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Apnoeic oxygenation with nasal cannula oxygen at different flow rates in anaesthetised patients – a study protocol for a randomised-controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025442
Article Type:	Protocol
Date Submitted by the Author:	23-Jul-2018
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Keywords:	apnoeic oxygenation, general anaesthesia, hypercapnia, nasal cannula

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Manuscripts

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3 1 **Apnoeic oxygenation with nasal cannula oxygen at different flow rates**
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9 3 **controlled trial**
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37 14 Short title: Physiology Regarding Apnoeic Oxygenation (PHARAO) using nasal cannula
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39 15 therapy at different flow rates
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50 20 Key Words: apnoeic oxygenation, general anaesthesia, hypercapnia, nasal cannula

52 21
53 22 Word count: 3324

55 23 Word count abstract: 303

24 **ABSTRACT**

25 **Introduction**

26 Apnoeic oxygenation using nasal high-flow oxygen delivery systems with heated and
27 humidified oxygen has recently gained popularity in the anaesthesia community. It has
28 been shown to allow a prolonged apnoea time of up to 65 minutes as CO₂ increase was
29 far slower compared to previously reported data from CO₂ increase during apnoea. A
30 ventilatory exchange due to the high nasal oxygen flow was proposed explaining that
31 phenomenon. However, recent studies in children did not show any difference in CO₂
32 clearance comparing high-flow to low-flow oxygen. To investigate this ventilatory
33 exchange in adults, we plan this study comparing different oxygen flow rates and the
34 increase of CO₂ during apnoea. We hypothesise that CO₂ clearance is non-inferior when
35 applying low oxygen flow rates.

36 **Methods and analysis**

37 In this single-centre, single-blinded, randomized-controlled trial we randomly assign 100
38 patients planned for elective surgery to either control (oxygen 70l/min, airway opened by
39 laryngoscopy) or one of three intervention groups: oxygen 70l/min, or 10l/min, or 2l/min,
40 all with jaw thrust to secure airway patency. After anaesthesia induction and
41 neuromuscular blockage, either one of the interventions or the control will be applied
42 according to randomisation. Throughout the apnoea period, we will measure the increase
43 of transcutaneous pCO₂ (tcpCO₂) until any one of the following criteria is met: time = 15
44 minutes, SpO₂ < 92%, tcpCO₂ > 10.67kPa, art. pH < 7.1, K⁺ > 6.0 mmol/l. Primary outcome is
45 the mean tcpCO₂ increase in kPa/min.

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3 46 **Ethics and dissemination**
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5 47 After Cantonal Ethic Committee of Bern approval (ID 2018-00293, 22.03.2018) all study
6
7 48 participants will provide written informed consent. Patients vulnerable towards hypoxia
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10 49 or hypercarbia are excluded. Study results will be published in a peer-reviewed journal
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12 50 and presented at national and international conferences.
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15 51 **Trial registration**
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18 52 This study was registered on www.clinicaltrials.gov (NCT03478774) and the Swiss Trial
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20 53 Registry KOFAM (SNCTP000002861).
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55 STRENGTHS AND LIMITATIONS OF THIS STUDY

- 56 ▪ Extensive measurements and rigorous study design on comparable groups
57 allows analysis of the physiologic response to apnoeic oxygenation and
58 increasing CO₂ over time to assess a possible ventilatory effect of nasal oxygen
59 delivery.
- 60 ▪ Randomised, direct comparison of different nasal oxygen flow rates to
61 investigate their subsequent effect on CO₂ clearance over time in order to
62 determine the existence of a ventilatory effect.
- 63 ▪ For this “proof of effect” study, we include an essentially healthy study
64 population, which limits the transfer of results to patients with compromised
65 lung function or other major health issues.
- 66 ▪ Due to obvious differences in devices, anaesthetists cannot be blinded but it is
67 unlikely, that this will influence our primary outcome (CO₂ increase).

69 INTRODUCTION

70 Apnoeic oxygenation was first scientifically described by F. Volhard in 1908.¹ He
71 sufficiently oxygenated paralysed dogs through a glass tube placed in the trachea
72 without ventilation or respiratory movements. This only worked when 100% oxygen was
73 provided, which was later confirmed by others.²⁻⁴ In 2015, Patel et al. applied the same
74 principle to high-flow nasal oxygenation (HFNO), but administered heated, humidified
75 oxygen through nasal cannulas at very high flow rates up to 70 l/min in adults. The study
76 group observed a lower-than-expected rise of CO₂ using this method. This allowed
77 extension in apnoea time of patients who underwent general anaesthesia, even if they
78 had difficult airways.⁵ A new term for this oxygen delivery technique was thus created by
79 the study authors: THRIVE – transnasal humidified rapid-insufflation ventilatory
80 exchange. The ventilatory effect is thought to happen by turbulences caused by the high-
81 flow oxygen combined with the open mouth. These turbulences are believed to continue
82 down through the trachea into the alveoli, which ultimately leads to a wash out of CO₂.
83 Thereafter, several studies described prolonged apnoea time without desaturation up to
84 65 minutes during continuous laryngoscopy or bronchoscopy⁵⁻⁷, or for laryngeal or
85 tracheal surgery, where a tracheal tube would block the surgical field.⁸
86 However, the physiologic effects of HFNO remain insufficiently understood. Especially
87 the ventilatory effect has not yet been proven with sufficient data. Rising CO₂ levels are
88 the time limitation for HFNO, as they result in effects such as marked acidosis, increased
89 blood pressure, increased heart rate and increased cerebral blood flow.⁹⁻¹¹ During the last
90 century, PaCO₂ increase in apnoeic patients has been repeatedly studied. According to
91 that literature, PaCO₂ increases rapidly during the first minute of apnoea (1.6-1.73 kPa),
92 while afterwards a linear increase of about 0.4-0.67 kPa/min sets in.^{4 11-13} This physiologic

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3 93 CO₂ increase is faster than the one described using HFNO, which is only about 0.15-0.24
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5 94 kPa/min.

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7 95 Recently, two studies showed that apnoeic oxygenation using low flow rates in children
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9 96 is equal to HFNO^{14 15} without difference regarding CO₂ increase. Given this new evidence,
10
11 97 it seems possible that nasal oxygen flow rate has little to no impact on CO₂ clearance in
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13 98 adults as well.

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16 99 Therefore, we will compare different nasal flow rates of 100% oxygen (70 l/min, 10 l/min
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18 100 and 2 l/min) with HFNO (70l/min). Furthermore, we will apply continuous laryngoscopy to
19
20 101 HFNO and compare it to normal jaw thrust in the intervention groups in order to
21
22 102 determine how mouth opening influences CO₂ clearance.

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25 103 We hypothesise that any of our intervention groups (70 l/min, 10 l/min and 2 l/min, all with
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27 104 jaw thrust) is non-inferior to the control group (HFNO with oxygen 70 l/min using
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29 105 continuous laryngoscopy).

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107 **METHODS AND ANALYSIS**

108 This study was approved by the Cantonal Ethics Committee of Bern (ID 2018-00293) and is
109 registered on www.clinicaltrials.gov (NCT03478774) as well as on the Swiss Trial Registry
110 KOFAM (SNCTP000002861).

111 **Aims**

112 Our primary aim is to better understand possible ventilatory effects during apnoeic
113 oxygenation using nasal cannulas at different flow rates. Our secondary aim is to
114 demonstrate the physiologic effects of increased CO₂ levels on human physiology during
115 general anaesthesia.

116 **Design**

117 This is a single-centre, single-blinded, prospective, randomised controlled trial at the Bern
118 University Hospital, Bern, Switzerland. After the study participant has enrolled in the
119 study by signing the informed consent, he or she will be randomised using a computer-
120 generated sequence. Once general anaesthesia is induced, and mask ventilation is
121 possible, the sealed envelope will be opened and oxygen flow will be provided according
122 to randomisation. Therefore, the participant is blinded towards his or her group
123 allocation, but anaesthesiologists cannot be blinded, because devices clearly differ from
124 each other. Once randomised, the participant will stay in the allocated group for analysis,
125 even if another intervention is applied (intention-to-treat).

126 **Study population**

127 Possible participants will be screened for eligibility during their preoperative interview as
128 well as checking the surgical schedule. We will include adults (> 18 years of age), who will

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3 129 undergo elective surgery requiring general anaesthesia, with an American Society of
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5 130 Anesthesiologists (ASA) physical health status I-III, SpO₂ ≥ 96% breathing room air, and
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7 131 who provide written informed consent in German.

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10 132 Because we intent to study the impact of apnoeic oxygenation on accumulation of CO₂,
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12 133 we will exclude all patients who – through their underlying condition – could bias or
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14 134 influence the normal physiologic response. Also, for patient safety reasons we will
15
16 135 exclude patients that might be harmed due to study related effects or measurements.
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18 136 Specifically, we exclude:

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21 137 • Patients with risk factors for difficult airway (indication for flexible optic
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23 138 intubation, high risk of regurgitation or expected difficult mask ventilation);
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26 139 • Vulnerability towards hypoxaemia (known coronary heart disease, peripheral
27
28 140 occlusive arterial disease, known stenosis of the carotid or vertebral arteries,
29
30 141 anaemia or pregnancy);
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33 142 • Vulnerability towards hypercarbia (pulmonary arterial hypertension, increased
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35 143 intracranial pressure, intracranial surgery or hyperkalaemia);
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38 144 • Obstructive sleep apnoea, nasal obstruction, body-mass index < 16 kg/m² or > 35
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40 145 kg/m² or known, suspected cervical spine instability, neuromuscular disorder,
41
42 146 absent power of judgement, limited knowledge of German language, allergies
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44 147 towards any of the used agents.

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46
47 148 In order to further reduce potential bias, we will stratify randomisation according to
48
49 149 body-mass index (BMI) into three groups (16-25 kg/m², 25-30 kg/m² and 30-35 kg/m²) and
50
51 150 according to smoker status into four groups (non-smokers, non-daily smokers, daily
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53 151 smokers < 40 years of age, daily smokers > 40 years of age).

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3 152 Participants will be randomized in a 1:1:1:1 ratio (25 patients per group) using a computer-
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5 153 generated sequence which will be executed by a study nurse.
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8 154 **Sample size**

9
10 155 Patel et al. showed an increase of only 0.15 kPa/min with a flow rate of 70L O₂/min and
11
12 156 maximal mouth opening⁵. However, end-tidal CO₂ was measured, not transcutaneous
13
14 157 tcpCO₂. Gustafson et al. measured both, tcpCO₂ as well as arterial pCO₂, and found a CO₂-
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16 158 increase of 0.24 kPa/min, with a standard deviation of 0.05 kPa, which was almost twice
17
18 159 as high as the tcpCO₂ value.⁶ Using a non-inferiority design, a difference of means of 0.04
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20 160 kPa/min, a standard deviation of 0.05 kPa/min, an alpha of 0.025 (one-sided) with a power
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22 161 of 80%, revealed a necessary sample size of 22 patients per group. We will include 25
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24 162 patients in each group (100 patients in total) to account for possible drop outs. A
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26 163 difference of means of 0.04 kPa/min CO₂ increase would still only result in an absolute
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28 164 difference of 1.2 kPa CO₂ after 30 minutes of apnoea time. We defined this as measurable,
29
30 165 but still clinically acceptable and therefore non-inferior, because the normal range of
31
32 166 standard arterial pCO₂ is 1.3 kPa (4.7-6.0 kPa).¹⁶
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39 167 **Procedure**

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41 168 Once written informed consent is obtained and pregnancy is excluded in female patients
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43 169 by a pregnancy test, we will extract demographic data from the hospital information
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45 170 system. This includes data collected through routine patients' workflow: age, sex, weight,
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47 171 height, BMI, airway risk factors (Mallampati score, mouth opening, thyromental distance,
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49 172 reduced neck movement, retrognathia, and dental status) underlying diseases, smoking
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51 173 habits, ASA physical health status and indication for surgery.
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3 174 On the day of surgery, we will place an arterial cannula into the radial artery under local
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5 175 anaesthesia and draw arterial blood gases from the awake study participant breathing
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7 176 room air as a baseline measurement. We will install 1) standard anaesthesia monitoring:
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9 177 EKG, pulse oximetry, invasive blood pressure, end-tidal O₂, end-tidal CO₂, train of four
10
11 178 (TOF), Narcotrend[®] EEG (Narcotrend[®], Hannover, Germany), and 2) study related
12
13 179 monitoring: cardiac output (LiDCO, LiDCO Ltd, London, UK), thoracic electric impedance
14
15 180 tomography (EIT; using PulmoVista[®] 500, by Dräger, Lübeck, Germany), bilateral near-
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17 181 infrared spectroscopy (NIRS; using Niro-200NX, Hamamatsu, Tokyo, Japan) and
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19 182 transcutaneous pCO₂ und pO₂ (tcpO₂) measurement (both via TCM5, Radiometer,
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21 183 Thalwil, Switzerland). After that, we will start bag-mask pre-oxygenation until end-tidal
22
23 184 O₂ has reached 90%. Patients will receive a fentanyl bolus of 2µg/kg, and induction of
24
25 185 anaesthesia will begin using a target-controlled infusion (TCI, Schnider model using
26
27 186 syramed[®] µSP6000, Arcomed AG, Regensdorf, Switzerland) for propofol with a target
28
29 187 concentration of 3.0 µg/ml and TCI for remifentanil (Minto model using syramed[®]
30
31 188 µSP6000, Arcomed AG, Regensdorf, Switzerland) with a target concentration of 2.0
32
33 189 ng/ml. We will administer rocuronium 0.9mg/kg to achieve neuromuscular blockage.
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35 190 After induction, general anaesthesia will be confirmed by absent end-tidal CO₂ readings,
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37 191 unconsciousness and Narcotrend[®]-values in the target range of 40 to 60 under bag-mask
38
39 192 ventilation.
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41 193 Once mask ventilation with a tidal volume of 6ml/kg and a respiratory rate of 12/min is
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43 194 successful, the previously sealed envelope containing the randomisation will be opened
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45 195 and the intervention will be prepared according to group allocation.
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47 196 For safety reasons the experiment will be discontinued if mask ventilation is impossible
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49 197 even after full neuromuscular blockage and placement of an oropharyngeal tube. The
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3 198 anaesthetist in charge would then intubate the trachea and no study-related
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5 199 measurements would take place.

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7 200 For all patients who show a cardiovascular reaction (increase of heart rate and blood
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9 201 pressure) to the study procedure (laryngoscopy or jaw thrust), we will titrate remifentanil
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11 202 to effect. Once steady state has set in, we will no longer interfere with remifentanil.

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14 203 Whenever Narcotrend[®] values rise above our target range, propofol will be increased. We
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16 204 will not correct dropping Narcotrend[®] values as this is likely to be caused by increasing
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18 205 CO₂ and therefore an effect we want to measure.

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21 206 When complete neuromuscular blockage has been confirmed by TOF = 0, we will stop
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23 207 mask ventilation and start the apnoea time. Arterial blood gas will be drawn and analysed
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25 208 at start of apnoea.

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28 209 If assigned to the control group, the study participant will receive high-flow humidified
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30 210 oxygen at 70l/min via Optiflow[™] (Fisher&Paykel, Auckland, NewZealand) throughout the
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32 211 apnoea period while the glottis will be visualised by videolaryngoscopy (MacGrath[™] MAC,
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34 212 Medtronic, Dublin, Ireland), thus assuring airway patency. If assigned to one of the
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36 213 intervention groups, we will apply jaw thrust and one of the following flow rates: 1) high-
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38 214 flow humidified oxygen at 70l/min via Optiflow[™]; 2) medium-flow humidified oxygen at
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40 215 10l/min (Carbamed digiflow, Switzerland; Aquapak[®] Hudson RCI[®], Teleflex[®], Wayne,
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42 216 Pennsylvania, USA; O2Star[™] nasal cannula curved, Dräger, Lübeck, Germany); or 3) low-
43
44 217 flow humidified oxygen at 2l/min (Carbamed digiflow, Switzerland; Aquapak[®] Hudson
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46 218 RCI[®], Teleflex[®], Wayne, Pennsylvania, USA; O2Star[™] nasal cannula curved, Dräger,
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48 219 Lübeck, Germany).

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51 220 During jaw thrust, upper airway patency will be visually confirmed by a nasopharyngeal
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53 221 fiberscope (EF-N slim, Acutronic, Hirzel, Switzerland).¹⁷ Only if the airway is obstructed,

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3 222 we will insert an oropharyngeal airway tube (Guedel airway, Intersurgical[®], Workingham,
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5 223 Berkshire, UK). We will not assess the degree of opening, as this would not have any
6
7 224 direct consequences for the study.
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9
10 225 During apnoea time, we will continuously measure invasive arterial blood pressure, pulse
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12 226 oximetry and EKG as part of standard monitoring. Furthermore, we will continuously
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14 227 measure tcpCO₂, tcpO₂ by applying a probe to the patient's chest, two fingers below the
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16 228 clavicle; depth of anaesthesia (Narcotrend[®]); bilateral brain oxygenation (NIRS); cardiac
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18 229 output by pulse contour analysis; and ventilation distribution changes by thoracic
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20 230 electrical impedance tomography. For this, resulting potential differences are measured,
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22 231 and impedance distribution sampled at 30 Hz will be calculated by an automated
23
24 232 linearized Newton-Raphson reconstruction algorithm¹⁸. Relative change in end-expiratory
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26 233 lung impedance (EELI) and measures of ventilation inhomogeneity such as the global
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28 234 inhomogeneity index (GI) will be calculated as described previously, using customised
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30 235 software (Matlab R2013a, The MathWorks Inc., Nattick, MA, USA).^{19,20}
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35 236 Furthermore, we will take arterial blood samples at the onset of apnoea, one minute after
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37 237 apnoea, and thereafter every two minutes to perform blood gas analysis (total of max. 10
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39 238 measurements). These blood samples will be analysed for PaO₂, SaO₂, PaCO₂, pH,
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41 239 bicarbonate and potassium.
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44 240 During the induction of anaesthesia, potential hypotension due to the anaesthetic drugs
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46 241 will be counteracted with a continuous infusion of norepinephrine. Thereafter, steady
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48 242 state will set in and any change in blood pressure is due to the vasoactive effect of CO₂.
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50 243 As we want to measure these effects we will no longer interfere with blood pressure,
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52 244 except for persisting hypotension.
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3 245 The experiment will end when any of the following criteria is met: SpO₂ <92%, p_tcCO₂
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5 246 >10.67 kPa, pH <7.1, K⁺ >6.0 mmol/l, t = 15 minutes. Thereafter the trachea will be
6
7 247 intubated according to the decision of the attending anaesthetists. With that the pre-
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9 248 surgical part of the study will end.
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11 249 Study participants will either be visited on the first postoperative day or contacted by
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13 250 phone to ask about the quality of recovery.²¹ This includes ability to breathe easily, feeling
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15 251 rested, being able to enjoy food, getting support from hospital doctors and nurses as well
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17 252 as any pain, nausea and vomiting, feeling worried or anxious, or feeling sad or depressed.
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19 253 Furthermore, we ask specifically for pain localised in the patient's throat, mandibular
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21 254 joint, or head; nasal dryness; lip injuries; dental damages; other injuries; or any other
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23 255 discomfort or complication. For assessing the severity of complications, we will use a
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25 256 (modified) visual analogue scale (VAS), where 0 is no pain (or discomfort), and 10 is
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27 257 maximum pain (or discomfort). We will also assess all injuries obtained during airway
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29 258 management and the study period. After this interview, no further data will be acquired,
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31 259 and the study ends.
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38 260 **Objectives**

39 261 **Primary objective**

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41 262 Our primary objective is to measure the increase of mean transcutaneous CO₂ over time
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43 263 in kPa/min and to determine the influence of nasal oxygen flow rate (70l/min, 10l/min and
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45 264 2l/min) and the presence of an open mouth (jaw thrust vs. continuous laryngoscopy).
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50 265 Secondary outcomes are: lowest O₂ saturation; changes in end-expiratory lung
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52 266 impedance, which will help quantify the degree of atelectasis after intubation; changes in
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54 267 cerebral perfusion using NIRS, and influence of increasing CO₂ on cardiac output and
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56 268 systemic blood pressure.
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269 **Statistical plan**

270 Distribution of data will be checked for normality using qq-plots and the Shapiro-Wilks
271 analysis using Stata (StataCorp LLC, College Station, Texas, USA). Normal distributed data
272 will be presented as means and standard deviation, otherwise median and interquartile
273 range will be used. Proportions will be presented as numbers and percentage. Analytical
274 statistics uses Mann-Whitney u-test and Student's t-test, according distribution, or
275 ANOVA and Kruskal-Wallis for multiple group comparisons. Each of the groups will a-
276 priory be compared to the control group independently, therefore no correction for
277 multiple comparisons will have to be used. Other multiple comparisons and any
278 subgroup-analyses will be performed using appropriate correction factors. Proportions
279 will be compared by Chi-square test or Fisher's exact test. As sensitivity analyses, we will
280 do regression analyses, using mixed effects linear regressions. All statistical analyses will
281 be performed on an intention-to-treat basis. A $p < 0.05$ will be considered as statistically
282 significant.

283 **Patient involvement**

284 No patients or patient representatives were involved in the design of this trial.

285

286 ETHICS AND DISSEMINATION

287 This study will be conducted in accordance with the ICH GCP Note for Guidance on Good
288 Clinical Practise and local regulations with approval of the Cantonal Ethics Committee
289 Bern, following the Swiss law for human research.²² The ethics committee already
290 approved our study (ID 2018-00293), including the safety end points. A drop in O₂-
291 saturation < 92% allows for timely securing the airway without risk of hypoxic damages of
292 the study participants. Furthermore, prior publications suggest it to be very likely that all
293 groups maintain stable O₂-saturation throughout the maximum apnoea time of 15
294 minutes.^{23 24} Rising CO₂ levels could lead to acidosis; therefore, patients vulnerable to
295 hypercarbia are excluded preliminarily (see section *study population*). As routinely stated
296 in the protocol for the ethics committee, the study can be terminated prematurely if new
297 evidence suggesting severe disadvantage or increased morbidity will arise during the
298 study period.

299 All study data will be directly recorded in the CRF, which should also be considered being
300 source data. These data will be transferred into the departmental research
301 documentation system – LabKey (LabKey Software, Seattle, WA, USA, version 14.3). All
302 study data will be archived for a minimum of 10 years after study termination or
303 premature termination of the clinical trial.

304 Data will be transferred into a secure, web-based data integration platform and
305 controlled independently by two members of the study team. Additionally, data are
306 double-checked by comparing the screening records with the digital anaesthesia
307 documenting system of the hospital.

308 A study nurse otherwise not involved in the study will be in charge of data monitoring
309 and auditing after every 20 patients.

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3 310 Important modifications to the protocol will have to reported to the ethics committee.
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5 311 Both, the principal investigator and sponsor investigator will have access to the final trial
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7 312 data set. Other researchers may be granted access to the dataset to answer scientific
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9 313 questions.
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11 314 Results will be presented at national and international scientific meetings and will be
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13 315 published in a peer-reviewed medical journal.
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16 17 316 **Informed Consent** 18

19
20 317 In order to be eligible for the study, all patients have to sign an ethics committee
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22 318 approved informed consent form. All potential risks and benefits will be thoroughly
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24 319 explained by study personnel and the patient will be given enough time to consider his or
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26 320 her study participation.
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322 DISCUSSION

323 Humidified high-flow nasal oxygenation is a widely used therapy in intensive care for both
324 adults and paediatric spontaneously breathing patients. The new use in patients under
325 general anaesthesia has revitalized the old concept of apnoeic oxygenation. Its use in
326 anaesthesiology spreads from oxygenating an awake patient, to pre-oxygenation, as well
327 as to apnoeic oxygenation during rapid-sequence intubation (RSI), or during micro
328 laryngoscopy, and bronchoscopy. More and more applications for humidified HFNO or
329 THRIVE are emerging and they show great potential.

330 However, there is only limited evidence explaining physiologic changes during HFNO,
331 especially the proposed mechanism of CO₂ elimination by a ventilatory effect in
332 anaesthetised patients. It remains unknown how different flow rates affect CO₂ clearance
333 and if a minimal flow rate (of 2l/min) is able to maintain oxygenation over 15 minutes.
334 There are a few studies suggesting lower flow rates could also be effective.^{23 24} However,
335 no prospective study compared high flow to low flow so far; and it has not yet been
336 determined how flow rate influences CO₂ clearance. As high CO₂ levels have a multitude
337 of effects, such as pulmonic arterial vasoconstriction, acidosis, and hyperkalaemia, a
338 better understanding of CO₂ clearance could lead to the definition of contraindications or
339 safety measurements for humidified HFNO/THRIVE, especially for longer apnoea periods
340 (e.g. during micro laryngoscopy).

341 It is not known, if changes of thoracic electric impedance tomography in anaesthetised
342 patients are similar to those in awake patients.²⁵ For example, it is already known that
343 end-expiratory lung impedance (EELI) is increased in awake patients. This is probably due
344 to a higher pharyngeal pressure observed in patients with HFNO who breath
345 spontaneously. The effect has never been evaluated in anaesthetised patients.^{26 27}

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3 346 Also, haemodynamic changes during apnoeic oxygenation and under increasing PaCO₂
4
5 347 have not yet been investigated rigorously. We only found studies describing increased
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7 348 PaCO₂ and its influence on cardiac output and brain perfusion in awake patients and
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9 349 healthy volunteers^{9 10 28}. It is very likely that anaesthetised patients have a different
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11
12 350 reaction due to the vasodilatory effect of most anaesthetic drugs, which could very easily
13
14 351 overweigh the vasoconstrictive effects of increased CO₂ levels.

15
16 352 Overall, knowledge of the underlying physiological mechanisms during HFNO in
17
18 353 anaesthetised patients is still very limited. This study investigates under rigorously
19
20 354 controlled circumstances the concept of humidified HFNO on prolonged apnoea time,
21
22 355 presumably without desaturation. With our findings, we hope to improve airway
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24 356 management safety as this study enables the medical community to better understand
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26 357 the physiology behind apnoeic oxygenation and the influence of different nasal flow
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28 358 rates on CO₂ clearance. Our study's extensive setup also allows us to measure the effects
29
30 359 of increased CO₂ on cerebral perfusion and cardiac output.

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33 360 If low-flow oxygen administration with standard nasal cannula is non-inferior compared
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35 361 to high-flow humidified HFNO, it could have direct clinical impact. Oxygen and standard
36
37 362 nasal cannula are ubiquitously available and it will be hard to argue against apnoeic
38
39 363 oxygenation during routine intubation. Especially for rapid sequence intubation (RSI) and
40
41 364 other emergency airway procedures, apnoeic oxygenation may be – and perhaps should
42
43 365 be – performed using a standard nasal cannula at a low flow rate.²⁹ For patients at risk of
44
45 366 desaturation, this has the potential to reduce complication of hypoxia and therefore will
46
47 367 improve patient safety with little additional resources.

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49 368 Due to the design of this trial, we will not be able to determine the influence of
50
51 369 pathophysiologic alterations of patients' underlying diseases, as we exclude severely ill

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3 370 patients from this study for safety reasons. Furthermore, although we include 100
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5 371 patients in this trial, we may still end up with an uneven distribution of risk factors. To
6
7 372 minimize this bias, we stratify according to BMI and smoking status, as we assume these
8
9 373 factors to be the most influential on our primary outcome.

11 374 Provided all groups have a similar CO₂ clearance, the inclusion of 100 patients will provide
12
13
14 375 a solid foundation to detect even smaller haemodynamic, thoracic EIT, or EEG changes.
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16 376 Nevertheless, all results are to be considered for anaesthetised patients using propofol
17
18 377 and remifentanyl. We do not know how other anaesthetic drugs would potentially
19
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21 378 interfere with patients' physiology.

23 379 All this leads us to the conclusion that this study will be able to provide highly interesting
24
25
26 380 results and urgently needed evidence on physiologic changes during HFNO and CO₂
27
28 381 increase in adult patients during apnoeic oxygenation. We will find an answer to our
29
30 382 question, if the application of nasal oxygen at 70l/min, 10l/min or 2l/min using jaw thrust is
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33 383 non-inferior compared to nasal oxygen at 70l/min using continuous laryngoscopy in
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35 384 regard to CO₂ clearance in anaesthetised patients.

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3 386 **AUTHOR CONTRIBUTIONS**
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6 387 RG and LT conceived the study. RG, LT, FS, HK, and TR wrote the study protocol. RG, LT,
7
8 388 FS and HK developed the practical approach to measurement and recruitment. LT
9
10 389 designed the statistical analysis plan for the protocol. All authors critically reviewed this
11
12 390 manuscript and agree to its final form.
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16 391 **FUNDING STATEMENT**
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19 392 This research is funded by a departmental research grant assigned to LT. For this study,
20
21 393 Fisher & Paykel (Auckland, New Zealand) provide all necessary breathing circuits and
22
23 394 nasal cannulas without costs. Fisher & Paykel are neither involved in the design nor have
24
25 395 they any influence on the data analysis and the presentation of results or their publication
26
27 396 nor do the study authors have any financial or any other collaborations with Fisher &
28
29 397 Paykel.
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34 398 **COMPETING INTERESTS**
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37 399 None declared.
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40 400 **FIGURE LEGENDS**
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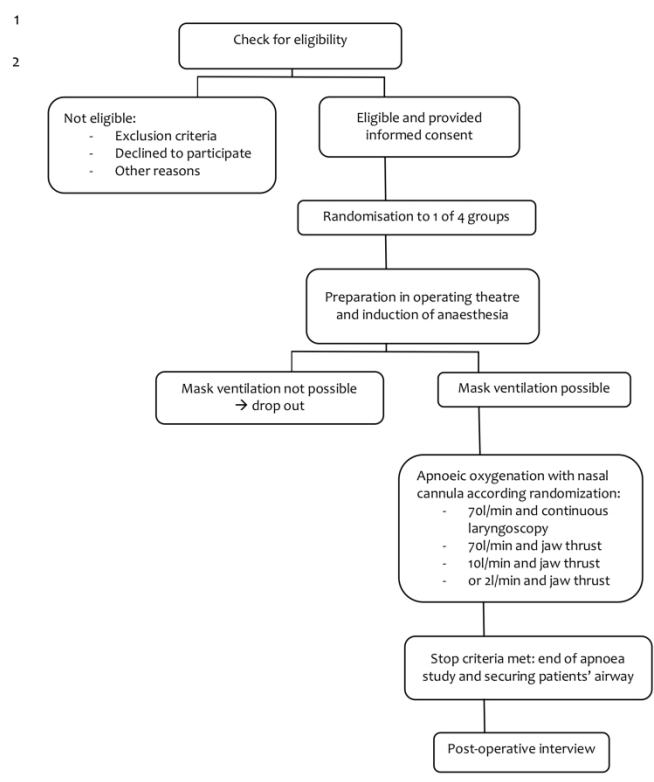
43 401 Figure 1: Study flow chart
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Figure 1

296x419mm (300 x 300 DPI)

BMJ Open

Apnoeic oxygenation with nasal cannula oxygen at different flow rates in anaesthetised patients – a study protocol for a non-inferiority randomised-controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025442.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Mar-2019
Complete List of Authors:	Theiler, Lorenz; Inselspital Bern Universitätsklinik für Anesthesiologie und Schmerztherapie Schneeberg, Fabian; Inselspital Bern Universitätsklinik für Anesthesiologie und Schmerztherapie Riedel, Thomas; Kantonsspital Graubünden Kaiser, Heiko; Inselspital Bern Universitätsklinik für Anesthesiologie und Schmerztherapie Riva, Thomas; Inselspital Bern Universitätsklinik für Anesthesiologie und Schmerztherapie Greif, Robert ; Inselspital Universitätsspital Bern, Anaesthesiology and PAin Therapy
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	apnoeic oxygenation, general anaesthesia, hypercapnia, nasal cannula

SCHOLARONE™
Manuscripts

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4 1 **Apnoeic oxygenation with nasal cannula oxygen at different flow rates**
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7 2 **in anaesthetised patients – a study protocol for a non-inferiority**
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10 3 **randomised-controlled trial**
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41 15 Short title: Physiology Regarding Apnoeic Oxygenation (PHARAO) using nasal cannula
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44 16 therapy at different flow rates
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56 21 Key Words: apnoeic oxygenation, general anaesthesia, hypercapnia, nasal cannula

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59 23 Word count: 4346
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24 Word count abstract: 300

For peer review only

25 **ABSTRACT**

26 **Introduction**

27 Apnoeic oxygenation using nasal high-flow oxygen delivery systems with heated and
28 humidified oxygen has recently gained popularity in the anaesthesia community. It has
29 been shown to allow a prolonged apnoea time of up to 65 minutes as CO₂ increase was far
30 slower compared to previously reported data from CO₂ increase during apnoea. A
31 ventilatory exchange due to the high nasal oxygen flow was proposed explaining that
32 phenomenon. However, recent studies in children did not show any difference in CO₂
33 clearance comparing high-flow to low-flow oxygen. To investigate this ventilatory
34 exchange in adults, we plan this study comparing different oxygen flow rates and the
35 increase of CO₂ during apnoea. We hypothesise that CO₂ clearance is non-inferior when
36 applying low oxygen flow rates.

37 **Methods and analysis**

38 In this single-centre, single-blinded, randomized-controlled trial we randomly assign 100
39 patients planned for elective surgery to either control (oxygen 70l/min, airway opened by
40 laryngoscopy) or one of three intervention groups: oxygen 70l/min, or 10l/min, or 2l/min, all
41 with jaw thrust to secure airway patency. After anaesthesia induction and neuromuscular
42 blockage, either one of the interventions or the control will be applied according to
43 randomisation. Throughout the apnoea period, we will measure the increase of
44 transcutaneous pCO₂ (tcpCO₂) until any one of the following criteria is met: time = 15
45 minutes, SpO₂ < 92%, tcpCO₂ > 10.67kPa, art. pH < 7.1, K⁺ > 6.0 mmol/l. Primary outcome is
46 the mean tcpCO₂ increase in kPa/min.

47 **Ethics and dissemination**

48 After Cantonal Ethic Committee of Bern approval (ID 2018-00293, 22.03.2018) all study
49 participants will provide written informed consent. Patients vulnerable towards hypoxia or
50 hypercarbia are excluded. Study results will be published in a peer-reviewed journal and
51 presented at national and international conferences.

52 **Trial registration**

53 This study was registered on www.clinicaltrials.gov (NCT03478774) and the Swiss Trial
54 Registry KOFAM (SNCTP000002861).

55

56 STRENGTHS AND LIMITATIONS OF THIS STUDY

- 57 ▪ Extensive measurements and rigorous study design on comparable groups
58 allows analysis of the physiologic response to apnoeic oxygenation and
59 increasing CO₂ over time to assess a possible ventilatory effect of nasal oxygen
60 delivery.
- 61 ▪ Randomised, direct comparison of different nasal oxygen flow rates to
62 investigate their subsequent effect on CO₂ clearance over time in order to
63 determine the existence of a ventilatory effect.
- 64 ▪ For this “proof of effect” study, we include an essentially healthy study
65 population, which limits the transfer of results to patients with compromised
66 lung function or other major health issues.
- 67 ▪ Due to obvious differences in devices, anaesthetists cannot be blinded but it is
68 unlikely, that this will influence our primary outcome (CO₂ increase).

70 INTRODUCTION

71 Apnoeic oxygenation was first scientifically described by F. Volhard in 1908.¹ He sufficiently
72 oxygenated paralysed dogs through a glass tube placed in the trachea without ventilation
73 or respiratory movements. This only worked when 100% oxygen was provided, which was
74 later confirmed by others.²⁻⁴ In 2015, Patel et al. applied the same principle to high-flow
75 nasal oxygenation (HFNO), but administered heated, humidified oxygen through nasal
76 cannulas at very high flow rates up to 70 l/min in adults. The study group observed a lower-
77 than-expected rise of CO₂ using this method. This allowed extension in apnoea time of
78 patients who underwent general anaesthesia, even if they had difficult airways.⁵ A new
79 term for this oxygen delivery technique was thus created by the study authors: THRIVE –
80 transnasal humidified rapid-insufflation ventilatory exchange. The ventilatory effect is
81 thought to happen by turbulences caused by the high-flow oxygen combined with the
82 open mouth. These turbulences are believed to continue down through the trachea into
83 the alveoli, which ultimately leads to a wash out of CO₂. Thereafter, several studies
84 described prolonged apnoea time without desaturation up to 65 minutes during
85 continuous laryngoscopy or bronchoscopy⁵⁻⁷, or for laryngeal or tracheal surgery, where a
86 tracheal tube would block the surgical field.⁸

87 However, the physiologic effects of HFNO remain insufficiently understood. Especially the
88 ventilatory effect has not yet been proven with sufficient data. Rising CO₂ levels are the
89 time limitation for HFNO, as they result in effects such as marked acidosis, increased blood
90 pressure, increased heart rate and increased cerebral blood flow.⁹⁻¹¹ During the last
91 century, PaCO₂ increase in apnoeic patients has been repeatedly studied. According to that
92 literature, PaCO₂ increases rapidly during the first minute of apnoea (1.6-1.73 kPa), while

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3 93 afterwards a linear increase of about 0.4-0.67 kPa/min sets in.^{4 11-13} This physiologic CO₂
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6 94 increase is faster than the one described using HFNO, which is only about 0.15-0.24 kPa/min.
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8 95 Recently, two studies showed that apnoeic oxygenation using low flow rates in children is
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10 96 equal to HFNO^{14 15} without difference regarding CO₂ increase. Given this new evidence, it
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13 97 seems possible that nasal oxygen flow rate has little to no impact on CO₂ clearance in adults
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15 98 as well.

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18 99 Therefore, we will compare different nasal flow rates of 100% oxygen (70 l/min, 10 l/min and
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20 100 2 l/min) with HFNO (70l/min). Furthermore, we will apply continuous laryngoscopy to HFNO
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23 101 and compare it to normal jaw thrust in the intervention groups in order to determine how
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25 102 mouth opening influences CO₂ clearance.

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27 103 We hypothesise that any of our intervention groups (70 l/min, 10 l/min and 2 l/min, all with
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30 104 jaw thrust) is non-inferior to the control group (HFNO with oxygen 70 l/min using
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32 105 continuous laryngoscopy) regarding mean transcutaneous CO₂ increase in kPa/min.
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107 **METHODS AND ANALYSIS**

108 This study was approved by the Cantonal Ethics Committee of Bern (ID 2018-00293) and is
109 registered on www.clinicaltrials.gov (NCT03478774) as well as on the Swiss Trial Registry
110 KOFAM (SNCTP000002861).

111 **Aims**

112 We want to better understand possible ventilatory effects during apnoeic oxygenation
113 using nasal cannulas at different flow rates and demonstrate the physiologic effects of
114 increased CO₂ levels on human physiology during general anaesthesia.

115 **Design**

116 This is a single-centre, single-blinded, prospective, non-inferiority randomised controlled
117 trial at the Bern University Hospital, Bern, Switzerland. After the study participant has
118 enrolled in the study by signing the informed consent, he or she will be randomised using
119 a computer-generated sequence. Once general anaesthesia is induced, and mask
120 ventilation is possible, the sealed envelope will be opened and oxygen flow will be
121 provided according to randomisation. Therefore, the participant is blinded towards his or
122 her group allocation, but anaesthesiologists cannot be blinded, because devices clearly
123 differ from each other. Once randomised, the participant will stay in the allocated group
124 for analysis, even if another intervention is applied (intention-to-treat).

125 **Study population**

126 Possible participants will be screened for eligibility checking the surgical schedule and we
127 invite them to participate during our pre-anaesthesia interview. To allow patients sufficient
128 time to consider participation, we contact eligible study participants the day before

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3 129 surgery. We will include adults (> 18 years of age), who will undergo elective surgery
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5 130 requiring general anaesthesia, with an American Society of Anesthesiologists (ASA)
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8 131 physical health status I-III, SpO₂ ≥ 96% breathing room air, and who provide written
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10 132 informed consent in German as this is the common language spoken in Bern, Switzerland.
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13 133 Because we intent to study the impact of apnoeic oxygenation on accumulation of CO₂,
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15 134 we will exclude all patients who – through their underlying condition – could bias or
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18 135 influence the normal physiologic response. Also, for patient safety reasons we will exclude
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20 136 patients that might be harmed due to study related effects or measurements. Specifically,
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23 137 we exclude:

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25 138 • Patients with risk factors for difficult airway (indication for flexible optic intubation,
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28 139 high risk of regurgitation or expected difficult mask ventilation);
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30 140 • Vulnerability towards hypoxaemia (known coronary heart disease, peripheral
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33 141 occlusive arterial disease, known stenosis of the carotid or vertebral arteries,
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35 142 anaemia or pregnancy);
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38 143 • Vulnerability towards hypercarbia (pulmonary arterial hypertension, increased
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41 144 intracranial pressure, intracranial surgery or hyperkalaemia);
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44 145 • Obstructive sleep apnoea, nasal obstruction, body-mass index < 16 kg/m² or > 35
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46 146 kg/m² or known, suspected cervical spine instability, neuromuscular disorder,
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49 147 absent power of judgement, limited knowledge of German language, allergies
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51 148 towards any of the used agents.

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53 149 In order to further reduce potential bias, we will stratify randomisation according to body-
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56 150 mass index (BMI) into three groups (16-25 kg/m², 25-30 kg/m² and 30-35 kg/m²) and
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59 151 according to smoker status into four groups (non-smokers, non-daily smokers, daily
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3 152 smokers < 40 years of age, daily smokers > 40 years of age). According to the BMI, smoking
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6 153 status and age group, the patient fits into one of the possible twelve strata. Within each
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8 154 strata, the groups are being randomised for the different flow rates. Participants will be
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11 155 randomized in a 1:1:1:1 ratio (25 patients per group) using a computer-generated sequence
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13 156 which will be executed by a study nurse.

16 157 **Sample size**

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19 158 Patel et al. showed an increase of only 0.15 kPa/min with a flow rate of 70L O₂/min and
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21 159 maximal mouth opening⁵. However, end-tidal CO₂ was measured, not transcutaneous
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23 160 tcpCO₂. Gustafson et al. measured both, tcpCO₂ as well as arterial pCO₂, and found a CO₂-
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25 161 increase of 0.24 kPa/min, with a standard deviation of 0.05 kPa, which was almost twice as
26
27 162 high as the tcpCO₂ value.⁶ Using a non-inferiority design, a difference of means of 0.04
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29 163 kPa/min, a standard deviation of 0.05 kPa/min, an alpha of 0.025 (one-sided) with a power
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31 164 of 80%, revealed a necessary sample size of 22 patients per group. We will include 25
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33 165 patients in each group (100 patients in total) to account for possible drop outs. A difference
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35 166 of means of 0.04 kPa/min CO₂ increase would still only result in an absolute difference of
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37 167 1.2 kPa CO₂ after 30 minutes of apnoea time. We defined this as measurable, but still
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39 168 clinically acceptable and therefore non-inferior, because the normal range of standard
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41 169 arterial pCO₂ is 1.3 kPa (4.7-6.0 kPa).¹⁶

42 170 **Procedure**

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45 171 Once written informed consent is obtained and pregnancy is excluded in female patients
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47 172 by a pregnancy test, we will extract demographic data from the hospital information
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49 173 system. This includes data collected through routine patients' workflow: age, sex, weight,
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51 174 height, BMI, airway risk factors (Mallampati score, mouth opening, thyromental distance,
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3 175 reduced neck movement, retrognathia, and dental status) underlying diseases, smoking
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6 176 habits, ASA physical health status and indication for surgery.
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8 177 On the day of surgery, we will place an arterial cannula into the radial artery under local
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10 178 anaesthesia and draw arterial blood gases from the awake study participant breathing
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13 179 room air as a baseline measurement. We will install 1) standard anaesthesia monitoring:
14
15 180 EKG, pulse oximetry, invasive blood pressure, end-tidal O₂, end-tidal CO₂, train of four
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17
18 181 (TOF), Narcotrend® EEG (Narcotrend®, Hannover, Germany), and 2) study related
19
20 182 monitoring: cardiac output (LiDCO, LiDCO Ltd, London, UK), thoracic electric impedance
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23 183 tomography (EIT; using PulmoVista® 500, by Dräger, Lübeck, Germany), bilateral near-
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25 184 infrared spectroscopy (NIRS; using Niro-200NX, Hamamatsu, Tokyo, Japan) and
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28 185 transcutaneous pCO₂ und pO₂ (tcpO₂) measurement (both via TCM5, Radiometer, Thalwil,
29
30 186 Switzerland). After that, we will start bag-mask pre-oxygenation until end-tidal O₂ has
31
32
33 187 reached 90%. Patients will receive a fentanyl bolus of 2µg/kg, and induction of anaesthesia
34
35 188 will begin using a target-controlled infusion (TCI, Schnider model using syramed® µSP6000,
36
37 189 Arcomed AG, Regensdorf, Switzerland) for propofol with a target concentration of 3.0
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40 190 µg/ml and TCI for remifentanyl (Minto model using syramed® µSP6000, Arcomed AG,
41
42 191 Regensdorf, Switzerland) with a target concentration of 2.0 ng/ml. We will administer
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44
45 192 rocuronium 0.9mg/kg to achieve neuromuscular blockage. After induction, general
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47
48 193 anaesthesia will be confirmed by absent end-tidal CO₂ readings, unconsciousness and
49
50 194 Narcotrend®-values in the target range of 40 to 60 under bag-mask ventilation.
51
52 195 Once mask ventilation with a tidal volume of 6ml/kg and a respiratory rate of 12/min is
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54
55 196 successful, the previously sealed envelope containing the randomisation will be opened
56
57 197 and the intervention will be prepared according to group allocation.
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3 198 For safety reasons the experiment will be discontinued if mask ventilation is impossible
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5
6 199 even after full neuromuscular blockage and placement of an oropharyngeal tube. The
7
8 200 anaesthetist in charge would then intubate the trachea and no study-related
9
10 201 measurements would take place.

12
13 202 For all patients who show a cardiovascular reaction (increase of heart rate and blood
14
15 203 pressure) to the study procedure (laryngoscopy or jaw thrust), we will titrate remifentanyl
16
17 204 to effect. Once steady state has set in, we will no longer interfere with remifentanyl.
18
19 205 Whenever Narcotrend® values rise above our target range, propofol will be increased. We
20
21 206 will not correct dropping Narcotrend® values as this is likely to be caused by increasing CO₂
22
23 207 and therefore an effect we want to measure.

24
25 208 When complete neuromuscular blockage has been confirmed by TOF = 0, we will stop mask
26
27 209 ventilation and start the apnoea time. Arterial blood gas will be drawn and analysed at start
28
29 210 of apnoea.

30
31 211 If assigned to the control group, the study participant will receive high-flow humidified
32
33 212 oxygen at 70l/min via Optiflow™ (Fisher&Paykel, Auckland, NewZealand) throughout the
34
35 213 apnoea period while the glottis will be visualised by videolaryngoscopy (MacGrath™ MAC,
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37 214 Medtronic, Dublin, Ireland), thus assuring airway patency. If assigned to one of the
38
39 215 intervention groups, one of the senior anaesthesia researchers will apply jaw thrust and
40
41 216 one of the following flow rates: 1) high-flow humidified oxygen at 70l/min via Optiflow™;
42
43 217 2) medium-flow humidified oxygen at 10l/min (Carbamed digiflow, Switzerland; Aquapak®
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45 218 Hudson RCI®, Teleflex®, Wayne, Pennsylvania, USA; O2Star™ nasal cannula curved, Dräger,
46
47 219 Lübeck, Germany); or 3) low-flow humidified oxygen at 2l/min (Carbamed digiflow,
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49 220 Switzerland; Aquapak® Hudson RCI®, Teleflex®, Wayne, Pennsylvania, USA; O2Star™ nasal
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51 221 cannula curved, Dräger, Lübeck, Germany) (see Figure 1).

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3 222 During jaw thrust, upper airway patency will be visually confirmed by a nasopharyngeal
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5 223 fiberscope (EF-N slim, Acutronic, Hirzel, Switzerland).¹⁷ Only if the airway is obstructed, we
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8 224 will insert an oropharyngeal airway tube (Guedel airway, Intersurgical[®], Workingham,
9
10 225 Berkshire, UK). We will not assess the degree of opening, as this would not have any direct
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12
13 226 consequences for the study.

14
15 227 During apnoea time, we will continuously measure invasive arterial blood pressure, pulse
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17 228 oximetry and EKG as part of standard monitoring. Furthermore, we will continuously
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19 229 measure tcpCO₂, tcpO₂ by applying a probe to the patient's chest, two fingers below the
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21 230 clavicle; depth of anaesthesia (Narcotrend[®]); bilateral brain oxygenation (NIRS); cardiac
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23 231 output by pulse contour analysis; and ventilation distribution changes by thoracic electrical
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25 232 impedance tomography. For this, resulting potential differences are measured, and
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27 233 impedance distribution sampled at 30 Hz will be calculated by an automated linearized
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29
30 234 Newton-Raphson reconstruction algorithm¹⁸. Relative change in end-expiratory lung
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32 235 impedance (EELI) and measures of ventilation inhomogeneity such as the global
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34 236 inhomogeneity index (GI) will be calculated as described previously, using customised
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36 237 software (Matlab R2013a, The MathWorks Inc., Nattick, MA, USA).^{19 20}

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38 238 Furthermore, we will take arterial blood samples at the onset of apnoea, one minute after
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40 239 apnoea, and thereafter every two minutes to perform blood gas analysis (total of max. 10
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42 240 measurements). These blood samples will be analysed for PaO₂, SaO₂, PaCO₂, pH,
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44 241 bicarbonate and potassium.

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46 242 During the induction of anaesthesia, potential hypotension due to the anaesthetic drugs
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48 243 will be counteracted with a continuous infusion of norepinephrine. Thereafter, steady
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50 244 state will set in and any change in blood pressure is due to the vasoactive effect of CO₂. As
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3 245 we want to measure these effects we will no longer interfere with blood pressure, except
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6 246 for persisting hypotension.

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8 247 The experiment will end when any of the following criteria is met: $SpO_2 < 92\%$, $p_{tC}CO_2 > 10.67$
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10 248 kPa, $pH < 7.1$, $K^+ > 6.0$ mmol/l, $t = 15$ minutes. Thereafter the trachea will be intubated
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12
13 249 according to the decision of the attending anaesthetists. With that the pre-surgical part of
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15 250 the study will end.

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18 251 Study participants will either be visited on the ward or contacted by phone on the first
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20 252 postoperative day in the morning to ask about the quality of recovery.^{21 22} This includes
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23 253 ability to breathe easily, feeling rested, being able to enjoy food, getting support from
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25 254 hospital doctors and nurses as well as any pain, nausea and vomiting, feeling worried or
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27
28 255 anxious, or feeling sad or depressed. Furthermore, we ask specifically for pain localised in
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30 256 the patient's throat, mandibular joint, or head; nasal dryness; lip injuries; dental damages;
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33 257 other injuries; or any other discomfort or complication. For assessing the severity of
34
35 258 complications, we will use a (modified) visual analogue scale (VAS), where 0 is no pain (or
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38 259 discomfort), and 10 is maximum pain (or discomfort). We will also assess all injuries
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40 260 obtained during airway management and the study period. After this interview, no further
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42 261 data will be acquired, and the study ends.

43 44 45 262 **Objectives**

46 47 48 263 **Primary outcome**

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52 264 Our primary outcome is to measure the increase of mean transcutaneous CO_2 over time in
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54 265 kPa/min and to determine the influence of nasal oxygen flow rate (70l/min, 10l/min and
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57 266 2l/min) and the presence of an open mouth (jaw thrust vs. continuous laryngoscopy).

58 59 267 **Secondary outcomes**

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3 268 Secondary outcomes are: lowest O₂ saturation; changes in end-expiratory lung impedance,
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6 269 which will help quantify the degree of atelectasis after intubation, and influence of
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8 270 increasing CO₂ on: cardiac output and systemic blood pressure, invasive arterial blood
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10 271 pressure, pulse oximetry and ECG as part of standard monitoring, tcpO₂, depth of
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12 272 anaesthesia, bilateral brain oxygenation (NIRS), arterial blood gas analysis (PaO₂, SaO₂,
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14 273 PaCO₂, pH, bicarbonate and potassium). Furthermore: postoperative pain, nausea and
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16 274 vomiting, feeling worried or anxious, or feeling sad or depressed, injurie or any other
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18 275 discomfort or complication.
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23 276 **Statistical plan**

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26 277 Distribution of data will be checked for normality using qq-plots and the Shapiro-Wilks
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28 278 analysis using Stata (StataCorp LLC, College Station, Texas, USA). For our primary outcome
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30 279 parameter, the rise of PtcCO₂, we will use a linear mixed model using groups and minutes.
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33 280 Normal distributed data will be presented as means and standard deviation, otherwise
34
35 281 median and interquartile range will be used. Proportions will be presented as numbers and
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37 282 percentage. Analytical statistics uses Mann-Whitney u-test and Student's t-test, according
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39 283 distribution, or ANOVA and Kruskal-Wallis for multiple group comparisons. Each of the
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41 284 groups will a-priory be compared to the control group independently, therefore no
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43 285 correction for multiple comparisons will have to be used. Other multiple comparisons and
44
45 286 any subgroup-analyses will be performed using appropriate correction factors.
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47 287 Proportions will be compared by Chi-square test or Fisher's exact test. As sensitivity
48
49 288 analyses, we will do regression analyses, using mixed effects linear regressions. All
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51 289 statistical analyses will be performed on an intention-to-treat basis. We will also include a
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53 290 per-protocol analysis in order to minimize bias for the standard treatment group. If the
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55 291 results of such an analysis are consistent with those from the intention-to-treat approach
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3 292 and if both lie below the non-inferiority threshold, the inference regarding non-inferiority
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6 293 is strengthened. A $p < 0.05$ will be considered as statistically significant.
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9 294 **Patient involvement**

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11 295 No patients or patient representatives were involved in the design of this trial.
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For peer review only

297 ETHICS AND DISSEMINATION

298 This study will be conducted in accordance with the ICH GCP Note for Guidance on Good
299 Clinical Practise and local regulations with approval of the Cantonal Ethics Committee Bern,
300 following the Swiss law for human research.²³ The ethics committee already approved our
301 study (ID 2018-00293), including the safety end points. A drop in O₂-saturation < 92% allows
302 for timely securing the airway without risk of hypoxic damages of the study participants.
303 Furthermore, prior publications suggest it to be very likely that all groups maintain stable
304 O₂-saturation throughout the maximum apnoea time of 15 minutes.^{24 25} Rising CO₂ levels
305 could lead to acidosis; therefore, patients vulnerable to hypercarbia are excluded
306 preliminarily (see section *study population*). As routinely stated in the protocol for the
307 ethics committee, the study can be terminated prematurely if new evidence suggesting
308 severe disadvantage or increased morbidity will arise during the study period.

309 All study data will be directly recorded in the CRF, which should also be considered being
310 source data. These data will be transferred into the departmental research
311 documentation system – LabKey (LabKey Software, Seattle, WA, USA, version 14.3). All
312 study data will be archived for a minimum of 10 years after study termination or
313 premature termination of the clinical trial.

314 Data will be transferred into a secure, web-based data integration platform and controlled
315 independently by two members of the study team. Additionally, data are double-checked
316 by comparing the screening records with the digital anaesthesia documenting system of
317 the hospital.

318 A study nurse otherwise not involved in the study will be in charge of data monitoring and
319 auditing after every 20 patients.

320 Important modifications to the protocol will have to reported to the ethics committee.

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3 321 Both, the principal investigator and sponsor investigator will have access to the final trial
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6 322 data set. Other researchers may be granted access to the dataset to answer scientific
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8 323 questions.

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10 324 Results will be presented at national and international scientific meetings and will be
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13 325 published in a peer-reviewed medical journal.

16 326 **Informed Consent**

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19 327 In order to be eligible for the study, all patients have to sign an ethics committee approved
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21 328 informed consent form. All potential risks and benefits will be thoroughly explained by
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24 329 study personnel and the patient will be given enough time to consider his or her study
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26 330 participation.

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DISCUSSION

Humidified high-flow nasal oxygenation is a widely used therapy in intensive care for both adults and paediatric spontaneously breathing patients. The new use in patients under general anaesthesia has revitalized the old concept of apnoeic oxygenation. Its use in anaesthesiology spreads from oxygenating an awake patient, to pre-oxygenation, as well as to apnoeic oxygenation during rapid-sequence intubation (RSI), or during micro laryngoscopy, and bronchoscopy. More and more applications for humidified HFNO or THRIVE are emerging and they show great potential.

However, there is only limited evidence explaining physiologic changes during HFNO, especially the proposed mechanism of CO₂ elimination by a ventilatory effect in anaesthetised patients. It remains unknown how different flow rates affect CO₂ clearance and if a minimal flow rate (of 2l/min) is able to maintain oxygenation over 15 minutes. There are a few studies suggesting lower flow rates could also be effective.^{24 25} However, no prospective study compared high flow to low flow so far; and it has not yet been determined how flow rate influences CO₂ clearance. As high CO₂ levels have a multitude of effects, such as pulmonic arterial vasoconstriction, acidosis, and hyperkalaemia, a better understanding of CO₂ clearance could lead to the definition of contraindications or safety measurements for humidified HFNO/THRIVE, especially for longer apnoea periods (e.g. during micro laryngoscopy).

It is not known, if changes of thoracic electric impedance tomography in anaesthetised patients are similar to those in awake patients.²⁶ For example, it is already known that end-expiratory lung impedance (EELI) is increased in awake patients. This is probably due to a higher pharyngeal pressure observed in patients with HFNO who breath spontaneously. The effect has never been evaluated in anaesthetised patients.^{27 28}

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2
3 356 Also, haemodynamic changes during apnoeic oxygenation and under increasing PaCO₂
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6 357 have not yet been investigated rigorously. We only found studies describing increased
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8 358 PaCO₂ and its influence on cardiac output and brain perfusion in awake patients and
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10 359 healthy volunteers^{9 10 29}. It is very likely that anaesthetised patients have a different
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13 360 reaction due to the vasodilatory effect of most anaesthetic drugs, which could very easily
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15 361 overweigh the vasoconstrictive effects of increased CO₂ levels.

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18 362 Overall, knowledge of the underlying physiological mechanisms during HFNO in
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20 363 anaesthetised patients is still very limited. This study investigates under rigorously
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23 364 controlled circumstances the concept of humidified HFNO on prolonged apnoea time,
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25 365 presumably without desaturation. With our findings, we hope to improve airway
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28 366 management safety as this study enables the medical community to better understand the
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30 367 physiology behind apnoeic oxygenation and the influence of different nasal flow rates on
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33 368 CO₂ clearance. Our study's extensive setup also allows us to measure the effects of
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35 369 increased CO₂ on cerebral perfusion and cardiac output.

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37 370 If low-flow oxygen administration with standard nasal cannula is non-inferior compared to
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40 371 high-flow humidified HFNO, it could have direct clinical impact. Oxygen and standard nasal
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43 372 cannula are ubiquitously available and it will be hard to argue against apnoeic oxygenation
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45 373 during routine intubation. Especially for rapid sequence intubation (RSI) and other
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47 374 emergency airway procedures, apnoeic oxygenation may be – and perhaps should be –
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50 375 performed using a standard nasal cannula at a low flow rate.³⁰ For patients at risk of
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52 376 desaturation, this has the potential to reduce complication of hypoxia and therefore will
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54 377 improve patient safety with little additional resources.

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57 378 Due to the design of this trial, we will not be able to determine the influence of
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59 379 pathophysiologic alterations of patients' underlying diseases, as we exclude severely ill
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3 380 patients from this study for safety reasons. Furthermore, although we include 100 patients
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5 381 in this trial, we may still end up with an uneven distribution of risk factors. To minimize this
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8 382 bias, we stratify according to BMI and smoking status, as we assume these factors to be
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10 383 the most influential on our primary outcome.

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13 384 Provided all groups have a similar CO₂ clearance, the inclusion of 100 patients will provide
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15 385 a solid foundation to detect even smaller haemodynamic, thoracic EIT, or EEG changes.
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17
18 386 Nevertheless, all results are to be considered for anaesthetised patients using propofol and
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20 387 remifentanyl. We do not know how other anaesthetic drugs would potentially interfere
21
22 388 with patients' physiology.

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25 389 All this leads us to the conclusion that this study will be able to provide highly interesting
26
27 390 results and urgently needed evidence on physiologic changes during HFNO and CO₂
28
29 391 increase in adult patients during apnoeic oxygenation. We will find an answer to our
30
31 392 question, if the application of nasal oxygen at 7l/min, 10l/min or 2l/min using jaw thrust is
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33 393 non-inferior compared to nasal oxygen at 7l/min using continuous laryngoscopy in regard
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35 394 to CO₂ clearance in anaesthetised patients.

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396 **AUTHOR CONTRIBUTIONS**

397 RG and LT conceived the study. RG, LT, FS, HK, and TR wrote the study protocol. RG, LT, FS
398 and HK developed the practical approach to measurement and recruitment. TRiv was
399 involved in the protocol development and manuscript review. LT designed the statistical
400 analysis plan for the protocol. All authors critically reviewed this manuscript and agree to
401 its final form.

402 **FUNDING STATEMENT**

403 This research is funded by a departmental research grant assigned to LT. For this study,
404 Fisher & Paykel (Auckland, New Zealand) provide all necessary breathing circuits and nasal
405 cannulas without costs. Fisher & Paykel are neither involved in the design nor have they
406 any influence on the data analysis and the presentation of results or their publication nor
407 do the study authors have any financial or any other collaborations with Fisher & Paykel.

408 **COMPETING INTERESTS**

409 None of the authors have any financial or any other competing interests concerning this
410 study.

411 **FIGURE LEGENDS**

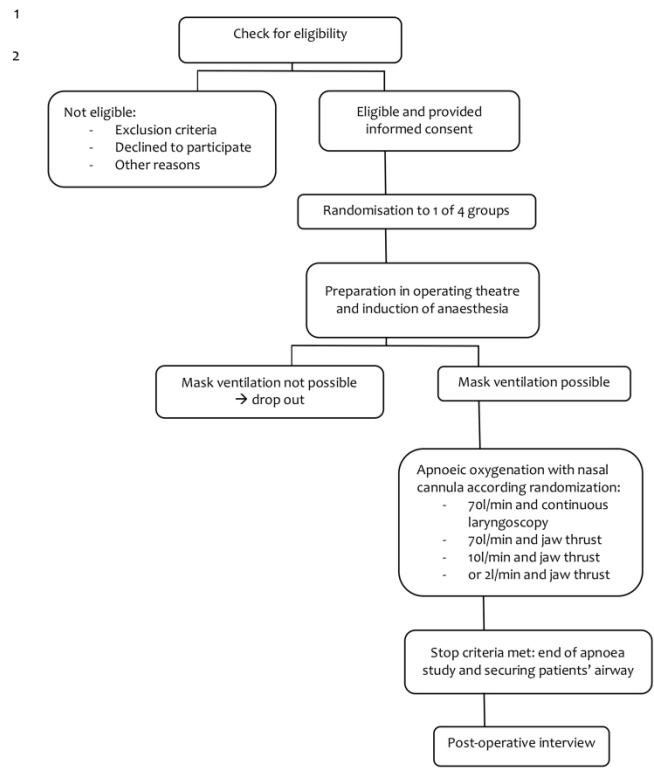
412 Figure 1: Study flow chart

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Figure 1

296x419mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set <i>Explanation: different registry used</i>	n/a
Protocol version	#3	Date and version identifier V4.5, February 2019	
Funding	#4	Sources and types of financial, material, and other support	22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities <i>Note: investigator-driven study</i>	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data	n/a

management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Explanation: Single-center study

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6	Background and	#6a	Description of research question and justification for undertaking	6
7	rationale		the trial, including summary of relevant studies (published and	
8			unpublished) examining benefits and harms for each intervention	
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11	Background and	#6b	Explanation for choice of comparators	7
12	rationale: choice of			
13	comparators			
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17	Objectives	#7	Specific objectives or hypotheses	6, 7
18				
19	Trial design	#8	Description of trial design including type of trial (eg, parallel	8
20			group, crossover, factorial, single group), allocation ratio, and	
21			framework (eg, superiority, equivalence, non-inferiority,	
22			exploratory)	
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26	Study setting	#9	Description of study settings (eg, community clinic, academic	8
27			hospital) and list of countries where data will be collected.	
28			Reference to where list of study sites can be obtained	
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31	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	8-10
32			eligibility criteria for study centres and individuals who will	
33			perform the interventions (eg, surgeons, psychotherapists)	
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37	Interventions:	#11a	Interventions for each group with sufficient detail to allow	11-14
38	description		replication, including how and when they will be administered	
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41	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for	14
42	modifications		a given trial participant (eg, drug dose change in response to	
43			harms, participant request, or improving / worsening disease)	
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46	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any	n/a
47	adherence		procedures for monitoring adherence (eg, drug tablet return;	
48			laboratory tests)	
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52			<i>Explanation: no compliance of patient necessary. Short duration</i>	
53			<i>of intervention (15 min)</i>	
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55	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or	n/a
56	concomitant care		prohibited during the trial	
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Explanation: short duration of trial (15 min), no additional interventions necessary

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5	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
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14	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
15			Figure 1
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20	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
21			10
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25	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size
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29	Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
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39	Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
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46	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
47			10
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49	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
50			8
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55	Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
56			n/a
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Explanation: blinding not possible

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3	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-14
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13	Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-14
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18	Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17-18
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25	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15, 16
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30	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15, 16
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34	Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15, 16
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39	Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
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49	Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17, 18
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55	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17, 18
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1	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17, 18
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6	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
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10	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17, 18
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17	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
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21	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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24	Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
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30	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
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34	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17, 18
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39	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
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43			<i>Explanation: no provisions</i>	
44				
45	Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
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53	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
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57			<i>Explanation: no professional writers</i>	
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1	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	n/a
2	reproducible research		participant-level dataset, and statistical code	
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5			<i>Explanation: none</i>	
6				
7	Informed consent	#32	Model consent form and other related documentation given to	n/a
8	materials		participants and authorised surrogates	
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11			<i>Explanation: only available in German. May be obtained upon</i>	
12			<i>request by the author</i>	
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15	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
16			biological specimens for genetic or molecular analysis in the	
17			current trial and for future use in ancillary studies, if applicable	
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20			<i>Explanation: not applicable</i>	
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23 3.0. This checklist was completed on 30. May 2018 using <http://www.goodreports.org/>, a tool made by the
24 [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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