ESCP Cohort Study:

An international cohort study of Wound Closure and Surgical Site Infection Prevention Strategies in Abdominal Surgery

(WOLVERINE)

Study Protocol 1.0

Version 30th January 2024

FUNDING AND SPONSOR

Funding and Support in Kind	
Ethicon	Unrestricted educational grant to the European Society of Coloproctology.
European Society of Coloproctology	Direct funding for study conduct.
This is an investigator-initiated and investigator-led study.	
Sponsor	
The University of Birmingham	
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Sponsor statement	
By signing the REC application for this study, the University of Birmingham, acting as the sponsor, confirms approval of this protocol. **Compliance statement** This protocol describes the *2023 ESCP Cohort Study*. The protocol should not be used as a guide for the treatment of patients not taking part in this study. The study will be conducted in compliance with the approved protocol, the General Data Protection Regulation (GDPR) and subsequent amendments, and the principles of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.	
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I, the Chief investigator, confirm that I have read and agreed the following protocol and that I will conduct the study in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Study Name	ESCP Wound closure and SSI prevention in abdominal surgery cohort study	Protocol Version Number	Version: 1.0
CI Name	Thomas Pinkney	Protocol Version Date	30 January 2024
Study Role	Chief Investigator		
Signature		Date	

DEPUTY CHIEF INVESTIGATOR

Gabrielle van Ramshorst	Associate Professor of Surgery

I, the Deputy Chief investigator, confirm that I have read and agreed the following protocol and that I will conduct the study in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Study Name	ESCP Wound closure and SSI prevention in abdominal surgery cohort study	Protocol Version Number	Version: 1.0
DCI Name	Gabrielle van Ramshorst	Protocol Version Date	30 January 2024
Study Role	Chief Investigator		
Signature		Date	

STUDY SUMMARY

Title: An international cohort study of Wound Closure and Surgical Site Infection Prevention Strategies in Abdominal Surgery

Background: The 2021 ESCP Wound Closure Survey found significant heterogeneity in common practices for abdominal wound closure and SSI prevention, including various types of fascial closure techniques and suture used, skin preparation and sterility measures taken during the surgical intervention.

Aim: To conduct a prospective, international cohort study in wound closure and SSI prevention following abdominal surgery. An international network will deliver the cohort study and collate clinical information on wound closure practices used and **patients** will provide their own short and longer-term outcomes on wound healing, recovery and return to normal function.

The data will also be used to inform the design of a future interventional trial on wound closure and SSI prevention.

Design: The study has two separate components:

1) Clinical data collection: clinician-derived baseline clinical data and short-term 30-day outcomes for patients undergoing elective and/or emergency general and colorectal surgery.
2) Cohort study: patient-reported additional outcome data for the period from 30 days to one year after surgery in the identical cohort of patients, provided that patient level informed consent is obtained.*

A parallel audit, overseen by ESCP, is ongoing. This audit collects only anonymised clinician-derived baseline clinical data and short-term 30-day outcomes for patients undergoing elective and/or emergency general and colorectal surgery. This is detailed in a separate protocol.

*** All sites have the option to participate in either the audit alone or the combined audit and cohort study. This protocol describes the cohort study only..**

Centre eligibility: Any hospital or surgical unit performing elective and/or emergency general and colorectal surgery.

Patient eligibility: Adults (age 18 years and above) undergoing surgery by abdominal approach are eligible, including elective, expedited or emergency surgery by open, laparoscopic or robotic approaches with a minimum (extraction) incision length of 5 cm.

Key outcome measures*:*

- Patient, disease and operation-related factors including detailed information on wound closure techniques and SSI prevention measures.
- Clinician-derived surgical outcomes data for up to 30 days post-operation.

- Patient-reported outcomes data at five time points: 30, 60 & 90 days, 6- & 12-months post- operation. Time-specific data collected on wound healing, post-operative recovery and return to normal activities, re-admissions and re-operations, development of incisional hernia at one year.

***Sample size*:** Based on previous studies, 1,000 patients are expected to participate in the cohort study.

List of abbreviations and definitions (in alphabetical order)

Abdominal wound dehiscence (also referred to as 'evisceration' or 'fascial dehiscence'). Defined as an unintended acute wound failure at the level of the fascia and a postoperative complication after primary closure of a laparotomy incision.

Degree of contamination during surgery
Clean: an incision in which no inflammation is encountered in a surgical procedure, without a break in sterile technique, and during which the respiratory, alimentary and genitourinary tracts are not entered
Clean-contaminated: an incision through which the respiratory, alimentary or.genitourinary tract is entered under controlled conditions but with no contamination encountered
Contaminated: an incision undertaken during an operation in which there is a major break in sterile technique or gross spillage from the gastrointestinal tract, or an incision in which acute, non-purulent inflammation is encountered. Open traumatic wounds that are more than 12 to 24 hours old also fall into this category
Dirty: An incision undertaken during an operation in which the viscera are perforated or when acute inflammation with pus is encountered during the operation (for example, emergency surgery for faecal peritonitis), and for traumatic wounds where treatment is delayed, and there is faecal contamination or devitalised tissue present.

Early abdominal wound failure. Defined as surgical site infection, surgical site occurrence or abdominal wound dehiscence diagnosed within 30 days postoperatively.

Incisional hernia. Defined by the European Hernia Society as "any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging".

Late abdominal wound failure. Defined as surgical site infection in presence of foreign body material or incisional hernia at one year postoperatively.

SSI: Surgical Site Infection. Defined by the CDC (Centers for Disease Control and Prevention) as infections related to a surgical procedure that occur near the surgical site within 30 days following surgery (or up to 1 year following surgery where synthetic implants are involved).

SSO: Surgical Site Occurrence. Defined as: wound cellulitis, non-healing incisional wound, skin or soft tissue ischemia, skin or soft tissue necrosis, serous wound drainage, stitch abscess, seroma, hematoma, infected or exposed mesh, surgical site infection, abdominal wound dehiscence.

INTRODUCTION

The *European Society of Coloproctology (ESCP) cohort studies group with Birmingham Surgical Trials Consortium* and *the Birmingham Centre for Observation and Prospective Studies* have developed an international network of hospitals and surgeons to deliver the *Wound Closure and Surgical Site Infection Prevention Strategies in Abdominal Surgery (WOLVERINE)* study; the last four audits conducted between 2015-2022 included thousands of surgeons from hundreds of hospitals. Our network has grown to 70 countries.

The impact of this study can be ground-breaking not only from the perspective of patient safety and quality of life, but also because of the methodology proposed. The data collected in this cohort study will be used in combination with the parallel audit findings. Collecting prospective, unselected patient data and providing feedback directly to the surgeons and hospitals can inform and harmonise practice across countries and continents. We additionally plan to use this data to populate an education platform (supported by Ethicon) that will be disseminated across the network and beyond. A previous study carried out using this methodology, EAGLE (ClinicalTrials.gov NCT04270721), is submitted for publication. It is envisaged that this pathway could be used to improve and standardise surgical quality for many other operations and processes around surgery in the future, in countries with both well developed and less developed surgical services.

BACKGROUND

Wound closure methods following surgical intervention is a major issue and has been the focus of interest ever since surgical interventions were introduced. Historical evidence dating back to Ancient Egypt shows an interest in differing closure techniques and the materials utilized (1). From Hippocrates and Galen to Lister and Fleming, the focus and improvement in wound management has been sought (2–4). However, despite considerable improvements in patient outcomes, failure of wound healing still remains the commonest cause of surgical morbidity worldwide. The occurrence of superficial wound infection and abdominal wound dehiscence influence incisional hernia rates, impairs quality of life (QoL) and impacts healthcare expenditure (5,6,7,8)

For years there has been considerable research into both the ideal methods of wound closure and the ideal suite of interventions to reduce surgical wound infections. The use of specific suture material, the distribution of tension across the wound, and the role of adjuncts (bowel preparation, antibiotics, prophylactic mesh) have all been investigated (9). Improving patient modifiable risk factors (body mass index, smoking status, medication use) are also important factors to consider (12-17). However, complete mitigation of all patient related risk factors is not feasible. Therefore, health organisations have focused on surgery related factors, such as patient pre-operative preparation, sterile environment and interventions proven to lower the risk for surgical site infections. For example, the World Health Organisation (WHO) has published guidelines on SSI prevention, with a most recent partial update in 2018 (18). The recommendations include commonly accepted interventions including prophylactic antibacterial perioperative therapy and

surgical site preparation prior to the surgical intervention, among others. However, although these guidelines are extensive, they are based on low to moderate evidence in the vast majority of recommendations, leading to limited uptake and implementation.

Several large prospective studies have reported on varying closure techniques and their impact on incisional hernia rates. The 2015 STITCH trial, compared small and large suture bites in abdominal wound closure (19). The authors observed that those with small bites had a lower risk of incisional hernia at one year follow-up. Alternatively, the PRIMA trial compared primary abdominal fascial closure to standard closure plus prophylactic mesh (onlay or sublay). These studies demonstrated that prophylactic onlay mesh significantly reduced incidence of incisional hernias (20). These studies have had several critiques and caused substantial debate in surgical communities across the world. Additionally, the studies to date have considerable heterogeneity and limited QoL outcome data. The Match review, a meta-analysis and systematic review aimed to evaluate fascial closure materials and techniques for emergency and elective laparotomies was published in 2015 (21). Although the authors found significant heterogeneity between included studies, small bites and stitches that absorb slowly seemed to have advantages in incisional hernia prevention. The most recent guidelines of the European Hernia Society (EHS) reflect these findings, as the current recommendation of the society is to close the fascia with a continuous, small bite, slowly absorbable suture. Most of the recommendations in these guidelines, however, rely on low to moderate quality evidence (22).

The aim of this current study is to provide global real-world data on patients, disease and operation-related factors and outcomes, which will also serve as benchmark data to set up a future interventional study on abdominal wound closure and SSI prevention.

STUDY RATIONALE

Need for research

In 2023, the ESCP conducted an international survey on common practices in abdominal wound closure and SSI prevention. (23) Over 500 ESCP members, colorectal and general surgeons participated in this study. Three common clinical scenarios were described, which included contaminated emergency surgery, clean contaminated laparoscopic and open surgery. Participants were asked to indicate how they would approach each case. The study found significant heterogeneity in common practices for abdominal wound closure and SSI prevention, including various types of fascial closure techniques and sutures used, skin preparation and sterility measures taken during the surgical intervention. This cohort study, and the parallel audit, will be the first large scale international study to investigate the impact of wound closure and early wound complications on the long term outcomes.

Justification of patient population

There are few prospective studies on variations of practice worldwide. Randomised studies on abdominal wound closure often focus on general and clean or clean-contaminated surgery, in absence of ostomies. Whether abdominal wound closure strategies can be fully extrapolated to colorectal surgery patients is questionable. This study will provide data on patients who are infrequently included in randomised studies, such as patients who undergo emergency surgery and dirty surgery. In addition, the study will provide the surgical community with data regarding global heterogeneity in the uptake of various recently proposed innovations including the small bites technique, and prophylactic mesh in colorectal surgery, as well as provide contemporaneous operative outcomes on an unselected population.

Rationale for study design

Cohort studies allow for the gathering of large numbers of unselected patients from many hospitals over a relatively short timeframe. There are two components to WOLVERINE that are being conducted: the WOLVERINE COHORT study, detailed within this protocol, and the WOLVERINE AUDIT, detailed in a separate protocol. Patient eligibility is the same within each study.

The cohort study will provide contemporaneously collected data on the impact of wound infection or long term wound failure on quality of life. This cohort study will also be the first study to collect and link data on short-term wound healing issues with longer-term wound failure.

The parallel prospective audit study will result in the generation of a large, international dataset of real-world data on wound closure and SSI prevention practices for patients undergoing abdominal surgery, and enable the first description of the global variability in practice.

This dataset will be used to explore how differences in patients, treatment practices and preventative measures may be associated with different clinical and patient-reported outcomes. The datasets will be analysed separately. They cannot fully control for selection bias and interaction effects; as such, they create hypothesis-generating information rather than true evidence of effect. The data collected as part of this study will be used to inform the design of a future interventional study on abdominal wound closure and SSI incidence in the elective and expedited/emergency general and colorectal surgery patient populations.

AIMS & OBJECTIVES

Main research question:

1. What is the relationship between differing wound closure materials and techniques, with the occurrence of early and late abdominal wound failure?

Abdominal wound failure includes surgical site infections according to Center for Disease Control classification, surgical site occurrences (which will be described excluding SSI,

abdominal wound dehiscence), abdominal wound dehiscence with or without evisceration, and incisional hernia formation. (24) Abdominal wound dehiscence (also referred to as 'evisceration' or 'fascial dehiscence') is an unintended acute wound failure at the level of the fascia and is a postoperative complication after primary closure of a laparotomy incision. (25) Incisional hernia is an example of late abdominal wound failure, occurring up to 65% in high-risk groups and up to at least 10 years after surgery (*long term follow-up of the PRIMA trial, accepted for publication in the Lancet.* (26) It was defined by the European Hernia Society as "any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging". (27, 28)

Further research questions:

1. What is the relation between early abdominal wound failure and late abdominal wound failure?
2. What is the impact of late abdominal wound failure, including incisional hernia, on the patient's quality of life?
3. What are the rates of early and late abdominal wound failure?
4. What are the effects of SSI prevention measures on the incidence of early and late abdominal wound failure?
5. What is the impact of a minimally invasive technique vs. open technique on the incidence of early and late abdominal wound failure?
6. What is the impact of early and late abdominal wound failure on the patient?
7. What is the impact of early and late abdominal wound failure on the duration of postoperative stay and the number of outpatient visits and unscheduled hospital visits?
8. What are the early and late abdominal wound failure associated costs (eg, hospital/ICU stay, unscheduled hospital visits and patient reported expenses)?
9. Which risk scores will have the highest predictive value for our primary outcomes within this cohort?

Summary of the cohort study key objectives

Short term:	***Longer-term*:**
Assessing the different practices of wound closure and surgical site prevention globally Assessing the effect of wound closure and surgical site infection prevention practices on the incidence of abdominal wound failure at 30 days.	Early phase: 30 days to 90 days Assessing the different practices of abdominal wound closure and surgical site prevention globally and their effect on wound healing, SSI, patient recovery and return to normal function. Later phase: 90 days to 1 year The incidence of abdominal wound failure, including the development of incisional hernia.

	Overall: Exploring the relationship between early adverse wound outcomes and longer-term patient-reported incisional hernia occurrence. Comparison of quality of life for patients with and without wound healing issues and/or incisional hernia.

Key outcome measures

Short term:	***Long-term:***
Methods of Wound Closure: ● Types and techniques of fascial, subcutaneous and skin closure ● Incidence and types of mesh use ● Use of SSI Prevention measures ● Incidence of abdominal wound failure at 30 days ● Length of postoperative stay ● Reoperations within 30 days ● 30-day mortality ● SSI diagnosis or management requiring ICU admission ● Unplanned readmissions within 30 days ● Need for interventional radiology procedures within 30 days ● Abdominal wound dehiscence within 30 days	Patient-reported outcomes and quality of life from 30 days to 1 year post-operation At all time points: ● EQ5D-5L ● SF-12 Early phase [wound healing / SSI / return to normal function]: 30 days to 90 days ● Bluebelle wound healing questionnaire at 30 days ● Patient reported Wound Recovery PROM - outpatient visits, unplanned hospital visits within 90 days, wound healing, return to work, satisfaction with wound at 30 days ● Repeat the Patient reported Wound Recovery PROM at 60 days and 90 days if wound is not fully healed at these time points Late phase [wound integrity, reintervention, incisional hernia]: 90 days to 1 year

• Clavien Dindo classification at 30 days • Surgical site occurrences at 30 days	• ESCP Incisional hernia PROM at 90 days, 6 months, 1 year • HerQles questionnaire at 1 year

STUDY DESIGN

International prospective cohort study.

The study will collect wound closure and SSI prevention measures employed, and short-term clinical outcomes up to 30 days and longer-term patient-reported outcomes.

Study Timelines

- The cohort study, will open within one month of being approved.
- Participating sites must have started recruitment within 3 months of the study being approved.
- The study is anticipated to close to recruitment in mid-2025.

ELIGIBILITY

Hospital inclusion criteria

Any hospital or surgical unit performing elective and/or emergency abdominal general and colorectal surgery.

Participating sites will be expected to recruit at least 10 consecutive eligible patients within a 4-week period.

At hospital level, data completeness of 95% will be required.

Patient eligibility

Inclusion criteria

- Adult patients (age 18 years and above) undergoing general or colorectal surgical procedures
- Elective (planned admission), expedited (within two weeks), or emergency (unplanned admission) surgery.
- General and colorectal procedures using any type of abdominal incision measuring at least 5 cm (including extraction sites).
- Able to give written informed consent

*For those patients who do not speak the national language of the country in which they are recruited for participation, normal hospital policies for translation to facilitate participation will be followed.

Exclusion criteria

- Patients undergoing incisional, ventral, umbilical, and inguinal/femoral hernia repair
- Simultaneous hyperthermic intraperitoneal chemotherapy (HIPEC) and/or cytoreductive surgery
- Stoma reversal without additional laparotomy incision
- Anyone who does not have an email address or who does not have access to the internet or a smart device.

Note: Each individual patient should only be included once. Following the index procedure (i.e. the procedure for study inclusion), patients undergoing additional procedures within the study window should not be included for a second time. Data on these additional procedures will be captured as part of patient follow-up.

Selection bias

Selection bias will be closely monitored by the Study Management Group. Study coordinators will regularly liaise with site Principal Investigators to ensure that all eligible patients are entered consecutively into the study. Recruitment rates will be monitored across individual sites and clarification will be sought in case of a drop in recruitment that might indicate that eligible patients were not included.

PATIENT IDENTIFICATION AND CONSENT

All consecutive adult patients who fulfil the eligibility criteria should be included. As this is an international study, each participating country and hospital will decide how best to identify and approach eligible patients. It is anticipated that potential participants may be identified as described below.

Potential participants may be identified:

- Pre-operatively:
    - Surgical outpatient clinics (e.g. when the patient is being booked for elective surgery)
    - Planned theatre lists (e.g. at the time of admission for surgery)
    - Emergency surgical admissions (e.g. at the time that a decision to operate is made)
- Intra-operatively
    - By operative team
- Post-operatively prior to discharge:
    - By the operating surgeon

**Ideally, potential participants will be identified pre-operatively.

SCREENING

The WOLVERINE Screening Log will be held on the REDCap data capture system. Each potential participant will be recorded by the site and a REDCap id number generated for every record entered. This REDCap ID number will then be used for those patients who are eligible and provisionally agree to enter the cohort study.

No specific screening visits or other screening procedures are planned.

INITIAL APPROACH TO PATIENT

Potential participants will be approached by either:

- The senior operating surgeon
- Any doctor involved in the patients' care (e.g. surgeon in training)
- Clinical nurse specialist (depending on local regulations)

Patients will be provided with background information about the study*, including the premise of the study, patient pathways, and what their participation would involve. The patient will have an opportunity to ask questions and a written WOLVERINE Study patient information sheet (PIS) will be provided as an adjunct to this conversation.

A record of the discussion with the patient will be kept in the patient's medical notes.

*The patient-facing documents will be available in the national language of each participating country.

PATIENT CONSENT

Informed consent within the WOLVERINE cohort study will be documented in REDCap.

WOLVERINE is a non-interventional study; there are no clinical interventions additional to those received as part of routine clinical care. Only routinely collected, anonymised data will be collected by the clinician at baseline and 30-days.

However, at the 30, 60, 90 days and 6-month, one-year post-op follow-up time points, patient reported outcomes will be collected remotely via REDCap, thus consent is required for the collection and analysis of this data.

Patient consent is therefore specifically sought for the permission to collect the follow-up data via the remote monitoring system and to contact the patient at the 30, 60, 90 days and 6-month, one-year post-operative follow-up time points via email or text reminders. Participants will be contacted up to three times at each timepoint to request completion of the questionnaires. Reminders will be sent via an automated email reminder from the central team at the University of Birmingham. As part of the consent process, patients will be asked to provide their email address and mobile phone number.

Process for consent for follow-up

Consent will be obtained remotely via REDCap.

Once a patient is identified as eligible, their surgeon or another member of their direct clinical care team will discuss the study with them. They will be provided with the PIS to facilitate the discussion.

The patient will be provided with a unique patient identification number by the person discussing the study with them (this is taken from the site-specific WOLVERINE REDCap LINK SHEET provided by the study office). This unique identifier will be recorded on the WOLVERINE PIS. Eligible patients will also be provided with a generic QR code. This QR code and unique identifier will be used by the potential participants to access the REDCap-WOLVERINE system and the consent form.

The potential participant will then be asked to access the online system at a time convenient to them, i.e. they do not need to access the system whilst in hospital. Upon access of the online REDCap system, they will be asked for consent for follow-up.

This unique REDCap ID will be the only identifier used to identify the patient in any correspondence between the coordinating centre and the participating site.

*Participating sites may download the consent form as a PDF if required for the WOLVERINE Site File.

STUDY FOLLOW-UP

Follow-Up Time points

After the baseline visit, there are no further study-specific visits. All study-specific follow-up is conducted via remote reporting.

There are 5 follow-up time points: 30-, 60- AND 90-days post-surgery; 6 months and one year post-surgery.

Short-term follow-up: 30-days post-surgery

- Clinician reported:
    - Conducted without the need for patient attendance.
    - No specific follow-up visit is mandated for participants.
    - The 30-day post-surgical outcomes form is undertaken by the clinical team, with routinely collected information from patient notes or electronic records, or other routinely collected data sources.
- Patient reported
    - Data is collected remotely from the participant via the WOLVERINE online REDCap system
    - Bluebelle wound healing questionnaire, EQ-5D5L, SF-12, the Patient reported Wound Recovery PROM QoL and the ESCP Incisional Hernia PROM.

Longer-term follow-up

At the 60-days, 90-days, 6-month and 1 year post-operative timepoints, data is collected remotely from the patient only. The following questionnaires will be requested:

- The EQ-5D5L and the SF-12 at each of the 4 timepoints.
- Bluebell wound healing questionnaire at 30 days.
- Patient reported Wound Recovery PROM at 60 days and 90 days.
- ESCP incisional hernia PROM at 3-, 6- and 12-months.
- HerQles questionnaire at 1 year

There is no clinical team involvement beyond 30-days post-surgery.

COHORT STUDY SCHEDULE OF EVENTS

		WOLVERINE COHORT STUDY								
		Study entry	Baseline data	After Surgery	30-day follow-up	30-day PROM	60-day PROM	90-day PROM	6-month PROM	1-year PROM
Clinician reported audit - <u>all patients</u>	Patient information		✓			NO FURTHER DATA COLLECTION / BEYOND 30 DAYS IN AUDIT STUDY				
	Surgery information			✓						
	Short-term Complications / reinterventions				✓					
Patient reported cohort study – <u>only patients who provide consent</u>, recorded via online PROMS system *N.B - these are **IN ADDITION to** the clinician-reported patient-level audit data*	Informed consent	✓								
	Wound healing questionnaire (Bluebelle)					✓				
	Patient reported Wound Recovery PROM					✓	✓ *if wound unhealed*	✓ *if wound unhealed*		
	ESCP incisional hernia PROM							✓	✓	✓
	HerQles questionnaire									✓
	EQ-5D-5L					✓	✓	✓	✓	✓
	SF-12					✓	✓	✓	✓	✓

PROMS targets for:

- 30 days -> 90 days
    - SSI, wound healing, return to normal function, patient satisfaction
- 90 days -> one year

- wound integrity, reintervention or readmission, incisional hernia, patient satisfaction

PATIENT WITHDRAWAL

Patients are free to withdraw from the study at any point and will be made aware from the beginning of their involvement in the study that they can withdraw at any time. Participants are given details on how to withdraw from the study in the Patient Information Sheet Before the start of each follow up questionnaire patients will be asked if they are happy to continue participating in the study.

Reasons for Withdrawal

Patients are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study subject's participation in the study if:

- Any medical condition, event or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion

Other reasons for withdrawal:

- Inability to contact the patient

Handling of Subject Withdrawals

If a patient withdraws from the study, then their record on REDCap will be closed and no further data will be collected. All data collected until that timepoint will be retained and these patients will be included in baseline analyses and reports.

SAFETY CONSIDERATIONS

There are no anticipated safety considerations relating to the WOLVERINE study. There is no risk of harm to either patients or investigators.

In the unlikely event that an incident occurs that is found to be serious, unexpected and possibly linked to the study procedures this will be reported in line with the sponsor's safety reporting procedures.

Any interventions that patients undergo will be as part of their routine clinical care; the study does not mandate any specific intervention.

The only study-specific activity is the collation of patient reported outcomes on the WOLVERINE REDCap database system.

Assessment of Risks

We do not anticipate any risks to study participants. Enrolment in the study will not have any impact on patient care as participants (unless there are significant concerns) will be receiving the same treatment that they would if they were not enrolled.

Study participants may find the follow-up contacts for completion of the questionnaires an inconvenience given that the follow-up period continues up to 12 months post study entry. We will mitigate any potential risk of attrition bias by ensuring that participants fully understand the time commitment at enrolment stage and that they know they may withdraw at any time.

In accordance with the University of Birmingham standard operating procedures (SOPs) this study has been risk assessed to clarify any risks relating uniquely to this study beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this study presents no higher risk than the risk of standard medical care.

Protocol Compliance

Protocol and GCP non-compliances should be reported to the Study Office on discovery.
The sponsor is responsible for ensuring the REC is notified of any serious breach of the conditions and principles of GCP in connection with that study or of the protocol relating to that study. Sites are therefore requested to notify the WOLVERINE Study Office of any suspected study-related serious breach of GCP and/or the study protocol as soon as they become aware of them. Where the WOLVERINE Study Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Study Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

STATISTICAL CONSIDERATIONS

SAMPLE SIZE – COHORT STUDY

Based on feasibility, we assume that each hospital provides data on at least 10 consecutive eligible patients over a 4-week recruitment period.

PROJECTED RECRUITMENT

Based on previous studies, 1,000 patients are expected to enter the cohort study.

ANALYSIS PLAN

Analysis will be performed after data has been cleaned and locked. The analysis will descriptively summarize the types of wound closure and SSI prevention measures, and the primary and secondary clinical outcomes in the audit and cohort study populations.

In the cohort study, there is potential for patients to be lost to follow-up, resulting in a variable duration of time over which outcomes may be ascertained for each patient. If follow-up varies systematically by site or wound closure techniques, this could introduce bias into the analyses of outcomes. To address this, each investigator/site should establish a plan to record the frequency, dates, and method/setting (e.g., phone, in-person) of contacts with patients when measuring outcomes over the course of the follow-up period. For example, if an investigator/research staff's last contact with a patient is completed 6 months into follow-up, but no subsequent contacts are successfully accomplished with the patient, the patient will be considered as lost to follow-up (censored) on the date of the last successful contact and will be considered as contributing 6 months of person-time to the analysis.

Upon completion of the cohort study data collection, we will examine the distribution of follow-up for all patients to determine its completeness and plan an appropriate course of action regarding statistical analysis, such as the use of complete case analysis with inverse probability of censoring weights or survival analysis methods (e.g., Cox proportional hazards models), if required. We will detail the specifics of these analyses in a statistical analysis plan after examining the empirical distributions of the data in a manner that is agnostic to the relationship between outcomes and treatment/wound closure exposure group.

Selected relevant risk scores for development of surgical site infections, surgical site occurrences, and abdominal wound dehiscence will be compared against the data collected in this study.

Planned additional analyses

A full statistical analysis plan will be published prior to study completion. Example of the analyses will include -

Pre-planned exploratory sub-group analyses of the primary outcome will be performed in the following groups:

At cluster (geographical) level:

Use of wound closure methods for Europe vs. non-Europe

Use of SSI prevention methods for Europe vs. non-Europe

At cluster (hospital) level:

Number of beds (<500 versus ≥500 total hospital beds).

Laparotomy volume (divided into tertiles).

Health service expenditure per capita in purchasing parity (top versus middle versus bottom tertile).

World Bank income group (high versus middle/low income country).

At patient level:

Indication for surgery (malignant versus benign, e.g. inflammatory bowel disease).

Procedure urgency (elective versus expedited/ emergency).

Age (≤65 years versus >65 years, possibly subanalysis for octogenarians).

Clinical Frailty score

National Nosocomial Infections Surveillance (NNIS) score

Operative approach (open versus minimally invasive (laparoscopy/robotic).

Primary operating surgeon experience as reported (trainee versus consultant).

Primary operating surgeon specialism as reported (general versus colorectal surgeon versus emergency surgeon).

Type and method of wound closure at fascial, subcutaneous and skin levels.

Pre-, intra-, and post-operative SSI prevention interventions used

Descriptive summary statistics will be provided for these aforementioned variables, with summaries presented by wound closure technique and other relevant groups. If possible, a separate estimated cost analysis will be performed to calculate the cost burden of SSI using a selection of available variables.

STUDY ORGANISATIONAL STRUCTURE AND OVERSIGHT

WOLVERINE Study Office

The coordinating centre for the WOLVERINE study is based at the University of Birmingham in the Birmingham Centre for Observational and Prospective Studies (BiCOPS). Members of this group also represent the European Society of Coloproctology (ESCP) and sit on both the research committee and cohort studies committee of ESCP.

Sponsor

The University of Birmingham is the Sponsor of the WOLVERINE cohort study in all collaborating countries. Sponsorship will be provided by the University of Birmingham upon signing of the Study Agreement with each site.

Local teams

Each site will appoint a local Principal Investigator (PI) who will take responsibility for the study at site. This will normally be an established and contracted employee working at the site, who is responsible for the overall conduct of the study. In many sites this local PI will be a consultant (attending) surgeon, but this is not mandated. If the local governance rules and regulations allow, any motivated and appropriately experienced healthcare professional could undertake the local PI role.

Each PI will appoint an additional local team of up to 5 more members, which may include surgical colleagues, trainee doctors, nurses, medical students, or others involved in the routine clinical care of eligible patients, depending on local circumstances. Members of this group will be designated local investigators and will be responsible for the local conduct of the study at their site, including helping to identify and approach potential patients and record data onto the WOLVERINE REDCap database.

WOLVERINE Study Management Group

The WOLVERINE Study Management Group (SMG) comprises those individuals who have created this protocol. This will include the Chief Investigator, WOLVERINE operations staff, and lead clinicians. The group will meet via teleconference approximately every twelve weeks to review ongoing progress. The role of the SMG is to monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard the quality of the study itself.

In addition to the SMG meetings, the Chief Investigator and the core team located within BiCOPS at the University of Birmingham will convene on a monthly basis for ongoing and continual review of study and progress.

International Advisory Committee

The remit of the International Advisory Committee (IAC) is to provide further international support, oversight and endorsement of the study through all key stages from concept and design through

to delivery and analysis. They will enhance the international dissemination of the study via their associated societies and groups throughout their respective countries and continents. The IAC members will ensure broad representation of study participants, both patients entering the study and clinicians collaborating as investigators.

The IAC will also provide a further layer of overall supervision for the study and ensure that it is being conducted in accordance with the protocol, the principles of Good Clinical Practice and other relevant regulations. The IAC will meet face-to-face or via teleconferencing at the start of the project and every twelve months thereafter.

The specific tasks of the IAC include:

- To agree the study protocol and any protocol amendments.
- To resolve problems brought to it by the WOLVERINE study management group.
- To provide advice to the investigators on all aspects of the study.

ETHICS & CONSENT

Patients will not undergo any additional investigations for the purposes of this study. Clinical follow-up will be limited to review of health records up to a maximum of 30 days postoperatively.

Additional patient contact (telephone, in-person, by email or by application) will take place between 30 days postoperatively and one year postoperatively to collect patient data.

The cohort study will be conducted and reported according to STROBE (Strengthening the Reporting of Observations studies in Epidemiology) guidelines.

DATA MANAGEMENT

Principal investigators at each participating site are responsible for obtaining necessary local approvals. Data will be collected in two phases. During the index admission, pre-operative and intra-operative data will be collected. Local Principal Investigators will establish pathways in their hospitals to ensure robust data collection; for example, pre-operative data could be collected in the morning prior to surgery, with intra-operative data fields completed in theatre immediately following completion of the procedure. Alternatively, all index data including patient registration could be collected in theatre, or in the post-operative ward.

Collection of post-discharge follow-up data

Patients who are discharged from hospital early may be more likely to develop a surgical site infection out of hospital and often fail to be noted or registered. A review of the participating patients' clinic visit notes and letters will therefore be mandatory for all participating hospitals. All

patients will be followed-up to a maximum of 30-days postoperatively (with Day 0 being the day of surgery) by a review of their inpatient health records, routine clinic visit notes/letters, and reports for postoperative radiological investigations arranged as part of normal patient care. The study is designed efficiently so that existing patient follow-up pathways and health records can be used, with only data that is routinely collected as part of normal clinical care being captured.

Patient reported outcomes.

After completing informed consent, the patient will be sent a link by email, mobile phone or text to report outcomes in REDCAP. Consent for the cohort study can be obtained either before or after surgery, unless local ethics guidance stipulates otherwise.

DATA HANDLING AND RECORD KEEPING

Source Data

Source data within the study will be kept as part of the participants' medical notes generated and maintained at site. As all clinical data collected and analysed within the study are routinely gathered in clinical practice, source data will be within the medical notes.

The patient-completed questionnaires form source data. As these are completed online via the WOLVERINE REDCap database, this data will form part of the source data.

Data Management

Information will be collected at the following times:

- At baseline (surgeon level)
- At 30 days after the operation (surgeon level)
- At 30 days after the operation (patient level)
- At 60 days after the operation (patient level)
- At 90 days after the operation (patient level)
- At 6 months after the operation (patient level)
- At one year after the operation (patient level)

Data will be entered directly onto the secure electronic REDCap database by members of the research team and by participants.

Site study collaborators will be provided with a paper copy of the eCRF to facilitate data collection. If this is used, they should then transfer data from the paper CRF into the online database (https://www.bistc.redcap.bham.ac.uk). Data management staff will check all incoming data CRFs for completeness, data consistency and compliance with the protocol. If discrepancies or missing data are identified, the data management staff will raise queries with the research team at the participating hospital via the study database.

Data Security and Data Protection

The security of the Study Database System is governed by the policies of the University of Birmingham. The study database will be hosted on the REDCap system managed and maintained by BiCOPS..

Data management and data security within BiCOPS will abide by the requirements of the General Data Protection Regulations (GDPR) and any subsequent amendments. The study will be conducted at collaborating sites in accordance with the country-specific data protection requirements.

Access to data will be restricted by usernames and passwords, at participating sites. Each participant will be allocated a unique study number at entry. All communication will use this as the identifier. All data will be analysed and reported in summary format. No individual will be identifiable.

Archiving

It is the responsibility of the PI to ensure all essential study documentation and source documents (e.g. Investigator Site Files, participants' hospital notes, copies of CRFs) at their site are securely retained for the contractual period. Archiving will be authorised by BiCOPS on behalf of UoB following submission of the end of study report. No documents should be destroyed without prior approval from the BiCOPS director.

The electronic TMF will be stored at BiCOPS for at least 3 years after the end of study. Long-term offsite data archiving facilities will be considered for storage after this time, data will be stored securely and confidentially for 10 years in accordance with the UoB Code of Practice for Research.

QUALITY CONTROL AND QUALITY ASSURANCE

Site set-up and site initiation

Once a site has local approvals in place and is nearly ready to open for recruitment, the final step will be to undertake a brief remote site initiation visit (SIV) via teleconference or videoconference. These SIVs will be run by central WOLVERINE study team members and may be conducted en-bloc with other sites at a similar stage of readiness to enhance efficiency. The SIV will cover details of local recruitment pathways, consent processes, data flow, and overall study conduct.

Investigator agreement form

Prior to opening, all participating local Principal Investigators will sign an Investigator's Agreement with the University of Birmingham to document acceptance of the responsibilities of the PI at the site.

Monitoring

Monitoring will be via data validation and range checks built into the REDCap database used to collect and manage the data; statistical monitoring techniques will be used to compare data from different sites to identify sites that may warrant further investigation, site monitoring and/or support and training. Review by the study oversight committees will also include the review of completion of primary and secondary outcomes.

Study staff from UoB will be in regular contact with the site research teams to check on progress and address any queries that they may have.

The Data Management Committee will check submitted CRFs from the participating hospitals for compliance with the protocol, data consistency and missing data. They will send participating hospitals data queries for missing data or clarification of inconsistencies or discrepancies.

END OF STUDY DEFINITION

Study participants will be followed-up by patient-completed questionnaires until 12-months post-surgery. Clinician-reported outcomes will be collected up to 30 days post-operatively. The end of study will be when the last enrolled participant completes their 12-month questionnaires, all database queries have been resolved and the database has been locked and analyses completed. The WOLVERINE Study Office will notify the REC and Sponsor within 90 days of the end of study. The WOLVERINE Study Office will provide the REC and Sponsor with a summary report of the study.

CONFIDENTIALITY AND DATA PROTECTION

At study entry, study participants will be asked for consent for the UoB to collect/hold their email address and mobile phone number. These identifiable details will be used by the central coordinating centre to contact participants to remind them to complete follow-up questionnaires and to obtain corresponding clinical data from the participant's treating centre.

Email addresses and mobile phone numbers will be deleted upon completion of the final study analysis. All data collected about participants will be identified using only the unique WOLVERINE study REDCap ID code.

Any correspondence between the WOLVERINE study office and hospital sites will use the anonymous ID code only.

The linkage between the study ID code and participants will be maintained in strict confidence at participating sites. This data will not be submitted to the WOLVERINE study office and will not be sent outside of the participating site.

Confidentiality of all participant's data will be maintained and there will be no disclosure of information by which participants may be identified to any third party other than those directly involved in the treatment of the participant.

Finance

WOLVERINE is an investigator-initiated and investigator-led study. The study has been funded by the ESCP through an unrestricted educational grant received from Ethicon.

INSURANCE AND INDEMNITY

The University of Birmingham has in place Clinical Trials indemnity coverage for UK sites for this study which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the study. For non-UK sites the University of Birmingham has in place a worldwide public liability policy.

The risk of the trial is no greater than the risk of the standard clinical care. Responsibility for the participants at sites remains with the organisation responsible for the clinical site and it is therefore indemnified through their normal arrangements.

PUBLICATION POLICY

The output from this research will be published under a single corporate authorship group: "European Society of Coloproctology (ESCP) collaborating group", manuscripts and authorships will be separated for those who contributed to the audit study and those who contributed to both the audit AND the cohort study. The following roles will be recognised within the collaborating authorship list: Study Protocol Writing group, Study Management Group, Data Management Committee, Statistical analysis, ESCP Cohort Studies and Audits Committee, ESCP Research Committee, study coordinators, Principal Investigators, co-Principal Investigators, Collaborators.

Specifically each participating hospital may include up to five collaborators for publication(s) regarding the audit study, and up to five (different or identical) collaborators for the (long term follow-up) of the cohort study on the condition that data for at least 10 consecutive patients is entered with at least 95% data completeness: the Principal Investigator; the surgical associate co-Principal Investigator; and three further collaborators supporting study delivery and data collection. An increase in the number of collaborators at a participating hospital is theoretically

possible but should be regarded as highly exceptional and prospectively agreed on a case-by-case basis with the Operations Committee. All co-authors will be PubMed searchable and citable.

No hospital-level or surgeon-level data will be published whereby an individual unit or surgeon could be identified. If local investigators would like a breakdown of their own unit's data for benchmarking purposes and local presentation/discussion, this will be available after the end of the study.

ACCESS TO FINAL DATASET

The ESCP Cohort Studies Working Group welcomes the use of the data for further research that benefits patients. Requests can be submitted to the ESCP Cohort Studies Working Group. Data Sharing is subject to ESCP approval and the appropriate safeguarding as determined by the ESCP. Any future subprojects should also comply with our policy of a single corporate authorship e.g. "European Society of Coloproctology (ESCP) collaborating group. However, authors' contributions will be highlighted in accordance with the recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals (commonly referred to as the Vancouver Convention) by the International Committee of Medical Journal Editors (ICMJE).

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