## PRISM Trial - Summary of Protocol Changes (version 1.6, dated 10 April 2017)

This document contains a summary of the minor updates to the PRISM trial protocol between the documents named PRISM Protocol dated 01 March 2016 (version 1.5) to the current final document version PRISM Protocol dated 10 April 2017 (version 1.6).

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| **Section:** | **Title Page (pg 1) and Chief Investigator Agreement (pg 4)** |
| **Formerly read:** | PRISM protocol version 1.5 01 March 2016 |
| **Amended to:** | PRISM protocol version 1.6 10 April 2017 |
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| **Section:** | **6.3 Exclusion criteria (pg 9 and 10)** |
| **Formerly read:** | • Participation in a clinical trial of a treatment with a similar biological mechanism or related primary outcome measure<br>• Clinician refusal |
| **Amended to:** | • Current participation in a clinical trial of a treatment with a similar biological mechanism or related primary outcome measure<br>• Clinician refusal<br>• Contraindication to continuous positive airway pressure (CPAP) |
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| **Section:** | **6.4 Study flow diagram (pg 10)** |
| **Formerly read:** | "Randomisation" followed by "surgery as planned" |
| **Amended to:** | "Surgery as planned" followed by "randomisation" |
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| **Section:** | **7.1 Recruitment and screening (pg 11)** |
| **Formerly read:** | This is an international randomised controlled trial in several European countries. |
| **Amended to:** | This is an international randomised controlled trial ~~in several European countries.~~ |
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| **Section:** | **7.3 Randomisation (pg 11)** |
| **Formerly read:** | Randomisation will occur after the participant has provided informed consent |

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| | and up to four hours after the end of surgery. |
| **Amended to:** | Patients will not be randomised before giving written informed consent. Randomisation will be performed immediately after surgery (up to four hours after the end of the surgical procedure). |
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| **Section:** | **7.4 Trial intervention (pg 12)** |
| **Formerly read:** | The trial intervention will commence immediately after the completion of surgery and continue for at least four hours. |
| **Amended to:** | The trial intervention period will ideally commence immediately after surgery. |
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| **Section:** | **7.4 Trial intervention (pg 12)** |
| **Formerly read:** | *Intervention group*<br>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. |
| **Amended to:** | The trial intervention is defined as CPAP for at least four hours, with minimal interruption, ideally started within four hours after the end of surgery. Where the start of CPAP has been delayed by exceptional circumstances (e.g. equipment failure, critical care admission, etc.), the intervention may be commenced up to twelve 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. Investigators may only use |

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| | CPAP equipment approved for routine use in their hospital to deliver the intervention. |
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| **Section:** | **7.7 Data collection** |
| **Formerly read:** | *Baseline data*<br>• Full name<br>• Gender<br>• Age/DOB<br>• ASA grade<br>• Planned surgical procedure<br>• Diagnosis of chronic lung disease (COPD, Asthma, Interstitial lung disease)<br>• Respiratory infection within the previous month<br>• Diagnosis of ischaemic heart disease<br>• Diagnosis of diabetes<br>• Diagnosis of stroke<br>• Diagnosis of heart failure<br>• Diagnosis of cirrhosis<br>• Diagnosis of active cancer<br>• Preoperative haemoglobin<br><br>*24 hours postoperative*<br>• Patient received CPAP within four hours of surgery? (Y/N) |
| **Amended to:** | *Baseline data*<br>• Full name<br>• Gender<br>• Age/DOB<br>• ASA grade<br>• Planned surgical procedure |

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| | • Diagnosis of chronic lung disease (COPD, Asthma, Interstitial lung disease, bronchiectasis)<br>• Respiratory infection within the previous month (including tuberculosis)<br>• Diagnosis of ischaemic heart disease<br>• Diagnosis of diabetes<br>• Diagnosis of stroke<br>• Diagnosis of heart failure<br>• Diagnosis of cirrhosis<br>• Diagnosis of active cancer<br>• Diagnosis of Human Immunodeficiency Virus (HIV) infection<br>• Preoperative haemoglobin<br><br>*24 hours postoperative*<br>• Patient received CPAP within twelve hours after the end of surgery? (Y/N) |
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| **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 or where CPAP is started more than four hours after the end of surgery<br>• Starting CPAP at a dose other than 5cm$H_2O$<br>• 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.<br>• 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 |

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| | minutes would usually be considered prolonged. |
| **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 twelve hours after the end of surgery<br>• Starting CPAP at a dose other than 5 $cmH_2O$.<br>• 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.<br>• Administration of CPAP for less than 4 hours duration for a patient in the intervention group.<br>• Administration of CPAP 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 relevant. |
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| **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. 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. |
| **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 |

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| | 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 NHS Digital or equivalent for UK participants. Prospective consent for ONS/HES data linkage will be sought before enrolment into the trial. |
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| **Section:** | **8.4 Secondary studies** |
| **Formerly read:** | The use of PRISM trial data for further secondary studies is encouraged. |
| **Amended to:** | The use of PRISM trial data for further secondary studies is encouraged. Secondary studies of UK data are detailed in the appendix. |
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| **Section:** | **10.3 Archiving** |
| **Formerly read:** | All trial documentation and data will be archived centrally by the Sponsor in a purpose designed archive facility for twenty years in accordance with regulatory requirements. |
| **Amended to:** | All central trial documentation and data will be archived centrally by the Sponsor in a purpose designed archive facility for twenty years in accordance with regulatory requirements. |
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| **Section:** | **11.1 CPAP delivery** |
| **Formerly read:** | CPAP machines are routinely used in secondary care. Investigators may only use commercially available CPAP equipment in this trial. |
| **Amended to:** | CPAP machines are routinely used in secondary care. Investigators may only use CPAP equipment approved for routine use in their hospital to deliver the intervention. |
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| **Section:** | **Appendix: National registry linkage (UK only)** |
| **Formerly read:** | |
| **Amended to:** | **1. Background**<br>More than 1.5 million patients undergo major surgery in the UK each year with reported hospital mortality between 1 and 4%.[1-3] Complications following major |

surgery are a leading cause of morbidity and mortality; respiratory complications, including pneumonia, are some of the most frequent and severe.[4-9] The PRISM trial aims to determine whether continuous positive airway pressure (CPAP), given immediately after surgery, can reduce the incidence of respiratory complications and improve long-term survival after major abdominal surgery.

In the United Kingdom (UK), individual patient consent will be sought to allow linkage of PRISM data to national registries for hospital episodes and mortality. This expands the scope of the trial, whilst putting no additional burden on individual participants.

**2. Data source**

In the UK mortality registry data is collated at a national level by the Office for National Statistics (ONS). Hospital Episode Statistics (HES) are collated at a national level by separate organisations for England, Scotland, Wales and Northern Ireland. These data include details of hospital admissions, hospital procedures, demographic information and hospital length of stay.

**3. Methods**

These analyses will utilise both ONS mortality statistics and hospital episode statistics. Individual patient consent will be obtained from UK participants for data linkage to national databases/registries. Individual applications for access to HES and mortality data will be made through national organisations in each of the devolved nations, e.g. NHS Digital for England. Patient identifiable data will be transferred to NHS Digital (or equivalent organisation) to facilitate data linkage. A dataset including linked data will be returned, either using patient identifiers or pseudo-identifiers, depending on data access rules. Alternatively, the full PRISM (UK) dataset with patient identifiers could be transferred to NHS Digital and a completely anonymised dataset returned after data linkage, i.e. with patient identifiable data removed.

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| | **4. Specific sub-studies**<br><br>**4.1. One-year mortality**<br>The majority of previous studies of postoperative CPAP have focused on short-term or in-hospital clinical outcomes. Therefore, the impact of CPAP on postoperative complications after hospital discharge is unclear. This sub-study aims to describe the impact of postoperative CPAP on mortality up to one year after surgery in a UK cohort.<br><br>**4.2. Long-term mortality**<br>Data from the USA suggests that there is a relationship between the presence of any postoperative complication and reduced long-term survival.[10] However, this relationship has not been confirmed in a UK surgical cohort. This sub-study aims to describe the incidence risk of mortality up to five years after surgery, to identify association between the presence of complications in the immediate postoperative period (up to 30 days after surgery) and survival up to five years after surgery, and the impact of postoperative CPAP on five-year postoperative mortality in a UK surgical cohort.<br><br>**4.3. Health Economic analysis**<br>Cost effectiveness is a key determinant of successful implementation of a new intervention. This sub-study aims to 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. The cost-effectiveness analysis will therefore take the form of a decision model with one-year and/or five-year mortality as an input in terms of treatment effectiveness. Quality adjusted life years (QALYs) over the patients' lifetime will be used as the primary outcome measure of the cost-effectiveness analysis. Trial mortality data will be quality-adjusted on the basis of EQ-5D data and allowing for non-fatal clinical events experienced in the two trial arms. |
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