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# BMJ Open

## The benefits and harms of perioperative high fraction inspired oxygen for surgical site infection prevention: a protocol for a systematic review and meta-analysis of individual patient data of randomised controlled trials

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Keywords:	ANAESTHETICS, WOUND MANAGEMENT, Infection control < INFECTIOUS DISEASES, SURGERY

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Manuscripts

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3 1 **TITLE PAGE**

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5 2 The benefits and harms of perioperative high fraction inspired oxygen for surgical site infection  
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7 3 prevention: a protocol for a systematic review and meta-analysis of individual patient data of  
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9 4 randomised controlled trials

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and references)

45 **Keywords:** general anaesthesia; hyperoxia; postoperative outcome; surgical site infection; surgical  
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wound infection

**ABSTRACT**

**Introduction:** The use of high fraction of inspired oxygen (FiO<sub>2</sub>) intraoperatively for the prevention of surgical site infection (SSI) remains controversial. Consequently, there is considerable practice variation in oxygen use. Early promising results have been replicated with varying success, and subsequent meta-analyses are equivocal. Since the initial promising results, perioperative care has changed considerably with consequences for hemodynamics, microcirculation, and peripheral oxygen delivery. These changes may explain the inconsistency in results, but the available published data provides insufficient detail on the participant level to test this hypothesis. The purpose of this individual participant data meta-analysis is to assess the described benefits and harms of intraoperative high (0.60-1.00) FiO<sub>2</sub> compared to regular (0.21-0.40) FiO<sub>2</sub> and its potential effect modifiers.

**Methods and analysis:** The initial search conducted for the WHO guidelines for the prevention of surgical site infection reviews will be updated. Medical databases and online trial registries will be searched to include all randomised and quasi-randomised controlled trials comparing the effect of intraoperative high FiO<sub>2</sub> (0.60-1.00) to regular FiO<sub>2</sub> (0.21-0.40) in patients undergoing surgery. Two researchers will independently assess articles retrieved by the search against the eligibility criteria for inclusion and methodological quality. Investigators of the identified trials will be invited to collaborate, comment on the study protocol, and supply the individual participant data of their initial trial and any additional follow-up data. The primary outcomes will be SSI within 90 days after surgery by the author's discretion, serious adverse events, and all-cause mortality within the longest available follow-up. Data will be analysed with the one-step approach. Additional analysis included exploration of effect-modifiers. The certainty of evidence will be assessed using GRADE methodology.

**Ethics and dissemination:** Ethics approval is not required. Investigators will de-identify individual participant data before it is shared. The results will be submitted to a peer-review journal.

**Trial Registration Number:** PROSPERO CRD42018090261

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3 76 **ARTICLE SUMMARY**  
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5 77 **Strengths and limitations of this study**  
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- 8 78 • Individual participant data meta-analysis (IPD MA) of (quasi-)randomised controlled trials is  
9 79 considered the gold standard of evidence-based medicine, providing the best possible  
10 80 analysis of the available data on the participant level, permitting the investigation of  
11 81 potential effect modifiers.  
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13 82 • IPD MA requires the collaboration of all investigators that have published data on the  
14 83 relevant topic and leads to a broad consensus on the outcome and interpretation of the  
15 84 analysis  
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17 85 • IPD MA depends on the quality of data that is made available by the authors of the original  
18 86 studies.  
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## 87 INTRODUCTION

88 Surgical site infection (SSI) is one of the most common healthcare-associated infections and leads to  
89 morbidity, mortality, and longer hospital stay.(1-4) The attributable costs can be more than €14.000  
90 per SSI, and European totals are estimated to range from €1.5 to €19 billion per year.(5, 6) In 2016-  
91 2017, both the World Health Organization (WHO) and the Centres of Disease Control and Prevention  
92 (CDC) independently released evidence-based guidelines on the prevention of SSI that included a  
93 recommendation in favour of the administration of high fraction of inspired ( $\text{FiO}_2$ ) for patients  
94 undergoing surgery under general anaesthesia.(7-9) This has led to a debate between opponents and  
95 proponents of the use of high  $\text{FiO}_2$  in several editorials and correspondences across medical  
96 speciality literature.(10-20) Concerns were raised on the safety of the use of high  $\text{FiO}_2$  as well as the  
97 different study results in supporting and not supporting use of high  $\text{FiO}_2$  to reduce SSI.(10-20)

98 In response to these concerns, the WHO conducted an independent systematic review on the safety  
99 of high intraoperative  $\text{FiO}_2$  and updated the systematic review on its effectiveness, excluding the  
100 disputed trials.(21, 22) No evidence of harm to discourage the use of high  $\text{FiO}_2$  was found, yet the  
101 evidence of an effect of SSI had become weaker, and the recommendation was adjusted  
102 accordingly.(23) Despite many randomised controlled trials, various meta-analyses, and guideline  
103 recommendations, uncertainty remains. This leads to practice variation that inevitably exposes  
104 patients to suboptimal care.(24) There is a need for better understanding and consensus on this  
105 issue.

106 Since the early promising results, perioperative care has changed considerably. Open abdominal  
107 surgery has been largely replaced by laparoscopic surgery, fluid management has moved from liberal  
108 to restrictive, to advanced goal directed regimens and active perioperative warming has become a  
109 mainstay.(25-27) All these changes have considerable consequences for hemodynamic,  
110 microcirculation, and eventually peripheral oxygen delivery.(28-30) These changes may explain the  
111 inconsistency in reproducibility, but the available data provides insufficient detail on the participant  
112 level to test the potential of high  $\text{FiO}_2$ . Meta-analysis of individual participant data uses the raw  
113 individual-level data from the original study for synthesis and overcomes this limitation.(31, 32) IPD  
114 MA enables analysis of uniform outcomes with more statistical power and assessment of potential  
115 effect modifiers.(33, 34) Importantly, IPD MA requires collaboration with all published researchers on  
116 the topic leading to a broad consensus on the outcome of data analysis and interpretation.  
117 The purpose of this IPD MA is to assess the potential benefits and harms of intraoperative high (0.60-  
118 1.00)  $\text{FiO}_2$  compared to traditional (0.21-0.40)  $\text{FiO}_2$  and its effect modifiers in patients undergoing  
119 surgery. This IPD MA is initiated by the University of Amsterdam / Amsterdam University Medical

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3 120 Center, and encouraged by the WHO and the World Federation of Societies of Anaesthesiologists  
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5 121 (WFSA) to provide patients and practitioners with the best possible evidence and guidance on this  
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7 122 disputed area and will give clearance of the disputed hypothesis that high FiO<sub>2</sub> reduces the incidence  
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9 123 of SSI.  
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## 124 **METHODS AND ANALYSIS**

### 125 **Protocol and registration**

126 This study protocol is registered with the International Prospective Register of Systematic Reviews  
127 (PROSPERO) on 7 March 2018 and was last updated on 15 July 2022 (registration number  
128 CRD42018090261). The study protocol is designed and written to adhere to the Preferred Reporting  
129 Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)(35) and the Preferred  
130 Reporting Items for Systematic Review Meta-Analysis of individual patient data (IPD) (PRISMA-  
131 IPD).(32)

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### 133 **Patient and Public Involvement Statement**

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135 This project is encouraged by the World Health Organization (WHO), and the World Federation of  
136 Societies of Anesthesiologists (WFSA) to provide patients and practitioners with the best possible  
137 evidence and guidance on this disputed area. WHO and WFSA have provided external independent  
138 review and advice on research direction and aim.

139

### 140 **Governance**

141 This study is an initiative of the Amsterdam University Medical Centre, encouraged by the WHO and  
142 the WFSA. Both organisations recognise the urgent need for this research and provide external  
143 independent review and advice. The writing committee consists of the study coordinator, two  
144 reviewers, a lead methodologist, and a principal investigator from both the surgery and the  
145 anaesthesiology department of the Amsterdam University Medical Centre and two external content  
146 matter experts. The writing committee is entirely independent of the initial trials and has full  
147 responsibility for all methodological decisions. A broader steering committee with representatives of  
148 the collaborating trial groups identified during the project will be invited to comment on and co-  
149 author the final protocol and IPD MA report. By sharing their IPD, collaborators will obtain one co-  
150 authorship on the IPD MA report and one additional co-authorship if data of more than 300  
151 participants is shared. For transparency and against intellectual bias, a record will be kept of all  
152 comments. Any important amendments to the protocol will be recorded in PROSPERO record and  
153 discussed in the methods section of the final report.

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### 155 **Eligibility criteria**

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3 156 We will include all randomised and quasi-randomised controlled trials comparing the effect of  
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5 157 intraoperative high FiO<sub>2</sub> (0.60-1.0) to traditional FiO<sub>2</sub> (0.21-0.40) in patients undergoing surgery.  
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7 158 These trials may include patients of any age undergoing surgery except for neonates, regardless  
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9 159 publication, language, or year of conduct and should include at least data on age, sex, mean FiO<sub>2</sub>  
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11 160 administered, method of oxygen administration, SSI, mortality, or other serious adverse events. Any  
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13 161 outcome found to be recorded in these trials will be included in the analysis. Studies without random  
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15 162 or quasi-random treatment allocation, animal studies, and studies outside of the intraoperative  
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17 163 period will be excluded.  
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### 19 165 **Identifying studies – information sources**

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21 166 The initial search conducted for the WHO guideline will be updated by a professional information  
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23 167 specialist.(21, 22) Medical databases will be searched, including MEDLINE, EMBASE, CENTRAL,  
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25 168 CINHAL, and the WHO regional databases. Online trial registries will be searched to identify potential  
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27 169 unpublished evidence or any ongoing trials. The search will not be limited by language or date of  
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29 170 publication. A final update will be conducted before the final round of revisions preceding submission  
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31 171 for publication. The reference list of all included studies will be hand searched for any additional  
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33 172 relevant trials not already identified through database searching. All corresponding authors of  
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35 173 relevant clinical trials will be contacted to review the list of identified studies for the omission of  
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37 174 potentially relevant studies missed by the search.  
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### 39 176 **Study selection process**

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41 177 Two reviewers will independently assess articles retrieved by the search against the eligibility criteria.  
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43 178 After screening the title and abstract, the full text of potentially eligible papers will be retrieved and  
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45 179 assessed. When no full paper exists, or trial eligibility is in doubt, the study authors will be contacted  
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47 180 to provide further information. Any discrepancies in study selection will be resolved through  
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49 181 consensus and discussion with a senior author. All studies that pass title and abstract screening but  
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51 182 were not eligible for inclusion will be listed with the reasons for exclusion.  
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### 54 184 **Study collaboration invitation**

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56 185 Authors of eligible studies will be contacted and invited to collaborate on the IPD MA. An email  
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58 186 invitation will be sent to the corresponding authors outlining the IPMDA goals. If no reply is received  
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60 187 within two weeks, a second email request will be sent to the corresponding and first author. If no

188 response is received again, we will try to contact all authors by email and telephone. IPD data will be  
 189 considered unavailable if numerous times (at least five) no reply is received if authors no longer have  
 190 access to the study data or consent to collaboration.

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## 192 **Data collection process**

193 The collaborating investigators will be requested to sign a data transfer agreement describing the  
 194 ownership and storage of the IPD before de-identified IPD is shared. Whenever possible, data  
 195 collection, interview on the protocol, and formal handoff on the data codebook will be done  
 196 electronically via email, videoconference, or a suitable alternative. Whenever requested by the  
 197 original investigator, a researcher will visit the investigators for a physical data transfer, in-person  
 198 interview, and data codebook handoff. In the unlikely event that individual patient data will not be  
 199 made available, the reason will be recorded. The aggregate data of the study will be used in a  
 200 sensitivity analysis. Aggregate data collection will be performed as appropriate for a regular meta-  
 201 analysis by two independent reviewers according to a predefined data extraction sheet and overseen  
 202 by a senior author to settle potential discrepancies. The University of Amsterdam's Clinical Research  
 203 Unit will facilitate secure data storage.

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## 205 **Data items**

206 Data items will include all data recorded by the initial trial investigators including, but not limited to  
 207 the items listed in table 1 and table 2.

209 <i>Baseline</i>	210 Sex, age, BMI (kg/m <sup>2</sup> ), ASA physical status score, smoking status, peripheral vascular disease, diabetes, (metastatic) cancer, congestive heart disease, (pulmonary) hypertension, chronic obstructive pulmonary disease, immunosuppressant use, peripheral oxygen saturation (%), glucose (mg/dL), indication for surgery, emergency procedure
211 <i>Preoperative</i>	212 Use of preoperative antibiotic prophylaxis (dose and agent), timing of preoperative antibiotic prophylaxis, use of mechanical bowel preparation, haemoglobin (g/dL), use of antibiotic bowel preparation, cytostatic chemotherapy, radiotherapy
213 <i>Intraoperative</i>	214 Surgical procedure(s), organ involvement, contamination (CDC wound classification(36)), laparoscopic surgery, mean arterial pressure (MAP) (mmHg), haemoglobin (g/dL), heart rate (beats/min), hemodynamic monitoring method, hemodynamic management algorithm, crystalloid infusion (ml), colloid Infusion (ml), red-cell transfusion (units), duration of surgery (min), duration of anaesthesia (min), mean core temperature (°C), lowest core temperature (°C), mean net fluid supplementation (ml/kg/hr), arterial oxygen saturation (%),

	peripheral oxygen saturation (%), subcutaneous oxygen tension (mm Hg), muscle oxygen tension (mm Hg), partial pressure of arterial oxygen (mmHg), mean FiO <sub>2</sub> (%), mean PEEP (cmH <sub>2</sub> O), ventilator flow (L/min), peak airway pressure (mmHg), plateau pressure (mmHg), tidal Volume (ml/kg predicted body weight), respiratory frequency, vasopressor agent, vasopressor agent used (mg), glucose (mg/dL), use of general anaesthesia, use of spinal or epidural anaesthesia, use of mechanical ventilation, use of nitrous oxide, total blood loss (ml), fluids (ml), end tidal CO <sub>2</sub>
<i>Postoperative</i>	Use of postoperative antibiotics (dose and agent), postoperative antibiotic duration (days), cytostatic chemotherapy, radiotherapy, haemoglobin (g/dL), VAS pain score, use of postoperative oxygen supplementation (duration, method and FiO <sub>2</sub> ), haemoglobin (g/dL), peripheral oxygen saturation (%), partial pressure of arterial oxygen (mmHg), subcutaneous oxygen tension (mmHg), muscle oxygen tension (mmHg), glucose (mg/dL), NNIS score(37), SSI risk score(38)
<i>Oxygen Administration &amp; Monitoring</i>	Total duration and concentration of oxygen exposure during the pre/intra/postoperative period (timing of initiation, concentration, duration), oxygen supply and mode of administration (Intubation, use and type of face mask, nasal prongs), carrier gas (N <sub>2</sub> , N <sub>2</sub> O, medical or room air), protocol-defined target or range of partial pressure of arterial oxygen (mmHg) or peripheral oxygen saturation (%)

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<i>Primary</i>	- SSI within 90 days after surgery by the author's discretion
<i>Secondary</i>	- All-cause mortality within the longest available follow-up
<i>Exploratory</i>	<ul style="list-style-type: none"> <li>- Survival within the longest available follow-up</li> <li>- Serious adverse events defined by the ICH guidelines for good clinical practice(39)</li> <li>- SSI monitored according to the CDC criteria and specified as either superficial, deep, organ/space(40)</li> <li>- Respiratory insufficiency: defined as the need for respiratory assistance provided as ventilator therapy or non-invasive ventilation within 90 days after surgery</li> <li>- Unplanned ICU admission (not part of routine postoperative care) (days)</li> <li>- Hospital readmissions within 90 days after surgery</li> <li>- Anastomotic leakage as defined by the international study group of rectal cancer(41)</li> <li>- Total duration of hospitalization, including readmissions related to the initial hospitalization</li> <li>- Any cardiovascular complication at any time after surgery</li> <li>- Any pulmonary complications at any time after surgery</li> <li>- Stroke at any time after surgery</li> <li>- New or recurrent cancer diagnosis at any time after surgery</li> <li>- Any further clinically relevant outcome reported in the IPD</li> </ul>
* When patients are reoperated within follow up for reasons other than surgical site infection these cases will be excluded from the analysis based on loss to follow up.	

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210 **Missing data**

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3 211 When variables are missing at the participant level and the missing at random assumption is  
4 212 plausible, multiple imputations by chained equations may be applied in each trial separately before  
5 213 proceeding with the analysis. Variables that miss systematically i.e., unknown for the entire study,  
6 214 will not be imputed. When this concerns variables included in pre-defined analysis, studies  
7 215 systematically missing this variable will be excluded from that analysis. When this concerns variables  
8 216 not included in pre-defined analysis, these variables will be dropped from the main outcome analysis  
9 217 as potential confounding variables. The set of available variables for the main analysis will thus be  
10 218 determined by the data set with the least available variables. Variables from richer sets will remain  
11 219 available for exploratory analysis among data sets with the variable available.  
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### 221 **Individual Participant Data integrity**

222 We will check IPD for potential missing, invalid, or out-of-range values, inconsistencies, and  
223 discrepancies with the aggregate publication. When identified, we will seek to resolve the issues with  
224 the trial investigators to improve data quality and ensure that trials are represented accurately. In  
225 addition, any modelling assumptions made in the initial analysis will be evaluated (i.e., missing at  
226 random in the case of multiple imputation or non-informative censoring and proportional hazards in  
227 the case of time to event data). In the case of any concerns on IPD integrity further prove of  
228 execution of the trial and substantiation of the results may be requested such as prove of  
229 institutional review board approval or original case record forms. If concerns cannot be resolved with  
230 the trial investigators, the data of the concerning study will not be included in the primary analysis  
231 and the reason for exclusion will be explicitly stated.  
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### 233 **Risk of bias**

234 Two reviewers will independently assess the quality of the included studies using the Cochrane risk-  
235 of-bias tool for randomised trials (Rob 2).(42) Studies will be judged as "*low risk*", "*some concerns*",  
236 or "*high risk of bias*". Publication bias will be assessed using a contour enhanced funnel plot.(43)  
237 Additionally, the IPD will be used to directly check process parameters of some of the bias domains.  
238 Randomization and allocation concealment will be assessed by checking baseline imbalances.  
239 Incomplete outcome data will be assessed by checking the IPD to ensure all randomized patients are  
240 included. All available clinically relevant outcomes in the IPD will be reported in the IPD MA. For time  
241 to event outcomes such as mortality, pattern and extent of follow up will be checked. When needed,

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3 242 additional follow up with original authors will be conducted to rectify any imbalances as far as  
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9 245 **Synthesis methods**

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11 246 All outcomes will be analysed according to the intention to treat principle and using a one-step  
12  
13 247 approach for IPD MA. In the one-step approach, IPD will be modelled from all studies simultaneously  
14  
15 248 using the generalised linear mixed model framework and the statistical model appropriate for the  
16  
17 249 type of outcome being analysed (i.e., logistic regression for binary outcome data, linear regression  
18  
19 250 for continuous outcome data, and Cox-regression for time to event data). A random treatment effect  
20  
21 251 term will be added to the model and all other parameters (intercepts, prognostic factor effects and  
22  
23 252 residual variances) will be stratified by trial to account for the clustering of patients within studies.  
24  
25 253 Maximum likelihood with quadrature will be used as estimation method and study-specific centering  
26  
27 254 of the variables.(44) Variables potentially affecting the outcome that, despite randomisation, show  
28  
29 255 baseline imbalances across treatment arms will be considered for adjustment based on the criteria  
30  
31 256 for confounder selection by VanderWeele and Shpitser.(45-48) Procedure duration is considered an  
32  
33 257 important proxy for the complexity of the procedure and will also be considered for adjustment  
34  
35 258 despite being measured during the exposure.(47, 48) We assume that the FiO<sub>2</sub> used does not affect  
36  
37 259 procedure duration. Benjamini-Hochberg correction will be used to account for multiple testing for  
38  
39 260 the primary and secondary outcomes when appropriate.(49)

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43 262 **Exploration of variation in effects**

44  
45 263 To explore the causes of heterogeneity and identify factors modifying the effects of high  
46  
47 264 intraoperative FiO<sub>2</sub>, we will perform pre-specified subgroup analyses by extending the one-step  
48  
49 265 meta-analysis framework to include treatment-covariate interaction terms. Subgroups will be  
50  
51 266 defined according to mean core temperature (<35°C), mean net fluid supplementation  
52  
53 267 (<15ml/kg/hr), use of mechanical ventilation, use of nitrous oxide, use of preoperative antibiotic  
54  
55 268 prophylaxis, and procedure duration (>2.5h). All subgroup variables have been proposed as effect  
56  
57 269 modifiers in previous studies and have a plausible biological substantiation.(50-61) Cut-offs are  
58  
59 270 driven by previously reported data.(50-61) Treatment-covariate interaction terms p <0.05 will be  
60  
271 considered statistically significant. Dose-response variation will be explored by total O<sub>2</sub> exposure  
272 duration for each primary outcome.

273

### 274 **Additional analysis**

275 A sensitivity analysis will be conducted to test the impact of excluding trials using N<sub>2</sub>O as a carrier gas  
276 on the pooled effect estimate. In the case of exclusion of trials due to concerns on IPD integrity, a  
277 sensitivity analysis will be conducted to test the impact of including the concerning data on the  
278 pooled effect estimate. When multiple imputation is performed, a complete case analysis will also be  
279 conducted. In studies with sufficiently detailed data on the intervention, all analyses will also be  
280 conducted according to the per-protocol principle after adjustment for confounding factors due to  
281 incomplete adherence to the assigned treatments or use of off-protocol concomitant therapies  
282 according to the variable selection principles described for the primary analysis. Per protocol  
283 treatment will be defined as an FiO<sub>2</sub> of 0.80 ± 0.05 for at least 75% of the ventilation time in the  
284 intervention group, and an FiO<sub>2</sub> smaller than 0.40 with a margin of 0.05, for 75% in the control group.  
285 Patients requiring more oxygen for medical reasons, for example to maintain adequate saturation,  
286 after initial ventilation with an FiO<sub>2</sub> of 0.45 are exempted and not considered a protocol deviation. A  
287 sensitivity analysis will be conducted according to the two-step approach. All studies will be  
288 reanalysed separately, similarly to the one-step approach but without the term for trial clustering.  
289 The new aggregate data of each study will then be synthesised in a second step synthesising an  
290 overall estimate using maximum likelihood method followed by the Hartung-Knapp Sidik-Jonkman  
291 correction assuming random effects.<sup>(62)</sup> Between-study variance will be evaluated using  $\tau^2$ ; in  
292 addition, the Chi<sup>2</sup> test for heterogeneity will be performed with  $p < 0.100$  considered statistically  
293 significant.. In the unlikely event that IPD will not be made available, aggregate study data will be  
294 included in the analyses during step two. Any unforeseen challenge during the analysis or choice that  
295 leads to discussion in the steering group that cannot be resolved by consensus will also be subjected  
296 to sensitivity analysis. For time to event outcomes a survival curve will be added to the Cox-  
297 regression analysis.

298

### 299 **Certainty of the cumulative estimate**

300 The Grading of Recommendations Assessment Development and Evaluation (GRADE) working group  
301 methodology will be used to assess the overall quality of evidence for the following domains: risk of  
302 bias, unexplained inconsistency, indirectness, imprecision, publication bias, and magnitude of effect.  
303 Additional domains may be considered where appropriate. Optimal information size, defined as the  
304 number of participants needed for a single adequately powered trial, was calculated assuming a  
305 type-1 error ( $\alpha$ ) of 0.05, a type 2 error ( $\beta$ ) of 0.2 and a relative risk reduction of 0.25.<sup>(63)</sup> If a  
306 confidence interval failed to exclude appreciable benefit or harm, defined as a relative risk reduction

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3 307 or increase of 0.25, the quality of evidence will be downgraded regardless of the optimal information  
4 308 size.<sup>(63)</sup> The overall certainty will be classified using four levels: high, moderate, low, and very  
5 309 low.<sup>(64)</sup>  
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## 11 311 **Software**

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13 312 Results will be processed using R 4.0.4.  
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## 18 314 **ETHICS AND DISSEMINATION**

### 20 315 **Ethical approval**

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23 316 Ethical approval is not deemed necessary for this study protocol.  
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25

26 317

### 27 318 **Dissemination**

28  
29  
30 319 This protocol and the results of this study will be submitted to a peer-reviewed medical journal  
31 320 regardless of the outcome. The protocol will be submitted before the data is gathered and analysed.  
32  
33

34 321

### 35 322 **Competing interests**

36  
37  
38 323 S.W.J. reports receipt of grants from Photonics in Healthcare, Integra LifeSciences, and Ethicon  
39 324 outside the submitted. P.S.M. reports receipt of grants or contracts from the Australian National  
40 325 Health and Medical Research Council (NHMRC), Practitioner Fellowship and Projects Grants, payment  
41 326 of expert testimony from Avant Medical Indemnity, and participation on a Data Safety Monitoring  
42 327 Board of Advisory Board for the SNAP, TOPIC-2 and BONANZA trials. A.F. reports receipt of  
43 328 institutional grants from the Australian Research Council Discovery Project and National Health and  
44 329 Medical Research Council Ideas outside the submitted work and participation on a Data Safety  
45 330 Monitoring Board or Advisory Board for the Australian Kidney Trials Research Network (INCH-HD,  
46 331 IMPEDE, TEQCH-PD, PHOSPHATE, BEST Fluids, N3RO trial, CKD-FIX, IMPROVE-FIX). R.G. reports  
47 332 participation on Steering Committee for the IntuBot Innosuisse Projekt and has a leadership role as  
48 333 ERC Director of Guidelines and ILCOR, and ILCOR Task Force Chair on Education, Implementation and  
49 334 Team, and Treasurer of European Airway Management society, and reports receipt without any  
50 335 payment of airway equipment for the research of the following: Intersurgical, Karl Storz, Verathon  
51 336 Inc, Aircraft Medical, Prodol Meditec, Venner Medical, Kingsystems, Medtronic, Ambu, VBM,  
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3 337 Radiometer, Sentec, and Fisher & Paykel. A.K. reports receipt of grants or contracts from Potrero  
4  
5 338 Medical, Rehabtronics and The 37company outside the submitted work and participation on a Data  
6  
7 339 Safety Monitoring Board of Advisory Board in Directedsystems, Potrero Medical and BioAgel  
8  
9 340 Laboratories. J.M. reports voluntary participation as a panellist in the updated WHO Guidelines on  
10  
11 341 high vs low FiO2 in 2018 and voluntary co-investigator in the PENGUIN trial of high versus low FiO2  
12  
13 342 for SSI prevention in abdominal surgery in low- and middle-income settings with GlobalSurg  
14  
15 343 Collaborative. M.G.W.D. reports participation on a Data Safety Monitoring Board or Advisory Board  
16  
17 344 for the following trials: DANCE, SPHINX, ICONIC, SAFE, PACER, LEARNS, RECAP, and BIOPEX2. C.F.  
18  
19 345 reports receipt fees for lectures and educational events from Getinge and Medtronic outside the  
20  
21 346 submitted work. C.S. reports receipts of institutional grants from NICHD outside the submitted work.  
22  
23 347 M.A.B. reports receipt of institutional grants from KCI/3M, Johnson & Johnson, New Compliance, BD  
24  
25 348 Bard, Gore, Telabio, GDM, Medtronic, and Smith & Nephew outside the submitted work, and  
26  
27 349 participation on the Data Monitoring Committee of the EXTEND trial. M.W.H. reports receipt of  
28  
29 350 institutional grants from ZonMw outside the submitted work, consulting institutional fees from IDD  
30  
31 351 Pharma outside the submitted work, institutional payment or honoraria for lectures, presentations,  
32  
33 352 speakers bureaus, manuscript writing or educational events from CSL Behring outside the submitted  
34  
35 353 work, and has a leadership role in DGAI, ISAP and IARS (Anaesthesia and Analgesia). The other  
36  
37 354 authors declare no conflict of interest.  
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40  
41  
42

### 43 **Contributions**

44  
45 360 MH and MB are the guarantors of the study. SJ conceived the study. SJ and RH drafted the study  
46  
47 361 protocol. All authors provided expertise from their respective area of interest, contributed to the  
48  
49 362 study protocol, provided critical feedback, and approved the final manuscript. JM and BA provided  
50  
51 363 independent advice on behalf of their respective organisations.  
52  
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54

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3 368 **Data sharing**  
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5 369 Data will be made available upon reasonable request and review and approval of all collaborators.  
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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	Reported on page
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplement01

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), processes for obtaining and confirming data from investigators	8
Data items	any 12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12-13

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*



# BMJ Open

## The benefits and harms of perioperative high fraction inspired oxygen for surgical site infection prevention: a protocol for a systematic review and meta-analysis of individual patient data of randomised controlled trials

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	Hollmann, Markus; Amsterdam UMC Locatie AMC, Anaesthesiology
<b>Primary Subject Heading</b> :	Anaesthesia
<b>Secondary Subject Heading</b> :	Surgery
<b>Keywords</b> :	ANAESTHETICS, WOUND MANAGEMENT, Infection control < INFECTIOUS DISEASES, SURGERY



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2  
3 **1 TITLE PAGE**

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6 **2 The benefits and harms of perioperative high fraction inspired oxygen for surgical site infection**  
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8 **3 prevention: a protocol for a systematic review and meta-analysis of individual patient data of**  
9 **4 randomised controlled trials**

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11 **5 S. W. de Jonge<sup>1a,b,2\*</sup>, R. H. Hulskes<sup>1a,2</sup>, M. Zokaei Nikoo<sup>11</sup>, R. P. Weenink<sup>2</sup>, C. S. Meyhoff<sup>3</sup>, K. Leslie<sup>4</sup>,**  
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54 **42 0031 (0)20 566 9111.**

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56  
57 **44 and references)**

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46 **Keywords:** general anaesthesia; hyperoxia; postoperative outcome; surgical site infection; surgical  
47 wound infection

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**48 ABSTRACT**

49 **Introduction:** The use of high fraction of inspired oxygen (FiO<sub>2</sub>) intraoperatively for the prevention of  
50 surgical site infection (SSI) remains controversial. Promising results of early randomized controlled  
51 trials (RCT) have been replicated with varying success and subsequent meta-analysis are equivocal.  
52 Recent advancements in perioperative care, including the increased use of laparoscopic surgery and  
53 pneumoperitoneum and shifts in fluid and temperature management, can affect peripheral oxygen  
54 delivery and may explain the inconsistency in reproducibility. However, the published data provides  
55 insufficient detail on the participant level to test these hypotheses. The purpose of this individual  
56 participant data meta-analysis is to assess the described benefits and harms of intraoperative high  
57 FiO<sub>2</sub> compared to regular (0.21-0.40) FiO<sub>2</sub> and its potential effect modifiers.

**59 Methods and analysis:**

60 Two reviewers will search medical databases and online trial registries, including MEDLINE, EMBASE,  
61 CENTRAL, CINHAL, and clinicaltrial.gov, for randomised and quasi randomised controlled trials  
62 comparing the effect of intraoperative high FiO<sub>2</sub> (0.60-1.00) to regular FiO<sub>2</sub> (0.21-0.40) on SSI within  
63 90 days after surgery in adult patients. Secondary outcome will be all-cause mortality within the  
64 longest available follow-up. Investigators of the identified trials will be invited to collaborate. Data  
65 will be analysed with the one step approach using the generalised linear mixed model framework  
66 and the statistical model appropriate for the type of outcome being analysed (logistic and cox  
67 regression respectively), with a random treatment effect term to account for the clustering of  
68 patients within studies. The certainty of evidence will be assessed using GRADE methodology. Pre-  
69 specified subgroup analyses include use of mechanical ventilation, nitrous oxide, preoperative  
70 antibiotic prophylaxis, temperature (<35°C), fluid supplementation (<15ml/kg/hr) and procedure  
71 duration (>2.5h).

72 **Ethics and dissemination:** Ethics approval is not required. Investigators will de-identify individual  
73 participant data before it is shared. The results will be submitted to a peer-review journal.

74  
75 **Trial Registration Number:** PROSPERO CRD42018090261

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3 76 **ARTICLE SUMMARY**  
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5 77 **Strengths and limitations of this study**  
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- 8 78 • Individual participant data meta-analysis (IPD MA) of (quasi-)randomised controlled trials  
9 79 provides the best possible analysis of the available data on the participant level, permitting  
10 80 the investigation of potential effect modifiers.  
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13 81 • IPD MA requires the collaboration of all investigators that have published data on the  
14 82 relevant topic and leads to a broad consensus on the outcome and interpretation of the  
15 83 analysis  
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18 84 • IPD MA depends on the quality of data that is made available by the authors of the original  
19 85 studies.  
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## 86 INTRODUCTION

87 Surgical site infection (SSI) is one of the most common healthcare-associated infections and leads to  
88 morbidity, mortality, and longer hospital stay.(1-4) The attributable costs can be more than €14.000  
89 per SSI, and European totals are estimated to range from €1.5 to €19 billion per year.(5, 6) In 2016-  
90 2017, both the World Health Organization (WHO) and the Centres of Disease Control and Prevention  
91 (CDC) independently released evidence-based guidelines on the prevention of SSI that included a  
92 recommendation in favour of the administration of high fraction of inspired ( $\text{FiO}_2$ ) for patients  
93 undergoing surgery under general anaesthesia.(7-9) This has led to a debate between opponents and  
94 proponents of the use of high  $\text{FiO}_2$  in several editorials and correspondences across medical  
95 speciality literature.(10-20) Concerns were raised on the safety of the use of high  $\text{FiO}_2$  as well as on  
96 the conflicting study results with some in support of the use of high  $\text{FiO}_2$  to reduce SSI and some  
97 not.(10-20) Finally, studies by of one of the authors that contributed to the body of evidence were  
98 retracted because of unreproducible statistics.

99 In response to these concerns, the WHO conducted an independent systematic review on the safety  
100 of high intraoperative  $\text{FiO}_2$  and updated the systematic review on its effectiveness, excluding the  
101 disputed trials.(21, 22) No evidence of harm to discourage the use of high  $\text{FiO}_2$  was found, yet the  
102 evidence of an effect of SSI had become weaker, and the recommendation was adjusted  
103 accordingly.(23) Despite various studies and recommendations, there is still no consensus on the  
104 safety and effectiveness of using high  $\text{FiO}_2$  during surgery with regard to SSI, all-cause mortality and  
105 other adverse events in adult patients. This leads to practice variation that inevitably exposes  
106 patients to suboptimal care.(24) There is a need for better understanding and consensus on this  
107 issue.

108 Since the early promising results, perioperative care has changed considerably. Open abdominal  
109 surgery has been largely replaced by laparoscopic surgery, fluid management has moved from liberal  
110 to restrictive, to advanced goal directed regimens and active perioperative warming has become a  
111 mainstay.(25-27) All these changes have considerable consequences for hemodynamic,  
112 microcirculation, and eventually peripheral oxygen delivery.(28-30) These changes may explain the  
113 inconsistency in reproducibility, but the available data provides insufficient detail on the participant  
114 level to test the potential of high  $\text{FiO}_2$ . Meta-analysis of individual participant data uses the raw  
115 individual-level data from the original study for synthesis and overcomes this limitation.(31, 32) IPD  
116 MA enables analysis of uniform outcomes with more statistical power and assessment of potential  
117 effect modifiers.(33, 34) Importantly, IPD MA requires collaboration with all published researchers on  
118 the topic leading to a broad consensus on the outcome of data analysis and interpretation.

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3 119 The purpose of this IPD MA is to assess the potential benefits and harms of intraoperative high (0.60-  
4 120 1.00) FiO<sub>2</sub> compared to traditional (0.21-0.40) FiO<sub>2</sub> and its effect modifiers in adult patients  
5  
6 121 undergoing surgery with SSI being the primary outcome. This IPD MA is initiated by the University of  
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8 122 Amsterdam / Amsterdam University Medical Center, and encouraged by the WHO and the World  
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10 123 Federation of Societies of Anaesthesiologists (WFSA) to provide patients and practitioners with the  
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12 124 best possible evidence and guidance on this disputed area and will give clearance of the disputed  
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14 125 hypothesis that high FiO<sub>2</sub> reduces the incidence of SSI.  
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## 126 **METHODS AND ANALYSIS**

### 127 **Protocol and registration**

128 This study protocol is registered with the International Prospective Register of Systematic Reviews  
129 (PROSPERO) on 7 March 2018 and was last updated on 15 July 2022 (registration number  
130 CRD42018090261). The study protocol is designed and written to adhere to the Preferred Reporting  
131 Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)(35) and the Preferred  
132 Reporting Items for Systematic Review Meta-Analysis of individual patient data (IPD) (PRISMA-  
133 IPD).(32)

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### 135 **Patient and Public Involvement Statement**

136  
137 This project is encouraged by the World Health Organization (WHO), and the World Federation of  
138 Societies of Anesthesiologists (WFSA) to provide patients and practitioners with the best possible  
139 evidence and guidance on this disputed area. WHO and WFSA have provided external independent  
140 review and advice on research direction and aim.

141

### 142 **Governance**

143 This study is an initiative of the Amsterdam University Medical Centre, encouraged by the WHO and  
144 the WFSA. Both organisations recognise the urgent need for this research and provide external  
145 independent review and advice. The writing committee consists of the study coordinator, two  
146 reviewers, a lead methodologist, and a principal investigator from both the surgery and the  
147 anaesthesiology department of the Amsterdam University Medical Centre and two external content  
148 matter experts. The writing committee is entirely independent of the initial trials and has full  
149 responsibility for all methodological decisions. A broader steering committee with representatives of  
150 the collaborating trial groups identified during the project will be invited to comment on and co-  
151 author the final protocol and IPD MA report. By sharing their IPD, collaborators will obtain one co-  
152 authorship on the IPD MA report and one additional co-authorship if data of more than 300  
153 participants is shared. For transparency and against intellectual bias, a record will be kept of all  
154 comments. Any important amendments to the protocol will be recorded in PROSPERO record and  
155 discussed in the methods section of the final report.

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### 157 **Eligibility criteria**

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3 158 We will include all randomised and quasi-randomised controlled trials comparing the effect of  
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5 159 intraoperative high FiO<sub>2</sub> (0.60-1.0) to traditional FiO<sub>2</sub> (0.21-0.40) in patients undergoing surgery.  
6  
7 160 Definitions for high and low FiO<sub>2</sub> were determined by literature review and consensus among the  
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9 161 IPDMA collaborators.(21, 22) These trials may include patients of any age undergoing surgery except  
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11 162 for neonates, regardless publication, language, or year of conduct and should include at least data on  
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13 163 age, sex, mean FiO<sub>2</sub> administered, method of oxygen administration, SSI, mortality, or other serious  
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15 164 adverse events. Any outcome found to be recorded in these trials will be included in the analysis.  
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17 165 Studies without random or quasi-random treatment allocation, animal studies, and studies outside of  
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19 166 the intraoperative period will be excluded.  
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### 22 168 **Identifying studies – information sources**

23 169 The initial search conducted for the WHO guideline will be updated by a professional information  
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25 170 specialist.(21, 22) Medical databases will be searched, including MEDLINE, EMBASE, CENTRAL,  
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27 171 CINHAL, and the WHO regional databases. Online trial registries will be searched to identify potential  
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29 172 unpublished evidence or any ongoing trials. The search will not be limited by language or date of  
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31 173 publication. A final update will be conducted before the final round of revisions preceding submission  
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33 174 for publication. The reference list of all included studies will be hand searched for any additional  
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35 175 relevant trials not already identified through database searching. All corresponding authors of  
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37 176 relevant clinical trials will be contacted to review the list of identified studies for the omission of  
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39 177 potentially relevant studies missed by the search.  
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### 42 179 **Study selection process**

43 180 Two reviewers will independently assess articles retrieved by the search against the eligibility criteria.  
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45 181 After screening the title and abstract, the full text of potentially eligible papers will be retrieved and  
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47 182 assessed. When no full paper exists, or trial eligibility is in doubt, the study authors will be contacted  
48  
49 183 to provide further information. Any discrepancies in study selection will be resolved through  
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51 184 consensus and discussion with a senior author. All studies that pass title and abstract screening but  
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53 185 were not eligible for inclusion will be listed with the reasons for exclusion.  
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### 56 187 **Study collaboration invitation**

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58 188 Authors of eligible studies will be contacted and invited to collaborate on the IPD MA. An email  
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60 189 invitation will be sent to the corresponding authors outlining the IPDMA goals. If no reply is received

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3 190 within two weeks, a second email request will be sent to the corresponding and first author. If no  
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5 191 response is received again, we will try to contact all authors by email and telephone. IPD data will be  
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7 192 considered unavailable if numerous times (at least five) no reply is received if authors no longer have  
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9 193 access to the study data or consent to collaboration.

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### 11 12 13 195 **Data collection process**

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15 196 The collaborating investigators will be requested to sign a data transfer agreement describing the  
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17 197 ownership and storage of the IPD before IPD is shared. Whenever possible, data collection, interview  
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19 198 on the protocol, and formal handoff on the data codebook will be done electronically via email,  
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21 199 videoconference, or a suitable alternative. Whenever requested by the original investigator, a  
22  
23 200 researcher will visit the investigators for a physical data transfer, in-person interview, and data  
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25 201 codebook handoff. IPD will be de-identified by the supplying collaborator. The IPD de-identification  
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27 202 code will not be shared. IPD will be transferred using one of the following secure methods:  
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29 203 SurfFilesender, a secure password protected data transfer service,(36) end-to-end encrypted and  
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31 204 password protected using email or send by courier on a physical storage media. Once transferred,  
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33 205 IPD will be stored securely on the local server of the Amsterdam UMC where appropriate data and  
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35 206 privacy policies will be maintained, as well as procedures and associated physical, technical and  
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37 207 administrative safeguards to assure that the IPD are accessed only by authorized personnel. In the  
38  
39 208 unlikely event that individual patient data will not be made available, the reason will be recorded.  
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41 209 The aggregate data of the study will be used in a sensitivity analysis. Aggregate data collection will be  
42  
43 210 performed as appropriate for a regular meta-analysis by two independent reviewers according to a  
44  
45 211 predefined data extraction sheet and overseen by a senior author to settle potential discrepancies.  
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47 212 The University of Amsterdam's Clinical Research Unit will facilitate secure data storage.

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### 49 214 **Data items**

50 215 Data items will include all data recorded by the initial trial investigators including, but not limited to  
51  
52 216 the items listed in table 1 and table 2. SSI within 90 days after surgery according to the authors  
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54 217 discretion will be the primary outcome, all-cause mortality within the longest available follow up will  
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56 218 be the secondary outcome. All other outcomes are exploratory.

57 **Table 1. Baseline and procedure characteristics**

58 <i>Baseline</i>	59 Sex, age, BMI (kg/m <sup>2</sup> ), ASA physical status score, smoking status, peripheral 60 vascular disease, diabetes, (metastatic) cancer, congestive heart disease, (pulmonary) hypertension, chronic obstructive pulmonary disease,
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	immunosuppressant use, peripheral oxygen saturation (%), glucose (mg/dL), indication for surgery, emergency procedure
<i>Preoperative</i>	Use of preoperative antibiotic prophylaxis (dose and agent), timing of preoperative antibiotic prophylaxis, use of mechanical bowel preparation, haemoglobin (g/dL), use of antibiotic bowel preparation, cytostatic chemotherapy, radiotherapy, Use of preoperative skin preparation prophylaxis (dose and agent), Timing of preoperative skin preparation prophylaxis.
<i>Intraoperative</i>	Surgical procedure(s), organ involvement, contamination (CDC wound classification(37)), laparoscopic surgery, mean arterial pressure (MAP) (mmHg), haemoglobin (g/dL), heart rate (beats/min), hemodynamic monitoring method, hemodynamic management algorithm, crystalloid infusion (ml), colloid Infusion (ml), red-cell transfusion (units), duration of surgery (min), duration of anaesthesia (min), mean core temperature (°C)*, lowest core temperature (°C)*, mean net fluid supplementation (ml/kg/hr), arterial oxygen saturation (%), peripheral oxygen saturation (%), subcutaneous oxygen tension (mm Hg), muscle oxygen tension (mm Hg), partial pressure of arterial oxygen (mmHg), mean FiO <sub>2</sub> (%), mean PEEP (cmH <sub>2</sub> O), ventilator flow (L/min), peak airway pressure (mmHg), plateau pressure (mmHg), tidal Volume (ml/kg predicted body weight), respiratory frequency, vasopressor agent, vasopressor agent used (mg), glucose (mg/dL), use of general anaesthesia, use of spinal or epidural anaesthesia, use of mechanical ventilation, use of nitrous oxide, total blood loss (ml), fluids (ml), end tidal CO <sub>2</sub>
<i>Postoperative</i>	Use of postoperative antibiotics (dose and agent), postoperative antibiotic duration (days), cytostatic chemotherapy, radiotherapy, haemoglobin (g/dL), VAS pain score, use of postoperative oxygen supplementation (duration, method and FiO <sub>2</sub> ), haemoglobin (g/dL), peripheral oxygen saturation (%), partial pressure of arterial oxygen (mmHg), subcutaneous oxygen tension (mmHg), muscle oxygen tension (mmHg), glucose (mg/dL), NNIS score(38), SSI risk score(39), Use of drains
<i>Oxygen Administration &amp; Monitoring</i>	Total duration and concentration of oxygen exposure during the pre/intra/postoperative period (timing of initiation, concentration, duration), oxygen supply and mode of administration (Intubation, use and type of face mask, nasal prongs), carrier gas (N <sub>2</sub> , N <sub>2</sub> O, medical or room air), protocol-defined target or range of partial pressure of arterial oxygen (mmHg) or peripheral oxygen saturation (%)
* Direct measurement or its approximation by peripheral measurement	

219

**Table 2. Outcome data and effect measure specification**

<i>Primary</i>	- SSI within 90 days after surgery by the author's discretion
<i>Secondary</i>	- All-cause mortality within the longest available follow-up
<i>Exploratory</i>	- Survival within the longest available follow-up - Serious adverse events defined by the ICH guidelines for good clinical practice(40) - SSI monitored according to the CDC criteria and specified as either superficial, deep, organ/space(41) - Respiratory insufficiency: defined as the need for respiratory assistance provided as ventilator therapy or non-invasive ventilation within 90 days after surgery - Unplanned ICU admission (not part of routine postoperative care) (days)

	<ul style="list-style-type: none"> <li>- Hospital readmissions within 90 days after surgery</li> <li>- Anastomotic leakage as defined by the international study group of rectal cancer(42)</li> <li>- Total duration of hospitalization, including readmissions related to the initial hospitalization</li> <li>- Any cardiovascular complication at any time after surgery</li> <li>- Any pulmonary complications at any time after surgery</li> <li>- Stroke at any time after surgery</li> <li>- New or recurrent cancer diagnosis at any time after surgery</li> <li>- Any further clinically relevant outcome reported in the IPD</li> </ul>
<p>* When patients are reoperated within follow up for reasons other than surgical site infection these cases will be excluded from the analysis based on loss to follow up.</p>	

220

### 221 **Missing data**

222 When variables are missing at the participant level and the missing at random assumption is  
 223 plausible, multiple imputations by chained equations may be applied in each trial separately before  
 224 proceeding with the analysis. Variables that miss systematically i.e., unknown for the entire study or  
 225 are deemed missing non-randomly after discussion in the writing committee, will not be imputed.  
 226 When this concerns variables included in pre-defined analysis, studies systematically missing this  
 227 variable will be excluded from that analysis. When this concerns variables not included in pre-defined  
 228 analysis, these variables will be dropped from the main outcome analysis as potential confounding  
 229 variables. The set of available variables for the main analysis will thus be determined by the data set  
 230 with the least available variables. Variables from richer sets will remain available for exploratory  
 231 analysis among data sets with the variable available.

232

### 233 **Individual Participant Data integrity**

234 We will check IPD for potential missing, invalid, or out-of-range values, inconsistencies, and  
 235 discrepancies with the aggregate publication. When identified, we will seek to resolve the issues with  
 236 the trial investigators to improve data quality and ensure that trials are represented accurately. In  
 237 addition, any modelling assumptions made in the initial analysis will be evaluated (i.e., missing at  
 238 random in the case of multiple imputation or non-informative censoring and proportional hazards in  
 239 the case of time to event data). In the case of any concerns on IPD integrity further prove of  
 240 execution of the trial and substantiation of the results may be requested such as prove of  
 241 institutional review board approval or original case record forms. If concerns cannot be resolved with  
 242 the trial investigators, the data of the concerning study will not be included in the primary analysis  
 243 and the reason for exclusion will be explicitly stated.

244

**245 Risk of bias**

246 Two reviewers will independently assess the quality of the included studies using the Cochrane risk-  
247 of-bias tool for randomised trials (Rob 2).(43) Studies will be judged as "*low risk*", "*some concerns*",  
248 or "*high risk of bias*". Publication bias will be assessed using a contour enhanced funnel plot.(44)  
249 Additionally, the IPD will be used to directly check process parameters of some of the bias domains.  
250 Randomization and allocation concealment will be assessed by checking baseline imbalances.  
251 Incomplete outcome data will be assessed by checking the IPD to ensure all randomized patients are  
252 included. All available clinically relevant outcomes in the IPD will be reported in the IPD MA. For time  
253 to event outcomes such as mortality, pattern and extent of follow up will be checked. When needed,  
254 additional follow up with original authors will be conducted to rectify any imbalances as far as  
255 possible.

256

**257 Synthesis methods**

258 All outcomes will be analysed according to the intention to treat principle and using a one-step  
259 approach for IPD MA. In the one-step approach, IPD will be modelled from all studies simultaneously  
260 using the generalised linear mixed model framework and the statistical model appropriate for the  
261 type of outcome being analysed (i.e., logistic regression for binary outcome data, linear regression  
262 for continuous outcome data, and Cox-regression for time to event data). A random treatment effect  
263 term will be added to the model and all other parameters (intercepts, prognostic factor effects and  
264 residual variances) will be stratified by trial to account for the clustering of patients within studies.  
265 Maximum likelihood with quadrature will be used as estimation method and study-specific centering  
266 of the variables.(45) Variables potentially affecting the outcome that, despite randomisation, show  
267 baseline imbalances across treatment arms will be considered for adjustment based on the criteria  
268 for confounder selection by VanderWeele and Shpitser.(46-49) Procedure duration is considered an  
269 important proxy for the complexity of the procedure and will also be considered for adjustment  
270 despite being measured during the exposure.(48, 49) We assume that the FiO<sub>2</sub> used does not affect  
271 procedure duration. Benjamini-Hochberg correction will be used to account for multiple testing for  
272 the primary and secondary outcomes when appropriate.(50)

273

**274 Exploration of variation in effects**

1  
2  
3 275 To explore the causes of heterogeneity and identify factors modifying the effects of high  
4  
5 276 intraoperative FiO<sub>2</sub>, we will perform pre-specified subgroup analyses by extending the one-step  
6  
7 277 meta-analysis framework to include treatment-covariate interaction terms. Subgroups will be  
8  
9 278 defined according to mean core temperature (<35°C), mean net fluid supplementation  
10  
11 279 (<15ml/kg/hr), use of mechanical ventilation, use of nitrous oxide, use of preoperative antibiotic  
12  
13 280 prophylaxis, and procedure duration (>2.5h). All subgroup variables have been proposed as effect  
14  
15 281 modifiers in previous studies and have a plausible biological substantiation.(51-62) Cut-offs are  
16  
17 282 driven by previously reported data.(51-62) Treatment-covariate interaction terms p <0.05 will be  
18  
19 283 considered statistically significant. Dose-response variation will be explored by total O<sub>2</sub> exposure  
20  
21 284 duration for each primary outcome. All exploratory analysis will be interpreted with caution  
22  
23 285 considering the limited power and potential of type 1 error when multiple interactions are tested.  
24  
25 286

286

### 287 **Additional analysis**

288 A sensitivity analysis will be conducted to test the impact of excluding trials using N<sub>2</sub>O as a carrier gas  
289 on the pooled effect estimate. Further, the choice of SSI definition will be evaluated in a sensitivity  
290 analysis applying the CDC definition as the primary outcome. In the case of exclusion of trials due to  
291 concerns on IPD integrity, a sensitivity analysis will be conducted to test the impact of including the  
292 concerning data on the pooled effect estimate. When multiple imputation is performed, a complete  
293 case analysis will also be conducted. In studies with sufficiently detailed data on the intervention, all  
294 analyses will also be conducted according to the per-protocol principle after adjustment for  
295 confounding factors due to incomplete adherence to the assigned treatments or use of off-protocol  
296 concomitant therapies according to the variable selection principles described for the primary  
297 analysis. Per protocol treatment will be defined as an FiO<sub>2</sub> of 0.80 ± 0.05 for at least 75% of the  
298 ventilation time in the intervention group, and an FiO<sub>2</sub> smaller than 0.40 with a margin of 0.05, for  
299 75% in the control group. Patients requiring more oxygen for medical reasons, for example to  
300 maintain adequate saturation, after initial ventilation with an FiO<sub>2</sub> of 0.45 are exempted and not  
301 considered a protocol deviation. A sensitivity analysis will be conducted according to the two-step  
302 approach. All studies will be reanalysed separately, similarly to the one-step approach but without  
303 the term for trial clustering. The new aggregate data of each study will then be synthesised in a  
304 second step synthesising an overall estimate using maximum likelihood method followed by the  
305 Hartung-Knapp Sidik-Jonkman correction assuming random effects.(63) Between-study variance will  
306 be evaluated using  $\tau^2$ ; in addition, the Chi<sup>2</sup> test for heterogeneity will be performed with p <0.100  
307 considered statistically significant. In the unlikely event that IPD will not be made available,

1  
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3 308 aggregate study data will be included in the analyses during step two. Any unforeseen challenge  
4 309 during the analysis or choice that leads to discussion in the steering group that cannot be resolved by  
5 310 consensus will also be subjected to sensitivity analysis. To assess robustness of the time to event  
6 311 outcomes a survival curve will be compared to the univariable version of the Cox proportional  
7  
8 312 hazards regression analysis.  
9  
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11

12 313

#### 14 314 **Certainty of the cumulative estimate**

16  
17 315 The Grading of Recommendations Assessment Development and Evaluation (GRADE) working group  
18 316 methodology will be used to assess the overall quality of evidence for the following domains: risk of  
19 317 bias, unexplained inconsistency, indirectness, imprecision, publication bias, and magnitude of effect.  
20 318 Additional domains may be considered where appropriate. Optimal information size, defined as the  
21 319 number of participants needed for a single adequately powered trial, was calculated assuming a  
22 320 type-1 error ( $\alpha$ ) of 0.05, a type 2 error ( $\beta$ ) of 0.2 and a relative risk reduction of 0.25.<sup>(64)</sup> If a  
23 321 confidence interval failed to exclude appreciable benefit or harm, defined as a relative risk reduction  
24 322 or increase of 0.25, the quality of evidence will be downgraded regardless of the optimal information  
25 323 size.<sup>(64)</sup> The overall certainty will be classified using four levels: high, moderate, low, and very  
26 324 low.<sup>(65)</sup>  
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#### 36 326 **Software**

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39 327 Results will be processed using R 4.0.4.  
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### 44 329 **ETHICS AND DISSEMINATION**

#### 46 330 **Ethical approval**

47  
48 331 Because this concerns a study on existing de-identified patient data, the medical research involving  
49 332 human subjects act does not apply and no formal medical ethics review is required.  
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53 333

#### 55 334 **Dissemination**

56  
57 335 This protocol and the results of this study will be submitted to a peer-reviewed medical journal  
58 336 regardless of the outcome. The protocol will be submitted before the data is gathered and analysed.  
59  
60



337

**338 Competing interests**

339 S.W.J. reports receipt of grants from Photonics in Healthcare, Integra LifeSciences, and Ethicon  
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348 participation on Steering Committee for the IntuBot Innosuisse Projekt and has a leadership role as  
349 ERC Director of Guidelines and ILCOR, and ILCOR Task Force Chair on Education, Implementation and  
350 Team, and Treasurer of European Airway Management society, and reports receipt without any  
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357 high vs low FiO<sub>2</sub> in 2018 and voluntary co-investigator in the PENGUIN trial of high versus low FiO<sub>2</sub>  
358 for SSI prevention in abdominal surgery in low- and middle-income settings with GlobalSurg  
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1314  
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16 377 designed the study, drafted the study protocol and provided statistical expertise. RH and MZ  
17  
18 378 provided input for the literature search and will coordinate the assembly of the data and perform the  
19  
20 379 screening, inclusion and assessment of risk of bias. RW, CM, KL, PM, AF, RG, OA, AK, DS, JM, KP, JB,  
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22 380 CF, GG, CS, DM, MC, PT, JO and BA provided substantial contributions to the study design, provided  
23  
24 381 critical feedback and approved the final version of the study protocol. All authors compliant with  
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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	Reported on page
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplement01

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I <sup>2</sup> , Kendall's τ)	12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12-13

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*



# BMJ Open

## The benefits and harms of perioperative high fraction inspired oxygen for surgical site infection prevention: a protocol for a systematic review and meta-analysis of individual patient data of randomised controlled trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-067243.R2
Article Type:	Protocol
Date Submitted by the Author:	30-Jun-2023
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	Hollmann, Markus; Amsterdam UMC Locatie AMC, Anaesthesiology
<b>Primary Subject Heading</b> :	Anaesthesia
<b>Secondary Subject Heading</b> :	Surgery
<b>Keywords</b> :	ANAESTHETICS, WOUND MANAGEMENT, Infection control < INFECTIOUS DISEASES, SURGERY



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3 **1 TITLE PAGE**

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6 **2 The benefits and harms of perioperative high fraction inspired oxygen for surgical site infection**  
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8 **3 prevention: a protocol for a systematic review and meta-analysis of individual patient data of**  
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12 **5 S. W. de Jonge<sup>1a,b,2\*</sup>, R. H. Hulskes<sup>1a,2</sup>, M. Zokaei Nikoo<sup>11</sup>, R. P. Weenink<sup>2</sup>, C. S. Meyhoff<sup>3</sup>, K. Leslie<sup>4</sup>,**  
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14 **6 P. S. Myles<sup>5</sup>, A. Forbes<sup>6</sup>, R. Greif<sup>7,8</sup>, O. Akça<sup>9</sup>, A. Kurz<sup>10</sup>, D. I. Sessler<sup>11</sup>, J. Martin<sup>12</sup>, M. G.**  
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18 **8 McKenna<sup>19</sup>, M. T. V. Chan<sup>20</sup>, P. Thibon<sup>21</sup>, J. Mellin-Olsen<sup>22</sup>, B. A. Allegranzi<sup>23</sup>, M. A. Boermeester<sup>1a, b</sup>,**  
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56 Word count: 2923 (excluding title page, abstract, article summary, tables, ethics and dissemination,  
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46 **Keywords:** general anaesthesia; hyperoxia; postoperative outcome; surgical site infection; surgical  
47 wound infection

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3 48 **ABSTRACT**  
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5 49 **Introduction:** The use of high fraction of inspired oxygen (FiO<sub>2</sub>) intraoperatively for the prevention of  
6 surgical site infection (SSI) remains controversial. Promising results of early randomized controlled  
7 50 surgical site infection (SSI) remains controversial. Promising results of early randomized controlled  
8 trials (RCT) have been replicated with varying success and subsequent meta-analysis are equivocal.  
9 51 Recent advancements in perioperative care, including the increased use of laparoscopic surgery and  
10 52 pneumoperitoneum and shifts in fluid and temperature management, can affect peripheral oxygen  
11 53 delivery and may explain the inconsistency in reproducibility. However, the published data provides  
12 54 insufficient detail on the participant level to test these hypotheses. The purpose of this individual  
13 55 participant data meta-analysis is to assess the described benefits and harms of intraoperative high  
14 56 FiO<sub>2</sub> compared to regular (0.21-0.40) FiO<sub>2</sub> and its potential effect modifiers.  
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23 59 **Methods and analysis:**  
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26 60 Two reviewers will search medical databases and online trial registries, including MEDLINE, Embase,  
27 61 CENTRAL, CINAHL, ClinicalTrials.gov, and WHO regional databases, for randomised and quasi  
28 62 randomised controlled trials comparing the effect of intraoperative high FiO<sub>2</sub> (0.60-1.00) to regular  
29 63 FiO<sub>2</sub> (0.21-0.40) on SSI within 90 days after surgery in adult patients. Secondary outcome will be all-  
30 64 cause mortality within the longest available follow-up. Investigators of the identified trials will be  
31 65 invited to collaborate. Data will be analysed with the one step approach using the generalised linear  
32 66 mixed model framework and the statistical model appropriate for the type of outcome being  
33 67 analysed (logistic and cox regression respectively), with a random treatment effect term to account  
34 68 for the clustering of patients within studies. The bias will be assessed using the RoB2 and the  
35 69 certainty of evidence using GRADE methodology. Pre-specified subgroup analyses include use of  
36 70 mechanical ventilation, nitrous oxide, preoperative antibiotic prophylaxis, temperature (<35°C), fluid  
37 71 supplementation (<15ml/kg/hr) and procedure duration (>2.5h).  
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47 72 **Ethics and dissemination:** Ethics approval is not required. Investigators will de-identify individual  
48 73 participant data before it is shared. The results will be submitted to a peer-review journal.  
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53 75 **Trial Registration Number:** PROSPERO CRD42018090261  
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3 76 **ARTICLE SUMMARY**  
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5 77 **Strengths and limitations of this study**  
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- 8 78 • Individual participant data meta-analysis (IPD MA) of (quasi-)randomised controlled trials  
9 79 provides the best possible analysis of the available data on the participant level, permitting  
10 80 the investigation of potential effect modifiers.  
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13 81 • IPD MA requires the collaboration of all investigators that have published data on the  
14 82 relevant topic and leads to a broad consensus on the outcome and interpretation of the  
15 83 analysis  
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18 84 • IPD MA depends on the quality of data that is made available by the authors of the original  
19 85 studies.  
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## 86 INTRODUCTION

87 Surgical site infection (SSI) is one of the most common healthcare-associated infections and leads to  
88 morbidity, mortality, and longer hospital stay.(1-4) The attributable costs can be more than €14.000  
89 per SSI, and European totals are estimated to range from €1.5 to €19 billion per year.(5, 6) In 2016-  
90 2017, both the World Health Organization (WHO) and the Centres of Disease Control and Prevention  
91 (CDC) independently released evidence-based guidelines on the prevention of SSI that included a  
92 recommendation in favour of the administration of high fraction of inspired ( $\text{FiO}_2$ ) for patients  
93 undergoing surgery under general anaesthesia.(7-9) This has led to a debate between opponents and  
94 proponents of the use of high  $\text{FiO}_2$  in several editorials and correspondences across medical  
95 speciality literature.(10-20) Concerns were raised on the safety of the use of high  $\text{FiO}_2$  as well as on  
96 the conflicting study results with some in support of the use of high  $\text{FiO}_2$  to reduce SSI and some  
97 not.(10-20) Finally, studies by of one of the authors that contributed to the body of evidence were  
98 retracted because of unreproducible statistics.

99 In response to these concerns, the WHO conducted an independent systematic review on the safety  
100 of high intraoperative  $\text{FiO}_2$  and updated the systematic review on its effectiveness, excluding the  
101 disputed trials.(21, 22) No evidence of harm to discourage the use of high  $\text{FiO}_2$  was found, yet the  
102 evidence of an effect of SSI had become weaker, and the recommendation was adjusted  
103 accordingly.(23) Despite various studies and recommendations, there is still no consensus on the  
104 safety and effectiveness of using high  $\text{FiO}_2$  during surgery with regard to SSI, all-cause mortality and  
105 other adverse events in adult patients. This leads to practice variation that inevitably exposes  
106 patients to suboptimal care.(24) There is a need for better understanding and consensus on this  
107 issue.

108 Since the early promising results, perioperative care has changed considerably. Open abdominal  
109 surgery has been largely replaced by laparoscopic surgery, fluid management has moved from liberal  
110 to restrictive, to advanced goal directed regimens and active perioperative warming has become a  
111 mainstay.(25-27) All these changes have considerable consequences for hemodynamic,  
112 microcirculation, and eventually peripheral oxygen delivery.(28-30) These changes may explain the  
113 inconsistency in reproducibility, but the available data provides insufficient detail on the participant  
114 level to test the potential of high  $\text{FiO}_2$ . Meta-analysis of individual participant data uses the raw  
115 individual-level data from the original study for synthesis and overcomes this limitation.(31, 32) IPD  
116 MA enables analysis of uniform outcomes with more statistical power and assessment of potential  
117 effect modifiers.(33, 34) Importantly, IPD MA requires collaboration with all published researchers on  
118 the topic leading to a broad consensus on the outcome of data analysis and interpretation.

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3 119 The purpose of this IPD MA is to assess the potential benefits and harms of intraoperative high (0.60-  
4 120 1.00) FiO<sub>2</sub> compared to traditional (0.21-0.40) FiO<sub>2</sub> and its effect modifiers in adult patients  
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6 121 undergoing surgery with SSI being the primary outcome. This IPD MA is initiated by the University of  
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8 122 Amsterdam / Amsterdam University Medical Center, and encouraged by the WHO and the World  
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10 123 Federation of Societies of Anaesthesiologists (WFSA) to provide patients and practitioners with the  
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12 124 best possible evidence and guidance on this disputed area and will give clearance of the disputed  
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14 125 hypothesis that high FiO<sub>2</sub> reduces the incidence of SSI.  
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## 126 **METHODS AND ANALYSIS**

### 127 **Protocol and registration**

128 This study protocol is registered with the International Prospective Register of Systematic Reviews  
129 (PROSPERO) on 7 March 2018 and was last updated on 15 July 2022 (registration number  
130 CRD42018090261). The study protocol is designed and written to adhere to the Preferred Reporting  
131 Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)(35) and the Preferred  
132 Reporting Items for Systematic Review Meta-Analysis of individual patient data (IPD) (PRISMA-  
133 IPD).(32)

134

### 135 **Patient and Public Involvement Statement**

136  
137 This project is encouraged by the World Health Organization (WHO), and the World Federation of  
138 Societies of Anesthesiologists (WFSA) to provide patients and practitioners with the best possible  
139 evidence and guidance on this disputed area. WHO and WFSA have provided external independent  
140 review and advice on research direction and aim.

141

### 142 **Governance**

143 This study is an initiative of the Amsterdam University Medical Centre, encouraged by the WHO and  
144 the WFSA. Both organisations recognise the urgent need for this research and provide external  
145 independent review and advice. The writing committee consists of the study coordinator, two  
146 reviewers, a lead methodologist, and a principal investigator from both the surgery and the  
147 anaesthesiology department of the Amsterdam University Medical Centre and two external content  
148 matter experts. The writing committee is entirely independent of the initial trials and has full  
149 responsibility for all methodological decisions. A broader steering committee with representatives of  
150 the collaborating trial groups identified during the project will be invited to comment on and co-  
151 author the final protocol and IPD MA report. By sharing their IPD, collaborators will obtain one co-  
152 authorship on the IPD MA report and one additional co-authorship if data of more than 300  
153 participants is shared. For transparency and against intellectual bias, a record will be kept of all  
154 comments. Any important amendments to the protocol will be recorded in PROSPERO record and  
155 discussed in the methods section of the final report.

156

### 157 **Eligibility criteria**

7

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2  
3 158 We will include all randomised and quasi-randomised controlled trials comparing the effect of  
4  
5 159 intraoperative high FiO<sub>2</sub> (0.60-1.0) to traditional FiO<sub>2</sub> (0.21-0.40) in patients undergoing surgery.  
6  
7 160 Definitions for high and low FiO<sub>2</sub> were determined by literature review and consensus among the  
8  
9 161 IPDMA collaborators.(21, 22) These trials may include patients of any age undergoing surgery except  
10  
11 162 for neonates, regardless publication, language, or year of conduct and should include at least data on  
12  
13 163 age, sex, mean FiO<sub>2</sub> administered, method of oxygen administration, SSI, mortality, or other serious  
14  
15 164 adverse events. Any outcome found to be recorded in these trials will be included in the analysis.  
16  
17 165 Studies without random or quasi-random treatment allocation, animal studies, and studies outside of  
18  
19 166 the intraoperative period will be excluded.  
20  
21 167

### 22 168 **Identifying studies – information sources**

23 169 The initial search conducted for the WHO guideline will be updated by a professional information  
24  
25 170 specialist.(21, 22) Medical databases will be searched, including MEDLINE, Embase, CENTRAL,  
26  
27 171 CINAHL, ClinicalTrials.gov, and the WHO regional databases. Online trial registries will be searched to  
28  
29 172 identify potential unpublished evidence or any ongoing trials. The search will not be limited by  
30  
31 173 language or date of publication. A final update will be conducted before the final round of revisions  
32  
33 174 preceding submission for publication. The reference list of all included studies will be hand searched  
34  
35 175 for any additional relevant trials not already identified through database searching. All corresponding  
36  
37 176 authors of relevant clinical trials will be contacted to review the list of identified studies for the  
38  
39 177 omission of potentially relevant studies missed by the search.  
40  
41 178

### 42 179 **Study selection process**

43 180 Two reviewers will independently assess articles retrieved by the search against the eligibility criteria.  
44  
45 181 After screening the title and abstract using Rayyan, the full text of potentially eligible papers will be  
46  
47 182 retrieved and assessed.(36) When no full paper exists, or trial eligibility is in doubt, the study authors  
48  
49 183 will be contacted to provide further information. Any discrepancies in study selection will be resolved  
50  
51 184 through consensus and discussion with a senior author. All studies that pass title and abstract  
52  
53 185 screening but were not eligible for inclusion will be listed with the reasons for exclusion.  
54  
55 186

### 56 187 **Study collaboration invitation**

57  
58 188 Authors of eligible studies will be contacted and invited to collaborate on the IPD MA. An email  
59  
60 189 invitation will be sent to the corresponding authors outlining the IPMDA goals. If no reply is received

1  
2  
3 190 within two weeks, a second email request will be sent to the corresponding and first author. If no  
4  
5 191 response is received again, we will try to contact all authors by email and telephone. IPD data will be  
6  
7 192 considered unavailable if numerous times (at least five) no reply is received if authors no longer have  
8  
9 193 access to the study data or consent to collaboration.

10 194

### 11 12 13 195 **Data collection process**

14  
15 196 The collaborating investigators will be requested to sign a data transfer agreement describing the  
16  
17 197 ownership and storage of the IPD before IPD is shared. Whenever possible, data collection, interview  
18  
19 198 on the protocol, and formal handoff on the data codebook will be done electronically via email,  
20  
21 199 videoconference, or a suitable alternative. Whenever requested by the original investigator, a  
22  
23 200 researcher will visit the investigators for a physical data transfer, in-person interview, and data  
24  
25 201 codebook handoff. IPD will be de-identified by the supplying collaborator. The IPD de-identification  
26  
27 202 code will not be shared. IPD will be transferred using one of the following secure methods:  
28  
29 203 SurfFilesender, a secure password protected data transfer service,(37) end-to-end encrypted and  
30  
31 204 password protected using email or send by courier on a physical storage media. Once transferred,  
32  
33 205 IPD will be stored securely on the local server of the Amsterdam UMC where appropriate data and  
34  
35 206 privacy policies will be maintained, as well as procedures and associated physical, technical and  
36  
37 207 administrative safeguards to assure that the IPD are accessed only by authorized personnel. In the  
38  
39 208 unlikely event that individual patient data will not be made available, the reason will be recorded.  
40  
41 209 The aggregate data of the study will be used in a sensitivity analysis. Aggregate data collection will be  
42  
43 210 performed as appropriate for a regular meta-analysis by two independent reviewers according to a  
44  
45 211 predefined data extraction sheet and overseen by a senior author to settle potential discrepancies.  
46  
47 212 The University of Amsterdam's Clinical Research Unit will facilitate secure data storage.

48 213

### 49 214 **Data items**

50  
51 215 Data items will include all data recorded by the initial trial investigators including, but not limited to  
52  
53 216 the items listed in table 1 and table 2. SSI within 90 days after surgery according to the authors  
54  
55 217 discretion will be the primary outcome, all-cause mortality within the longest available follow up will  
56  
57 218 be the secondary outcome. All other outcomes are exploratory.

58  
59  
60  
**Table 1. Baseline and procedure characteristics**

<i>Baseline</i>	Sex, age, BMI (kg/m <sup>2</sup> ), ASA physical status score, smoking status, peripheral vascular disease, diabetes, (metastatic) cancer, congestive heart disease, (pulmonary) hypertension, chronic obstructive pulmonary disease,
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	immunosuppressant use, peripheral oxygen saturation (%), glucose (mg/dL), indication for surgery, emergency procedure
<i>Preoperative</i>	Use of preoperative antibiotic prophylaxis (dose and agent), timing of preoperative antibiotic prophylaxis, use of mechanical bowel preparation, haemoglobin (g/dL), use of antibiotic bowel preparation, cytostatic chemotherapy, radiotherapy, Use of preoperative skin preparation prophylaxis (dose and agent), Timing of preoperative skin preparation prophylaxis.
<i>Intraoperative</i>	Surgical procedure(s), organ involvement, contamination (CDC wound classification(38)), laparoscopic surgery, mean arterial pressure (MAP) (mmHg), haemoglobin (g/dL), heart rate (beats/min), hemodynamic monitoring method, hemodynamic management algorithm, crystalloid infusion (ml), colloid Infusion (ml), red-cell transfusion (units), duration of surgery (min), duration of anaesthesia (min), mean core temperature (°C)*, lowest core temperature (°C)*, duration hypothermia (<35°C), mean net fluid supplementation (ml/kg/hr), arterial oxygen saturation (%), peripheral oxygen saturation (%), subcutaneous oxygen tension (mm Hg), muscle oxygen tension (mm Hg), partial pressure of arterial oxygen (mmHg), mean FiO <sub>2</sub> (%), mean PEEP (cmH <sub>2</sub> O), ventilator flow (L/min), peak airway pressure (mmHg), plateau pressure (mmHg), tidal Volume (ml/kg predicted body weight), respiratory frequency, vasopressor agent, vasopressor agent used (mg), glucose (mg/dL), use of general anaesthesia, use of spinal or epidural anaesthesia, use of mechanical ventilation, use of nitrous oxide, total blood loss (ml), fluids (ml), end tidal CO <sub>2</sub>
<i>Postoperative</i>	Use of postoperative antibiotics (dose and agent), postoperative antibiotic duration (days), cytostatic chemotherapy, radiotherapy, haemoglobin (g/dL), VAS pain score, use of postoperative oxygen suppletion (duration, method and FiO <sub>2</sub> ), haemoglobin (g/dL), peripheral oxygen saturation (%), partial pressure of arterial oxygen (mmHg), subcutaneous oxygen tension (mmHg), muscle oxygen tension (mmHg), glucose (mg/dL), NNIS score(39), SSI risk score(40), Use of drains
<i>Oxygen Administration &amp; Monitoring</i>	Total duration and concentration of oxygen exposure during the pre/intra/postoperative period (timing of initiation, concentration, duration), oxygen supply and mode of administration (Intubation, use and type of face mask, nasal prongs), carrier gas (N <sub>2</sub> , N <sub>2</sub> O, medical or room air), protocol-defined target or range of partial pressure of arterial oxygen (mmHg) or peripheral oxygen saturation (%)
* Direct measurement or its approximation by peripheral measurement	

219

<b>Table 2. Outcome data and effect measure specification</b>	
<i>Primary</i>	- SSI within 90 days after surgery by the author's discretion
<i>Secondary</i>	- All-cause mortality within the longest available follow-up
<i>Exploratory</i>	- Survival within the longest available follow-up - Serious adverse events defined by the ICH guidelines for good clinical practice(41) - SSI monitored according to the CDC criteria and specified as either superficial, deep, organ/space(42) - Respiratory insufficiency: defined as the need for respiratory assistance provided as ventilator therapy or non-invasive ventilation within 90 days after surgery - Unplanned ICU admission (not part of routine postoperative care) (days)

	<ul style="list-style-type: none"> <li>- Hospital readmissions within 90 days after surgery</li> <li>- Anastomotic leakage as defined by the international study group of rectal cancer(43)</li> <li>- Total duration of hospitalization, including readmissions related to the initial hospitalization</li> <li>- Any cardiovascular complication at any time after surgery</li> <li>- Any pulmonary complications at any time after surgery</li> <li>- Stroke at any time after surgery</li> <li>- New or recurrent cancer diagnosis at any time after surgery</li> <li>- Any further clinically relevant outcome reported in the IPD</li> </ul>
<p>* When patients are reoperated within follow up for reasons other than surgical site infection these cases will be excluded from the analysis based on loss to follow up.</p>	

220

### 221 **Missing data**

222 When variables are missing at the participant level and the missing at random assumption is  
 223 plausible, multiple imputations by chained equations may be applied in each trial separately before  
 224 proceeding with the analysis. Variables that miss systematically i.e., unknown for the entire study or  
 225 are deemed missing non-randomly after discussion in the writing committee, will not be imputed.  
 226 When this concerns variables included in pre-defined analysis, studies systematically missing this  
 227 variable will be excluded from that analysis. When this concerns variables not included in pre-defined  
 228 analysis, these variables will be dropped from the main outcome analysis as potential confounding  
 229 variables. The set of available variables for the main analysis will thus be determined by the data set  
 230 with the least available variables. Variables from richer sets will remain available for exploratory  
 231 analysis among data sets with the variable available.

232

### 233 **Individual Participant Data integrity**

234 We will check IPD for potential missing, invalid, or out-of-range values, inconsistencies, and  
 235 discrepancies with the aggregate publication. When identified, we will seek to resolve the issues with  
 236 the trial investigators to improve data quality and ensure that trials are represented accurately. In  
 237 addition, any modelling assumptions made in the initial analysis will be evaluated (i.e., missing at  
 238 random in the case of multiple imputation or non-informative censoring and proportional hazards in  
 239 the case of time to event data). In the case of any concerns on IPD integrity further prove of  
 240 execution of the trial and substantiation of the results may be requested such as prove of  
 241 institutional review board approval or original case record forms. If concerns cannot be resolved with  
 242 the trial investigators, the data of the concerning study will not be included in the primary analysis  
 243 and the reason for exclusion will be explicitly stated.

244

**245 Risk of bias**

246 Two reviewers will independently assess the quality of the included studies using the Cochrane risk-  
247 of-bias tool for randomised trials (RoB2).(44) Studies will be judged as "*low risk*", "*some concerns*", or  
248 "*high risk of bias*". Publication bias will be assessed using a contour enhanced funnel plot.(45)  
249 Additionally, the IPD will be used to directly check process parameters of some of the bias domains.  
250 Randomization and allocation concealment will be assessed by checking baseline imbalances.  
251 Incomplete outcome data will be assessed by checking the IPD to ensure all randomized patients are  
252 included. All available clinically relevant outcomes in the IPD will be reported in the IPD MA. For time  
253 to event outcomes such as mortality, pattern and extent of follow up will be checked. When needed,  
254 additional follow up with original authors will be conducted to rectify any imbalances as far as  
255 possible.

256

**257 Synthesis methods**

258 All outcomes will be analysed according to the intention to treat principle and using a one-step  
259 approach for IPD MA. In the one-step approach, IPD will be modelled from all studies simultaneously  
260 using the generalised linear mixed model framework and the statistical model appropriate for the  
261 type of outcome being analysed (i.e., logistic regression for binary outcome data, linear regression  
262 for continuous outcome data, and Cox-regression for time to event data). A random treatment effect  
263 term will be added to the model and all other parameters (intercepts, prognostic factor effects and  
264 residual variances) will be stratified by trial to account for the clustering of patients within studies.  
265 Maximum likelihood with quadrature will be used as estimation method and study-specific centering  
266 of the variables.(46) Variables potentially affecting the outcome that, despite randomisation, show  
267 baseline imbalances across treatment arms will be considered for adjustment based on the criteria  
268 for confounder selection by VanderWeele and Shpitser.(47-50) Procedure duration is considered an  
269 important proxy for the complexity of the procedure and will also be considered for adjustment  
270 despite being measured during the exposure.(49, 50) We assume that the FiO<sub>2</sub> used does not affect  
271 procedure duration. Benjamini-Hochberg correction will be used to account for multiple testing for  
272 the primary and secondary outcomes when appropriate.(51)

273

**274 Exploration of variation in effects**

1  
2  
3 275 To explore the causes of heterogeneity and identify factors modifying the effects of high  
4  
5 276 intraoperative FiO<sub>2</sub>, we will perform pre-specified subgroup analyses by extending the one-step  
6  
7 277 meta-analysis framework to include treatment-covariate interaction terms. Subgroups will be  
8  
9 278 defined according to mean core temperature (<35°C), mean net fluid supplementation  
10  
11 279 (<15ml/kg/hr), use of mechanical ventilation, use of nitrous oxide, use of preoperative antibiotic  
12  
13 280 prophylaxis, and procedure duration (>2.5h). All subgroup variables have been proposed as effect  
14  
15 281 modifiers in previous studies and have a plausible biological substantiation.(52-63) Cut-offs are  
16  
17 282 driven by previously reported data.(52-63) Treatment-covariate interaction terms p <0.05 will be  
18  
19 283 considered statistically significant. Dose-response variation will be explored by total O<sub>2</sub> exposure  
20  
21 284 duration for each primary outcome. All exploratory analysis will be interpreted with caution  
22  
23 285 considering the limited power and potential of type 1 error when multiple interactions are tested.  
24  
25 286

286

### 287 **Additional analysis**

288 A sensitivity analysis will be conducted to test the impact of excluding trials using N<sub>2</sub>O as a carrier gas  
289 on the pooled effect estimate. Further, the choice of SSI definition will be evaluated in a sensitivity  
290 analysis applying the CDC definition as the primary outcome. In the case of exclusion of trials due to  
291 concerns on IPD integrity, a sensitivity analysis will be conducted to test the impact of including the  
292 concerning data on the pooled effect estimate. When multiple imputation is performed, a complete  
293 case analysis will also be conducted. In studies with sufficiently detailed data on the intervention, all  
294 analyses will also be conducted according to the per-protocol principle after adjustment for  
295 confounding factors due to incomplete adherence to the assigned treatments or use of off-protocol  
296 concomitant therapies according to the variable selection principles described for the primary  
297 analysis. Per protocol treatment will be defined as an FiO<sub>2</sub> of 0.80 ± 0.05 for at least 75% of the  
298 ventilation time in the intervention group, and an FiO<sub>2</sub> smaller than 0.40 with a margin of 0.05, for  
299 75% in the control group. Patients requiring more oxygen for medical reasons, for example to  
300 maintain adequate saturation, after initial ventilation with an FiO<sub>2</sub> of 0.45 are exempted and not  
301 considered a protocol deviation. A sensitivity analysis will be conducted according to the two-step  
302 approach. All studies will be reanalysed separately, similarly to the one-step approach but without  
303 the term for trial clustering. The new aggregate data of each study will then be synthesised in a  
304 second step synthesising an overall estimate using maximum likelihood method followed by the  
305 Hartung-Knapp Sidik-Jonkman correction assuming random effects.(64) Between-study variance will  
306 be evaluated using  $\tau^2$ ; in addition, the Chi<sup>2</sup> test for heterogeneity will be performed with p <0.100  
307 considered statistically significant. In the unlikely event that IPD will not be made available,

1  
2  
3 308 aggregate study data will be included in the analyses during step two. Any unforeseen challenge  
4 309 during the analysis or choice that leads to discussion in the steering group that cannot be resolved by  
5 310 consensus will also be subjected to sensitivity analysis. To assess robustness of the time to event  
6 311 outcomes a survival curve will be compared to the univariable version of the Cox proportional  
7  
8 312 hazards regression analysis.  
9  
10  
11

12 313

#### 14 314 **Certainty of the cumulative estimate**

16  
17 315 The Grading of Recommendations Assessment Development and Evaluation (GRADE) working group  
18 316 methodology will be used to assess the overall quality of evidence for the following domains: risk of  
19 317 bias, unexplained inconsistency, indirectness, imprecision, publication bias, and magnitude of effect.  
20 318 Additional domains may be considered where appropriate. Optimal information size, defined as the  
21 319 number of participants needed for a single adequately powered trial, was calculated assuming a  
22 320 type-1 error ( $\alpha$ ) of 0.05, a type 2 error ( $\beta$ ) of 0.2 and a relative risk reduction of 0.25.<sup>(65)</sup> If a  
23 321 confidence interval failed to exclude appreciable benefit or harm, defined as a relative risk reduction  
24 322 or increase of 0.25, the quality of evidence will be downgraded regardless of the optimal information  
25 323 size.<sup>(65)</sup> The overall certainty will be classified using four levels: high, moderate, low, and very  
26 324 low.<sup>(66)</sup>  
27  
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#### 36 326 **Software**

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38  
39 327 Results will be processed using R 4.0.4.  
40  
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43 328

### 44 329 **ETHICS AND DISSEMINATION**

#### 46 330 **Ethical approval**

47  
48 331 Because this concerns a study on existing de-identified patient data, the medical research involving  
49 332 human subjects act does not apply and no formal medical ethics review is required.  
50  
51  
52

53 333

#### 55 334 **Dissemination**

56  
57 335 This protocol and the results of this study will be submitted to a peer-reviewed medical journal  
58 336 regardless of the outcome. The protocol will be submitted before the data is gathered and analysed.  
59  
60



337

**338 Competing interests**

339 S.W.J. reports receipt of grants from Photonics in Healthcare, Integra LifeSciences, and Ethicon  
340 outside the submitted. P.S.M. reports receipt of grants or contracts from the Australian National  
341 Health and Medical Research Council (NHMRC), Practitioner Fellowship and Projects Grants, payment  
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346 Monitoring Board or Advisory Board for the Australian Kidney Trials Research Network (INCH-HD,  
347 IMPEDE, TEQCH-PD, PHOSPHATE, BEST Fluids, N3RO trial, CKD-FIX, IMPROVE-FIX). R.G. reports  
348 participation on Steering Committee for the IntuBot Innosuisse Projekt and has a leadership role as  
349 ERC Director of Guidelines and ILCOR, and ILCOR Task Force Chair on Education, Implementation and  
350 Team, and Treasurer of European Airway Management society, and reports receipt without any  
351 payment of airway equipment for the research of the following: Intersurgical, Karl Storz, Verathon  
352 Inc, Aircraft Medical, Prodol Meditec, Venner Medical, Kingsystems, Medtronic, Ambu, VBM,  
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355 Safety Monitoring Board of Advisory Board in Directedsystems, Potrero Medical and BioAgel  
356 Laboratories. J.M. reports voluntary participation as a panellist in the updated WHO Guidelines on  
357 high vs low FiO<sub>2</sub> in 2018 and voluntary co-investigator in the PENGUIN trial of high versus low FiO<sub>2</sub>  
358 for SSI prevention in abdominal surgery in low- and middle-income settings with GlobalSurg  
359 Collaborative. M.G.W.D. reports participation on a Data Safety Monitoring Board or Advisory Board  
360 for the following trials: DANCE, SPHINX, ICONIC, SAFE, PACER, LEARNS, RECAP, and BIOPEX2. C.F.  
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367 Pharma outside the submitted work, institutional payment or honoraria for lectures, presentations,  
368 speakers bureaus, manuscript writing or educational events from CSL Behring outside the submitted  
369 work, and has a leadership role in DGAI, ISAP and IARS (Anaesthesia and Analgesia). The other  
370 authors declare no conflict of interest.

1  
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10 37411  
12 375 **Contributions**13  
14  
15 376 SJ conceived the study. SJ, MH, MB and RH secured funding for the study. SJ, MH, MB, MD, and RH  
16 377 designed the study, drafted the study protocol and provided statistical expertise. RH and MZ  
17  
18 378 provided input for the literature search and will coordinate the assembly of the data and perform the  
19  
20 379 screening, inclusion and assessment of risk of bias. RW, CM, KL, PM, AF, RG, OA, AK, DS, JM, KP, JB,  
21  
22 380 CF, GG, CS, DM, MC, PT, JO and BA provided substantial contributions to the study design, provided  
23  
24 381 critical feedback and approved the final version of the study protocol. All authors compliant with  
25  
26 382 their responsibilities according to the research protocol, meet authorship criteria as defined by the  
27  
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29 384

30  
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35  
36 38737  
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40 389 Data will be made available upon reasonable request and review and approval of all collaborators.  
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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	Reported on page
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplement01

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I <sup>2</sup> , Kendall's τ)	12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12-13

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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