Pragmatic multicentre factorial randomized controlled trial testing measures to reduce surgical site infection in low- and middle-income countries

NIHR Global Health Research Unit on Global Surgery

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European Colorectal Congress

29 November – 2 December 2020, St.Gallen, Switzerland

Sunday, 29 November 2020

MASTERCLASS

Introduction & course objectives
Michel Adamina, Winterthur, CH

Myths and facts about oral antibiotics, bowel preparation, and timing of iv antibiotics to reduce surgical site infection
Frédéric Ris, Geneva, CH

Management of colorectal GIST – all you should know from diagnosis to handling recurrences
Paris Tekkis, London, UK

Do and don't in taTME surgery – a decade of experience explaned
Roel Hompes, Amsterdam, NL

What your pathologist can do for you: from standard margins recommendations to molecular pathology, liquid biopsies, and the microbiome
Phil Quirke, Leeds, UK

Prehabilitation, patient blood management, frailty index – welcome addition or resource wasting
Des Winter, Dublin, IE

Selective use of neoadjuvant and adjuvant radiotherapy for rectal cancer
Chris Cunningham, Oxford, UK

Handling large rectal adenoma and malignant polyps
Willem Bemelman, Amsterdam, NL

All techniques to avoid staple line intersections in colorectal surgery
Antonino Spinelli, Milano, IT

Management of pelvic sepsis after colorectal / coloanal anastomosis and oncological outcomes of the GRECCAR 5 trial
Quentin Denost, Bordeaux, FR

Best practices in colostomy construction and repair of parastomal hernia
Eva Angenete, Göteborg, SE

The EBSQ Coloproctology Examination
Michel Adamina, Winterthur, CH

Wrap-up
Michel Adamina, Winterthur, CH

Sunday, 29 November 2020

COURSE OF PROCTOLOGY

Introduction & course objectives
Bruno Roche, Geneva, CH

Complex pelvic fistula revisited: established wisdom and innovative approaches
Alexander Herold, Mannheim, DE

Obstretrical trauma: assessment, timing and options to repair
Patrick Hohlfeld, Lausanne, FR

The painful bottom – Proctalgia beyond the classical abscess, fissures, and hemorrhoids
Bruno Roche, Geneva, CH

Sexually transmitted diseases in proctology
Karel Skala, Geneva, CH

Anorectal trauma and foreign bodies
Richard Cohen, London, UK

Pilonidal sinus – strategies and outcomes
Frédéric Ris, Geneva, CH

Fecal incontinence: investigations and conservative treatment
Beatrice Salvioli, Milano, IT

Fecal incontinence: neuromodulation and interventional options
Joan Robert-Yap, Geneva, CH

The pelvic floor revealed: transperineal / transvaginal / transanal repairs explained
Bruno Roche, Geneva, CH

The pelvic floor revealed: investigations and pelvic floor therapy
Jacqueline de Jong, Bern, CH

Obstructed defecation and IBS: investigations, differential diagnosis, and treatment strategies
Daniel Pohl, Zurich, CH

Obstructed defecation: surgical options
André d'Hoore, Leuven, BE

Wrap-up
Alexander Herold, Mannheim, DE

Monday, 30 November 2020

SCIENTIFIC PROGRAMME

Opening and welcome
Jochen Lange, St. Gallen, CH

Is cancer an infectious disease: role of the microbiome
Philip Quirke, Leeds, UK

Ethical considerations in crisis – lessons from Covid-19
Omar Faiz, London, UK

SATELLITE SYMPOSIUM
Medtronic

Prophylactic mesh in colorectal surgery
René H. Fortelny, Wien, AT

Lars Pahlman lecture: Extending the limits of liver surgery
Markus Büchler, Heidelberg, DE

Multimodal approaches to colorectal liver metastases
Mohammed Abu Hilal Brescia, IT

SATELLITE SYMPOSIUM
Ethicon

Urogenital dysfunction in patients treated for rectal cancer – what do we know and what can we do?
Eva Angenete, Göteborg, SE

Hemorrhoids – new options and time-tested solutions
Alexander Herold, Mannheim, DE

Anal pain and emergency proctology: what every surgeon should know & do
Richard Cohen, London, UK

All you need to know about anorectal fistula
Bruno Roche, Genève, CH

Strategies and outcomes for obstructive cancers of the colon and rectum
Willem Bemelman, Amsterdam, NL

Tuesday, 1 December 2020

BREAKFAST SYMPOSIUM
Karl Storz

Lessons learned along the robotic learning curve: a video guide for colorectal surgeons
Jim Khan, Portsmouth, UK

EAES presidential lecture: Strategies for lifelong learning and implementation of new technologies
Andrea Pietrabissa, Pavia, IT

SATELLITE SYMPOSIUM
Intuitive

A journey in global surgery – why getting out of the comfort zone
Raffaele Rosso, Lugano, CH

Enhanced recovery pathwaysreloaded – a practical guide to success
Roberto Persiani, Roma, IT

Cancer at the extremes of age: are there any differences in handling youngsters and seniors
Des Winter, Dublin, IE

Management pearls for early rectal cancer
Roel Hompes, Amsterdam, NL

Ventral rectopexy: indications, tricks of the trade, and long-term results
Chris Cunningham, Oxford, UK

SATELLITE SYMPOSIUM
BBraun

Total neoadjuvant therapy for colon and rectum cancers
Ronan O'Connell, Dublin, IE

Randomized trial evaluating chemotherapy followed by pelvic reirradiation vs chemotherapy alone as preoperative treatment for locally recurrent rectal cancer (GRECCAR 15)
Quentin Denost, Bordeaux, FR

Timeline of surgery following neoadjuvant radiotherapy – balancing morbidity and efficacy
Torbjörn Holm, Stockholm, SE

Poster award
Michel Adamina, Winterthur, CH

Wednesday, 2 December

Place and outcome of total colectomy in the surgical armentarium
Neil Mortensen, Oxford, UK

Kono S anastomosis and over the valve stricturoplasties: hope for better outcomes
André D'Hoore, Leuven, BE

New drugs, old fears: state of the art management of IBD patients
Gerhard Rogler, Zurich, CH

SATELLITE SYMPOSIUM
Takeda

Do resection of the mesentery in Crohn's & appendectomy in ulcerative colitis alter the course of disease
Christianne Buskens, Amsterdam, NL

The septic abdomen: getting out of misery and closing the case
Marja Boermeester, Amsterdam, NL

Management strategies for patients with advanced colorectal cancers
Paris Tekkis, London, UK

Anastomotic leak in colorectal surgery: insights, perspectives, and practical strategies
Antonino Spinelli, Milano, IT

Closing words
Michel Adamina, Winterthur, CH

Information & Registration

www.colorectalsurgery.eu

Trial protocol

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Pragmatic multicentre factorial randomized controlled trial testing measures to reduce surgical site infection in low- and middle-income countries: study protocol of the FALCON trial

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Abstract

Aim Surgical site infection (SSI) is the commonest postoperative complication worldwide, representing a major burden for patients and health systems. Rates of SSI are significantly higher in low- and middle-income countries (LMICs) but there is little high-quality evidence on interventions to prevent SSI in LMICs.

Method FALCON is a pragmatic, multicentre, 2 x 2 factorial, stratified randomized controlled trial, with an internal feasibility study, which will address the need for evidence on measures to reduce rates of SSI in patients in LMICs undergoing abdominal surgery. To assess whether either (1) 2% alcoholic chlorhexidine versus 10% povidone-iodine for skin preparation, or (2) triclosan-coated suture versus non-coated suture for fascial closure, can reduce surgical site infection at 30-days post-surgery for each of (1) clean-contaminated and (2) contaminated/dirty surgery. Patients with predicted clean-contaminated or contaminated/dirty wounds with abdominal skin incision ≥ 5 cm will be randomized 1:1:1:1 between (1) 2% alcoholic chlorhexidine and noncoated suture, (2) 2% alcoholic chlorhexidine and triclosan-coated suture, (3) 10% aqueous povidone–iodine and noncoated suture and (4) 10% aqueous povidone–iodine and triclosan-coated suture. The two strata (clean-contaminated versus contaminated/dirty wounds) are separately powered. Overall, FALCON aims to recruit 5480 patients. The primary outcome is SSI at 30 days, based on the Centers for Disease Control definition of SSI.

Conclusion FALCON will deliver high-quality evidence that is generalizable across a range of LMIC settings. It will influence revisions to international clinical guidelines, ensuring the global dissemination of its findings.

Keywords randomized controlled trial, surgery, surgical site infection, wound infection

Background

The Lancet Commission on Global Surgery highlighted the need to improve surgical outcomes as a global health priority [1]. Surgical site infection (SSI) is the most common postoperative complication worldwide, representing a major burden for patients and health systems. Patients who develop SSI experience pain, disability and prolonged recovery time prior to a return to normal activities [2]. SSIs are associated with increased resource use: in the UK they incur additional costs of GBP 5000–10 000 per patient [3,4]. The impact of increased healthcare costs is greatest in communities with high rates of poverty where patients are required to cover their healthcare costs. In many low- and middle-income countries (LMICs) the financial burden of SSI can increase the risk of catastrophic expenditure and impoverishment [5].

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Clinical trial registration**:** Clinicaltrials.gov: NCT03700749.

Trial sponsor**:** University of Birmingham reference RG_17-126 (Research Governance Team, University of Birmingham, Birmingham B15 2TT; e-mail: researchgovernance@contacts.bham.ac.uk). This manuscript is based on FALCON protocol 1.0, dated 14 August 2018.

Collaborating authors are listed in Appendix S1 in the online Supporting Information.

How frequently do SSIs occur?

A prospective study of 12 539 patients undergoing abdominal surgery across 343 hospitals in 66 countries found that rates of SSI were almost double in LMICs compared with high-income countries (16.3% *vs* 9.4%) [6]. Following risk adjustment for patient, disease, operative and hospital factors, patients in low-income countries remained at greater risk of SSI than those in high-income countries. Overall, rates of SSI in children (12.1%) and adults (12.3%) were similar.

The need for the FALCON trial

In 2016, the World Health Organization (WHO) made 29 recommendations for the prevention of SSI [7,8]. However, none were supported by high-quality evidence for LMICs, leading to uncertainty about their implementation in resource-limited settings. A large-scale multi-country randomized controlled trial (RCT) is needed to evaluate multiple interventions in LMICs in order to establish generalizable high-quality evidence that can inform future clinical guidelines.

Selection of interventions

Surgeons representing 16 LMICs (Fig. 1) participated in a Delphi process to select interventions to be tested in the FALCON trial, with a longlist based on the WHO recommendations. A consensus was reached to select two interventions: 2% alcoholic chlorhexidine skin preparation and triclosan-coated sutures for closure of the abdominal fascial sheath.

The WHO recommendation for alcoholic chlorhexidine as the skin preparation was based on meta-analyses of RCTs [9]. However, only one RCT was of high quality and this was limited to contaminated surgery [10]. Evidence for alcoholic chlorhexidine in middle-income countries was limited, and absent for dirty or emergency surgery, paediatric surgery and in all situations in low-income country settings [11–14].

The WHO recommendation for triclosan-coated sutures was conditional because only low- to moderate-quality evidence was available. Meta-analyses demonstrated no evidence of a benefit for triclosan-coated sutures in clean-contaminated or contaminated surgery [15]. Evidence to support the use of triclosan-coated sutures in dirty or paediatric surgery was limited [16,17]. One trial, completed in a LMIC, included patients undergoing open appendicectomy and found no advantage for triclosan-coated sutures [18].

Method

This protocol has been reported in compliance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline [19].

The FALCON hypothesis is that in (1) clean-contaminated and (2) contaminated/dirty abdominal wounds, 2% alcoholic chlorhexidine is superior to 10% povidone–iodine skin preparation and fascial closure with triclosan-coated suture is superior to closure with noncoated suture as strategies to reduce the rate of SSI at 30 days postsurgery.

Study design

FALCON is a pragmatic, multicentre, 2 x 2 factorial, stratified RCT to evaluate measures to reduce rates of SSI in patients undergoing abdominal surgery. FALCON is stratified according to the anticipated category of wound contamination, with two separately powered strata: (1) clean-contaminated and (2) contaminated/dirty. Eligible patients will be randomized to four groups: (1) 2% alcoholic chlorhexidine and noncoated suture, (2) 2% alcoholic chlorhexidine and triclosan-coated suture, (3) 10% aqueous povidone–iodine and noncoated suture and (4) 10% aqueous povidone–iodine and triclosan-coated suture (Fig. 2).

FALCON has two stages, an internal pilot and the main trial.

Internal pilot

The aim of the 6-month internal pilot is to assess: (1) the feasibility of recruitment to the randomized interventions; (2) compliance with treatment allocation and (3) patient retention and follow-up.

The internal pilot is anticipated to take 6 months, with at least 100 patients randomized. The independent Data Monitoring Committee and Trial Steering Committee will convene at the end of the pilot to advise on continuation to the main trial.

Main trial

The primary objective of the main trial is to assess whether 2% alcoholic chlorhexidine versus 10% povidone–iodine for skin preparation or triclosan-coated suture versus noncoated suture for fascial closure reduce SSI at 30 days postsurgery for (1) clean-contaminated and (2) contaminated/dirty abdominal wounds.

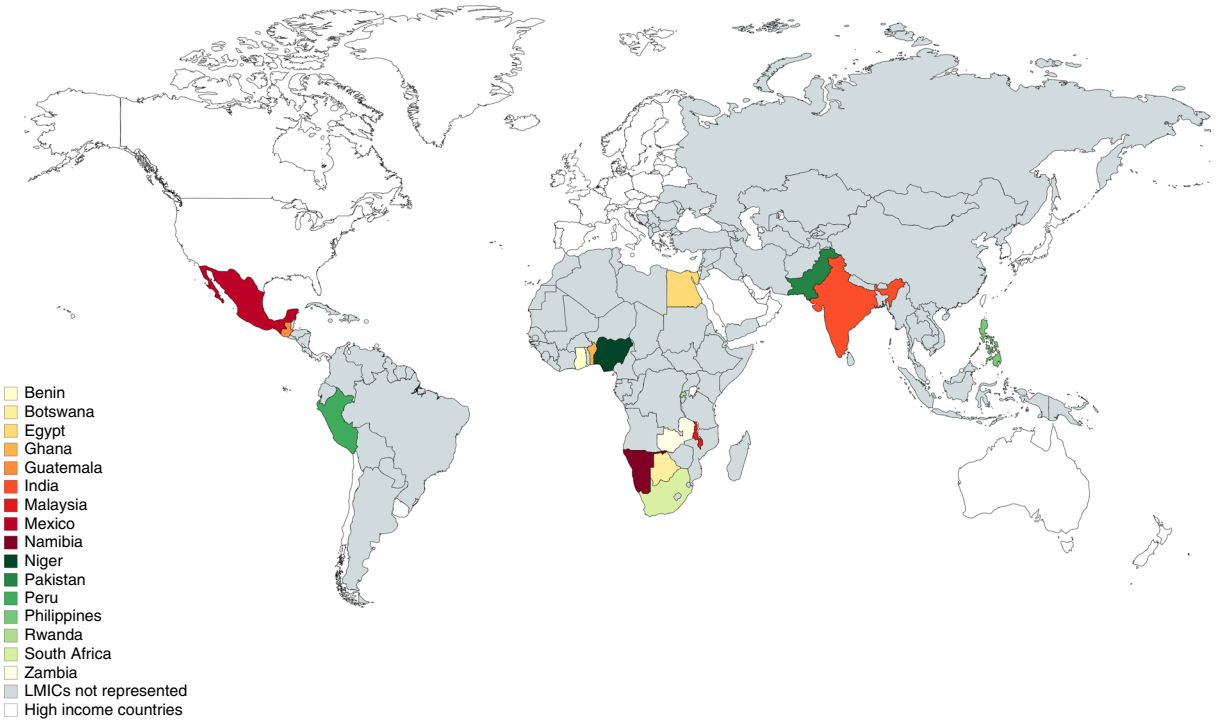

Figure 1 Countries represented by participants of Delphi which prioritized the interventions to be tested in the randomized controlled trial. Countries represented: Benin, Botswana, Egypt, Ghana, Guatemala, India, Malawi, Mexico, Namibia, Nigeria, Pakistan, Peru, Philippines, Rwanda, South Africa, Zambia.

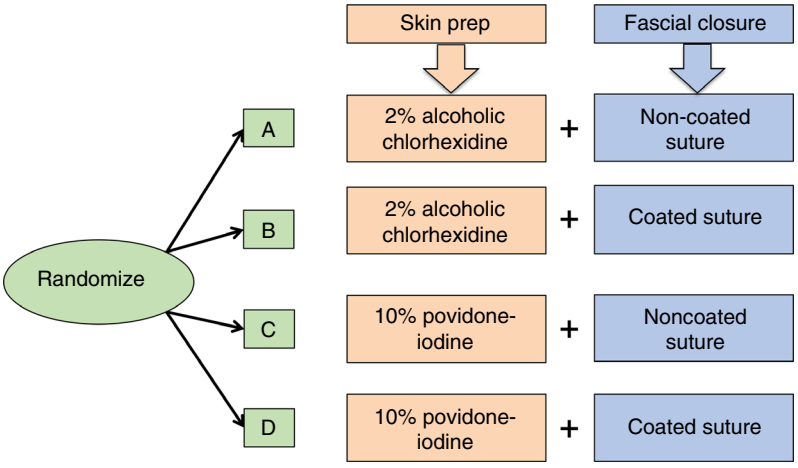

Figure 2 Trial schema.

The secondary objectives are to assess the impact of the interventions on: (1) secondary clinical outcomes (SSI at hospital discharge, length of index hospital admission, 30-day unplanned wound opening, 30-day reoperation, 30-day readmission, 30-day mortality, return to normal activities within 30 days); (2) resistance of organisms isolated from wound swabs to prophylactic antibiotics administered; (3) patient healthcare resource use and costs.

Study setting

Hospitals LMICs that perform abdominal surgery are eligible to participate in FALCON. LMICs are defined

as countries in the bottom two tertiles of the Human Development Index [20].

Eligibility criteria

Patients are eligible for inclusion if their wounds are predicted to be clean-contaminated or contaminated/dirty, with a predicted abdominal skin incision of 5 cm or greater. The baseline SSI rate in clean wounds is low and the potential benefits of research into interventions targeting SSI in those patients are limited, so FALCON focuses on clean-contaminated and contaminated/dirty wounds. Since eligibility must be determined preoperatively, it is based on the surgeon's prediction for contamination category and incision size. The study includes patients undergoing emergency or elective surgery. This can be for any indication and includes trauma surgery.

Patients must be able and willing to provide written informed consent. Patients with a documented or suspected allergy to iodine, shellfish or chlorhexidine skin preparation solution are excluded. Patients anticipated to be unable to complete either in-person or telephone follow-up are excluded.

FALCON will have no overall age restrictions, but each participating country will select age criteria based on country-specific regulatory approval processes.

Interventional products

The interventional product for skin preparation is 2% alcoholic chlorhexidine solution. The comparator skin preparation will be 10% aqueous povidone–iodine, identified through the consensus process as the most widely used and readily available skin preparation across participating hospitals. If necessary where national regulatory approvals are in place, preprepared 2% alcoholic chlorhexidine applicators can be used (e.g. ChloraPrep™ sticks, 2% chlorhexidine gluconate with 70% isopropyl alcohol, Carefusion).

The interventional arm for closure of the fascial sheath of the abdominal wall is the use of triclosan-coated sutures. Triclosan is a bactericidal and fungicidal triclocarban that aims to reduce bacterial colonization and biofilm formation on absorbable suture materials. Polydioxanone (Ethicon PDS Plus) and Vicryl (Ethicon Vicryl Plus) triclosan-coated sutures are commercially available and either can be used according to surgeon preference. The comparator fascial sutures are noncoated PDS or noncoated Vicryl.

Participating hospitals either procure skin preparations and sutures locally or the intervention products are supplied centrally.

Outcomes

The primary outcome is SSI at 30 days postsurgery using the Centers for Disease Control (CDC) definition of deep incisional or superficial incisional SSI as follows:

1 The infection must occur within 30 days of the index operation;
2 The infection must involve the skin, subcutaneous, muscular or fascial layers of the incision;
3 The patient must have at least one of the following: purulent drainage from the wound; organisms detected by wound swab; diagnosis clinically or at imaging; wound opened spontaneously or by a clinician;
4 The patient has at least one of the following: pain, tenderness, localized swelling, redness, heat at the wound site, systemic fever (> 38°C).

The secondary outcomes are:

1 SSI at discharge from hospital, based on the CDC definition;
2 length of index hospital admission;
3 readmission within 30 days of surgery;
4 unplanned wound opening within 30 days of surgery;
5 re-operation for SSI within 30 days of surgery;
6 mortality within 30 days postsurgery;
7 return to normal activities within 30 days of surgery;
8 resistance to prophylactic antibiotics administered within 1 h of incision;
9 health resource usage.

Patient identification and consent

Each participating hospital should develop a local pathway to recruit eligible patients. This can be in outpatient or inpatient settings, including emergency departments. Potential recruits may be identified by any member of the surgical team (consultant, surgical trainee, nonsurgical trainee on the unit or a research nurse).

Once a patient is identified, they are provided with a patient information sheet (PIS) (Appendix S2), following which they are asked to give informed consent to participate in the trial. The PIS has been translated into appropriate languages, as advised by local research ethics committees. Trial consent is required in addition to operative consent and must be obtained prior to surgery. Patients indicate their agreement either by signing or thumb printing the trial consent form. Trial consent can be taken by the local principal investigator (PI),

another surgeon or surgeon in training, or a research nurse, if permitted by country-specific regulations.

Randomization and blinding

Patients are randomized 1:1:1:1 to the following allocations: (1) 2% alcoholic chlorhexidine and noncoated suture, (2) 2% alcoholic chlorhexidine and triclosan-coated suture, (3) 10% aqueous povidone–iodine and noncoated suture, (4) 10% aqueous povidone–iodine and triclosan-coated suture (Fig. 2). Randomization is stratified by predicted wound contamination (clean-contaminated versus contaminated/dirty). Within each stratum, a minimization algorithm ensures balance in urgency (elective versus emergency procedures), age (children < 18 years of age versus adults aged ≥ 18 years) and hospital.

Randomization can be performed by a member of the research team who will not be involved in patient follow-up. For example, this can be the operating surgeon, surgical assistant, anaesthetist or theatre nurse. Randomization is preferentially performed on a password-protected online system, provided by a third party. Alternatively, a telephone randomization service is available 24 h a day, 7 days a week. In exceptional circumstances when neither online nor telephone randomization is possible, sequentially numbered, opaque, sealed envelopes have been prepared centrally for local distribution as back-up randomization.

The operating surgeon, surgical assistant and theatre team are aware of the randomized allocation. The patient and outcome assessors are blinded to the randomized allocation. In-theatre randomization minimizes the risk of unblinding. For cases where it is anticipated that in-theatre randomization will not be possible (e.g. no internet or phone access), randomization should be performed preoperatively and as close to surgery as possible., Ideally, operation notes will not include details of specific skin preparation or type of suture to maintain blinding, unless specifically required by the local research ethics committee or local regulatory body.

General operative considerations

The WHO Surgical Safety Checklist [2] will be used during the period of the study in order to standardize perioperative care [21]. Those centres currently not using this programme will need to familiarize themselves with it this prior to recruiting patients. Compliance with the individual components of the checklist is not mandated in this pragmatic trial but is recorded on the intra-operative case report form.

Trial technique: skin preparation

PIs are responsible for training surgeons and theatre staff at their hospitals to use the same standardized technique to apply both the 2% alcoholic chlorhexidine and 10% aqueous povidone–iodine skin preparations. The skin can be cleaned initially using normal saline or water to remove any gross contamination. If appropriate, any hair removal is performed using skin clippers (or equivalent) immediately prior to skin preparation. After pouring 50–100 ml into a sterile container, the randomized skin preparation is applied using a swab on a stick (e.g. Rampley sponge forceps) or, with alcoholic chlorhexidine, a Chloraprep stick if this is available. The skin preparation is initially applied at the planned skin incision site and this area is scrubbed for 30 s. Next, the preparation is applied in concentric circles going outward from the incision site to the sides of the abdomen. Only one layer of skin preparation is applied. The preparation solution is allowed to dry for at least 2 min before draping the patient and making the skin incision.

As regards closure of the abdominal fascia sheath, the randomization is to triclosan-coated or noncoated sutures. Other suture characteristics (suture size, loop or nonloop PDS) are selected at the surgeon's discretion. Similarly, surgeons can use their choice of technique, interrupted or continuous. The skin is approximated with sutures (again any type or technique) or staples or can be left open to heal by secondary intention.

All other aspects of intra-operative care are determined by the surgeon and anaesthetist. Technical aspects of the procedure, such as the skin closure method, are captured on the intra-operative case report form (CRF).

Assessment schedule

Trial data are recorded on CRFs and then entered on to a secure online REDCap server hosted by the University of Birmingham. Data are pseudo-anonymized on the REDCap server with only a unique trial number used to identify each patient. CRFs are stored in a locked cabinet in a locked office at the local site. Data are collected at patient entry, intra-operatively, at discharge from hospital and at 30 days postsurgery (Table 1).

Clinical follow-up

Follow-up will be performed by trained, blinded outcome assessors. All patients who have been randomized and operated on should be followed up. This includes patients who were predicted to have a clean-contaminated, contaminated or dirty wound but whose

Table 1 Schedule of assessments.

Processes	CRF	Time point			
		Trial entry	Intra-operative	Day of discharge	Postoperative day 30
Informed trial consent	Consent form	X			
Eligibility check and baseline data collection Randomization	Randomization notepad	X			
Adherence to allocated interventions	Intra-operative CRF		X		
Clinical examination for SSI and return to normal activities Death	Follow-up at discharge CRF			X	
	Follow-up at postoperative day 30 CRF				X

CRF, case report form.

operation was clean (e.g. a planned bowel resection which was not necessary). It also includes those with a predicted incision ≥ 5 cm who had a smaller incision (e.g. a planned laparoscopic extraction site not created).

The primary outcome will be captured from the time of index surgery until postoperative day 30. If follow-up is not possible on postoperative day 30, patients will be followed up as soon after this as possible. If a patient develops SSI before postoperative day 30 they will still be reviewed on postoperative day 30 to record secondary outcomes.

If it is local practice that patients do not routinely return for in-hospital review at around postoperative day 30, their travel costs will be refunded to encourage them to attend review. Additional incentives can be offered, based on local practices. If patients are unable to return for in-person review, a member of the research team will attempt to visit them in the community. If this is not possible, a telephone interview will be arranged.

Sample size

The two trial strata (clean-contaminated and contaminated/dirty surgery) will be separately powered based on different baseline SSI rates. The clinical impact of an intervention may differ in clean-contaminated compared with contaminated/dirty surgery where infection is less likely to have an overall impact on recovery. Therefore, different intervention effects are specified for each stratum based upon the perceived differences in clinical impact. The sample sizes are based on 90% power, a 5% two-sided significance level and 15% loss to follow-up or death prior to reaching the primary end-point, and assuming no intervention interaction. The pooled sample size combining both strata is 5480 and is calculated as follows:

1 For the clean-contaminated stratum, a control group SSI event rate of 12% is anticipated based on GlobalSurg 2 data [6]. A 4% absolute reduction to 8% (i.e. relative risk of 0.67) is considered clinically important and would require 2780 patients in total (1390 per arm for the comparison of a main effect);
2 For the contaminated/dirty stratum, a control group SSI event rate of 30% is anticipated based on GlobalSurg 2 data [6]. A 6% absolute reduction to 24% (i.e. relative risk of 0.80) is considered clinically important and would require 2700 patients in total (1350 per arm for the comparison of a main effect).

Statistical data analysis

All analyses will be based on the intention to treat principle. For all outcome measures, summary statistics will be presented, with the relevant adjusted effect measures, 95% confidence intervals and *P*-values from two-sided tests. The effect of each intervention will be adjusted for the other intervention as well as the variables minimized on at randomization where possible. No adjustment for multiple comparisons will be made. For all binomial outcomes, log-binomial regression models will be used where possible to calculate adjusted relative risks and 95% confidence intervals. For all time to event outcomes, Cox proportional hazards models will be used if the assumptions of proportionality are met, and adjusted hazards ratios with 95% confidence intervals presented. For continuous outcomes, linear regression methods will be used if the outcome is sufficiently normally distributed (or where data can be suitably transformed) to calculate an adjusted mean difference and 95% confidence interval. For skewed continuous outcomes, unadjusted median differences and 95% confidence intervals will be presented. An intervention

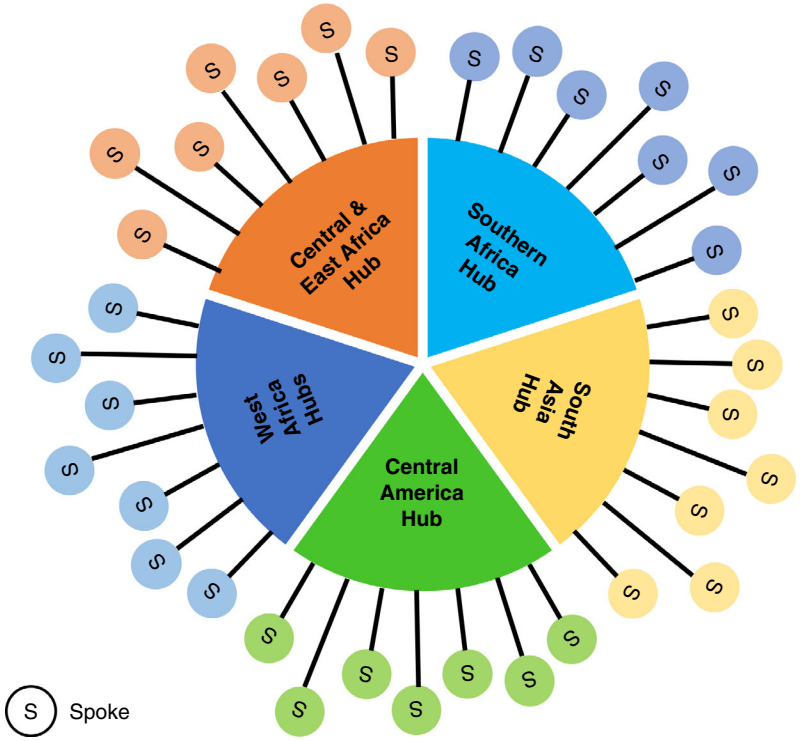

Figure 3 'Hub and spoke' network (S, spoke hospital). Hub locations: a West Africa Hub is at Lagos University Teaching Hospital, Lagos, Nigeria; a second West Africa Hub is at Tamale Teaching Hospital, Tamale, Ghana; the Central and East Africa Hub is at the University Central Hospital of Kigali, Kigali, Rwanda; the Southern Africa Hub is at the University of the Witwatersrand, Johannesburg, South Africa; the South Asia Hub is at the Christian Medical College Ludhiana, Punjab, India; and the Central America Hub is at Hospital Español de Veracruz, Veracruz, Mexico.

interaction effect is not anticipated; however, an estimate of the intervention interaction effect for the primary outcome will be presented as is recommended for all factorial trials [22]. The primary analysis of all outcomes will be based on the separate treatment effects for each of the two strata (clean-contaminated and contaminated/dirty). A secondary analysis for all outcomes will be based on pooled data for both strata.

Subgroup analyses will be limited to the same variables used in the minimization algorithm, with the exception of hospital. This will include urgency (elective, emergency) and age (child, adult). Tests for statistical heterogeneity will be presented alongside the effect estimate within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

Resource use

Data will be collected at 30 days for adult patients (aged ≥ 18 years) at preselected hospitals: length of stay in hospital; readmission to hospital; discharge from hospital with (1) pain killers, (2) antibiotics, (3) wound dressings; cost of postoperative visit to (1) hospital, (2) a community doctor, (3) a nurse or other health worker, (4) a home visit by a nurse or other health worker.

Ethics and dissemination

The FALCON trial has been approved by the University of Birmingham Research Ethics Committee (ERN_18-0230).

The trial has been disseminated through a 'hub–spoke' structure (Fig. 3). In each participating country, a central hospital acts as a national coordinating centre with a senior surgeon acting as the national coordinating investigator. Hubs are responsible for recruiting regional and district-level hospitals to create a representative, country-wide network of spoke hospitals. Hubs coordinate FALCON across their network, taking responsibility for securing national clearances, oversight of spokes and governance, and financial reporting. In collaboration with the International Coordinating Centre based at the University of Birmingham, each hub has also established safety reporting processes and

monitoring plans which are acceptable to local and overall regulatory requirements. Each spoke is responsible for ensuring it completes local regulatory processes, such as securing research ethics and/or institutional review board approvals.

Dissemination of data and data sharing

A meeting will be held after the end of the trial to allow discussion of the main results among the collaborators prior to publication. Results of the trial will be submitted for publication in a peer-reviewed journal. The success of FALCON depends on the collaboration of a large number of clinicians across several countries. For this reason, all publications arising from this work will be attributed to the 'FALCON Collaborative and NIHR Global Research Health Unit on Global Surgery', with the writing committee and order approved by the National Institute for Health Research (NIHR) Unit on Global Surgery Executive Committee. The collaborative authorship will include PIs and investigators who have consented or completed follow-up for a minimum of 10 patients. Any secondary publications and presentations prepared by investigators must be reviewed and approved by the trial management group. Manuscripts must be submitted to the trial management group in a timely fashion prior to submission for publication in order to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of The University of Birmingham and funding from the NIHR. Intellectual property rights will be addressed in the clinical study site agreement between the sponsor and the national coordinating centre. Individuals may make a formal request for the full dataset along with a proposed statistical analysis plan. Such requests will be considered by the trial management group. Although individual countries will be allowed to publish their efficacy results, the publication of efficacy results from the pooled analysis will take precedence unless the trial management group decides otherwise.

Discussion

FALCON will be the largest international RCT of interventions aimed at reducing the incidence of SSI across a diverse range of indications and procedures in LMICs. A finding that either 2% alcoholic chlorhexidine or triclosan-coated sutures reduces the incidence of SSI would influence international clinical guidelines such as those of the WHO [7,8] and the Global Surgery Guidelines [23]. Furthermore, any recommendations from this study could be applied to routine practice by incorporating them into the 'SSI bundle' already embedded in many local versions of the WHO Surgical Safety Checklist [21].

A key factor determining the adoption of alcoholic chlorhexidine or triclosan-coated sutures if they reduce SSIs, is their cost-effectiveness. FALCON will be the first multi-country RCT to determine the cost-effectiveness of specific interventions aimed at reducing SSI in LMICs. Furthermore, the high-quality, generalizable multi-country SSI cost data that FALCON will generate will be valuable to the development of pretrial models for future prevention of SSI in LMICs.

At the time of submission, both patient recruitment and follow-up are ongoing.

Writing Group

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Conflicts of interest

The authors have no competing interests to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. List of collaborating authors of the FALCON Collaborative.

Appendix S2. FALCON adult patient information sheet.