguard the interests of trial participants, including assessing the safety of the intervention, reviewing relevant new external evidence, and monitoring the overall conduct of the trial. The DMEC will provide recommendations about stopping, modifying or continuing the trial to the Trial Steering Committee. The DMEC may also make recommendations regarding selection, recruitment, or retention of participants, their management, protocol

	adherence and retention of participants, and procedures for data management and quality control. The Trial Steering Committee will be responsible for promptly reviewing the DMEC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required. The DMEC will review trial data relating to patient safety and the quality of trial conduct. The DMEC will perform a single interim analysis during the recruitment period. In the light of this analysis, the DMEC will advise the chief investigator if, in their view, the randomised comparisons have provided both (i) 'proof beyond reasonable doubt' that for all, or some specific types of patient, one particular treatment is clearly contra-indicated in terms of a net difference in adverse events or serious morbidity, and (ii) evidence that might reasonably be expected to materially influence future patient management. The trial will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile. The DMEC functions primarily as a check for safety by reviewing adverse events.
Section:	**15. FINANCE AND FUNDING**
Formerly read:	This is an investigator led trial. This trial is supported by a project grant from the Association of Anaesthetists of Great Britain and Ireland and the National Institute for Academic Anaaesthesia (UK). Additional funding will be sought from the National Institute for Health Research (UK) and from industry.
Amended to:	This is an investigator led trial. This trial is supported by unrestricted grants from the Association of Anaesthetists of Great Britain and Ireland, the National Institute for Health Research (UK) and Intersurgical Ltd who will also provide CPAP consumables.
Section:	**DEFINITIONS APPENDIX**
Formerly read:	***Other definitions***

	Cancer surgery *Intended to be a curative treatment* The surgical procedure is intended to cure the cancer. *Intended to be palliative treatment* The surgical procedure is not intended to cure the cancer. For example surgical de-bulking in metastatic disease, partial removal of a tumour or for the purpose of pain or other symptom control. **Levels of care after surgery** *Level 3 care: Critical care unit* A clinical area capable of providing invasive mechanical ventilation or support to at least two organ systems. *Level 2 care: Critical care unit or step-down unit* A clinical area capable of providing support to a single organ system, but not including invasive mechanical ventilation, which is considered level 3 care. *Post-anaesthesia care unit (PACU)* Short-stay clinical area dedicated to caring for patients that are recovering from anaesthesia. If the PACU is providing level 2 care then level 2 care should be recorded on the CRF. *Surgical ward* Hospital ward environment not offering single-organ support or dedicated to

	patients recovering from anaesthesia. **High flow nasal oxygen** Humidified oxygen therapy delivered via large-bore nasal prongs at flow rates greater than 50 litres per minute. **Intraoperative recruitment manoeuvre** A technique used by the anaesthetist to transiently increase the transpulmonary pressure. This is usually by increasing tidal volume or inspiratory pressure for one or more breaths.
	Aspiration of gastric contents **Inhalation of regurgitated gastric contents directly related to CPAP. (added to pg 42)** ***Other definitions*** **Active cancer** **A current diagnosis of cancer excluding non-melanoma skin cancers. A previous diagnosis of cancer where the patient underwent curative treatment with remission is not considered active cancer. A surgical procedure where the indication is a presumed diagnosis of cancer, but which has not yet been confirmed with histology, should be considered active cancer.** **Cancer surgery** *Intended to be a curative treatment* The surgical procedure is intended to cure the cancer. *Intended to be palliative treatment*

	The surgical procedure is not intended to cure the cancer. For example surgical de-bulking in metastatic disease, partial removal of a tumour or for the purpose of pain or other symptom control. **End of surgery** **Completion of surgery. Usually marked by suturing of the wound and application of dressing(s).** **Intraoperative recruitment manoeuvre** **A technique used by the anaesthetist to transiently increase the transpulmonary pressure. This is usually by increasing tidal volume or inspiratory pressure for at least one breath**. **Levels of care after surgery** *Level 3 care: Critical care unit* A clinical area capable of providing invasive mechanical ventilation or support to at least two organ systems. *Level 2 care: Critical care unit or step-down unit* A clinical area capable of providing support to a single organ system, but not including invasive mechanical ventilation, which is considered level 3 care. *Post-anaesthesia care unit (PACU)* Short-stay clinical area dedicated to caring for patients that are recovering from anaesthesia. If the PACU is providing level 2 care then level 2 care should be recorded on the CRF. *Surgical ward* Hospital ward environment not offering single-organ support or dedicated to

	patients recovering from anaesthesia. *Critical care unit admission* Either level two or level three care, as defined above. **Open surgical technique** **Open abdominal surgery is usually distinguished from laparoscopic by the fact that for laparoscopic surgery the incision is only large enough to remove the resected specimen. Some procedures may involve the use of a laparoscope as well as an open incision, where the incision is larger than required to remove the specimen – this is considered open surgery.** **Preoperative oxygen saturation (SpO_2)** **Pulse-oximetry on room air before surgery.** **Primary hospital admission** **The hospital admission for elective surgery during which the participant was randomised as part of the PRISM trial. The duration of the primary hospital stay should be calculated from the date of randomisation.** **Respiratory support** ***Invasive mechanical ventilation*** **Positive pressure ventilation via an endotracheal tube or supraglottic airway device.**

	Non-invasive mechanical ventilation **Positive pressure mechanical ventilation via a face-mask, hood or helmet, or nasal device. However, Continuous Positive Airway Pressure (CPAP) is not considered non-invasive mechanical ventilation.** ***High flow nasal oxygen*** **Humidified oxygen therapy delivered via large-bore nasal prongs at flow rates greater than 50 litres per minute.** **Maximum positive end expiratory pressure (PEEP) during surgery** **The maximum pressure, above atmospheric pressure, that exists at the end of expiration and provided by mechanical ventilation.** **Maximum set tidal volume (Vt) during surgery** **The maximum volume of air displaced between inspiration and expiration during mechanical ventilation as set on the ventilator.** **Start of surgery** **Time of the induction of anaesthesia before the surgical procedure.**