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Pilot study

PILOT STUDY

PErioperative respiratory care aNd outcomes for patients underGoing hIgh risk abdomiNal surgery (PENGUIN): a randomised international internal pilot trial

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Abstract

Background: Infections are a common complication of abdominal surgery in low- and middle-income countries (LMICs). The role of a high fraction of inspired oxygen (FiO_2) and chlorhexidine mouthwash in preventing post-operative infections is unconfirmed.

Methods: Internal pilot phase of an international outcome assessor-blinded, 2x2 factorial randomised trial of patients aged ≥10-years undergoing midline laparotomy in LMIC hospitals. The main trial objectives are to compare the clinical effectiveness of preoperative 0.2% chlorhexidine mouthwash in preventing pneumonia versus no mouthwash, and 80–100% perioperative FiO_2 to prevent surgical site infection (SSI) versus 21–35% FiO_2. This 12-month internal pilot assessed feasibility of hospital site opening, patient recruitment, intervention adherence, patient follow-up and safety. Patients were randomised in a 1:1:1:1 ratio to the four intervention group combinations and followed up for 30 days.

Results: We recruited 927 patients from seven hospitals in India and South Africa over 12 months from November 2020. There were 907 adults (97.8%) and 20 children aged ten or over (2.2%): 89/927 (9.6%) patients died. Site opening reached 70% of our target (7/10) hospitals, and patient recruitment 107% (927/870). 917/927 (99%) patients in the mouthwash arm, and 840/927 (91%) patients in the oxygen arm received the allocated intervention. Lower adherence to the oxygen intervention related mainly to clinically necessary FiO_2 increases in the 21–35% FiO_2 arm. 30-day follow-up was completed appropriately for 924/927 (99%) patients. and was performed by a masked assessor for all patients. There were no reported safety events.

Conclusion: This pilot showed the feasibility and safety of a major phase III trial in post-operative infection prevention in LMICs.

Trial registration: ClinicalTrials.gov NCT04256798.

Keywords: Pilot trial; feasibility study; perioperative care; abdominal surgery; surgical site infection; postoperative pneumonia; global health

Infection is a common and serious complication of surgery, with a significant burden for patients and health systems. Two globally important postoperative infections are pneumonia and surgical site infection (SSI). Pneumonia affects around 1 in 30 patients after abdominal surgery, but accounts for as many as one in four postoperative deaths.[1,2] The incidence is greater still in high-risk populations such as those undergoing midline laparotomy where mortality rates are more than 10%.[1,3] SSIs are the most frequent healthcare-associated infection in LMICs, affecting one in three patients undergoing

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contaminated surgery.[4] The risk of postoperative mortality and complications such as SSI is three times greater in low- and middle-income countries (LMICs) than in high-income countries.[3,5,6] High-quality randomised trials including patients from the Global South are required to identify evidence-based methods to reduce the harms of surgery and improve the resilience of surgical systems.[7]

The PErioperative respiratory care aNd outcomes for patients underGoing hIgh risk abdomiNal surgery (PENGUIN) trial has been designed to evaluate two interventions to reduce infections complicating surgical recovery. A modified Delphi consensus process evaluated prioritised perioperative care interventions by importance, relevance, and acceptability by GlobalSurg collaborators representing 15 LMICs. The evaluation of chlorhexidine mouthwash to reduce the incidence of pneumonia and inspired oxygen concentration to reduce surgical site infection were identified as the top priorities. No likely biological mechanism for interaction exists between the two interventions, allowing evaluation within a factorial design.

Aspiration of bacteria in oral and pharyngeal secretions during tracheal intubation may lead to colonisation of the lower respiratory tract, and pneumonia following surgery.[8,9] One potential method to prevent pneumonia after surgery involves an oral rinse with 0.2% chlorhexidine mouthwash immediately prior to anaesthesia. Experimental data show that a single administration of 0.2% chlorhexidine mouthwash reduces the total oral microbial numbers by >80% within one minute.[10] The findings of four randomised trials in elective cardiac surgery in high-income settings suggest that this approach may reduce the relative risk of pneumonia by up to 40%.[11–14] However, no high-quality, randomised evaluation has been performed in patients undergoing abdominal surgery, nor in low-middle income countries. An internal pilot study is required to test whether mouthwash can be reliably delivered per-protocol across very varied hospital types and resource settings.

Low tissue oxygenation in the surgical wound is associated with an increased incidence of SSI.[15] It is hypothesised that a higher fraction of inspired oxygen (FiO_2) during and after surgery could prevent SSI.[15–17] World Health Organisation (WHO) guidelines recommend that adult patients undergoing general anaesthesia with tracheal intubation for surgical procedures should receive 80% FiO_2 intraoperatively and, if feasible, in the immediate postoperative period for 2–6 hours to prevent SSI.[18] However, this recommendation has been hotly debated for three reasons: 1) there is good evidence to believe high FiO_2 may cause harm, which has not been properly assessed in the perioperative setting[19]; 2) The delivery of high FiO_2 during anaesthesia is technically difficult and expensive in resource-poor settings.[20] The fragility of oxygen supply systems in LMICs was critically exposed during the pandemic (see WHO Access to COVID-19 Tools Accelerator (ACT-A) Oxygen Emergency Taskforce),[21] and 3) there are key flaws in the evidence on which the WHO recommendation is based.[22] The retraction of a number of studies by one group has further heightened concerns.[18,23,24] An updated evidence synthesis of the effect of high FiO_2 on SSI was undertaken on behalf of the WHO.[22] Previous trials were conducted almost exclusively in HICs, they used heterogeneous definitions for SSI, and none was powered to detect an effect on mortality. The findings do not provide strong evidence for routine use of high FiO_2, and the WHO advises that a large randomised trial is needed to resolve this.[18] High FiO_2 may even increase mortality amongst acutely unwell patients.[25] Our preliminary cost-effectiveness analysis using current LMIC data suggests high FiO_2 would be a cost-effective intervention to prevent SSIs.[26] There is an urgent need for a large high-quality trial in LMIC hospitals to confirm the clinical and cost-effectiveness of high FiO_2 to prevent SSIs. Again, an internal pilot study is required to test whether high and low FiO_2 can be delivered across environments with different procurement and supply systems, clinical pathways, and practices.

The aims of this randomised internal pilot trial were to assess site opening, patient recruitment, intervention adherence and safety, and patient follow-up, to inform delivery of the main trial.[27,28]

Methods

Overview of phase III PENGUIN trial

PENGUIN is an international, multi-centre, pragmatic, outcome assessor-blinded, 2x2 factorial randomised controlled trial (ClinicalTrials.gov NCT04256798). The primary objectives for the phase III trial are to assess whether (1) preoperative 0.2% chlorhexidine mouthwash reduces the rate of postoperative pneumonia at 30-days compared to no mouthwash, and (2) 80–100% FiO_2 used during surgery reduces the rate of postoperative SSI at 30-days compared to 21–35% FiO_2 amongst patients undergoing midline laparotomy. Outcome assessment was performed at day 7 or the day of discharge (whichever was sooner) and again at 30-days after surgery, and analysed together as an overall event rate at 30-days. Post-discharge follow-up at 30-days was permitted in-person or over the telephone in accordance with a validated, pre-specified protocol, with the outcome assessor masked to the randomised allocation.[29,30] Allowing for 15% loss to follow-up, a total sample size of 12,942 patients (11,000/0.85) (6,471 per intervention arm) will allow the following differences to be detected with 90% power and 5% significance level: (1) 30-day surgical site infection: 20.0%–17.6% (RRR: 12%); (2) 30-day pneumonia: 3.50%–2.45% (RRR: 30%); (3) 30-day mortality: 5.00%–3.74% (RRR: 25.2%). The full protocol is available at: https://www.globalsurgeryunit.org/clinical-trials-holding-page/project-penguin/. This paper reports an internal pilot study within the PENGUIN trial, reporting feasibility outcomes only in the first 12-months of the PENGUIN trial. An internal pilot forms the first part of a trial and the outcome data generated will contribute to the final analysis. This study is reported in accordance with CONSORT extension for pilot and feasibility studies.[31]

Ethics and regulatory approvals

The primary ethics approval was from the International Ethics Committee at University of Birmingham (ERN_19–1376). National ethics approval was submitted by International Coordinating Centres (ICCs) in each country, and local centre Principal Investigators (PIs) ensured adherence to local hospital research approvals, reflecting differences in processes across settings.

Eligibility criteria

Pilot trial eligibility included both centre- and patient-level criteria. Hospitals in an LMIC (as defined by the Development Assistance Committee (DAC)) that routinely provided abdominal surgery and with facilities to deliver inspired oxygen

concentrations of both 21–35% and 80–100% during surgery were eligible to include patients. Adults and children aged 10 years or over undergoing elective or emergency abdominal surgery via midline laparotomy incision with an anticipated abdominal incision of at least 5cm in length and with the capacity to provide written (or fingerprint) informed consent were eligible. Patients were excluded if they were undergoing Caesarean section, were American Society of Anesthesiologists (ASA) grade V (moribund patient, not expected to survive 24h without the operation), had a documented or suspected allergy to chlorhexidine, were unlikely to be contactable after discharge or if they'd been enrolled into PENGUIN within the previous 30 days. No major changes to the trial eligibility criteria were made after commencement of the pilot study.

Recruitment and randomisation procedures

Each participating country and hospital created local pathways to identify potentially eligible patients. This included surgical outpatient clinics, planned theatre lists, emergency surgical admissions, and emergency theatre lists. Researchers in each participating country, with advice from their research ethics committee(s), created contextually appropriate pathways to provide information to potential patients about the trial and seek informed consent. Patient Information Sheets (PIS) were made available to all centres in appropriate languages and were used to facilitate the trial informed consent process. After providing written (or fingerprint) informed consent, patients were randomly allocated by local site investigators in a 1:1:1:1 ratio to chlorhexidine mouthwash or usual care (control group) and a FiO_2 of 80–100% ('Liberal') or FiO_2 of 21–35% ('Restrictive') (control group). A minimisation procedure using a computer-based algorithm was used to avoid chance imbalances in the following prognostic variables: i) age: child (10–17 years) or adult (≥18 years), ii) urgency: elective (planned) surgery or emergency (unplanned) surgery, iii) indication for surgery (malignant disease or benign disease or trauma), and iv) hospital.

Trial interventions

Two interventions were used in this pilot trial. The mouthwash intervention was defined as two 30-second mouthwashes with 15ml 0.2% chlorhexidine both administered within 30 minutes immediately before induction of anaesthesia. The intervention was observed by the anaesthesia provider to confirm adherence. This was compared to usual care (i.e., no mouthwash before induction of anaesthesia). The oxygen intervention was defined according to the FiO_2 administered after induction of anaesthesia and throughout surgery. Anaesthesia was either administered with a high FiO_2 of 80–100% ('Liberal'), or with a low FiO_2 of 21–35% ('Restrictive'). Where possible, the intervention was continued after surgery for up to four hours. Higher fractions up to 100% were used at the discretion of the anaesthesia provider during induction and cessation of anaesthesia, and if clinically indicated at other times for the treatment of hypoxia in the low FiO_2 (restrictive) group. It was not possible to fully blind either the patient or operating room staff to either intervention, however clinical outcome assessment was performed by an assessor masked to the randomised allocation. Trial investigators were an established network of clinicians and trialists. They were trained in intervention delivery in Site Initiation Visits and visual intervention 'cards' were posted in anaesthetic rooms as an aide-memoire. They were given feedback, and opportunity for discussion with the trial management group in the event of non-adherence.

Outcome measures

We defined four outcomes related to trial processes over the 12-month pilot period. Site opening and recruitment targets were based upon our experience within a previous large, randomised trial across similar patients and settings, and the required rate required to recruit all patients within a four-year period.[32]

1. Site opening: The number and time of participating sites that opened to recruitment. The pre-specified target was 10 centres open at 12-months in at least two countries.
2. Recruitment: The number of patients who consented to inclusion and were allocated into the trial. The pre-specified target was 870 patients at 12 months.
3. Intervention adherence: The proportion of patients who received either or both intervention or control in accordance with their randomised allocation. Adherence to the oxygen intervention was complete if patients received the correct oxygen concentration for all or all but one measured 10-minute intraoperative time epochs. If patients received an oxygen concentration for more than one epoch they were labelled as non-adherent, although it was recognised *a priori* that changes in FiO_2 may be clinically necessary to treat hypoxia among patients in the 21–35% FiO_2 arm. Evaluated time epochs excluded the first and last epochs where a high FiO_2 would typically be recommended for the induction of anaesthesia and tracheal extubation. Wherever non-adherence was recorded a site was required to complete a specific Case Report Form. Sites were asked to select and describe their reason for non-adherence, which was proactively monitored and adjudicated by the trial management group. Adherence to the mouthwash intervention was defined as complete if patient received two or more administrations in-hospital and prior to tracheal intubation. The number of administrations was also monitored.
4. Completion of follow-up: The proportion of patients with a complete, blinded assessment of the two primary clinical outcome measures (pneumonia, surgical site infection) at 30-days after surgery. These were defined according to US Center for Disease Control Criteria definitions, and quality assured through investigator training, site opening visits and a standardised assessment tool. Wherever possible these were assessment in-person by a masked, trained assessor. Sites were permitted to use telephone or clinical notes review for outcome assessment where patients were unable to travel back to hospital (for example, during the SARS-CoV-2 pandemic). Clinical outcome definitions are described in full in the study protocol (NCT04256798).

The frequencies and percentages of protocol deviations, and the number and percentage of patients experiencing any serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) were presented by intervention group.

Statistical analysis

As recommended by guidance for pilot and feasibility studies, we have not accessed or presented primary outcome data

either overall or by arm.[27,28,33] A statistical analysis plan was written prior to data access and approved by the trial management and steering groups, and Data Monitoring Committee prior to data access. Data cleaning and analyses were performed using Stata V16.0 (StataCorp LLC, TX, USA). Categorical data are summarised by number of patients, counts and percentages. Continuous data were summarised by the number of patients, mean and standard deviation if deemed to be normally distributed or number of patients, median and interquartile range if data are skewed, and ranges if appropriate. Reflecting the exploratory nature of analyses, tests of statistical significance were not undertaken, nor are confidence intervals presented.

Community engagement and involvement (CEI)

Community members and patients in participating LMICs were involved throughout the research cycle, guided by a dedicated Patient and Public Involvement manager. The impact of CEI before and during the internal pilot study is reported in accordance with the GRIPP-2 short form.[34]

Results

Site opening and patient recruitment

In the first 12-months from trial opening, patients were recruited from seven hospitals in two upper-middle income countries (India and South Africa). Predicted and observed rates of patient recruitment and site opening by month and overall is shown in Fig 1. In total, 927 patients were recruited and allocated in the internal pilot period, between 13 November 2020 and 12 November 2021. Site opening reached 70% of the pre-specified target (7/10) and patient recruitment 107% (927/870). A CONSORT diagram for the pilot trial is presented in Fig 2. Case report form return rates and completeness was very high (>95% return rate for all forms, and with completeness >99% for all forms; Supplementary table 1).

Baseline characteristics

The characteristics of patients in the PENGUIN pilot are shown in Tables 1 and 2. In terms of the minimisation variables, 97.8% (907/927) of patients were adults and 2.2% (20/927) were children; 65.7% (609/927) of operations were elective and 34.3% (318/927) were emergency: 49.2% (452/927) of operations were for malignant, 44.8% (415/927) for benign and 6.0% (56/927) for traumatic indications. Overall centre recruitment varied from 1 patient to 313 patients, with a rate per month between 0.5 per month and 26.1 per month. 28.1% patients were ASA grade III or IV (260/927), and a majority (81.8%) had never smoked (757/927). Most patients had a tracheal tube placed for airway management (99.7%, 914/917, 10 missing). The rate of preoperative SARS-CoV-2 test positivity was very low (0.1%, 1/927). There was a very low rate of missingness in baseline data overall (1.0%, 10/927).

Intervention adherence

464 patients were randomly allocated to receive chlorhexidine mouthwash and 463 to receive no mouth wash (control), with 98.9% adherence (n=458) to mouthwash administration. The common reasons cited for lack of adherence was wrongly identifying the patient as a control patient (n=3). One patient received mouthwash but had been allocated to control. All patients that received mouthwash had a minimum of two oral rinses. The adherence to oxygen arm allocation was 840/927 (90.6%); non-adherence by number of time epochs and characteristics of oxygen delivery can be seen in Table 3. Non-adherence was clinically indicated for 56 of 77 patients (72.4%) recorded as non-adherent to the allocated oxygen intervention (10 patients missing data). Examples of clinical indications for non-adherence included anaesthetist concerns about patient instability and oxygenation at the lower end of the acceptable normal range i.e., temporary clinician responses to patients' physiology as opposed to increasing the FiO2 as part of a strategy to prevent surgical site infection. Only 18 of 927 patients (1.9% of those allocated) were non-adherent for a non-clinical reason.

Intervention safety

The overall safety of intervention delivery was high. There were no safety events (SAEs or SUSARs) recorded for the chlorhexidine mouth intervention, including aspiration or allergy. There was no SAE related to oxygen delivery.

Completion of follow-up

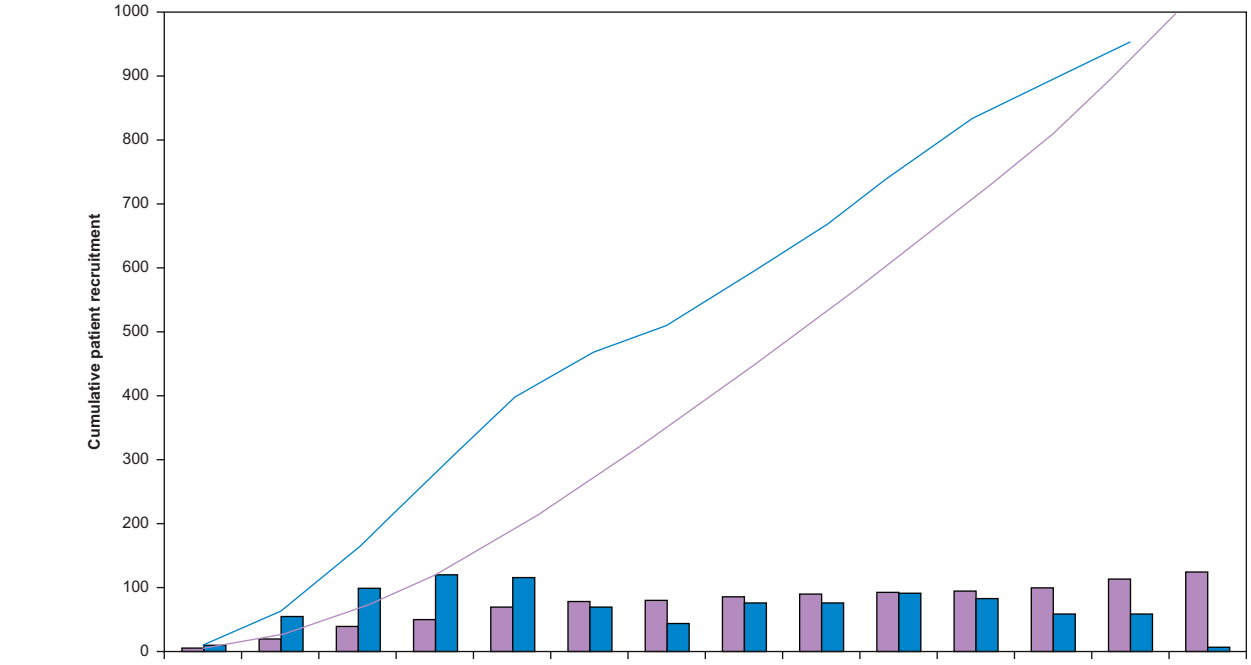
Of the 94 patients without a complete 30-day Case Report Form, 76 (80.1%) died within 30-days before having recorded SSI or pneumonia (i.e., where death acted as a competing risk), 2 were discharged after 30 days, 9 were allocated to a group but did not have surgery, 4 withdrew consent and 3 were lost to follow up after discharge. 30-day follow-up was therefore appropriately completed for 924/927 (99%) patients. In total, 89/927 (9.6%) patients died within 30 days. 30-day outcome assessment was performed by an assessor masked to the randomised allocation for all patients. Most follow-ups were performed over the telephone (82.4%, 686/833), with 15.4% (126/833) in person. For 19 patients (2.3%), this assessment was made from the clinical notes only.

Community engagement and involvement

Patients were involved in prioritisation of the trial topic in perioperative care, and a patient lead partner was part of the Trial Development and Management group after undergoing training in research methods.[35] Patient-facing materials were drafted and refined with support from this lead patient partner, ensuring that intervention delivery (e.g., mouthwash procedure) was also comprehensible and acceptable. We also worked with CEI partners to co-design an optimised, culturally acceptable telephone follow-up procedure for the co-primary outcome.[30]

Discussion

This internal pilot trial has demonstrated that the PENGUIN trial is feasible, and deliverable to a high-quality, with no safety concerns identified for patients taking part. Patient recruitment was above our target despite the pilot running through periods of the pandemic. Site and country opening was slightly below target, reflecting challenges in COVID-19 'surge' pressures across candidate LMICs within our pilot network. We have proactively addressed this during the COVID-recovery phase by performing further national site investigator



	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21
Pts - projected, monthly	6	21	40	52	71	79	81	87	89	93	94	100	114	124
Pts - actual, monthly	10	54	99	118	114	70	44	76	76	91	83	60	58	
Pts - projected, cumulative	6	27	67	119	190	269	350	437	526	619	713	813	927	1051
Pts - actual, cumulative	10	64	163	281	397	467	511	587	663	754	837	897	955	
Sites - projected, cumulative	2	4	5	5	5	5	5	5	5	5	5	9	11	13
Sites - actual, cumulative	2	5	5	5	5	5	5	5	5	5	6	6		

Figure 1. PENGUIN pilot recruitment graph.

meetings and extending recruitment to five further LMICs (Mexico, Nigeria, Rwanda, Brazil, Uganda). Adherence was very high for the mouthwash intervention, and acceptable for the oxygen intervention, noting that 56 of 77 (72%) who were deemed non-adherent to the allocated oxygen arm had received a clinically indicated increase in FiO_2 to treat hypoxia in the 21–35% FiO_2 treatment arm. There were no intervention safety events. Follow-up rates were high suggesting a low risk of attrition bias. In light of these data, the Trial Steering Committee and Data Monitoring Committee made a recommendation to continue into the main phase III trial.

The high postoperative mortality risk observed in the PENGUIN pilot trial demonstrates that an appropriate case-mix of high-risk patients has been included in the study, as would be required for a generalisable trial in patients undergoing midline laparotomy. This mortality rate is similar to that observed in prospective cohort studies across our networks.[5,36] One third of recruitment was in the emergency setting despite this being typically a harder-to-reach cohort than in planned surgery. We will continue to monitor the mortality rate and rate of recruitment in the emergency setting during the main phase of the trial and report this back to our oversight committees. This does, however, pose a problem of competing risk of mortality with both primary outcome measures.[37,38] If a patient has an SSI or pneumonia event recorded before they die, this is classified as complete follow-up, but those that die with an unknown status for the primary outcome measures represent an important source of missing data. We will pre-plan to address this using sensitivity analyses in the Statistical Analysis Plan for the main phase trial.[32,39]

Feasibility of this trial has important implications for other trials in global surgery and perioperative care in the future. PENGUIN adopts an efficient 2x2 factorial design, which allows two interventions to be tested in parallel against co-primary outcome measures, where no interaction between treatment effects is anticipated or biologically plausible. This demonstrates that patients, clinicians, and ethics committees are likely to be receptive to novel designs, with lower costs and higher potential benefits for patients and health systems. Other novel efficient trial designs such as platform or multi-arm multi-stage trials would allow greater flexibility to evaluate multiple interventions, test treatment effects across defined sub-groups and overcome inefficiencies in trial set up and site opening.[40,41] This trial also demonstrates synergy of surgical and anaesthetic research and clinical networks in trial development and delivery. This represents an exciting area for future development. Currently, there is one other trial (HOT-ROX) being conducted which addresses outcomes between restrictive, standard of care and liberal oxygen strategy across

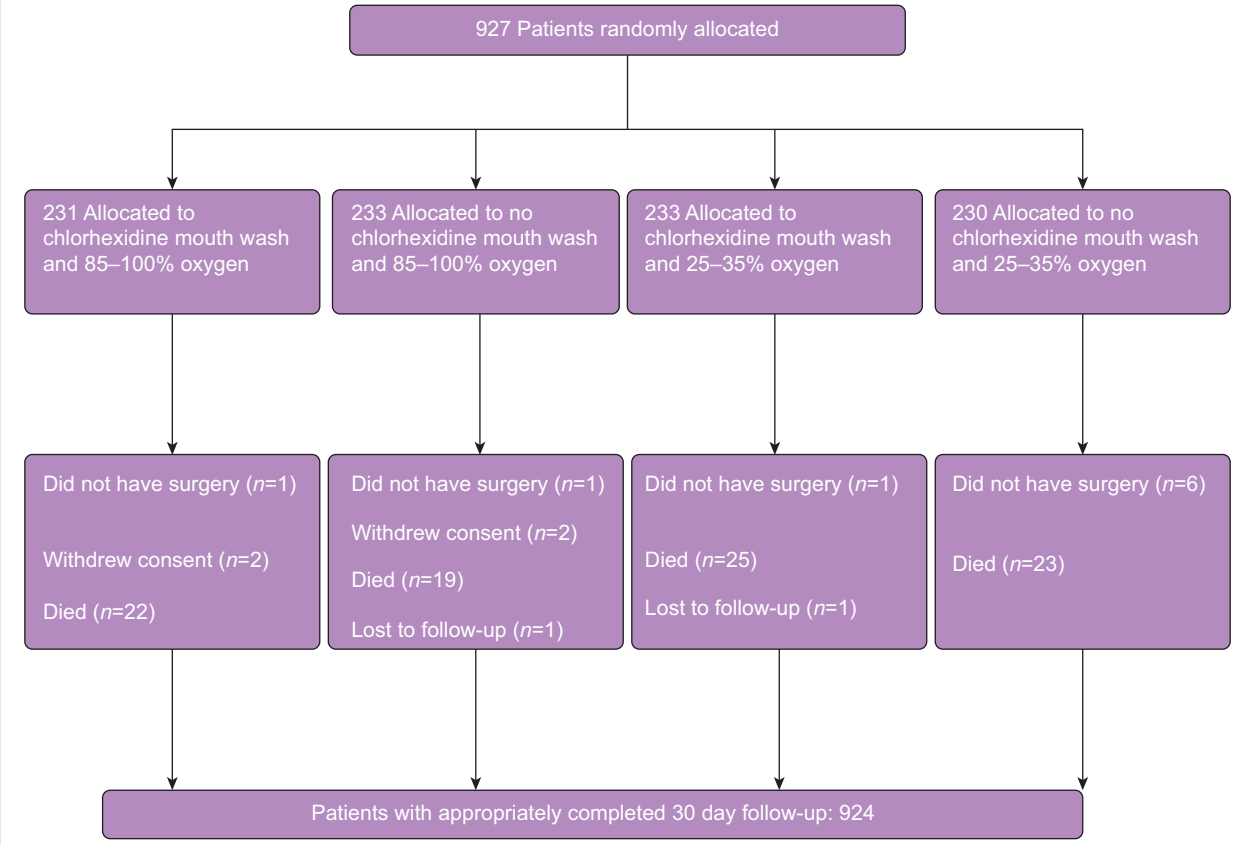


Figure 2. CONSORT diagram for PENGUIN pilot.

three randomised groups.[42] HOT-ROX differs in the following respects to PENGUIN, suggesting that there is value in continuing both trials: i) it includes a broader range of patients in the trial i.e., lower risk patients, ii) it has a quality of life outcome i.e., days alive and at home. Therefore, the trials are fundamentally different with PENGUIN addressing the effectiveness of a perioperative oxygen intervention in higher risk surgical patients, with objective surgical complications i.e. SSI, and hard outcomes i.e. mortality.

PENGUIN has some limitations. Upon recommendation of our data monitoring committee (DMC), we have not presented any baseline or process outcome data by arm. Whilst this maintains the integrity of the primary outcome assessment, it reduces the utility of data presented in highlighting variability by arm and further optimising trial delivery. We are not able to check the balance of randomisation between arms; however, we have pre-planned a minimisation procedure which will force balance across four key co-variables. We did not aim, or attempt, to present primary outcome data, nor estimate effect sizes; we will reserve the first unblinded analysis for the main phase III trial. The DMC has full access to unblinded outcome data and has not made any post-pilot recommendations to change our sample size or trial conduct. Our factorial trial relies on an assumption of no interactions between interventions leading to heterogeneity of treatment effect between randomised groups; our DMC is monitoring any statistical evidence of this to ensure the validity of our design. Whilst the main phase trial aims to be delivered across five countries, we only have data from five centres in two countries from the pilot trial. These are likely to be self-selected as 'high achieving centres'. Care must be taken to maintain signals of high-quality delivery when scaling the trial across centres with less research experience and resourcing. As the pilot was conducted during the SARS-CoV-2 pandemic, a high proportion of the follow-up was performed on the telephone, which is atypical when applying the US Centre for Disease Controls (CDC) criteria. To quality assure telephone assessment, we developed, adapted and validated a standardised schedule.[30,43]

The PENGUIN trial is feasible and safe, and once completed will provide high-quality prospective data on two low-cost interventions to reduce common and serious infection complications of abdominal surgery. This pilot trial has not identified any major amendments required to the trial protocol. The key learning has been qualitative in terms of shared experience of participating hospitals, establishing anaesthetic leads in each site, recognising challenges around low dose oxygen delivery, and learning of the trial management team to collaborate across perioperative teams. Ongoing patient recruitment is now taking place across a diverse network of

Table 1 Preoperative characteristics of patients in PENGUIN pilot (n=927).

Factor	Levels	Frequency
Minimisation variables		
Age	Child (<18y)	20 (2.2%)
	Adult (≥18y)	907 (97.8%)
Timing of surgery	Elective (planned)	609 (65.7%)
	Emergency (unplanned)	318 (34.3%)
Indication for surgery	Malignant	456 (49.2%)
	Benign	415 (44.8%)
	Trauma	56 (6.0%)
Hospital	1	54 (5.8%)
	2	313 (33.8%)
	3	118 (12.7%)
	4	204 (22.0%)
	5	235 (25.4%)
	6	2 (0.2%)
	7	1 (0.1%)
Other characteristics		
Age group	10 to 17	20 (2.2%)
	18 to 29	120 (12.9%)
	30 to 49	277 (29.9%)
	50 to 69	402 (43.4%)
	70 and above	108 (11.7%)
Sex	Male	520 (56.2%)
	Female	406 (43.8%)
	Missing	1
ASA grade	Grade I	256 (27.7%)
	Grade II	410 (44.3%)
	Grade III	207 (22.4%)
	Grade IV	53 (5.7%)
	Missing	1
Smoking status	Ex-smoker (stopped >6 weeks ago)	69 (7.5%)
	Current smoker (or stopped smoking < 6 weeks ago)	100 (10.8%)
	Never smoked	757 (81.8%)
	Missing	1
Comorbidities	Diabetes Mellitus	126 (13.6%)
	COPD or asthma	20 (2.2%)
	Bronchiectasis	0 (0.0%)
	Pneumonia in past month	2 (0.2%)
	Known HIV infection	12 (1.3%)
	Stroke or TIA	5 (0.5%)
	Any listed co-morbidity	165 (17%)
Tuberculosis (TB)	No	906 (97.8%)
	Yes, on active treatment	5 (0.5%)
	Yes, not actively treated	1 (0.1%)
	Yes, previously treated	14 (1.5%)
	Missing	1
Preoperative COVID-19 status	Asymptomatic: no SARS-CoV-2 test performed	16 (1.7%)
	Asymptomatic: SARS-CoV-2 test negative	901 (97.3%)
	Asymptomatic: SARS-CoV-2 test positive	8 (0.9%)
	Symptomatic: COVID-19, with SARS-CoV-2 testing	1 (0.1%)
	Unknown	1
Preoperative resting oxygen saturation	>96%	813 (87.70%)
	93–96%	64 (6.90%)
	88–92%	5 (0.54%)
	<87%	3 (0.32%)
	Not measured	41 (4.4%)
	Missing	1
Preoperative serum Haemoglobin	Not anaemic (≥12g/dL for women, ≥13g/dL for men)	250 (27.1%)
	Anaemic (<12g/dL for women, <13g/dL for men)	671 (72.9%)
	Missing	1
Active cancer	Yes	492 (53.1)
	No	424 (45.7)
	Missing	11

Table 2 Intraoperative characteristics of patients in PENGUIN pilot (n=927).

Factor	Levels	Frequency
Intra-operative contamination	Clean	133 (14.5%)
	Clean-contaminated	504 (55.0%)
	Contaminated	59 (6.4%)
	Dirty	221 (24.1%)
	Missing	10
WHO Surgical Safety Checklist used?	No	1 (0.1%)
	Yes	916 (99.9%)
	Missing	
Pulse oximetry used during surgery?	Yes	917 (100.00%)
	Missing	10
Prophylactic antibiotics given before surgery?	No	6 (0.7%)
	Yes	911 (99.3%)
	Missing	10
Temperature monitored during surgery?	No	420 (45.8%)
	Yes	497 (54.2%)
	Missing	10
Skin preparation for surgery	Chlorhexidine	306 (33.4%)
	Iodine	610 (66.5%)
	Other	1 (0.1%)
	Missing	10
Hair removal at site of wound?	No hair at site of wound	192 (20.9%)
	In theatre, electric	202 (22.0%)
	In theatre, razor/blade	10 (1.1%)
	Before theatre arrival	450 (49.1%)
	Not done	63 (6.9%)
	Missing	10
Anaesthetic technique	General anaesthesia	914 (99.7%)
	Spinal	14 (1.5%)
	Epidural	352 (38.4%)
	Missing	10
Airway management	Endotracheal tube	914 (99.7%)
	Laryngeal mask airway	1 (0.11%)
	Other	2 (0.22%)
	Missing	10
Indication of surgery	Malignant Disease	453 (49.4%)
	Benign Disease	411 (44.8%)
	Trauma	53 (5.8%)
	Missing	10

Table 3 Adherence to and delivery of inspired oxygen intervention.

Factor	Levels	Frequency (%) N=927
Number of 10-minute epochs outside allocated oxygen concentration range[a]	0	791 (85.3%)
	1	49 (5.3%)
	2	35 (3.8%)
	3	17 (1.8%)
	4	10 (1.1%)
	5	2 (0.2%)
	6	13 (1.4%)
	Missing	10 (1.1%)
Oxygen supply	Pipeline	903 (98.6%)
	O2 cylinder	7 (0.8%)
	O2 concentrator in operating room	6 (0.7%)
	Missing	11 (1.1%)
Medical gases used during anaesthesia[b]	02	915 (99.8%)
	Medical Air	453 (49.4%)
	Nitrous oxide	456 (49.7%)
	Missing	10 (1.1%)

[a] Adherence was defined as 0 or 1 epochs outside of the protocolised oxygen concentration range.
[b] Patients could receive one or more medical gases during anaesthesia, in accordance with local practice.

hospitals in LMICs around the world. The findings will be highly generalisable, and will directly inform national and international guidelines, including those issued by the World Health Organisation.

Contributions statement

Conceptualization & Study Design: AA, AB, ABB, BB, SC, RC, JD, CG, DG, JG, PH, BH, DK, MK, HK, IL, RL, LM, JM, DM, OO, RP, ARDM, TR, ER, DS, MS, AS, ST, NW. Data Curation &; Management: AB, BK, DK, DS, MS, NW, OO, PH, RL. Statistical Analysis: BK, OO, PH. Investigation & Data Collection: AA, AB, AS, BB, CG, DG, JD, JG, HK, PH, RC, ARDM, ST. Hub Leads: ARDM, DG, RM. Supervision & Project Administration: AB, BB, DM, RP. Writing – Original Draft Preparation: JG, RP, BB, CG. Writing – Review & Editing: AA, AB, ABB, BB, SC, RC, JD, CG, DG, JG, PH, BH, DK, MK, HK, IL, RL, LM, JM, DM, OO, RP, ARDM, TR, ER, DS, MS, AS, ST, NW. Funding Acquisition: AA, JG, DM, LM, PH. Ethics & Regulatory Approvals: AA, AB, AS, BB, CG, DG, JD, JG, HK, PH, RC, ARDM, ST. All NIHR Global Health Research Unit on Global Surgery collaborators contributed to local ethics and regulatory approvals and date curation and management.

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Declaration of interest

No authors have interests to declare with direct relevance to this trial or its reporting. This pilot trial was investigator initiated, developed and reported. Rupert Pearse has received research grants and/or consultancy fees from Edwards Lifesciences, Intersurgical and GlaxoSmithKline. Janet Martin has consulted for the WHO on projects related to surgical site infection.

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Appendix A. Supplementary data

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