MD (Doctor of Medicine)

The Impact of Standardising Intra-Operative Variables on the Incidence of Surgical Site Infections in Colorectal Surgery in Wales.

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Summary

Background and Aims

Surgical site infections (SSIs) are infections of the incisional wound made during the operation or an infection within the area/organ space of the operation. SSIs affect up to 40% of patients post-operatively and are a burden both for the patient and the NHS due to resource consumption and cost on average £10,523 per patient. Within Wales, the colorectal SSI rate is unknown. The aim of this thesis was to establish the rate of colorectal SSIs in Wales, to assess the impact of the implementation of an SSI bundle and to investigate the impact of the hypothermia on SSIs.

Materials and Methods

A national all Wales prospective observational study was conducted to establish the colorectal SSI rate. This led to the development and implementation of an SSI bundle to assess the impact on SSIs. Despite this patient hypothermia was present in over 50% of patients. The HEAT study was designed to evaluate the use of warmed, humidified laparoscopic insufflation on intra-abdominal temperatures and impact on SSI rates.

Results

The Welsh colorectal and emergency general surgery SSI rate was 13%, with a colorectal SSI rate of 21.1%. The implementation of the SSI bundle reduced the SSI rate in one centre from 24.3% to 10.0%. Despite the bundle, hypothermia was identified as being present in over 50% of the patients. The HEAT study demonstrated that the intra-abdominal temperatures were often lower than the recorded core temperatures, and that SSIs mainly happened in those patients who were hypothermic.

Discussion

Overall, this thesis has demonstrated that the colorectal SSI rate in Wales could be halved through targeting interventions including an SSI bundle, and warming and humidifying laparoscopic insufflation gas. This is the first all Wales study to define the colorectal SSI rate, but to also demonstrate an evidence-based approach to reducing SSI rates.

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Publications and Presentations

Peer-Reviewed Publications

Reeves N, White J, Bird S, Shinkwin M, Cornish J, Torkington J. Warmed and humidified insufflation to prevent perioperative hypothermia and improve quality of recovery in elective laparoscopic colectomy patients: A feasibility, triple blind randomised controlled trial. Submitted to Colorectal Disease May 2021

Reeves N, Cuff S, Boyce K, Harries R, Roberts C, Harrison W, Torkington J. Welsh Barbers SSI Research Collaborative. Diagnosis of colorectal and emergency surgical site infections in the era of enhanced recovery: an all-Wales prospective study. Colorectal Dis 2021 Feb 5 (PMID: 33544977)

Ryczek E, White J, Poole RL, *Reeves N*, Torkington J, Carolan-Rees G. Normothermic Insufflation to Prevent Perioperative Hypothermia and Improve Quality of Recovery in Elective Colectomy Patients: Protocol for a Randomized Controlled Trial. JMIR Research Protocols, 2019 Dec 20;8(12):e14533. (PMID: 31859685)

Presentations

WICS – Wound Infection in Colorectal Surgery an All Wales Prospective Snapshot Audit of SSIs After Colorectal Surgery

- Welsh Surgeons Spring Meeting May 2019; Invited Podium Presentation
- Infection Prevention Society, Welsh Branch Conference June 2019; Invited Podium Presentation
- SiS 23rd European annual congress on surgical infections June 2021; Oral Presentation

List of Abbreviations

°C	Degrees Centigrade
ACPBGI	Association of Coloproctology of Great Britain and Ireland
AE	Adverse Events
ASA	American Society of Anesthesiologists physical status classification system.
CD	Crohn's Disease
CDC	Centre for Disease Control and Prevention
CHG	Chlorhexidine gluconate
CI	Confidence Intervals
CM	Centimetres
CO_2	Carbon dioxide
ERAS	Enhanced Recovery After Surgery
FiO_2	Fraction of Inspired Oxygen
GP	General Practice/practitioner
HCAI	Healthcare Associated Infections
HEAT Study	Quality of recovery and perioperative Hypothermia in Elective colectomy patients: A feasibility study of a blinded randomised controlled trial
IBD	Inflammatory Bowel Disease
IMA	Inferior Mesenteric Artery
IQR	Interquartile ranges
MBP	Mechanical Bowel Preparation
MBP/OAB	Mechanical Bowel Preparation and Oral Antibiotic Combination
MDT	Multi-Disciplinary Team

MRSA	Methicillin resistant staphylococcus aureus
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NPWT	Negative pressure wound therapy
ODP	Operating department practitioner
OR	Odds Ratio
PHE	Public Health England
PHW	Public Health Wales
PIS	Patient information sheet
POD	Post-operative day
PVP-I	Povidone-iodine
QoL	Quality of Life
RCSEng	Royal College of Surgeons England
RCT	Randomised controlled trial
ROS	Reactive oxygen species
RR	Risks Ratio
SC	Standard Care
SMA	Superior Mesenteric Artery
SSI	Surgical Site Infection
UC	Ulcerative Collitis
UHB	University Health Board
UHW	University Hospital of Wales
WHO	World Health Organisation

| **WICS** | Wound Infections in Colorectal Surgery |

"When a clean operated wound suppurates, the surgeon should put his house in order"

Mr. J Lynn Thomas
President of Cardiff Medical Society
1905

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1 Introduction

1.1 Colorectal Surgery and Enhanced Recovery After Surgery

1.1.1 Colorectal Surgery

Colorectal surgery is the surgical speciality that manages pathology of the colon, rectum and anus. There are many different aspects to the surgical management of colorectal patients including the approach – open, laparoscopic, robotics; and the urgency of the surgery – elective planned surgery versus emergency unplanned surgery. It is a subspecialty of the broader 'General' surgical specialty which manages general surgery patients including emergency surgery, hernia repairs and gallbladder operations and has the following subspecialties (1,2):

- o Breast
- o Colorectal
- o Upper Gastrointestinal – liver, stomach, and oesophagus
- o Endocrine – thyroid, parathyroid and adrenals
- o Hepato-pancreatic and biliary – liver, pancreas, and gallbladder
- o Transplant
- o Vascular
- o Trauma

1.1.2 Colorectal Anatomy

Colon

The colon originates at the caecum, where the terminal ileum joins the colon, and ends at the rectum, where the sigmoid colon joins the rectum at the rectosigmoid junction. The different sections of the colon, from proximal to distal, are the caecum, appendix, ascending/right colon, transverse colon, descending/left colon, and the sigmoid colon. The right colon and the left colon are attached to the posterior retroperitoneum, whereas the transverse and sigmoid colon are relatively free on their mesentery within the abdominal cavity (3).

The colon is a long tubular structure of approximately 150cm in length, which has an inner mucosal layer, connective tissue layer and an outer muscle layer. There are distinct features of the colon which include the appendices epiploicae, the taeniae coli, and the haustra. The appendices epiplocae are non-mesenteric fat on the serosal surface of the colon, the taeniae coli are three thickened outer bands of longitudinal muscle and the haustra are the colon pouches caused by the taenia coli (3).

The vascular supply of the colon is from the two main arteries, the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA), and the venous drainage follows the arterial drainage but drains into the portal vein (Figure 1-1 and 1-2) (3).
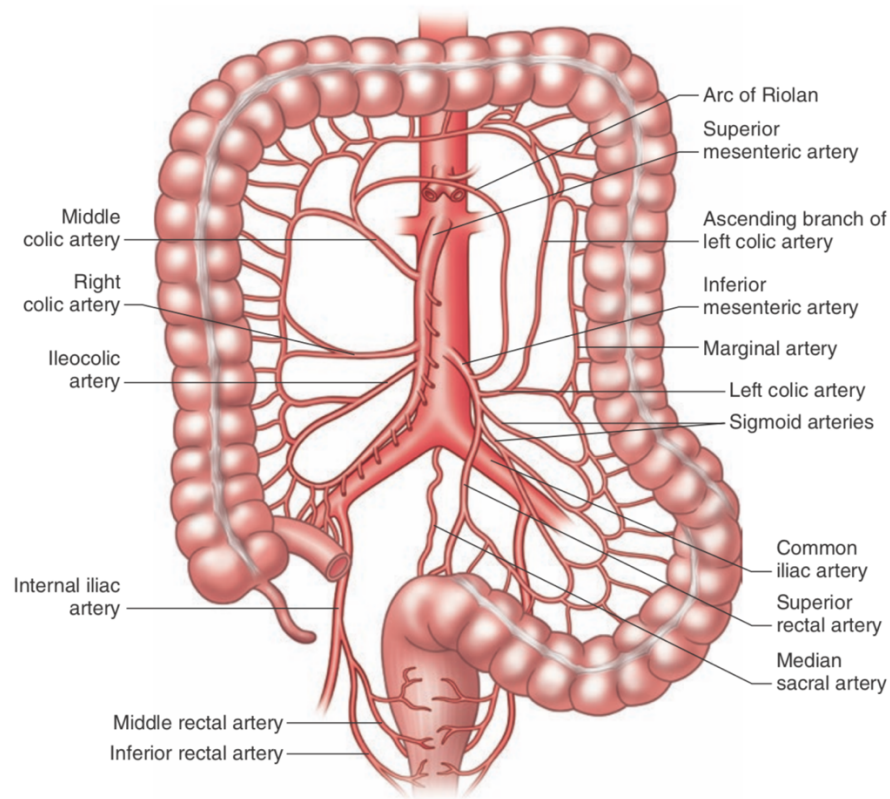
Figure 1-1 - Arterial Supply of the Colon and Rectum (3)
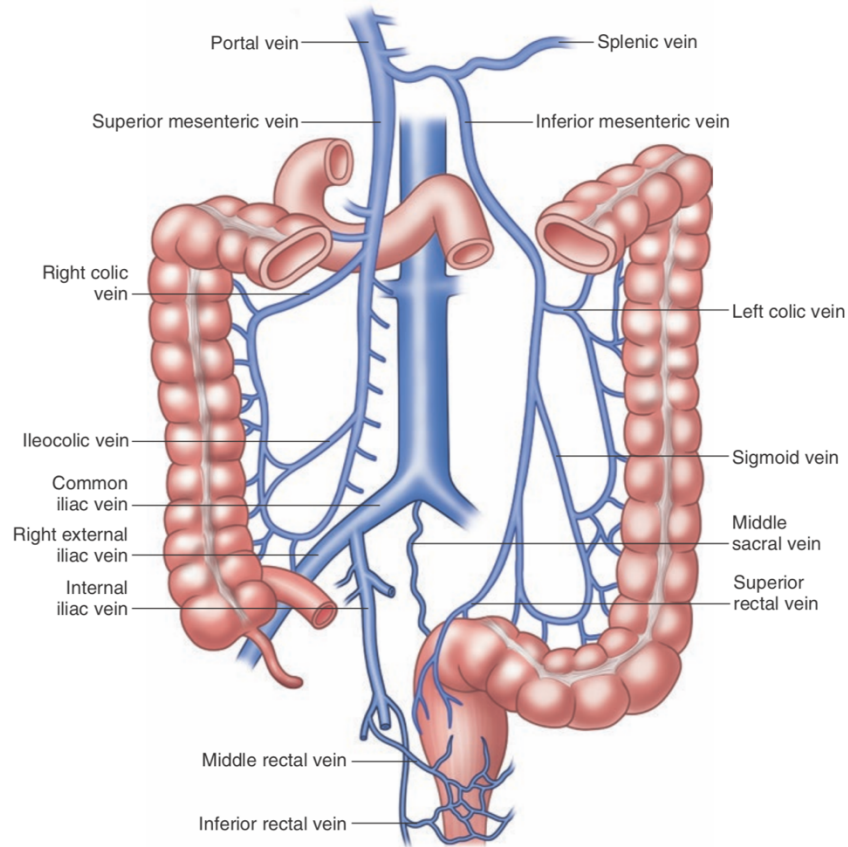
Figure 1-2 - Venous drainage of the Colon and Rectum (3)

Rectum

The rectum starts proximally at the rectosigmoid junction and ends at the anal canal just past the pelvic hiatus. The rectum is divided into three parts measured from the anal verge, lower at 0-7cm, middle at 7-12cm and upper at 12-15cm. The parts are not able to be distinguished anatomically but is important in the surgical management of rectal tumours. The upper part of the rectum is covered with visceral peritoneum on the anterior and lateral aspects, but the rest of the rectum is outside the peritoneum, below the peritoneal reflection (3).

The arterial and venous supply are seen in Figures 1-1 and 1-2. The upper part of the rectum is supplies by the superior rectal artery which is a continuation of the IMA, with the middle and lower parts supplies by the middle and inferior rectal arteries which originate from the internal iliac artery. The venous drainage is via the superior rectal vein into the portal

system, and the middle and inferior rectal veins drain systemically via the internal iliac vein (3).

Anal Canal

The anatomical definition of the anal canal is formed from its embryological development and begins at the dentate line, extended to the anal verge. However in surgical practice the surgical anatomy of the anus was first described by Milligan and Morgan in 1934 (4). The rectum passes through the pelvic hiatus and joins with the puborectalis as the proximal start to the anal canal at the anorectal ring. The anal canal then extends to the anal verge, encompassing the musculature of the internal anal sphincter, the external anal sphincter and the puborectalis (3). Figure 1-3 is a diagrammatic representation of the anal canal.
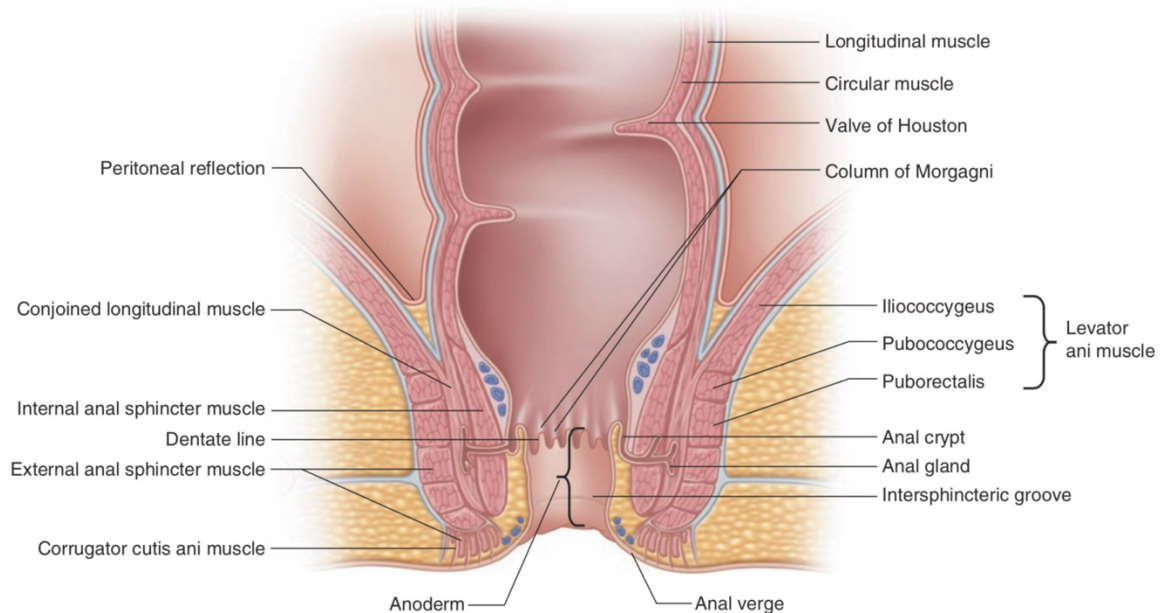
Figure 1-3 - Anal Canal (3).

Abdominal Wall

The anterolateral abdominal wall consists of the skin, fascial and musculature layers overlaying the abdominal cavity. It provides protection to the underlying organs, but the muscles also assist in with respiration, defecation, micturition and movement. During general and colorectal surgery, access to the underlying organs of the abdominal cavity involves an incision through the anterolateral abdominal wall (5,6).

The layers of the abdominal wall, seen in Figure 1-4, are:

- o Skin – the epidermis and dermis
- o Superficial Fascia – a single fatty connective tissue layer. Below the umbilicus it divides into the superficial fatty Camper's fascia, and the deeper Scarpa's fascia
- o Investing Fascia – a connective tissue layer that covers the muscles
- o Abdominal muscles – External abdominal oblique muscle, internal abdominal oblique muscle and the transversus abdominus muscle which form a flat muscle layer that is continuous with the thoracic wall muscles; and the rectus abdominus muscles that is vertical pair of muscle that extend centrally from the pubis symphysis to the xiphoid process.
- o Extraperitoneal fat – a variable fat layer
- o Peritoneum – a thin serous layer consists of parietal peritoneum that lines the inner aspect of the abdominal wall, and the visceral peritoneum that covers partially or completely the abdominal organs/viscera.

The aponeurosis of the three flat muscles (external oblique, internal oblique and transversus) form the rectus sheath which encloses the rectus abdominus muscle, blood vessels, lymphatics and nerves. Figure 1-4 displays the two configurations of the rectus sheath dependent on its position is relation to the arcuate line (5). Despite this recognised anatomical configuration there can always be variations which need to be considered (7).
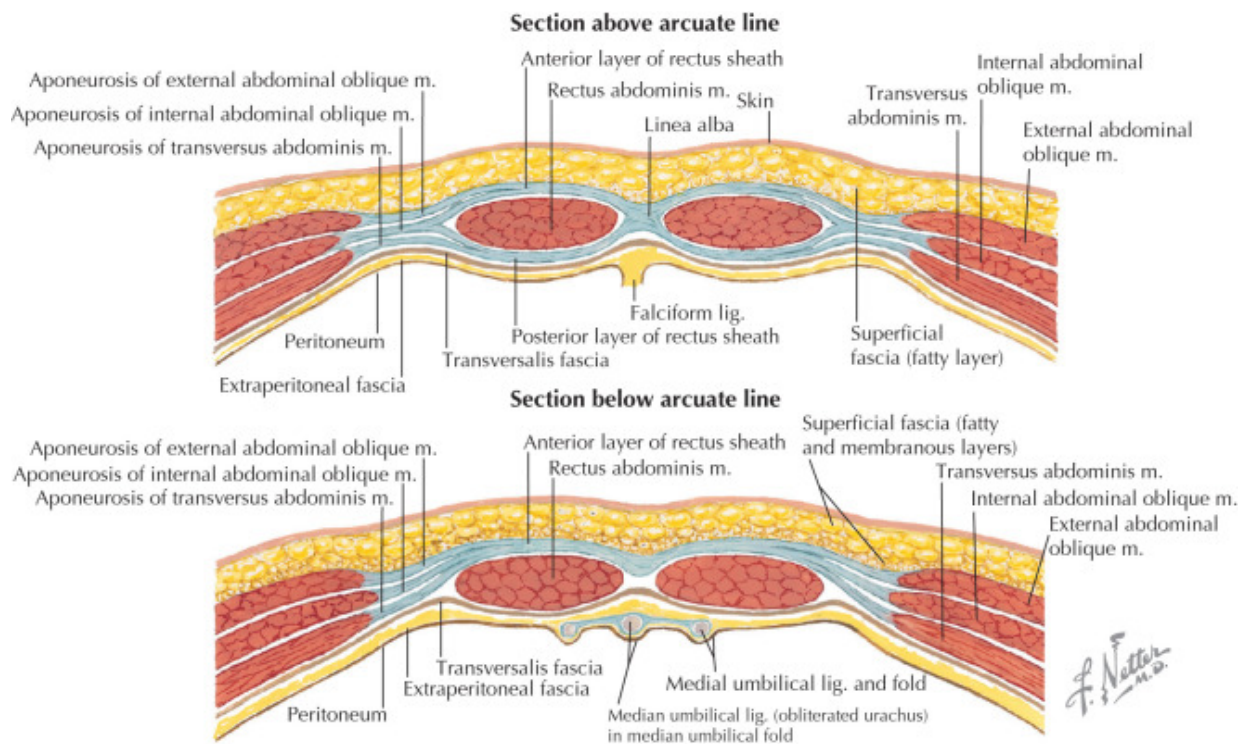
Figure 1-4 - Layers of the Anterolateral Abdominal Wall (5)

1.1.3   Principles of Colorectal Surgery

There are many conditions that affect the colon and rectum that are managed by colorectal surgeons. The conditions and surgery are broadly divided into the following groups:

- Benign and Malignant
- Emergency and Elective
- Open, Laparoscopic and Robotic (Surgical Approaches)

The urgency of surgery and the surgical approach, have an impact on surgical wounds particularly their size, location, potential intra-operative contamination, infection rates and time for wound healing.

1.1.3.1   Emergency and Elective Colorectal Surgery

Emergency surgery as a broad term encompasses many aspects of care provided by a multidisciplinary team. Surgery performed as an emergency is for patients that present to the surgical service with an acute abdominal pathology requiring immediate to urgent surgery at any time of day, or surgery that is performed for a complication of planned

surgery that has happened recently. Approximately 25% of patients presenting to the acute surgical team will require some operative management (8). The Royal College of Surgeons England (RCSEng) published a report in 2011 that set out the minimum recommended standards that should be met to deliver safe emergency surgical care (9).

Emergency surgery is prioritised based on the time frame of the urgency of surgery required, and this was developed from the NCEPOD (National Confidential Enquiry into Patient Outcome and Death) recommendations of 2004 (10):

- o Category 1 – Immediate life, limb or organ saving intervention. Time frame 0-2 hours.
- o Category 2a – Urgent intervention for deterioration of conditions that threaten life, limb or organ. Time frame 2-6 hours.
- o Category 2b – As 2a, but a patient who is more stable than 2a. Time frame – 6-18 hours
- o Category 3 – Expediated procedure for a stable patient requiring early intervention. Time frame 18hours to days.
- o Category 4 – Elective surgery.

Elective procedures are those considered to be for non-acute conditions or presentations, which is scheduled in a planned manner by the surgical team.

1.1.3.2 Surgical Approaches

Open Surgery

Surgical treatment of abdominal pathology via an open surgical procedure is when there is a surgical incision through the abdominal wall. There are different types of surgical incisions dependent upon the access required to the abdomen for the target surgery. The choice of incision will be dependent on surgeon's decision, minimising risk to other structures, cosmetic appearance, pain, and most importantly safe and adequate surgical access.

The main type of open incision used for colorectal surgery is a midline laparotomy incision. although there are other types of incisions such as the Pfannesteil low transverse incision used often for pelvic conditions and the Kockers right sided upper abdominal incision used

for gall bladder surgery. The midline laparotomy incision is an incision through the linea alba along the midline from the pubis symphysis to the xiphoid process. It can be the full length or a partial smaller incision along the midline. It gives maximal exposure to the four quadrants of the abdominal cavity but leaves a long scar and is associated with development of an incisional hernia in 12.8% of cases at 2 years (11,12).

The Pfannenstiel incision is used most commonly within colorectal surgery for access to the pelvis for rectal surgery and can be used together with laparoscopic surgery. The incision was originally described by Hermann Johannes Pfannenstiel in 1900 (13), with the skin incision being a curved transverse incision just above the pubic hair line and a similar transverse incision along the rectus sheath. The muscle layer is split and retracted with a vertical incision in the underlying fascia transversalis and peritoneum. This gives good access to the pelvic organs, and is associated with a lower incidence of complications including a lower, 0-2%, incisional hernia incidence (13).

Laparoscopic Surgery

The principles of laparoscopic surgery are to perform an operation within the abdominal cavity via small incisions on the abdominal wall and using a laparoscopic camera and instruments. It was first described in the early 1900s, but it was development of the computer chip camera that displayed the laparoscopic images on a television in 1986 that allowed more complex gastrointestinal surgeries to be performed (14).

The use of laparoscopic surgery to perform colorectal oncological operations underwent much scrutiny when initially implemented due to the risks of port site metastases and ensuring adequate resection margins and lymphadenectomies. Three large studies have demonstrated that laparoscopic surgery had equivalent oncological results to open surgery but with reduced post-operative analgesia, complications and hospital stays:

- Clinical Outcomes of Surgical Therapy Study Group trial (COST trial) (15)
- Conventional versus Laparoscopic-Assisted Surgery in Patients with Colorectal Cancer (CLASICC) trial (16)
- Colorectal cancer Laparoscopic or Open Resection (COLOR II) trial for rectal cancer (17).

Robotic Surgery

The use of robotic surgery within colorectal surgery is at the start of its journey, but the use is expanding exponentially with the full potential still to be recognised. The first recorded robotic surgery was within the field of neurosurgery with a neurosurgical biopsy in 1985 (18). Robotic surgery then developed with two main models, the da Vinci® and the Zeus, which are based on a 'master-slave' system where the robot translates the movement of the surgeon to laparoscopic instruments that mimic the movements intracorporeal. The da Vinci® robot has the added benefit of seven degrees of movement at the wrists of its arms, which is able to translate the wrist movements of the surgeon. This is deemed the advantage over laparoscopic surgery as there is more wrist-like movements of the robotic instruments through the same incision size. The first cholecystectomy was performed in 1997 and has now progressed to have multiple uses multispecialty, including prostatectomies in urology, and rectal surgery in colorectal surgery (19–21).

Within colorectal surgery, the most significant potential benefits for robotic surgery may be with rectal cancer surgery and the mesorectum dissection because of the greater freedom of movement of the instruments in comparison to traditional laparoscopic approaches. There was a randomised controlled study, published in 2017, investigating the 'Effect of Robotic-Assisted vs Conventional Laparoscopic Surgery on Risk of Conversion to Open Laparotomy Among Patients Undergoing Resection for Rectal Cancer' (ROLARR study) (22). The study demonstrated that there was no significant difference in conversion to open procedures when considering robotic to laparoscopic rectal resections, and no significant difference in the secondary end points. This confirms that robotic surgery is as safe as laparoscopic, but with the added extra cost per case for robotics, there remains the question of cost efficiency of the procedure. The study did however find that within the male group there was a lower rate of conversion in the robotic group, and this may be due to the advantages of robotics in the male narrower pelvis, with the authors suggesting that this may be an area to explore in the future (22).

1.1.4   Enhanced Recovery After Surgery

1.1.4.1   Background

With the development of surgical practice over the years there has been great variability in the management of surgical patients at each step of their pathway – preoperative, intraoperative and postoperative. The care that the patient received at each step was dependent on the individual anaesthetist and surgeon's prior experience and preferences. During the 1990s, the average stay after an open colonic resection was approximately 9 days (23), and this was reduced with the introduction of minimally invasive surgery/laparoscopic surgery to 4-6 days (15). This was felt to be a big step forward in improving the care of surgical patients, reducing the incidence of post-operative complications and thus reducing their length of stay. However, there was still a lack of a consensus on the optimal management of patients from a combined anaesthetic and surgical point of view.

Kehlet first published in 2000 a small study that looked at the impact of a multi-modal accelerated pathway for colonic resection patients (24). The pathway included epidural analgesia started during the anaesthetic and continued for 48 hours, standardising intraoperative fluid management and medication administrations and normothermia strategies. Post operatively the patients followed a standardised nursing care programme which involved early oral intake and mobilisation. The median postoperative stay was 2 days, however 27% of patients felt they had been discharged too early and 11.6% had a serious complication or death. This was the first study that had demonstrated a successful multi-modal approach could reduce length of stay post-operatively (24,25).

Following Kehlet's work, there was increased focus on the optimal management of colorectal patients using an evidence-based approach. In 2001, Professor Ken Fearon, Edinburgh, and Professor Olle Ljungqvist, Sweden, met and formed the Enhanced Recovery after Surgery - ERAS® study group and started to define the ERAS® pathway. A consensus from the ERAS® group was formed in 2005 defining the principles of the pathway (26). There was some hesitancy in the implementation of the pathway, and the ERAS group found in 2007 that within 5 centres there was compliance between 13-100% of the individual

components of the pathway (27). Consequently, the ERAS Society was founded in 2010 and the main aims were on the implementation and development of the pathway in centres, and this ran implementation programmes to improve the compliance with all aspects of the pathway. Now ERAS has been expanded and adapted to included most surgical specialities, and most hospitals in the UK use some form of ERAS protocol.

1.1.4.2   Principles

The main principles of the ERAS protocol are to optimise the patient pathway from pre-operative to intra-operative through to post-operative and discharge as illustrated in Figure 1-8 (26). This optimisation is through a multi-disciplinary approach involving many health professionals including surgeons, anaesthetists, nurses, specialist nurses, physiotherapists, dieticians, geriatricians and many more. With the implementation of the pathway, it means that every patient undergoing the same operation should receive the same care irrespective of health care professionals involved in the care. This is of increasing importance with trainee doctors and introduction of the European working time directive and loss of the traditional surgical team structures.

The full original colorectal ERAS guidelines are seen in Figure 1-9. The start of the ERAS pathway is in the months to weeks before the admission for surgery, particularly with a large focus on education of the patients, for self-optimisation or prehabilitation (e.g stopping smoking, weight management and exercise programmes) and management of patient expectations including stoma education, discussions about post-operative pain and preparing the patient for discharge home (28). There are some thoughts that this process should be started upon initial referral from primary care to the colorectal team; including weight and smoking management, and starting to medically optimise the patient, for example correcting anaemia or diabetic control.
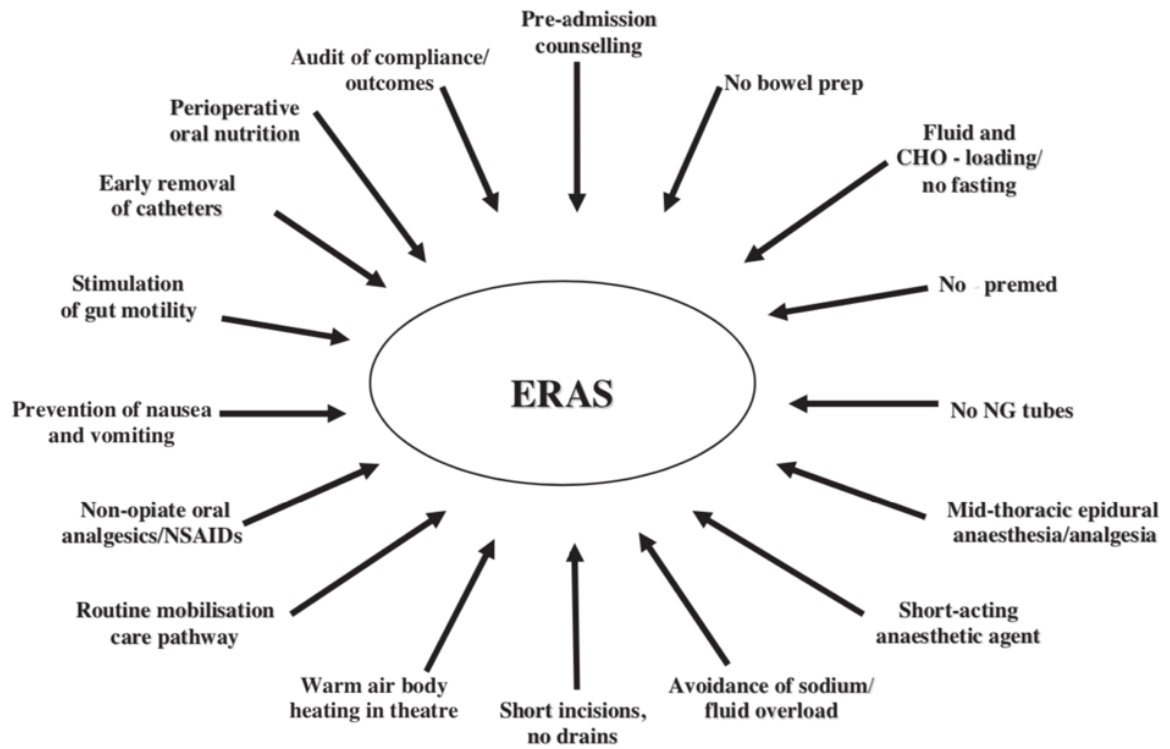
Figure 1-5 - Main Elements of the ERAS Pathway (26)

Element	Target Effect and/or Comment
Preadmission	
Cessation of smoking and excessive intake of alcohol	Reduce complications
Preoperative nutritional screening and, as needed, assessment and nutritional support	Reduce complications
Medical optimization of chronic disease	Reduce complications
Preoperative	
Structured preoperative information and engagement of the patient and relatives or caretakers	Reduce anxiety, involve the patient to improve compliance with protocol
Preoperative carbohydrate treatment	Reduce insulin resistance, improve well-being, possibly faster recovery
Preoperative prophylaxis against thrombosis	Reduce thromboembolic complications
Preoperative prophylaxis against infection	Reduce infection rates
Prophylaxis against nausea and vomiting	Minimize postoperative nausea and vomiting
Intraoperative	
Minimal invasive surgical techniques	Reduce complications, faster recovery, reduce pain
Standardized anesthesia, avoiding long-acting opioids	Avoid or reduce postoperative ileus
Maintaining fluid balance to avoid over- or underhydration, administer vasopressors to support blood pressure control	Reduce complications, reduce postoperative ileus
Epidural anesthesia for open surgery	Reduce stress response and insulin resistance, basic postoperative pain management
Restrictive use of surgical site drains	Support mobilization, reduce pain and discomfort, no proven benefit of use
Removal of nasogastric tubes before reversal of anesthesia	Reduce the risk of pneumonia, support oral intake of solids
Control of body temperature using warm air flow blankets and warmed intravenous infusions	Reduce complications
Postoperative	
Early mobilization (day of surgery)	Support return to normal movement
Early intake of oral fluids and solids (offered the day of surgery)	Support energy and protein supply, reduce starvation-induced insulin resistance
Early removal of urinary catheters and intravenous fluids (morning after surgery)	Support ambulation and mobilization
Use of chewing gums and laxatives and peripheral opioid-blocking agents (when using opioids)	Support return of gut function
Intake of protein and energy-rich nutritional supplements	Increase energy and protein intake in addition to normal food
Multimodal approach to opioid-sparing pain control	Pain control reduces insulin resistance, supports mobilization
Multimodal approach to control of nausea and vomiting	Minimize postoperative nausea and vomiting and support energy and protein intake
Prepare for early discharge	Avoid unnecessary delays in discharge
Audit of outcomes and process in a multiprofessional, multidisciplinary team on a regular basis	Control of practice (a key to improve outcomes)

Figure 1-6 - The ERAS Society Guideline Elements for Colonic Resection (29)

Clinical Outcomes

The ERAS protocol's clinical outcomes have been studied extensively, with systematic reviews evaluating several aspects (30,31). Nicholson *et al.* found that the mean length of stay was reduced by 1.14 days, and 30% reduction in complications with no difference in readmission rates, major complication rates and risk of death (30). Greer *et al.*, incorporated surgical approach into a sub-analysis, but also found that the mean length of stay was reduced by 2.6 days and a reduction in morbidity by RR of 0.66 (31). ERAS has also been shown to be effective in the an increasingly frail elderly group of patients, with age itself not impacting compliance to ERAS or length of stay (32).

The clinical effectiveness of the ERAS protocol is evidenced in many studies. However, the studies may often be biased by the selection of patients included and systematic reviews demonstrate that there is much heterogeneity between the studies included. The impact of the earlier discharge of patients is difficult to fully evaluate as some complications, including wound infections, may not cause readmission but can put increased pressure on primary care services.

Financial Outcomes

The main benefit of ERAS has been clinical with shorter length of stays and reduced morbidity. Reduced hospital stays and reduced resource usage has a large financial benefit which makes ERAS cost effective (33). A further evaluation of the ERAS pathway, highlighted that the societal costs of ERAS are reduced, driven by patients returning to work earlier; and the reduced financial burden from reduced complications (34). The cost benefits from ERAS do need to be weighed against the cost of implementation and running of a successful ERAS programme including the extra dedicated staff time to particular aspects such as patient and staff education (29,33,34).

1.2   Surgical site infection

1.2.1   Definition of Surgical Site Infections

A surgical site infection (SSI) is part of a group of infections known as health care associated infections (HCAI) or nosocomial infections which are infections that happen after 48 hours of admission to hospital not directly related to their primary admission (35). HCAI affect 7% of patients in developed and 10% in developing countries. They have a significant impact on patients by increasing their length of stay and their morbidity and may contribute to antimicrobial resistance by requiring more antibiotic use (36,37). HCAI include SSIs, catheter associated infections, ventilator associated pneumonia and central venous line access associated infections, in addition to others (35,37,38). SSIs are the second most common HCAI after catheter related infections (35).

SSIs are infections of the incisional wound made during the operation or an infection within the area/organ space of the operation. The Centre for Disease Control and Prevention (CDC) have defined SSIs to have occurred within 30 days of surgery unless an implant (e.g. hip prothesis) is used at which point it is one year (39–41). They are still a frequent and adverse complication of both emergency and elective surgery that increases the morbidity of the operation and negatively impact the patient experience post-operatively (40,42).

1.2.2   Categories of Surgical Site Infections

SSIs are broadly defined based on their location within the skin layers, superficial/deep/organ space, but can also be defined on the type of surgery that is performed, categorised as clean, clean-contaminated, contaminated or dirty.

1.2.2.1   Superficial, deep, organ space

Figure 1-10 illustrates the definition of the SSI locations, superficial/deep/organ or space, based on the anatomical locations in schematic form based on the CDC's definition (39,43).
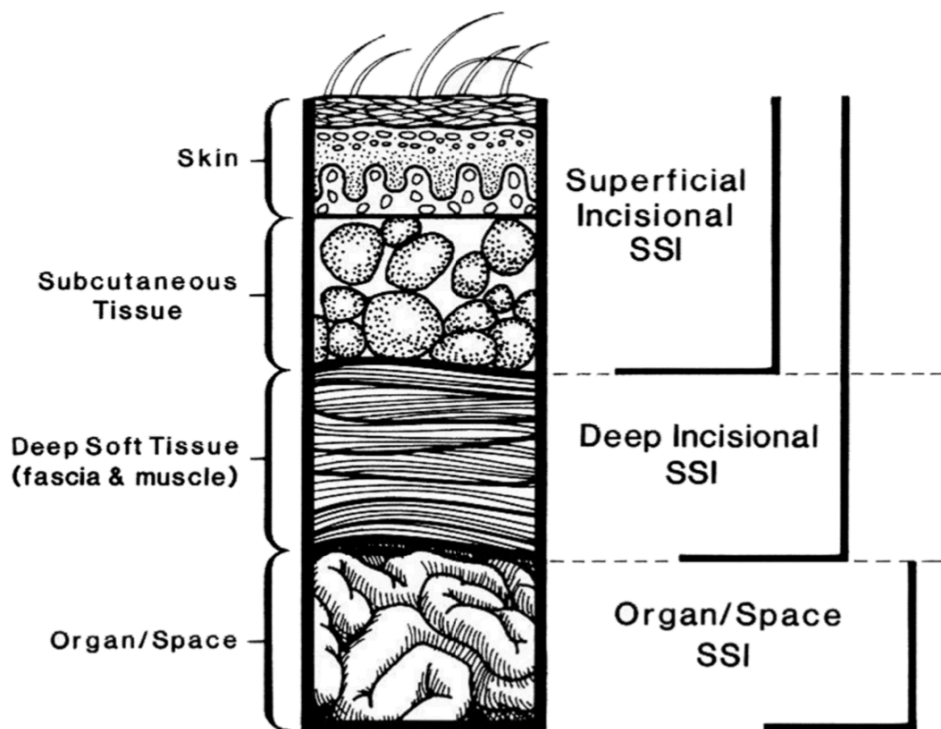
Figure 1-7 - Centre for Disease Control and Prevention's National Healthcare Safety Network Schematic of SSI anatomy and appropriate classification (39)

Superficial SSI

A superficial SSI is an infection of the surgical incision that involves only the skin or subcutaneous tissues. In addition to the location, there must be **at least one** of the following: purulent discharge; organisms cultured from aseptically obtained swabs or fluid; symptoms or signs – erythema, tenderness, swelling, heat; incision opened by the surgeon; or diagnosis of superficial SSI by a surgeon (39,41).

Deep SSIs

A deep SSI is an infection that is within the fascial or muscle layers of the incision. Aside from the location it must have **at least one** of the following signs or symptoms: purulent drainage from the deep incision, not from organ/space; a deep incision that spontaneously dehisces; deep incision opened by the surgeon; pyrexia greater than 38°C, tenderness or

pain; an abscess present on examination, re-operation or radiological imaging; or diagnosis of a deep SSI by the surgeon. A deep SSI often occurs with a superficial SSI, if this is the case the wound is defined as only a deep SSI (39,41).

Organ/Space SSI

An organ/space SSI is any anatomical area that is opened or manipulated during the surgery that is not the incision, for example the abdominal cavity or a joint space. When reporting an organ/space SSI, it is important that the location is specified (e.g., intra-abdominal SSI). It must meet **at least one** of the following, aside from the location: purulent drainage into a drain placed through a stab wound; aseptically cultured organisms from the organ/space; an abscess present on examination, re-operation or radiological imaging; or diagnosis by a surgeon. An organ/space SSI can by diagnosed along with a deep or superficial SSI (39,41).

1.2.2.2   Clean, clean contaminated, contaminated and dirty wounds

Operations can be broadly classified as clean, clean contaminated, contaminated or dirty dependent on different features as shown in Table 1-1 (44–46). The classification of the resultant wound is dependent on the presence of infection/inflammation (none present is clean), whether a hollow viscus is opened in a controlled manner (clean-contaminated), whether there is more contamination from a viscus tract opening (contaminated) and whether there is widespread pus or contamination or the wounds are traumatic wounds (dirty). The classification of the wound can predict the risk of developing an SSI (45–47). For colorectal surgery the majority of the operations are classified as clean-contaminated or contaminated, and thus the SSI rate should be 10-20%.

5Class	Type	Definition	Example	Infection Rate
I	Clean	No entry into viscus, no infection or inflammation	Joint replacement, breast surgery, hernia	1-2%
II	Clean-Contaminated	Controlled opening of hollow viscus, minimal contamination	Cholecystectomy, elective colorectal resection	<10%
III	Contaminated	Viscus tract opened with significant contamination	Accidental enterotomy	15-20%
IV	Dirty	Gross contamination due to pus or perforation of viscus, old traumatic wounds	Perforated diverticular disease	40%

Table 1-1 - Wound Types and Infection Rates(46,47)

1.2.3 Pathophysiology

For an SSI to develop there needs to be microbial contamination of a wound. The risk of then developing an SSI is dependent upon the bacterial species, the virulence of the bacteria, the dose of the bacteria and finally the resistance of the bacteria to the treatment involved (48). If there is contamination of the wound by more than 10^5 microorganisms per gram of tissue, then the risk of an SSI is greatly increased (49). However, if a foreign material is used within the wound including sutures, mesh or protheses, the number of microorganisms required for infection is much lower (50).

The contamination of the wound can be from the endogenous flora of the skin, mucous membranes, and hollow viscus. The contaminating bacteria are then dependent on the location of the skin incision and/or hollow viscus that is opened (48). This is the basis of the risk from the type of surgery – clean, clean-contaminated, contaminated and dirty (46,47). The other routes of contamination of a wound are via exogenous sources including surgical personnel, surgical sterility, and operating theatre environment. There can be contamination intraoperatively but also during the postoperative wound care by both the clinical team and the patient (48).

1.2.4 History of Surgical Site Infections

Infections have had a significant impact on morbidity and mortality, particularly in childbirth and post operatively since 1500BC. Methods of reducing infection were started to be developed in the nineteenth century, with the growth in knowledge of the origin and transmission of infectious diseases (51). In 1841 in Vienna, Austria, Ignaz Semmelweiss was a physician working on a maternity ward who noticed that there was a high rate of mortality from childbed fever or puerperal sepsis – infection after childbirth causing sepsis. Semmelweiss also noted that the deliveries that were assisted with midwives compared to medical students had a much lower rate of sepsis (2% compared to 16%) (51,52). It was noted that the midwives were not involved in the autopsies in the morning, of which the doctors and medical students were. It was not until a colleague of Semmelweiss died of a similar sepsis to the patient he had performed an autopsy on and contaminated his hand wound, that Semmelweiss appreciated that there was contamination from soiled hands of the cadaver's poison. As a result, Semmelweiss made hand decontamination before vaginal examination compulsory, and the mortality rate of puerperal sepsis dropped to 3% (51,52).

Joseph Lister and Louis Pasteur independent work on bacteria, sterilisation and wounds led to the develop of antisepsis with Carbolic Acid in the late 1800s. Pasteur identified that sterilised broth did not contain bacteria until it was in contact with contamination/bacteria. This further reinforced to Lister that wound became infected from contact with bacteria (in this case skin flora). Lister then soaked dressings, and later sutures, in Carbolic Acid which reduced the rate of wound infections (51).

1.2.5 Risk Factors for development of Surgical Site Infections

The risk factors for development of an SSI can be broadly divided into groups of infective micro-organism, wound environment and patient factors, and these will have modifiable and non-modifiable aspects (45–47). The extent to which the micro-organism colonises and infects the area is dependent on the exposure and virulence of the organism. Table 1-2 illustrates the other risk factors. Some of the risk factors will depend on the operation type and urgency and whether they are modifiable. For example, nutritional status can be

improved if there is some time before an elective operation with input from nutritional teams but not before an emergency procedure.

	Non Modifiable	Modifiable
Wound Environment	Mechanism of wound Clean/clean-contaminated/contaminated/dirty Anatomical site	Sterility Technique Use/type of prothesis Procedure duration Wound haematoma
Patient Factors	ASA Age Immunosuppression Malnutrition (emergency) Obesity (emergency) Diabetes (emergency) Ascites Renal Failure Jaundice	Hyperglycaemia Hypothermia Hypoxia Anaemia Blood Transfusion Smoker Nutrition (elective) Weight management (elective) Diabetes (elective)

Table 1-2 - Risk factors for surgical infections(45–47) (ASA - American Society of Anaesthesiologists physical status classification system).

1.2.5.1   Patient Host Immunology and risk of developing an SSI

Patient factors, or host factors, are an important consideration when considering SSI development. Surgical methods of preventing SSIs in the perioperative period are partially aimed at preventing colonisation of the surgical wound with bacteria. However, the presence of bacteria within the surgical wound does not always result in an SSI, and this is likely due to host factors and immunology. The patients immunological response should eradicate the bacterial contaminates of the wound and result in low SSI rates, but when there is compromise of this immunological response SSIs can develop (53).

Surgery and anaesthesia initiates a series of immunological responses that are broadly divided into proinflammatory responses to opportunistic causative microbes hence reducing SSIs, but also deactivation of the immune system impairing normal responses increasing the risk of SSIs (54). Acquired impairment of the hosts immunological response to wound contamination, has been studied more extensively and can be broadly divided into three areas as seen in figure 1-8 – naturally occurring variables (age), acute physiological events (hypothermia) and treatments given to patients (steroids) (53,54).
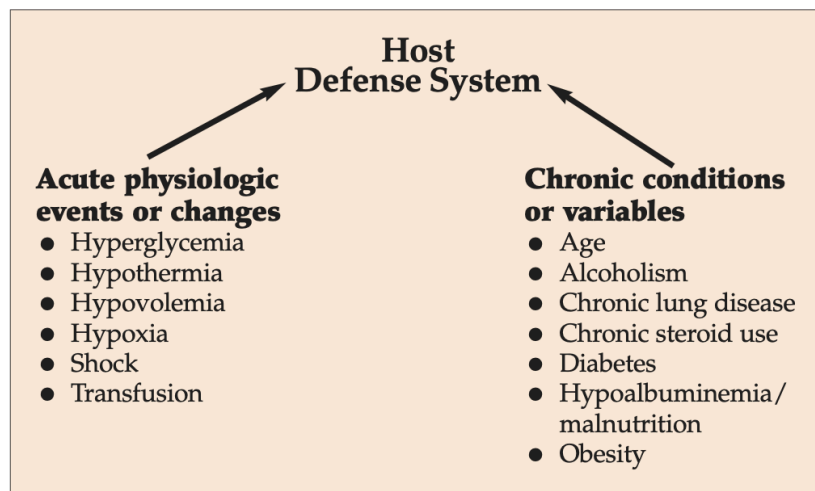
Figure 1-8 Factors influencing Host Immunology (53)

Multiple studies have looked at identifying the factors that increase the SSI rate. These include length of operation, presence of chronic diseases like diabetes and chronic obstructive pulmonary disease, receiving a blood transfusion (55–57).

The main objectives of SSI preventative methods are to minimise surgical wound contamination – skin preparation – but by also minimising the acute physiologic changes that occur during surgery like hypothermia and hypoxia through targeted interventions (53).

1.2.5.2   Role of Prophylactic Antibiotics and Reducing SSIs.

Surgical antibiotic prophylaxis is the administration of antibiotics prophylactically before the surgical incision is made. The aim is to minimise the wound contamination during the operation, particularly in clean-contaminated, contaminated and dirty operations (58). Through minimising wound contamination with causative bacteria, the risk of SSI is lower. There are many studies that have demonstrated that prophylactic antibiotics reduce the

incidence of SSIs, with a Cochrane Review in 2014 of pregnant woman found that those women who received prophylactic antibiotics before a caesarean were 60-70% less likely to have an infectious post-operative complication including SSIs (59,60).

Antibiotic choice for surgical prophylaxis is dependent on local microbiology guidance based on local resistance patterns and specific causative bacterial profiles. Generally, for colorectal surgery (and all gastrointestinal surgery) the antibiotics will be selected for an agent with action against skin flora bacteria like staphylococcus aureus, and an agent with good gram-negative activity for bacteria like enterococcus species (61). It is important that in patients who have had multiple operations or hospital admissions, that specific antibiotic regimes are used based on previous bacterial cultures and microbiology advice. Further to antibiotic action upon individual patients, it is important to consider antimicrobial resistance overall within hospital practice. This can be minimised by following local microbiology protocols, preventing SSIs and individualising treatment for those high risk patients who have previous microbiology cultures (61).

1.2.6   Diagnosis of Wound Infections

1.2.6.1   Clinical diagnosis

Clinical diagnosis of SSIs happens within 30 days post-operatively (up to 1 year if an implant is used) by either the surgical clinical care team on the patient's initial admission for surgery or during readmission, or by the primary care team (general practitioners (GP) and nursing staff) post discharge. A clinical diagnosis is based on the definitions of superficial, deep and organ space SSIs in section 1.2.2.1 – presence of erythema, pain, purulent discharge, and microbiology positive cultures. The difference of the three types of SSIs is the location of the SSI (39). The difficulty of clinical diagnosis of SSIs is often based on the experience of the assessing clinician. Non healing wounds, which are not infected, and normal healing wounds can exhibit the similar features of an SSI like erythema and pain but are not infected wounds. The accuracy and sensitivity of positively diagnosing SSIs depend on the training of the individual assessing the wound (62).

Within current NHS practice, the assessment of a surgical wound is performed by a multi-disciplinary team for signs of healing and infection. Microbiological culture remains the gold-standard for bacterial identification, but despite this, there is no standardised swabbing technique. For example, the Levine swab technique focuses on a localised 1cm^2 area of the wound for 5 seconds, whereas a Z-technique adopts a 10-point Z-pattern trace on the entire wound site (63); such different approaches to sample collection may result in the positive identification of different microorganisms within the same wound (64).

The major limitations of microbiological swabs are the 2-5 days required for accurate results to be communicated to treating clinicians, and that results include only commonly cultured bacteria; thus, most clinicians will treat infections empirically with broad spectrum antibiotics in the first instance (65). This is of particular importance in community management of wounds, when it can be difficult to ascertain the difference between a wound that is infected by bacteria, in comparison to one that is colonised and healing. This has led to the misuse and overuse of antibiotics within chronic wounds and has contributed to the development of antibiotic-resistant microorganisms which further complicates wound management (66).

1.2.6.3   Diagnosis within different health care settings

Within the secondary care setting, the patient is primarily cared for by the surgical medical team (consisting of a consultant/s, a speciality trainee, and junior doctors), and nursing staff that are usually trained surgical nurses with experience in caring for surgical wounds. In addition to these direct patient healthcare professionals, within most hospitals there is access to expertise with 'Infection Prevention and Control' Specialist Nurses, and Tissue Viability Nurses. These allied services will not only provide training to the surgical doctors and nurses but will provide support to the teams in diagnosing and caring for patients with SSIs. In addition, if a patient develops an SSI whilst an inpatient, there is daily reviews of the wound progression with the treatments instigated and the SSI is fed back to the operating surgeon in a timely fashion. There is evidence that the feedback of SSI rates to the operating surgeon and surgical departments, can decrease SSI rates (62,67).

Within the primary care setting, patients have access to GPs and senior nurses – Practice or District. There are also community tissue viability services available. Usually post discharge, a patient with a wound problem will present to their GP who may prescribe antibiotics based on their assessment of the wound, with nursing care to manage the dressings of the wound. The main difficulties with community led wound care, is that during the development of an SSI, the patient will choose to engage with their GP and at the time point they choose, which may not reflect on the start of the SSI. Their GP will likely see the wound on a single occasion with no further clinical input, unless requested from nursing staff. Also, the GP will record the SSI in their record, but there is often no direct detailed communication with the operating surgeon to provide that essential feedback. Patients will be referred to secondary care, and the surgical team, if the wound is more complex and required surgical wash outs.

The difficulties faced in post-discharge surveillance of SSI development in well documented in the literature, however a large proportion of SSIs (up to 40%) develop in this time period and are not always fed back to the secondary care setting and/or surveillance programmes (68).

1.2.6.4   Patient reporting tools

One option for SSI diagnosing and reporting, is to use a patient self-reporting tool that could be done electronically or via paper methods and sent back to the operating team. Telephone calls to patients from the surgical team can be conducted on the 30th day post-operatively, but when these are unscripted phone calls, there is unreliability in the accuracy of the data collected (62,69). There are patient questionnaires available that can be returned via post, however these have previously tended towards clinical questionnaires designed for healthcare professionals, but the more recent BLUEBELLE study has designed a patient focused questionnaire that has good reliability when compared to an expert assessor of the wound (70).

The challenges with patient reporting tools are the extra workforce time needed to distribute, collect, and collate the data (67). For this reason, these tools are used more frequently for research trials where there is funding for dedicated nursing time. The

incorporation of patient reporting tools into standard practice has been very slow to implement.

1.2.6.5   Review of Surveillance Methods

One of the biggest limitations of SSI diagnosis, and hence surveillance, is the assessments of post-operative wounds by independent experienced and/or trained assessors with adequate experience and not the operating surgeon who has inbuilt biases. Therefore, for successful surveillance programmes, the definition of SSI must be pre-defined, clear and standardised, which can be adopted by less experienced staff (71).

Methods of surveillance include:

- Retrospective or prospective clinical notes review
- Daily clinical inpatient reviews
- Microbiology results review
- Prescribing of antibiotics
- Patient reported tools
- Telephone calls
- Primary care data

Each of these methods have strengths and limitations, which impact on sensitivity and specificity (figure 1-9). For example an SSI diagnosis should not be made based on microbiology results in isolation without a clinical examination of the wound as not all positive microbiology are from infected wounds and could be from a colonised wound (62). CDC recommend that there should be two methods of surveillance used together to ensure there is reliable data – clinical review and microbiology results for example (69).

The biggest indicator of a successful SSI surveillance programme is when there is ownership of the project by an individual or a team within the healthcare setting (62,71). Successful surveillance programmes in the UK, including Wales, are for orthopaedic joint replacement surgery, and obstetric caesarean surgery which are largely due to the mandatory data collection requirement. The success of the orthopaedic surgery surveillance programme and

subsequent improvements in perioperative care, has resulted in SSI rates less that 1% for joint replacement surgery (71).

Method	Potential advantages	Potential disadvantages
Routine direct wound examination by trained professionals	High sensitivity and specificity	Labour intensive
Outpatient chart review by trained professionals	Acceptable sensitivity and specificity	Labour intensive, suboptimal documentation
Surgeon-reporting:		
Self-initiated	High specificity, resource efficient	Poor sensitivity
By survey (mail)	Acceptable specificity, relatively resource efficient	Suboptimal sensitivity
Patient reporting:		
By mail	Relatively resource efficient	Unreliable sensitivity and specificity
By telephone	Good public relations	Labour intensive, unreliable sensitivity and specificity
Microbiology data	Relatively resource efficient, may 'flag' potential SSIs	Unreliable sensitivity and specificity when used in isolation

Figure 1-9 - Surveillance methods and their advantages and disadvantages, adapted from Smyth et al. 2000 (62)

1.2.7   Impact on Patient Outcomes

Patients that develop SSIs postoperatively have an increased short- and long-term morbidity and mortality profile.

1.2.7.1   Short-term

The development of an SSI can affect the patient on their index admission due to several reasons. Firstly, the length of stay increases if there is an SSI (72), which is reported in general surgery to be increased by an average of 2 to 14 days (68,73). There are an increased number of surgical procedures and antibiotic prescribing, alongside an increase in readmission rates (68,72). A surgical incision that does not heal in the expected way is associated with increased scaring superficially which has a cosmetic impact, something which is visible to the patient and others (74).

All these immediate complications from developing an SSI contributes to the patient experience of the surgical process and can ultimately affect their quality of life (QoL). There

are significantly lower scores on the different measures of QoL used in the literature when a patient develops an SSI (42,72,73,75). There is also an decrease in the patients utility post SSI (76).

There are long term impacts on developing an SSI, alongside the psychological impacts discussed above. The main long-term impacts are due to the impacts of the SSI on colorectal cancer outcomes, and also due to the development of an incisional hernia.

Many studies, including a large cohort study of the American Veterans Affairs registries found that infectious postoperative complications after colorectal cancer surgery were associated with decreased long-term survival irrespective of age, stage of cancer and whether they received adjuvant chemoradiotherapy (77). Another retrospective study based in Ljubljana, Slovenia also identified that SSIs were associated with worse 5 year survival but the cause was likely multifactorial (78)

Further to this, a 2020 meta-analysis has shown that infective postoperative complications have a negative impact on long term survival of patients (79). SSIs had a significant negative effect on overall survival in colorectal cancer patient with a hazard ratio (HR) 1.37 and cancer specific survival with a HR 2.58. The meta-analysis did not show a significant impact on disease free survival (79).

The infectious postoperative complication associated with the poorest long-term survival are deep or organ space SSIs. The reasons behind this are likely to be multifactorial but an important consequence of SSIs is the subsequent delay in receiving adjuvant chemotherapy for cancer patients (77–79).

Post-operative SSIs are an independent risk factor for developing an incisional hernia following abdominal surgery. Incisional hernias are prevalent after 12.8% of all midline laparotomies (11), and it is important to reduce any potential risk factors for their development. The long-term impacts of incisional hernias are on the patient's cosmesis, comfort particularly with clothes wearing, pain and the potential to develop small and large bowel obstruction which can result in emergency surgery with its own morbidity and

mortality profile. Incisional hernias are the aetiology of 4.5% of those that present as an emergency with small bowel obstruction (80,81).

Additionally, the increased rate of SSIs lead to increased usage of antibiotics which contributes to antibiotic resistance (48). This is particularly important for those patients who have multiple surgeries as the development of resistant causative bacteria can make treatment of future infections more difficult.

1.2.8 Resource Usage and Financial Cost

SSI infections have a cost to the NHS in both a financial and resource usage manner, alongside the personal financial cost to the patient with lost workdays from increased length of stay, readmissions and primary care interactions (75). Studies within the literature have demonstrated that each colorectal SSI costs the NHS on average £10,523 each in extra bed days, doctor and nursing time and resources (dressings and medications) (68,82). Over the year, this could result in a cost of approximately £50 million to the NHS (68).

Although the economic burden of SSIs is significant there needs to be a consideration of resource usage due to an SSI. Tanner *et al*. showed that each infection had on average 19 visits from a District Nurse in the primary care setting (68). For each patient who has an increase in length of stay that is a bed occupied which could be utilised for another patient within the NHS. There is also the environmental impact of each wound infection on the number of disposables used with treating an SSI from dressings to gloves(83).

1.2.9 Colorectal Surgical Site Infection Rates

Colorectal surgery has a high incidence of SSIs primarily due to the nature of the surgery being clean-contaminated or contaminated. The number of colorectal patients affected by SSIs are variable, with reported rates as high as 27% (68,84–88).

There are only a few multicentre prospectively collected SSI rates that have been published including from Hawaii with a 12.08% SSI rate from both acute and elective colorectal procedures (89); New South Wales Australia had a colorectal SSI rate of 9.64% but this was a retrospective review using hospital cost coding to determine inpatient SSIs or readmissions due to SSIs (85); and Switzerland had a national SSI rate of 17.9% for colonic surgery only

(86). Both the studies from Switzerland and Hawaii used 30-day follow up methods including telephone calls to ensure that all SSIs were captured even if the patient had been discharged into the community. There have also been large clinical trials evaluating SSI prevention interventions. An example of such a clinical trial is the ROSSINI study which evaluated the use of wound edge protectors (Figure 2-1) in lowering the SSI rate in laparotomy wounds in both elective and emergency surgery. The superficial SSI rate was 25.4% in the control arm and 24.7% in the intervention arm (73). Within the ROSSINI trial, each patient was reviewed at 30 days by a trained assessor to ensure accurate SSI diagnosis.

In England, colonic surgery has an SSI rate of 8.7% as published in the public domain by Public Health England (PHE) (87). However, this rate is calculated from inpatient SSI rates and re-admissions from SSIs, and thus does not include primary care diagnosis. The data entered are non-continuous and based on quarterly data, of which each hospital is only required to submit one quarter per year (90). Moreover, only 50 hospitals, who had chosen to voluntarily partake in data entry, entered data, which is less than 40% of all English hospitals. The variance of SSI rates between these hospitals ranged from 1.6 to 20.7% (87).

1.3 Surgical Site Infections within Wales

1.3.1 Demographics of Wales

Wales has a population of 3.06 million over a land size of 20,782 square kilometres (91). The population is increasing, with an increase of 5.3% between the consensus of 2001 and 2011 (92).

Wales is one of the four countries that form the United Kingdom, but it has devolved powers with limited self-government powers subject to the UK Parliament in Westminster. As a consequence, the Senedd Cymru (Welsh Parliament) has responsibility for NHS provisions in Wales after it was devolved in 1999, and therefore the funding structure of the NHS in Wales is different to NHS England (93). NHS Wales delivers services through 7 Local Health Boards and 3 NHS Trusts with a map of the local health boards in Figure 1-11 (94).

Health Boards (HBs) in Wales

Legend:
- Betsi Cadwalader University HB
- Hywel Dda HB
- Powys Teaching HB
- Abertawe Bro Morgannwg University HB
- Cwm Taf HB
- Cardiff & Vale University HB
- Aneurin Bevan HB

Cities labelled on map: Holyhead, Colwyn Bay, Rhyl, Bangor, Caernarfon, Wrexham, Welshpool, Newtown, Aberystwyth, Brecon, Haverfordwest, Carmarthen, Abergavenny, Llanelli, Merthyr Tydfil, Cwmbran, Swansea, Port Talbot, Caerphilly, Pontypridd, Newport, Bridgend, Cardiff, Barry

Figure 1-10 - A map on the Local Health Boards within Wales (94)

1.3.2 Current National Initiatives (Obstetric and Orthopaedics)

Within Wales, Public Health Wales (PHW) has a programme of change to reduce the incidence and impact of HCAI. PHW has recently completed a 10-year programme of change to reduce the SSI rate after caesarean section within the obstetric departments from over 12% in 2007 to 3.4% to 2017 as seen in Figure 1-12 (95).
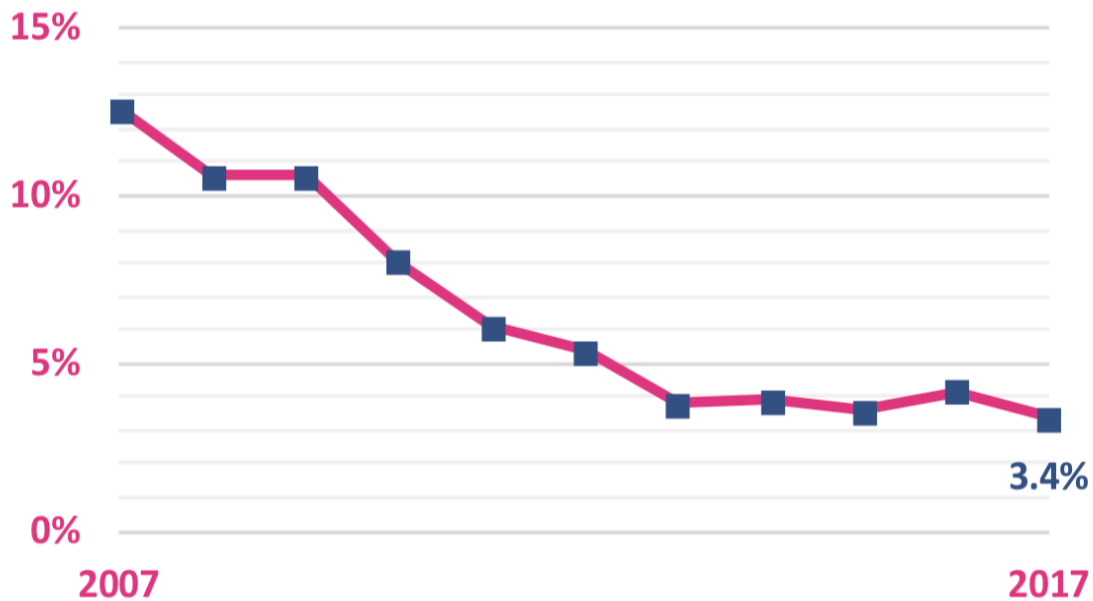
Figure 1-11 The Caesarean Section SSI rate for all of Wales from 2007 to 2017 (74).

PHW targeted the high caesarean SSI rate in a multi-faceted approach. Firstly, they improved documentation and recording of SSIs through engagement with midwifes and post-natal health care visitors to improve the accurate 30-day post-operative reporting of SSIs. Since 2006 it has been a requirement by the Welsh Government for all health boards that have patients who undergo caesarean section to participate in the national data collection to ensure both an accurate number of SSIs and an accurate number of patients who have a caesarean, the denominator. Patient details and operative details were also collected to establish the risk factors of those who develop an SSI. Using this data, it allowed PHW to work with each health board to instigate a programme of change to improve the SSI rate. This was focused on patient education, health care professional education and

changing practices in theatre, for example closing the skin with subcuticular sutures instead of surgical clips (95).

Since 2003, all health boards within Wales have been required to participate in SSI surveillance of primary hip and knee arthroplasty surgery by the Welsh Government. In 2015 the surveillance became electronic and was a normal practice of departments to prospectively record and monitor patients for SSI development. There was then a review of each case that developed an SSI often through a multi-disciplinary team (MDT) approach. This has resulted in a drop in SSI rate to 0.22%, or 12 SSIs out of 5501 procedures performed in 2018 (Figure 1-13) (96).
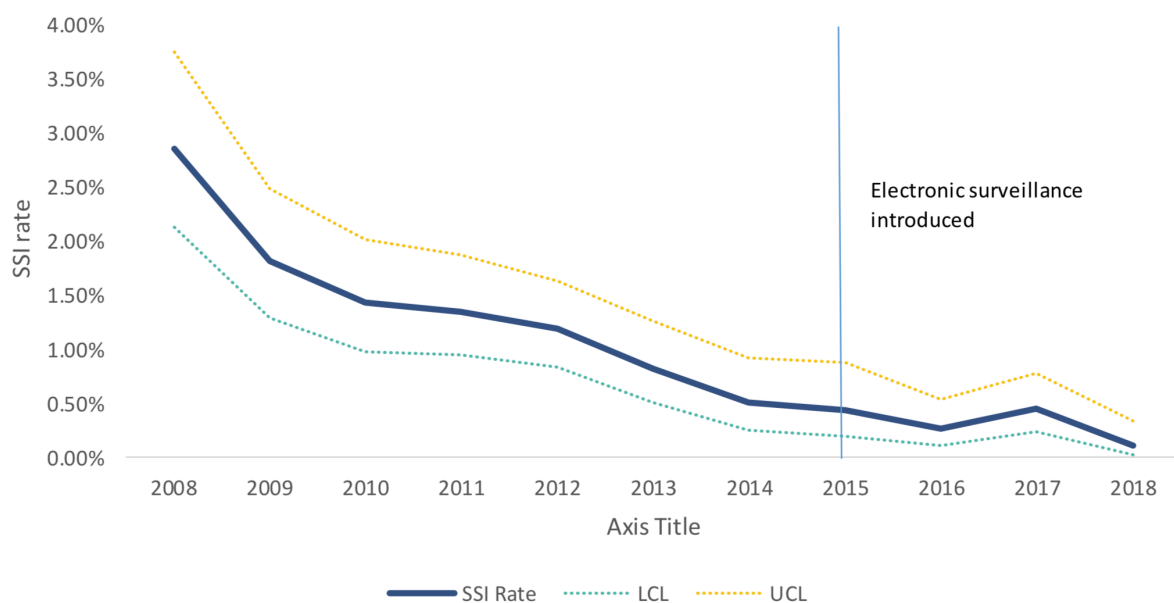
Figure 1-12 Orthopaedic SSI rate of primary joint replacement surgery in Wales (96)*.*

1.3.2.1   Lessons learnt from National Initiatives in Orthopaedics and Obstetrics

PHW has ran SSI surveillance for over 10 years in both areas, and although there has been great success in establishing a robust surveillance programme and reducing SSI rates, there have been challenges along the way. The biggest lesson learnt from their work, must be active engagement of the multi-disciplinary team in diagnosing and recording SSIs is essential. Without engagement of all members accurate data collection is not possible, and the success of the project is now reflected in the standard practice of completing the required data for PHW. Within each department, in each hospital, they designated an SSI

champion member of staff, who then took ownership of the data collection and running the surveillance programme.

Another aspect that was noted is that prompt feedback to departments on their individual SSI rate, but also the rate in comparison to the average Wales SSI rate, helped in part with compliance with preventative methods and subsequently reduced the SSI rate. This evolved into a SSI Dashboard within Wales, where up to date data is accessible. Regular meetings with clinical staff (surgeons, theatre staff, midwives, and community health care workers) continued to promote the engagement with the project and contributed to its success.

1.3.3   Colorectal Surgical Site Infections in Wales

The previous SSI rate published within University Hospital of Wales (UHW) Cardiff was 8.6%, which was based on a retrospective analysis of a prospectively collected database of 647 emergency and elective operations during 2011 (1st January to 31st December) which equated to 56 SSIs (44). However, this study only included the SSIs diagnosed during primary admission or if the patient was re-admitted. Consequently, SSIs diagnosed and treated in primary care were missed from this data set, an important limitation, as a proportion of SSIs requiring antibiotics are diagnosed and treated by primary care physicians.

This published colorectal SSI rate is the largest data set published from a Welsh hospital. The Welsh national SSI rate of colorectal surgery is unknown, with no published data available. Any improvements or interventions aimed at reducing the SSI rate are difficult to implement as it is difficult to measure their success against an unknown baseline SSI rate.

2 Hypothesis and Aims

Colorectal surgery patients have had their post-operative care optimised by the ERAS programme, reducing incidence of complications and their length of stay. Currently, some of the main complications facing colorectal patients are infective, largely SSIs which includes anastomotic leaks, and these patients have a larger morbidity and mortality profile and increased length of stay. Within Wales, there are successful SSI surveillance programmes run by PHW for orthopaedic joint replacement surgery and obstetric caesarean surgery, but there is no programme in place for colorectal and general surgery SSIs.

It is hypothesised that the implementation of surveillance of colorectal surgery SSIs and then the implementation of targeted improvements in intraoperative variables will reduce the incidence of SSIs in colorectal patients in Wales.

2.1 Aims

To be able to address the hypothesis and reduce the incidence of SSIs in Welsh colorectal patients, the following three aims have been formulated:

1. A literature review of the evidence for the current SSI prevention recommendations - Chapter 3

2. To determine the Colorectal Surgery SSI rate in Wales, with an evaluation on plans to reduce the SSI rates – Chapters 4-6. This will contain the following objectives:

    a. An All-Wales prospective observational study to establish the SSI incidence in colorectal patients – The Wound Infection in Colorectal Surgery (WICS) study

    b. The development and introduction of a standardised approach, 'An SSI Bundle', to reduce SSIs

    c. An Evaluation of the SSI Bundle – Compliance, strengths, and limitations

3. Assessing the Impact of Hypothermia on SSIs – investigating the concept of intra-abdominal temperatures during laparoscopic surgery and methods to counteract this – a novel way to reduce SSIs – Chapter 7.

Section One – Literature Review

3 Literature Review

3.1 Introduction

There are several guidelines for the prevention of SSIs that have been published worldwide. The World Health Organisations (WHO), the CDC and the National Institute for Health and Care Excellence (NICE) guidelines are all used to guide clinical practice within the UK (97–99). The evidence for each of these guidelines is from a mixture of randomised controlled trials (RCT), clinical observational studies and translational research. This is a literature review of the evidence on each on the perioperative factors in SSI prevention. The literature was searched for any recent systematic reviews and clinical trials, including the major, seminal studies that have contributed to that guideline. All the literature in the review has been critically appraised highlighting potential limitations, and future research in each area has been identified. Relevant statistical results from the studies have been expressed using odds ratio (OR), risks ratio (RR) and confidence intervals (CI). The guidelines from the three bodies will be summarised at the end of each section, with a commentary from myself included. A formal GRADE assessment was not included as the literature review was an appraisal of different types of studies and included the main systematic reviews that formed the WHO, CDC and NICE guideline. The commentary will summarise strengths and weaknesses of the studies which form the basis of the guidelines.

3.2 Antibiotic Prophylaxis

Surgical antibiotic prophylaxis involves the administration of antibiotics before the surgical incision is made to minimise the wound contamination during the operation, particularly in clean-contaminated, contaminated and dirty operations (58). A 2014 Cochrane review of antibiotic prophylaxis in colorectal surgery included 30 trials of 2,435 patients and demonstrated that antibiotic prophylaxis significantly reduced SSI risk compared to placebo or no antibiotics (RR 0.34; 95% CI 0.28-0.41) (100). The studies included were often small, with unclear randomisations with other methodological flaws. This Cochrane review evaluated 260 studies for benefit of antibiotic regimes, and within the 260 studies there

were 68 different antibiotics used, demonstrating the heterogeneity of the studies in this area.

3.2.1 Timing of Antibiotic Prophylaxis

There have been many observational studies examining the timing of surgical prophylactic antibiotics and the subsequent risk of SSI. An observational study from 1992 of 2,847 patients found that those who had their prophylactic antibiotics within 2 hours of surgical incision had a lower risk of SSI (101). However, this was a prospective cohort study and not an RCT and they found little difference in SSIs when antibiotics were administered between 60-120 minutes and 0-60 minutes before surgery. Steinberg *et al.* (2009) analysed the prophylactic antibiotic dosing of 4,472 patients (cardiac surgery, hysterectomies and joint arthroplasty), and found that antibiotics given after the incision was made was associated with an increased risk of SSIs (OR 2.20; 95% CI 1.03-4.66; p=0.02)(102).

A 2017 systematic review of 14 studies of 54,552 patients confirmed these findings, if antibiotic prophylaxis was administered greater than 120 minutes prior to incision or anytime post incision then there was an increased risk of SSIs. It further confirmed that there is no significant difference in administering antibiotics at different time points within 120 minutes to surgical incision (103). The studies included within this systematic review were heterogenous, particularly in the different antibiotic regimes used, and were all observational studies resulting in no controlling of possible confounding variables. Overall, this systematic review, and its individual studies, strongly agreed that antibiotic prophylaxis needed to be administered so that the tissue concentration is at its maximal at time of incision when considering the individual antibiotic half-life (58,102,103).

3.2.2 Intraoperative Redosing of Antibiotics

Further to ensuring that prophylactic antibiotics are given prior to incision, there is evidence that maintaining serum concentration of the antibiotic is also important in the prevention of SSIs. This is of increased importance in cases of increased operative times and increased blood loss. A 2002 study that looked at the serum level of gentamicin intraoperatively found that if there was a serum gentamicin level lower than 0.5mg/litre at the time of wound closure there was an 80% SSI rate (p=0.003) (58). Further to this a 2019 observational study

of over 9,000 patients found that SSI incidence significantly correlated with the duration of surgery (p=0.021) but that redosing of antibiotics significantly reduced the SSI incidence (OR 0.60, 95% CI 0.37–0.96, p = 0.034) (104).

Although there is a lack of robust RCT data on redosing of surgical antibiotic prophylaxis, these observational cohort studies are of a reasonable sample size, and relate to blood serum levels of the antibiotic, thus the results are fairly robust. There needs to be further research in defining the optimal dosing regimens, including timings and redosing, for the different antibiotics and combinations used for surgical prophylaxis.

3.2.3   Current Guidelines

NICE (NG125) guidelines: prophylactic antibiotics should be given up to 60 minutes before the surgical incision and not after the incision. NICE recommends re-dosing antibiotics in procedures greater than four hours (105).

WHO guidelines: Administration of prophylactic antibiotics prior to the surgical incision when indicated; administration should be within 120 minutes of the incision dependent upon the antibiotic half-life (97)

CDC guidelines: Administer preoperative antimicrobial agents only when indicated based on published clinical practice guidelines and timed such that a bactericidal concentration of the agents is established in the serum and tissues when the incision is made. No evidence for re-dosing antibiotics intra-operatively (98).

Commentary: The evidence base on prophylactic antibiotic is made from many studies, mainly observational in nature, and are heterogenous in their methodology including the antibiotics used. Despite this, the majority of the literature is in agreement that prophylactic antibiotics decrease the risk of SSIs, and the most important factor is ensuring that the tissue concentration is at the maximal prior to the incision reinforcing that antibiotics should be given in the immediate time period before a surgical incision. The guidelines all agree on this, however the optimal window of time for administration of antibiotics does vary. This would be improved, if future research was focused on defined the time point of maximal tissue concentration post administration for each antibiotic,

and thus there would be a specific antibiotic dosing time, which would be the most accurate.

3.3   Patient Hair Removal

Traditionally, patient hair is removed from the operating site for various reasons. This has mainly been for practical reasons including adequate exposure for operating, skin marking, skin preparation, wound suturing, and ease of dressing applications. There are conflicting thoughts about patient hair and the risk of SSIs, with the presence of hair having an impact on cleanliness due microbial contamination versus the thought that hair removal can lead to skin microtrauma which can increase the risk of an SSI. It has been shown that 25% of cutaneous bacterial populations are found in the hair follicles, with 75% on the epidermal layers, however there is little evidence to demonstrate that these bacteria subsequently cause SSIs (106). There are three main ways of removing skin – shaving with a razor, clipping or depilatory creams. Many studies and systematic reviews have examined the evidence for each.

There are 4 systematic reviews within the literature, of which one is a Cochrane review and three included a meta-analysis (107–110). The Cochrane review, which was updated in 2011, found that in the 6 studies included, there was no significant statistical difference in SSI rates between hair removal or no hair removal, however the studies that were included in this review were small and underpowered (107). When comparing shaving to hair clipping, there were three studies that overall demonstrated significantly more SSIs associated with shaving (RR 2.09, 95% CI 1.15 to 3.80) (107). The systematic review by Lefebvre *et al.* (2015) confirmed the findings by the Cochrane review, in that there were significantly fewer SSIs with hair clipping compared to shaving (RR 0.55; 95% CI 0.38 to 0.97) but that there was no difference in SSIs between no hair removal and hair clipping groups (RR1.05, 95% CI 0.55 to 2.00) (108). Shi *et al*. (2017) however included the Chinese studies that had been excluded from the other systematic reviews and found that there was no difference between the three methods of hair removal, but also when comparing these methods to no hair removal (109). The final systematic review, Poirot *et al.* (2018), was of poorer quality compared to the other three, as there were fewer methodological details. Poirot *et al.* found similar findings to the other reviews (110).

Upon further searching of the literature there have been three further studies that add to the evidence on hair removal. Kowalski *et al.* (2016) conducted a prospective, randomised non-inferiority clinical trial to evaluate if hair clipping was non inferior to no hair removal in the prevention of SSIs. Despite the study recruiting 1,543 patients who completed follow up, 768 in the clipped group and 775 in the no hair removal group, there was no difference in SSI rates – 6.12% in the clipped group, and 6.32% in the no hair removal group (absolute risk difference -0.20%; 95% CI -2.61% to 2.21%) (111). This study included only general surgical procedures; however, the study was underpowered because the resultant SSI rate was approximately 6% which was higher than the 2% SSI rate used in the design of the study. This was further confirmed as the predefined SSI rate of 2% was within the absolute risk difference confidence interval. Despite this, it was a large study with similar SSI rates between the two groups, indicating that hair clipping is not superior to no hair removal in the prevention of SSIs.

The remaining two studies do not add to the evidence base already formed. A retrospective analysis of 755 Mexican patients undergoing open abdominal surgery by Guzmán-García *et al.* (2019), found that there was a significantly lower number of SSIs if there was no hair removal or if the hair removal was done 12-24 hours preoperatively compared to hair removal immediately prior to surgery (112). However the study does no explain the methods of hair removal, does not specify statistical analysis of the hair removal data and is a retrospective case series (112). Similarly, a RCT of 109 patients published by Okoli *et al.* (2020) demonstrated no significant difference between shaving and depilatory creams. However there is not a clear explanation of how the sample size was calculated, there was an 8% drop out rate and the SSI rate in the study was much higher than expected at 18% (113).

The main difficulties when interpreting the systematic reviews is that although the included studies did not have methodological heterogeneity, the patient groups were often different, particularly with operation types and anatomical locations. This makes it more difficult to utilise the findings when considering one type of patient, for examples, those undergoing abdominal surgery. However, all the studies collectively have formed the conclusion that hair removal does not reduce the risk of an SSI, but if hair removal has to be performed for other reasons, then hair clipping is associated with a lower rate of SSIs. This is with the

caveat that further research is needed to completely define the optimal timing of hair removal, and further larger definitive RCTs to evaluate the 3 methods of hair removal with no hair removal.

3.3.1 Current Guidelines

NICE (NG125) guidelines: Do not use hair removal routinely to reduce the risk of SSI, but if hair must be removed, use electric clippers with a single-use head on the day of surgery. Do not use razors for hair removal (105).

WHO guidelines: Hair should either not be removed or, if necessary, it should be removed only with a clipper. Shaving is strongly discouraged at all times. (97)

CDC guidelines: Do not remove hair preoperatively unless the hair at or around the incision site will interfere with the operation. If hair removal is necessary, remove immediately before the operation, with clippers.(98).

Commentary: The literature has demonstrated that hair removal does not reduce the risk of SSIs, however it has shown that if hair removal is required for other reasons then it should be done via clipping. There is consensus with the guidelines on this. However from reading the literature the evidence base for this is not the strongest, and a well designed, three arm, powered RCT would be able to definitively answer if hair clipping is the superior method of hair removal.

3.4 Surgical Site Skin Preparation

Surgical site skin preparation happens immediately before the start of the operation within the operating theatre, and its main purpose is to reduce the microbial contamination of the skin which is to be incised and the skin in its immediate proximity – the surgical field. The macroscopic cleaning of skin should be performed prior to the patient arriving to the operating theatre by a patient shower. Skin preparation is mainly performed using two types of skin preparation - povidone-iodine (PVP-I) or chlorhexidine gluconate (CHG); which are either in an alcohol-based solution or an aqueous based solution.

3.4.1 Type of Skin Preparation

PVP-I is the most widely used skin antiseptic pre-operatively. Iodine has been used for more than 150 years, not only in skin disinfection but also in treating infected wounds, however iodine is a highly aggressive skin irritant. PVP-I is iodine bonded via hydrogen bonds to the synthetic polymer polyvinylpyrrolidone, which is used in an aqueous formula, as there is a slow release of the iodine when applied (114). Its action is via oxidative effects on the cell structure and enzymes of micro-organisms, leading to the disruption of the cell wall and denaturation of enzymes. This makes it effective against a wide range of micro-organisms including bacteria, viruses and fungi, and importantly antibiotic resistant bacteria (114).

CHG has been used for 50 years as a topical antiseptic solution (115). Its mode of action is via binding to the cell wall of micro-organisms, increasing the cell wall permeability, and causing cellular apoptosis due to the alteration of the osmosis equilibrium of the cellular components (115). There are several formulations available (0.5-5%), and it can be used in either an aqueous or alcohol solution. It has an action against bacteria, yeasts, and some viruses; including antibiotic resistant bacteria (115). It also works when exposed to blood or serum. The alcohol based CHG dries quicker, which is useful in surgical skin preparation (116).

There have been two Cochrane reviews on the effectiveness of CHG or PVP-I on skin preparation and subsequent SSI rates (117,118), one based on clean surgery and one based on caesarean section surgery. Dumville *et al*. (2015) included 13 studies, of 2,623 patients. However, the studies were largely heterogenous in nature, and they compared different antiseptic solutions, leading to 11 different comparisons. There were no significant differences found in SSI rates between any of the preparations compared, except in one preparation. Five studies compared PVP-I solutions with CHG solutions and one study found that there was a reduced SSI rate with alcohol based 0.5% CHG compared with alcohol based PVP-I (RR 0.47, 95% CI 0.27 to 0.82) (117,119). The study, Berry *et al.* (1982), does have some risk of bias from allocation and outcome assessment blinding alongside with the patients only being followed up until discharge with wound assessments on day 3-4 post-operatively, which is not in line with the CDC recommended 30 day reporting guidelines (98,119). The second Cochrane review by Hadiati *et al.,* updated in 2020, included 8 trials of

4,324 women that compared CHG with PVP-I, finding that CHG reduced the rate of SSIs (RR 0.72, 95% CI 0.58 to 0.91)(118).

There have been two more recent systematic reviews and meta-analysis published in 2020, Wade *et al.,* and Chen *et al.* (116,120). Wade *et al.* (2020) included 17 studies of 14,493 patients, comparing 5 different antiseptic preparations in clean surgery, and performed a network meta-analysis to allow more direct comparisons of the preparations. Alcohol based 4-5% CHG was ranked the most effective preparation, with less bias in the study analysis, as it halved the risk of SSI when compared to aqueous PVP-I (RR 0.49; 95% CI 0.24 to 1.02) (120). Alcohol based CHG 2-3% was ranked second most effective but there was increased bias and uncertainty in the studies included in the meta-analysis (120). Wade *et al.* does recognise some limitations to their review including that most studies were of poor quality using different time-points and definitions for SSI diagnosis and that there were no studies that were directly comparing the different concentrations of CHG. This review has provided clearer evidence for the use of alcohol based CHG, but it has only considered clean surgery, and this limits its applicability to colorectal surgery.

Chen *et al.* (2020) included 30 studies of 29,006 patients. The studies were of all types and not exclusively RCTs, and also included clean and clean-contaminated surgery. It found that overall the use of CHG reduced the risk of SSIs compared to PVP-I (RR 0.65; 95% CI, 0.55–0.77; p < 0.00001) (116). When analysis of clean contaminated surgeries was performed, CHG was again superior to PVP-I in reducing SSIS (RR 0.58; 95% CI, 0.47–0.73; p < 0.00001) (116). The limitation of this review was the large heterogeneity between the studies included in two aspects, the study types (RCTs, observational, cohort and retrospective studies) and that all types of surgery were considered as one cohort (anatomical, clean, clean-contaminated).

Despite the limitations of the two recent systematic reviews, their meta-analysis have provided increased evidence that CHG is the superior skin preparation and reduces the risk of SSIs in both clean and clean-contaminated surgery. In comparison to the Cochrane review of Dumville *et al.* (117), there were 6 more studies included by Wade *et al.* (120) and 16 more studies included by Chen *et al.* (116) although these also included clean-contaminated studies. As the number of patients and studies has increased, it has added to the statistical

analysis and significance. The network meta-analysis has also allowed more direct comparisons, further adding to the evidence of the superiority of CHG. However, there continues to be research in the area of skin preparation with both the CLEAN 2 (Clinical Trials: NCT03560193) study and ROSSINI 2 (Clinical Trials: NCT03838575) studies currently recruiting, comparing CHG with PVP-I and/or surgeon's usual preparation (121,122).

3.4.2 Alcohol or Aqueous Solutions

Both CHG and PVP-I can be in either solute, alcohol, or aqueous solution. Dumville *et al.,* (2015) included data from 6 trials of 1,400 patients, and showed no significant difference between the two solutes, but that it tended towards favouring alcohol solutions (RR 0.77, 95% CI 0.51 to 1.17) (117). Many studies in the literature have compared alcohol CHG with PVP-I in either aqueous or alcohol preparations with little direct comparisons of CHG in alcohol with CHG in aqueous solutions.

3.4.3 Current Guidelines

NICE (NG125) guidelines: Alcohol-based CHG is first choice unless contraindicated or the surgical site is next to a mucous membrane. There is specific guidance on the percentage strength of CHG - 0.5% chlorhexidine in 70% alcohol solution (Hydrex; Prevase) is only licensed for preoperative skin disinfection prior to minor surgical procedures and 2.0% chlorhexidine in 70% alcohol applicators (ChloraPrep^{TM}) was licensed for 'disinfection of the skin prior to invasive medical procedures'. If the surgical site is next to a mucous membrane then use aqueous CHG or alcohol based PVP-I (105).

WHO guidelines: Recommends alcohol-based antiseptic solutions based on CHG for surgical site skin preparation, however due to heterogeneity of the studies unable to recommend on the concentrations of CHG (97).

CDC guidelines: Perform intraoperative skin preparation with an alcohol-based antiseptic agent, unless contraindicated. There is no specific guidance on the concentration of CHG (98).

Commentary: The choice of skin preparation has been looked at by systematic reviews and the network meta-analysis provided the most comparisons to allow judgement on which

preparation is superior. Overall, the evidence indicates that alcohol CHG is the superior skin preparation. There are few studies that directly compare the different strengths of CHG, however the NICE guidance states that only 2% CHG is licensed, which is different the WHO and CDC who do not comment on the concentration of CHG. Hopefully the ROSINNI II study which is evaluating 2% CHG against other preparation types and strengths will give further indication of the superior skin preparation.

3.5   Perioperative Oxygenation

Tissue perfusion and oxygenation is an essential requirement for wound healing. In the early stages of wound healing, neutrophils release reactive oxygen species (ROS) that target micro-organisms and destroy them with a 'respiratory burst'(123). Oxygen is also required for new tissue angiogenesis and deposition of collagen fibres in the remodelling phase (123). This knowledge has led to clinical trials investigating the effect of hyperoxia on reducing SSIs and thus improving wound healing.

WHO guidelines published in 2016 recommended the use of 80% fraction of inspired oxygen (FiO_2) in the immediate post-operative period of 2-6 hours to reduce the risk of SSIs (97,124). This guidance was based on a meta-analysis of the literature that included 11 RCTS that considered only patients who underwent a general anaesthesia with endotracheal intubation. The meta-analysis found that a FiO_2 of 80% reduced SSIs compared to a FiO_2 of 30-35% (OR 0.72; 95% CI 0.55-0.94) (97,124). However, this meta-analysis and subsequent recommendation of 80% FiO_2 guideline by WHO faced criticism and scrutiny largely from the anaesthetic community (125–131).

There are two main criticisms of the WHO guideline. Firstly, there are aspects of the methodology of the meta-analysis which have been questioned and secondly, the WHO guideline does not fully appreciate the potentially harmful other effects that a high inspiratory FiO_2 can have on patients. The meta-analysis included 11 RCTS in its analysis, but it is a sub analysis based only on those patients that had endotracheal intubation. There is a lack of a pre-planned statistical analysis within the methodology, and yet it is a strong recommendation by WHO (125,128–130). It is also not clear on the rationale as to why some studies were excluded, in particular a 2015 RCT by Kurz *et al.* (132) of 555 patients,

which did not find any difference in SSI rates between 30% and 80% FiO_2. A further meta-analysis performed by Volk *et al.* (126) and Myles *et al.* (131)*,* which included studies excluded in the meta-analysis used by WHO, found that there was no benefit to using the higher 80% FiO_2 (Volk *et al.* found a OR 0.84, 95% CI 0.62–1.12, p = 0.242 while Myles *et al.* found a OR 0.93, 95% CI 0.73–1.18, p=0.54). Overall, the response by the anaesthetic community was concern that a strong recommendation had been made in the absence of a large robust RCT that is powered to accurately assess the potential benefits of inspired FiO_2, and at which concentration, on SSIs.

Secondly, the potentially harmful effects of high inspired FiO_2 had not been fully explored by the WHO guidelines. It has been demonstrated that ventilating patients with high levels of FiO_2 during all aspects of the anaesthesia (pre-oxygenation, ventilation and extubation) is associated with atelectasis, with the effect being more pronounced at 100%, then 80%, then 60% FiO_2 (133). The development of atelectasis affects the patients in the post-operative period, increasing the likelihood of a chest infection, but can also affect oxygenation of the blood and thus the tissue partial pressure of oxygen that is beneficial in wound healing (133). Animal studies have demonstrated that higher inspired FiO_2 results in higher levels of ROS, which do not only damage lung tissue but also other organs including liver, brain and kidneys (127). There has been a move away from using supplementary oxygen in other conditions including acute coronary syndrome, traumatic brain injuries and post cardiac arrests. The AVOID trial demonstrated that if a patient received supplementary oxygen in the absence of hypoxia in acute coronary syndrome, then they had a higher incidence of arrythmias, reinfarction and myocardial lesions after 6 months (134). In addition, there are worldwide guidelines about the avoidance of hyperoxia post return of spontaneous circulation post cardiac arrest due to an increase in mortality (135).

An updated systematic review and meta-analysis in response to the concerns raised by the anaesthetic community was performed in 2019, comprising two parts, the effectiveness of high FiO_2 on reducing SSIs but also on the safety of using high FiO_2 in patients undergoing surgery (136,137). The updated review on efficacy identified 21 RCTs, which included 6 new RCTs published since the 2016 WHO guideline (136). Four previously included studies were excluded as one study had been retracted and three other studies by the same authors were under investigation. In the final meta-analysis of the 17 studies including all patients

having anaesthesia irrespective of oxygen delivery method (endotracheal intubation, face make, nasal cannula) there was no reduction in SSIs after the use of 80% FiO_2 (RR 0.89; 95% CI 0.73 – 1.07). A subgroup analysis of those patients who had endotracheal intubation showed a small benefit in reduction of SSIs with 80% FiO_2 (RR 0.80; 95% CI 0.64-0.99) (136). The systematic review considering the safety of high inspired FiO_2 reviewed the studies included to define the risk of clinically relevant adverse events including atelectasis, cardiovascular events, intensive care admissions and death. It was found that there was no significant difference in the number of adverse events between the patients who inspired 80% FiO_2 compared to 30-35% FiO_2 (137). Overall, the two systematic reviews concluded that there was no harm from a higher inspired FiO_2 but that the evidence for the beneficial effects on SSIs had become weaker and thus the WHO guidance should reflect this.

Despite the updated systematic reviews, there continues to be ongoing debate in this field from the anaesthetic community (138) and further systematic reviews (139,140). The important aspect that all stakeholders have acknowledged is that achieving optimal tissue oxygenation and the high tissue partial pressure of oxygen that favours wound healing is multifactorial. The optimal patient conditions are a combination of normovolemia, normothermia and normoxia as this will facilitate delivery of oxygen to the surgical wound site.

3.5.1   Current Guidelines

NICE (NG125) guidelines: Maintain optimal oxygenation during surgery. In particular, give patients sufficient oxygen during major surgery and in the recovery period to ensure that a haemoglobin saturation of more than 95% is maintained (105).

WHO guidelines: recommends that adult patients undergoing general anaesthesia with endotracheal intubation should receive an 80% fraction of inspired oxygen (FiO_2) intraoperatively and, if feasible, in the immediate postoperative period for 2-6 hours to reduce the risk of SSIs (97).

CDC guidelines: RCT evidence suggested uncertain trade- offs between the benefits and harms regarding the administration of increased FIO_2 via endotracheal intubation during the intraoperative period in patients with normal pulmonary function undergoing general

anaesthesia for the prevention of SSI. However, there is a lack of evidence that evaluated the optimal target level, duration, and delivery method of FIO_2 for the prevention of SSIs (98).

Commentary: There continues to be debate amongst the anaesthetic and surgical communities about the role of high FIO2 during the peri-operative period in reducing SSIs. The CDC guideline summarises this well, and states that there is a likely trade-off between the benefits and harm on increased FIO2. The most important thing noted by all guidelines, is that the maintenance of optimal tissue oxygenation is important in reducing SSIs, and that is achieved via a combination of factors. There needs to be more research in this area to define the reduction in SSIs and the potential harm and adverse effects of high FIO_2. Further to that, the exact concentration and duration of delivery of O_2 needs to be evaluated to ensure the best possible benefits with the least possible harms.

3.6 Normothermia

Intraoperative hypothermia, a temperature lower than 36°C, can influence the patient's normal physiology and can increase the risk of postoperative complications, including adverse cardiovascular events, postoperative pain, analgesic use and increased wound infections (141,142). It has been shown that despite active warming pre- and intra-operatively up to half of patients will develop hypothermia in the first 60 minutes of surgery (143). Further to this, 53% of patients are still hypothermic in the postoperative phase despite active warming intraoperatively (144).

There have been 3 RCTs that were included in a Cochrane Review in 2016; Kurz *et al.* (1996), Melling *et al.* (2001) and Pu *et al.* (2014) (145–147). Kurz *et al.* conducted a RCT between two groups of patients undergoing colorectal surgery, a hypothermic group with no active intraoperative warming (standard care) and a normothermic group with active intraoperative warming (145). The study was stopped early at 200 patients instead of the planned 400 patients as there was a significant difference in the SSI rate, with 6 SSIs in the normothermic group and 18 in the hypothermic group (p=0.009) (145). This was despite the limitations in the study, including a 4-day course of post-operative antibiotics in both

groups, and SSIs were only measured if diagnosed up to day 15 post-operatively, instead of the widely accepted, and recommend by WHO and CDC, 30-day time point (97,98).

A further RCT by Melling *et al.* (2001) demonstrated the same finding, where there was a significant difference (p=0.001) in SSIs between the warmed and non-warmed patients of 5% to 14% (146). However, the RCT was looking at active pre-warming for at least 30 minutes immediately before surgery, either locally to the wound site or systemically. SSIs could be diagnosed up to 6 weeks post operatively which deviates from the CDC guidance of 30 days (98). A RCT by Pu *et al.* (2014) compared surgical post-operative complications between a control group and an intervention group, where the intervention was the use warming underbody blanket and a forced air warmer (147). There were no SSIs in either group despite a significant reduction in post-operative complications in the intervention. However, the study was not powered to detect a difference in SSI rates.

The Cochrane review showed a significant benefit of forced air warming in reducing the rate of SSIs (RR 0.36; 95% CI 0.20-0.66; P = 0.0008)(148). The review was from the above 3 RCTs of 589 participants, and it was felt that the evidence was low quality (148).

Further studies have evaluated the use of pre-operative warming on intra-operative hypothermia, by increasing the temperature of peripheral tissues mitigating for redistribution hypothermia (149). Prewarming thus reduces the drop in temperature during the initial hour of anaesthesia and a more recent meta-analysis in 2020, which included 7 studies , demonstrated that pre-warming reduces SSIs post-operatively (RR 0.60, 95% CI 0.42–0.87, P = 0.072) (150).

3.6.1 Current Guidelines

NICE (CG65) guidelines: Patient temperature should be maintained above 36°C throughout the pre, intra and post-operative phases. Active warming methods should be used 30 minute before surgery and through the intraoperative period (151).

WHO guidelines: Recommends the use of warming devices in the operating room and during the surgical procedure for patient body warming with the purpose of reducing SSI. (97)

CDC guidelines: Maintain perioperative normothermia but does not make guidance on normothermic strategies (98).

Commentary: The evidence for maintenance of normothermia is limited but robust. As half of patient will become hypothermic within 60 mins of surgery, this is a factor that needs to be considered regularly by the peri-operative team. The first RCT in 1996 had to be stopped early due the hypothermic group having much higher adverse events. Hypothermia should be avoided to reduce SSIs, and all the guidelines reflect this.

3.7   Intensive perioperative blood glucose control

During surgery, the body has a 'stress response' which includes a rise in the circulating levels of cortisol, glucagon, catecholamines, and growth hormones (152). This causes hyperglycaemia due to increased catabolic hormones resulting in endogenous glucose production. This is combined with reduced insulin secretion and transient insulin resistance due to the increased hormones. This hyperglycaemia happens in patients with or without diabetes mellitus(152). The transient hyperglycaemia usually lasts for 24 hours post-operatively and is associated with increased post-operative complications including increased SSIs and impaired wound healing(153). Hyperglycaemia can affect neutrophil function, and chronic hyperglycaemia pre-operatively can inhibit the PI3K-Akt signalling pathway, which can impair phagocytosis by neutrophils. Treatment of chronic hyperglycaemia in diabetic mice with intensive insulin regimes can normalise neutrophil function (154).

A systematic review, in 2017, evaluated intensive and conventional glucose control protocols in relation to reduction of SSIs but also with the occurrence of hypoglycaemic episodes, which has a different morbidity profile. The meta-analysis included 15 RCTs of 2,836 patients demonstrating a significant benefit for an intensive glucose control protocol in reducing SSI (OR 0·43, 95% CI 0·29-0·64; p < 0·001)(155). Sub-analysis of the data demonstrated that the benefit in reducing SSIs was greater when the intensive protocol was applied extending through the immediate post-surgery period (155). There was a significantly higher number of hypoglycaemic events in the intensive glucose protocol groups, but this was with no increase in morbidity (death or stroke) (155). There was

increased heterogeneity between the studies, with different groups of patients in studies (exclusively diabetics, or diabetics and non-diabetics); different surgical groups, and a variety of SSI definitions, and with no study having SSI as a primary outcome. Another limitation of the studies included is that the majority of included patients were having major surgery requiring a higher level of care, ITU, post-operatively.

Treating non-diabetics with insulin intra-operatively for stress-induced hyperglycaemia has been found to reduce SSIs in a large cohort study in 2020. An Australian surgical improvement programme evaluated the effects of introducing an insulin infusion if the blood glucose was greater than 10 mmol/L. They found that the SSI incidence significantly decreased from 25% in the pre-intervention group to 6.1% in the intervention group (OR 5.17; 95% Cl 1.92–16.08, p <0.001) (156). There are limitations to using the NSQIP data as there was selective data entry, and it was not a prospective trial with defined outcomes.

Despite the studies demonstrating that intensive glucose control protocols improve SSI outcomes, there has been hesitancy to implement these protocols, with NICE not recommending insulin treatment in those patients who do not have diabetes. Further research needs to be conducted as there is a lack of robust RCTs looking at the effects of intensively managing stress induced hyperglycaemia where the primary outcome is SSIs, particularly to define the blood glucose level that treatment should be initiated at.

3.7.1   Current Guidelines

NICE (NG125) guidelines: Do not give insulin routinely to patients who do not have diabetes to optimise blood glucose postoperatively as a means of reducing the risk of surgical site infection (105,157).

WHO guidelines: Recommends the use of protocols for intensive perioperative blood glucose control for both diabetic and non-diabetic adult patients undergoing surgical procedures to reduce the risk of SSI (97)

CDC guidelines: Implement perioperative glycaemic control and use blood glucose target levels less than 200 mg/dL in patients with and without diabetes, however it does not suggest the optimal blood glucose blood level range (98).

Commentary: Intensive perioperative blood control is a further SSI preventative method that is debated by surgeons, endocrinologists, and anaesthetists. Patient's physiological response to anaesthetic elicits a stress response, which causes hyperglycaemia. This happens in all patients and not exclusively those that are diabetic. As such the studies have demonstrated that blood glucose control does reduce SSIs. However, in these studies SSIs have been a secondary outcome. As such, NICE does not recommend the use of intensive perioperative glucose control in those without diabetes, whilst WHO and CDC do recommend it. Further RCTS with SSIs as a primary outcome are needed to definitely answer the question, however I believe that the existing evidence and the underlying physiology indicate that intensive blood glucose control in all will reduce SSIs.

3.8 Incision Drapes

Once the surgical site has had skin preparation applied and the surgical field draped, the operating field can have an incision drape applied. These incision drapes can be non-antimicrobial adhesive clear drapes or can be iodine-impregnated drapes that are believed to have antimicrobial effects. The incision drapes are applied for two main reasons, firstly to ensure that there is no inadvertent contamination into the surgical wound from unprepped skin by the surgical team and secondly, as a microbial barrier to prevent contamination of the surgical incision by migrating skin flora/microorganisms. The mode of action of the iodine-impregnated drape is through the continued action of iodine on the skin to decolonise of micro-organisms and through penetration of the skin layers to ensure that there is not recolonisation of the skin. Casey *et al.* (2015) performed ex vivo studies using human skin samples and found that the iodine-impregnated drapes had significantly superior antimicrobial action compared to the non-impregnated drapes, and that the iodine penetrated 1,500 µm below the skin surface (158).

The 2015 Cochrane review included 7 studies that reviewed the use of incision drapes (non-impregnated or iodine-impregnated). The 5 studies comparing non-impregnated adhesive incision drapes with no incision drapes, involved 3,082 patients, and the meta-analysis found that more patients with an incision drape developed a SSI (RR 1.23, 95% CI 1.02-1.48, P = 0.03) (159). The other 2 studies of 1,113 patients compared iodine-impregnated incision drapes with no incision drapes and found no difference in SSIs (RR 1.03, 95% CI 0.06 to 1.66,

P = 0.89) (159). There were no studies directly comparing the two types of adhesive incision drapes. The main finding of the review was that overall incision drapes did not reduce SSI rates and could be associated with a higher SSI rate. However the review included studies that were published up to 40 years ago, and the authors stated that there was an unclear publication bias (159).

A systematic review by Eckler *et al.* (2019) included 2 RCTs of incision drapes in caesarean section. The meta-analysis of 1,943 patients confirmed the finding in the Cochrane review, that there is a statistically significant increase in SSIs in the group using adhesive incision drapes (RR: 1.29, 95% CI: 1.02–1.65) compared to the control group (160). The 2 RCTS were also in the Cochrane meta-analysis, and on reviewing the 2 studies the follow up period was 4 days in one and 15 days in the other, which was not compliant with the CDC recommendation of 30 days (98).

Since the Cochrane review there have been further studies in the use of incision drapes. For clean surgery, particularly orthopaedic joint arthroplasty surgery, further studies have focused on bacterial contamination of the surgical field. The benefits of iodine-impregnated incision drapes may be of more importance in clean surgery, as skin flora is often the causative organism of SSIs in comparison to clean-contaminated surgery where the causative organism could originate from the opened viscus (bowel, urinary tract). Two studies looking at knee and hip arthroplasty found that there was significantly less bacterial contamination of the surgical wound on swab cultures when an iodine-impregnated adhesive incision drape was used (161,162). Hesselvig *et al.* (2020) found 10% wound contamination with iodine-impregnated incision drapes, compared to 15% with no drapes (OR 0.61; 95% CI 0.43-0.87; P=0.005) in knee arthroplasty. There was a big loss to follow-up of 500 patients, which the authors attributed to a change in computer systems and 'forgetful' surgeons, but this was almost a third of all the patients recruited. Rezapoor *et al.* (2018) found that in hip arthroplasty, there was bacterial colonisation in 12% of incisions with iodine-impregnated incision drapes compared to 27.4% without incision drapes (162). Both studies did not report SSIs as their primary outcome and thus the difficulty interpreting these studies is that it is unclear how bacterial colonisation translated into clinical complications. However, rates of SSIs in orthopaedic surgery, particularly joint arthroplasty are very low so it would require a very large trial to evaluate this.

Within cardiothoracic surgery, two recent studies have shown the benefit of iodine-impregnated incision drapes in reducing SSIs. A large retrospective case control study showed that the patients in the iodine-impregnated incision drape group had a lower SSI rate of 2.9% compared to 9.12% in the no incision drapes control group (OR 0.30; 95% CI 0.14-0.61; p=0.001) (163). Bejko *et al.* (2015) evaluated the overall cost effectiveness of iodine-impregnated drapes. They retrospectively analysed a prospectively collected dataset and used propensity matched analysis to take into account co-morbidities that contribute to SSI risk, and found that the SSI rate in the iodine-impregnated incision drapes was 1.9% compared to 6.5% in non-impregnated incision drape group, and that due to the cost of managing the SSIs (treatments and increased length of hospital stay), the use of iodine-impregnated incision drapes was cost-effective (164). Despite the results of this study, and the design of the study to reduce to impact of the variables (co-morbidities) on SSIs, only 31% of patients operated on during the time period were included in the analysis due to the nature of propensity matched samples. This is a methodological flaw.

Overall, the evidence is not favourable for the usage of incision drapes including the iodine-impregnated drapes as demonstrated by the meta-analysis in the literature. There may be some role for iodine-impregnated incision drapes in clean surgery, particularly joint arthroplasty in reducing bacterial contamination, but the literature lacks well designed, correctly powered for SSIs, prospective RCTs which would provide an answer to the use of incision drapes in both clean, and clean-contaminated surgery. Currently, ROSSINI 2 has an iodine-impregnated incision drape as part of its three interventions being used in isolation or with other interventions including CHG (122).

3.8.1 Current Guidelines

NICE (NG125) guidelines: Do not use non-impregnated incision drapes routinely for surgery as they may increase the risk of SSI, but if an incision drape is required then an iodine-impregnated incision drape should be used (105).

WHO guidelines: Recommends not to use plastic adhesive incision drapes with or without antimicrobial properties for the purpose of preventing SSI (97).

CDC guidelines: The use of plastic adhesive incision drapes with or without antimicrobial properties, is not necessary for the prevention of SSI (98).

Commentary: The literature does not support the use of incision drapes for reducing SSIs and this is reflected in the guidelines. The studies performed in clean surgery, evaluating the bacterial contamination with the drapes are interesting and raise the possibility that the incision drapes may have a small protective effect in joint replacement surgery. However the studies were not powered to detect a change in SSI rates due to the large sample size that would be required to detect a change in already low SSI rates.

3.9   Wound protector devices

During an abdominal incision or laparotomy there is concern that there is contamination of the wound edge by bowel flora and/or abdominal pus either directly from contact or indirectly from the surgeon's gloves and instruments. The principles of wound protectors are that it forms a plastic barrier over the edge of the wound to protect the incision from colonisation from intra-abdominal micro-organisms (Figure 2-1). The wound protectors can be in the form of single or dual ring (Figure 2-2). There have been 2 well designed, large, multicentre RCTs conducted over the same time period, to try and define the effectiveness of wound protectors which have contrasting outcomes – ROSSINI and BaFO.
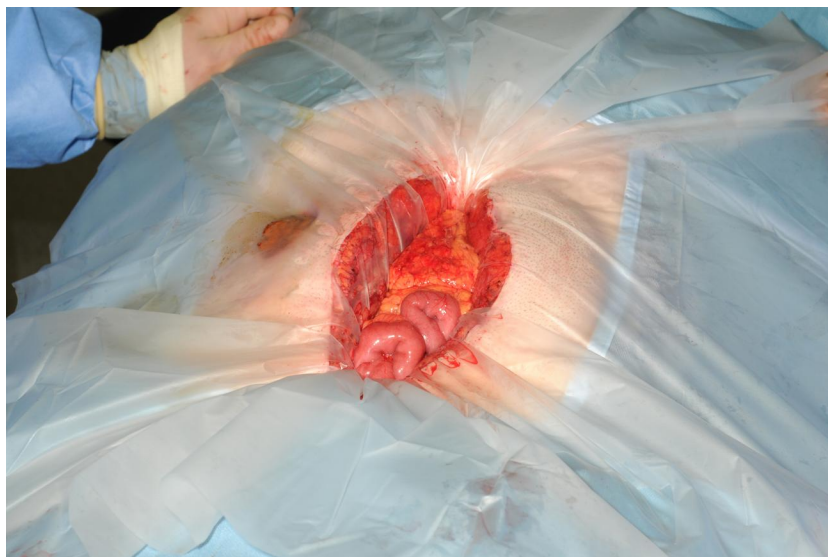
Figure 3-1 Wound protection device used in ROSSINI(73) - 3M Steri-Drape Wound Edge Protector

Figure 3-2 A dual ring wound protector - Alexis O wound retractor/protector

ROSSINI was a UK prospective, multicentre, observer blinded, RCT using the 3M Steri-Drape wound edge protector (Figure 2-1) in the intervention group that randomised 749 patients to two groups (73). They included both emergency and elective abdominal laparotomies for any surgical indication and employed a minimisation strategy to randomisation that happened in theatre post anaesthetic. The trial was pragmatic and allowed surgeons normal practice in regard to antibiotic prophylaxis, skin preparation, etc. Blinded wound assessors reviewed the wounds at day 5-7 or discharge if earlier, then again at day 30, and patients were asked to fill in a questionnaire for the period between days 7-30. The end point was the rate of superficial SSIs as defined by the CDC (98). The power calculation was based on a baseline SSI rate of 12% and a 50% reduction in SSIs with a 5% drop out rate. The authors believed the study was performed well, providing adequate training to wound assessors and there was a low number of patients that were lost to follow up. The results of the RCT demonstrated no difference in superficial SSIs in the 2 arms, 24.7% in the device group and 25.4% in the control arm (OR 0.97, 95% CI 0.69-1.36; P=0.85) (73).

BaFO was a German multicentre, observer and patient blinded, RCT using the 3M Steri-Drape wound edge protector (Figure 2-1) that randomised 608 patients to the two groups (165). They included only patients undergoing elective open abdominal surgery requiring a

median or transverse laparotomy, which were classified as clean or clean contaminated preoperatively. They excluded patients of ASA (American Society of Anesthesiologists physical status classification system) greater than 3. They used block randomisations that occurred after consent but before the day of surgery. Blinded wound assessors reviewed the wound at days 2, 4, 6, 8, 10 to 14 and 30 to 45 for the presence of all types of SSIs (superficial, deep and organ/space) as per CDC guidance (98). The power calculation was based on an SSI rate of 16% and a reduction of 50% with a 15% dropout. This study had a higher loss to follow up than ROSSINI, but the intention to treat analysis demonstrated an SSI rate of 25.5% in the control group and 17.7% in the device group (OR 0.64, 95% CI 0.429-0.949, P = 0.026). The authors performed multiple sensitivity analysis due to the loss to follow up, and all showed a significant difference in SSIs being lower in the device group except for their 'worst case scenario' analysis. The groups were comparable including the type of SSIs in each group. A subgroup analysis of only colorectal surgery found that there was a larger reduction in SSIs from 22.4% in the control to 9.7% in the device group (OR = 0.374; 95% CI: 0.190–0.735; P = 0.003) (165).

Judging if a protector truly reduces the rate of SSIs in abdominal laparotomies is difficult when two large, well designed RCTs conducted over the same time period have conflicting results. Both studies had some methodological flaws which need to be considered. It is unclear why ROSSINI only considered superficial SSIs, and if this is the case why their rate of SSI was approximately 25% overall, when BaFO had a 7.1% superficial SSI rate overall. Admittedly, the studies had slightly different patient groups with ROSSINI including a large proportion of emergency surgery of which 20% was classified as contaminated or dirty surgery, while BaFO had much tighter inclusion criteria. BaFO did not utilise a patient reported outcome, and many studies have demonstrated that SSIs happen between day 15-30 and are only detectable with a robust patient reported tool (70). The differences in the trials may be explained by the differences in surgical practices between Germany and the UK, however the SSI rate in ROSSINI was much higher than expected, emphasised in the clean surgery group of 7.3% compared to an expected 1-2% (Table 1-1).

There have been several meta-analysis published, including one by the study team of ROSSINI and one by the study team of BaFO, that have found that wound protectors reduce the incidence of SSIs (166–170). Four of the five meta-analysis all performed a sub-group

analysis of double ring wound protectors (Figure 2-2) and found they had a greater effect on SSI reduction (RR 0.31; 95% CI 0.15–0.58) (170).

Overall, there is evidence that wound edge protectors reduce the risk of SSIs, however the ROSSINI study has indicated that there continues to be debate about the effectiveness in all patients, and that the singe ring wound protector system may not be the most efficient.

3.9.1   Current Guidelines

NICE (NG125) guidelines: No guidance(105).

WHO guidelines: Recommends considering the use of wound protector devices in clean-contaminated, contaminated and dirty abdominal surgical procedures for the purpose of reducing the rate of SSI (97)

CDC guidelines: No guidance (98).

Commentary: Due to the two large RCTs demonstrating conflicting results, each with their own flaws, it is very difficult to make a conclusion about the role of wound protectors in reducing SSI rates. As such neither NICE nor CDC have guidance on the use of wound protectors.

3.10 Incisional wound irrigation

Many pan-speciality surgeons use surgical wound irrigation as an intraoperative technique to reduce the risk of SSIs. The macroscopic principles behind wound irrigation is that it removes tissue debris, contamination from pus and removal of blood clots to create a better environment for wound healing (171,172). The wound irrigation may also have a microscopic role in reducing the bacterial colonisation through the action of a wash or by using an antimicrobial agent, for example PVP-I (172). Despite many surgeons employing incisional wound irrigation, there has been little agreement and standardisation in the type of solution used for irrigation, the amount and the delivery of the wash (171). There have been many studies in the literature published over the last 40 years, however many of these remain small studies with results at high risk of bias. There is a 2017 Cochrane review that has addressed the question, with further recent systematic reviews and meta-analysis.

The 2017 Cochrane review found that there were 20 studies of 7,192 patients comparing wound irrigation (mixture of irrigants) with no irrigation and found there was no difference in SSIs between the two groups (RR 0.87, 95% CI 0.68-1.11; 14 studies, 6,106 patients) (173). The authors felt that the included studies were of poor quality due to methodological design flaws and imprecision. The subgroup analysis that was performed to determine if differences seen with different irrigants (saline or antiseptics), or with different class of surgery (clean, clean-contaminated etc) did not show any significant difference in SSIs. 36 studies (6,163 patients) included in the review compared antibacterial irrigation with non-antibacterial irrigation. This found that there may have been reduced SSIs in those that received the antibacterial irrigation (RR 0.57, 95% CI 0.44-0.75: 30 studies, 5,141 participants). Again, the studies included were low quality and at risk of bias (173). The Cochrane review had a similar meta-analysis results compared to the earlier 2015 meta-analysis by Mueller *et al.* (174), which found that wound irrigation was beneficial over no irrigation but that the effect was greater when the irrigant was an antibiotic.

The WHO guidelines are based upon a systematic review published in 2017 (175) which included 21 studies. It was found that wound irrigation by PVP-I resulted in reduced SSIs in clean and clean-contaminated surgeries (OR 0.31; 95% CI 0.13–0.73; p = 0.007). It was also stated that there was no benefit to antibiotic irrigation in reducing SSIs (OR 1.16; 95% CI 0.64– 2.12; p = 0.63). This systematic review included studies that only used wound irrigation prophylactically on primary wound to prevent SSIs, and not as a therapeutic irrigation of infected wounds. The authors felt that by only including prophylactic wound irrigation it would provide more evidence on the use of wound irrigation to prevent SSIs.

In 2020, there has been a further systematic review which has included a network meta-analysis to compare the 4 wound irrigation options (no irrigation, saline, antiseptics, antibiotics) more directly despite the paucity of studies that have included direct irrigant comparisons in their intervention arms (176). They included 42 eligible RCTs with 11,726 participants evaluating the effectiveness of the 4 irrigants. The network meta-analysis compared antiseptic, antibiotic, and no irrigation to irrigation with saline. Antibiotic irrigation was the most effective (OR 0.439; 95% CI 0.282-0.667) followed by antiseptic agents (OR 0.573; 95% CI 0.321-0.953) (176). No irrigation was similar to non-antibacterial

irrigation (OR 0.959; 95% CI 0.555-1.660) (176). The nature of the network meta-analysis is that it is at low risk of bias, and the authors felt that the results are robust.

The difficulty with interpreting all the systematic reviews that have been published is that the studies included were mainly single centre studies, with unclear or high risk of bias and include a mixture of surgery (orthopaedics, general, gynaecology), which makes it difficult to apply the findings to the colorectal cohort. However, the systematic reviews, including the Cochrane review found that an antibiotic wash of the wound reduced the risk of SSIs the most, following by antiseptics including PVP-I. In the era of antibiotic stewardship and resistance it would be reasonable that wound irrigation is performed using PVP-I.

3.10.1 Current Guidelines

NICE (NG125) guidelines: Do not use wound irrigation to reduce the risk of surgical site infection (105).

WHO guidelines: There is insufficient evidence to recommend for or against saline irrigation of incisional wounds before closure for the purpose of preventing SSI; however they recommend to consider the use of irrigation of the incisional wound with an aqueous PVP-I solution before closure for the purpose of preventing SSI, particularly in clean and clean-contaminated wounds (97)

CDC guidelines: Consider intraoperative irrigation of deep or subcutaneous tissues with aqueous iodophor solution for the prevention of SSI. (98).

Commentary: NICE guidance does not recommend wound irrigation and this is different to both CDC and WHO, who do recommend the use of wound irrigation with PVP-I to reduce SSIs. Even though the literature is heterogenous and includes all types of surgery, a systematic review and network meta-analysis have demonstrated that there is a benefit to wound irrigation.

3.11 Prophylactic negative pressure wound therapy

Negative pressure wound therapy (NPWT) has been used therapeutically to manage open wounds in the clinical setting to aid healing by secondary intention. It has been postulated

that NPWT may have a role in the prophylactic setting with surgical incisions in preventing SSIs and wound dehiscence, thus aiding the preventing of the chronic non healing wound. NPWT creates negative pressure over the surgical incision to aid prevention of seroma and fluid collections but may also promote normal healing mechanisms. A review of molecular studies have shown that NPWT attenuates the acute inflammatory response locally through angiogenesis, cell recruitment and reduced metalloproteinase expression (177). The exact mechanisms of actions is complex and not completely understood (177).

A 2020 Cochrane review added 15 RCTs to its previous systematic review, and this is reflective of the many studies that are being completed on the use of NPWT prophylactically. The meta-analysis of 31 studies of 6,204 patients stated that NPWT reduces the incidence of SSIs (RR 0.66; 95% CI 0.55-0.80)(178). The limitations of the review are that there have not been comparisons of the different types of NPWT. The studies included in the meta-analysis were of mixed surgical specialities, and also a large proportion were funded by the manufacturers of the NPWT, raising concerns on the impartiality of the studies.

Zwanenburg *et al*. (2019) performed a meta-analysis that is the basis of the WHO guidance (179). They found that NPWT reduced SSIs in a meta-analysis of 28 RCTS of 4,398 patients (RR 0.61, 95% CI 0.49–0.76, P < 0.0001). Sub analysis of the types of surgery, showed that NPWT significantly reduced vascular surgical SSIs, but that there was no significant reduction in SSIs in abdominal surgery (RR 0.56, 95% CI: 0.30, 1.03) (179). The weakness of the review is the heterogeneity of surgeries included but also that the funnel plot of the RCTs shows that there is likely to be a publication bias, and this in part may be due to the large number of studies that were funded by the manufactures.

Despite the many RCTs already in the literature, there are some large, well designed and appropriately powered studies currently recruiting. There is a UK multicentre RCT '*SUNRRiSE*' (ISRCTN reference number 17599457) of NPWT dressings in emergency laparotomies that is being conducted that may give a better answer on NPWT role in colorectal surgery (180). There is a similar multicentre RCT '*PROPEL*' (Clinicaltrials.gov reference number NCT03871023) recruiting in Ireland for laparotomy patients (181) and a

multicentre RCT '*CYGNUS*' (Australian and New Zealand Clinical Trials Registry ACTRN12618002006224p). recruiting for caesarean patients in Australia (182).

3.11.1 Current Guidelines

NICE (MTG43) guidelines: recommends the use of PICO dressings in those at high risk for an SSI, and particularly in orthopaedic and caesareans (183).

WHO guidelines: Recommends the use of NPWT in adult patients on primarily closed surgical incisions in high-risk wounds, for the purpose of the prevention of SSI, while taking resources into account (97).

CDC guidelines: No guidance (98).

Commentary: There is literature indicates that NPWT reduces the risk of SSIs in high risk patients. However, a large part of the evidence is from studies that are funded by the manufacturer which raises questions on the impartiality. The independent RCTs currently being recruited too will hopefully provide further evidence for NPWT.

3.12 Use of surgical gloves

Surgical gloves, which have become a routine part of operative attire, were worn for the first time in the UK by Lynn Thomas, a Cardiff surgeon, in 1905 (184,185). The main reason that gloves were first worn as standard practice was to protect the staff from blood-borne diseases; however, gloves also protect the surgical patient from transmission of micro-organisms from the surgeon (185). During surgery, the surgeon can wear single gloves, double gloves or triple gloves depending on the degree of contamination risk for the patient. For the majority of procedures that are less than an hour in duration single gloves are appropriate but longer procedures or higher risk procedures including joint arthroplasty should be double gloved due to the increased risk from perforations (185). A Cochrane review 2006 included two RCTs that evaluated glove perforations of which 14 trials of double gloving showed that there were significantly more perforations to the single glove than the innermost of the double gloves (OR 4.10, 95% CI 3.30-5.09) (186). Although the number of perforations correlate to the risk of potential contamination of the surgical wound, there was no association with SSI rates within those 14 studies.

Misteli *et al.* (2009) analysed a prospective observational cohort study to evaluate the rate of SSIs in the presence of perforated gloves in 4,147 patients undergoing a vascular or general surgical procedure (187). The overall SSI rate was 4.5% but it was 7.5% in patients with a glove perforation (OR 2.0; 95% CI 1.4-2.8; p<0.001) (187). There was an overall glove perforation rate of 16.3% but this was increased in those cases lasting longer than 2 hours to 34%. A further analysis of the same data set by Junker *et al.* (2012) found that if glove perforation happened in those patient who had not had prophylactic antibiotics immediately before surgery then they were more likely to develop an SSI (OR 2.0; CI 1.4–2.8; p <0.001) (188).

Although glove perforations increase with longer operating times, there is also an increase in recolonisation of the surgeons hands, and Hosseini *et al.*(2016) found that at 5 hours hand recolonisation had reached pre-scrubbed levels (189). Despite the evidence for glove perforation and hand recolonisation, a small study by Ortiz *et al.* (2012) actually found that complete surgical rescrubbing prior to laparotomy closure significantly increased the SSI rate (190).

Overall, there is a lack of clear evidence on the different aspects for optimal surgical glove practice. Firstly, it seems that if an operation is to take longer than 2 hours double gloving is recommended, or a change of gloves to mitigate for the increased perforation rate. Secondly, glove perforation in the absence of prophylactic antibiotics increases the risk of SSIs. Thirdly, there is no RCTs to evaluate the optimal time of glove change, if at all.

3.12.1 Current Guidelines

NICE (NG125) guidelines: Consider wearing 2 pairs of sterile gloves when there is a high risk of glove perforation and the consequences of contamination may be serious. (105).

WHO guidelines: No recommendation due to the lack of evidence to assess whether double-gloving or changing of gloves during the operation or using specific types of gloves is more effective in reducing the risk of SSI. (97)

CDC guidelines: No guidance(98).

Commentary: Overall there is a lack of evidence in the role of surgical gloves in preventing SSIs. There is some weak evidence that double gloving in longer operations may reduce SSIs, but to further evaluate the exact specifics such as role of glove changes, timing of glove changing and double gloving will exactly define best practice for reducing SSIs.

3.13 Antimicrobial-coated sutures

Sutures are used to approximate wound edges to facilitate healing of a surgical incision. However, the suture does provide a surface on which bacterial colonisation can occur. The different suture materials and type, particularly mono-filament and braided, have different affinities for microbial colonisation. To try and combat the bacterial colonisation, sutures have been coated with Triclosan, which can prevent colonisation and reduce the risk of an SSI post-operatively (191). Triclosan interferes with lipid synthesis which leads to weaker cell membranes in bacterial cells. It has a broad spectrum of action and is effective against selected Gram negative and Gram positive bacteria leading to a significant reduction of bacterial colonisation in *in vitro* and *in vivo* studies (191–193). Ming *et al*. demonstrated that there was activity against bacteria up to 3 weeks including action against *Staphylococcus aureus*, MRSA (methicillin resistant *Staphylococcus aureus*) and *Escherichia coli* (192). The main concern of using triclosan in sutures is the potential development of resistance (191) but this has not been demonstrated in laboratory or clinical studies as of yet.

Two large systematic reviews have evaluated the literature for the effectiveness of antimicrobial sutures on SSIs (194,195). A systematic review by de Jonge *et al.* (2016) included 21 RCTS of 6,462 patients and found that triclosan coated sutures reduced the risk of SSIs (RR 0.72; 95% CI 0.60-0.86; p<0.001) (194). This was pan-speciality and contained operations of all classes (clean to dirty). The RCTs included were of a variety of methodological quality, but only 4/21 had no conflict of interest, with many studies funded by the manufacturer of the sutures. An updated systematic review by Ahmed *et al.* (2019) included 25 RCTS of 11,957 patients, 4 more than the 2016 review of which one study was a large RCT of 2,546 patients (195). The meta-analysis found that triclosan coated sutures significantly reduced the risk of SSIs (RR 0.73; 95% CI 0.65-0.82), and that this was the case in both clean and contaminated surgery (195). A main point of methodological differences in the studies included is which surgical layers the triclosan coated sutures were used.

Despite the results of the meta-analysis, there continues to be further trials to evaluate triclosan coated sutures. Future research needs to be focused on contaminated surgeries, of which numbers are low in the previous studies, and to investigate the surgical layer of importance for the triclosan coated sutures.

3.13.1 Current Guidelines

NICE (NG125) guidelines: When using sutures, consider using antimicrobial triclosan-coated sutures, especially for paediatric surgery, to reduce the risk of surgical site infection. (105).

WHO guidelines: The panel suggests the use of triclosan-coated sutures for the purpose of reducing the risk of SSI, independent of the type of surgery (97).

CDC guidelines: Consider the use of triclosan-coated sutures for the prevention of SSI (98).

Commentary: There are two strong systematic reviews that have demonstrated that triclosan-coated sutures reduce the risk of SSIs, however the majority of the studies included in these systematic reviews were funded by the manufactures, which may impact impartiality. On the strength of the systematic reviews, NICE, WHO and CDC recommend the use of triclosan coated sutures.

3.14 Mechanical Bowel Preparation and Oral Antibiotics

The use of mechanical bowel preparation (MBP) is used in colorectal surgery has been controversial within colorectal surgery, particularly after the introduction of ERAS which advocated the limited use of bowel preparation (28). The use of MBP is consequently varied between surgeons, hospitals and countries. Those that do prescribe MBP do so due to its perceived benefit of reducing the intraluminal bacterial load of the colon and thus reducing SSIs, whilst also having some benefit for the colorectal anastomosis through its construction by ensuring the bowel is free of faeces and then maintaining its post-operative structure by limiting the passage of hard stool.

In 1973, Nichols *et al.* published that combining MBP with an oral antibiotic regime (MBP/OAB) reduced SSI rates after colorectal surgery (196). However, it has been argued that the introduction of oral antibiotics has a potential harmful profile, particularly since

antibiotic prophylaxis is also given intravenously immediately prior to the surgical incision. Since this study there has continued to be much debate about the role of MBP alone, MBP/OAB or no bowel preparation. More recently there has been an analysis of the American College of Surgeons National Surgical Quality Improvement Program database, which is a prospectively collected database of all types of surgical outcomes, comparing SSI rates in different MBP regimes (197). A total of 27,804 patients were included, where 23.5% received no bowel preparation, 32.7% received MBP alone, 5.9% received oral antibiotics alone and 38% received MBP/OAB combination. It concluded that the MBP/OAB combination reduced SSI (OR 0.39, p < 0.001), wound dehiscence (OR 0.43, P = 0.001) and anastomotic leaks (OR 0.53, P < 0.001). It subsequently reported that oral antibiotics alone SSIs also, but that MBP alone had no beneficial effect on SSIs and infectious complications (197). The use of oral antibiotics was also not associated with increase in post-antibiotic complications like *Clostridium Difficile* infections. There are limitations with this data via the nature of a prospective collected national database and some lack of data completeness.

Within the literature there has been two recent systematic reviews with meta-analysis, whilst the WHO has conducted a systematic review to provide guidance on this controversial issue (97,198,199). Rollins *et al.* (2019) included 40 studies within their meta-analysis and found that the MBP/OAB combinations versus MBP alone significantly reduced SSIs (RR 0.51, 95% CI 0.46–0.56, p < 0.00001) with no difference in *Clostridium Difficile* infections (199). They found there were no RCTs comparing MBP alone with oral antibiotics alone and comparing oral antibiotics alone with no MBP. These comparisons are important to fully answer the questions about efficacy of the MBP/OAB combination in the reduction of SSIs.

The systematic review by Nelson *et al*. (2020) takes the question further by analysing the effect of using intravenous antibiotics with/or oral antibiotics with/or MBP (198). Some of the controversy around the use of oral antibiotics is that prophylactic intravenous antibiotics are routine practice for colorectal surgery, and thus these patients would then have a double dose of prophylactic antibiotics. The combinations of antibiotic and MBP evaluated in this meta-analysis found that the combined oral and intravenous antibiotic regime were superior in reducing the risk of SSIs. They then weakly confirmed by a meta-analysis of 2 studies that this was independent to MBP (198). Both systematic reviews are

further confirming that the action of oral antibiotic bowel preparation, and not the action of MBP that reduces the rate of SSIs.

WHO has conducted a systematic review with the primary question of comparing MBP alone with no bowel preparation to reduce SSIs, but secondarily reviewed the impact of adding in oral antibiotics to MBP to reduce SSIs (97). 24 RCTs were included, and it was found that MBP/OAB regime reduced SSIs compared to MBP alone (OR 0.56; 95% CI 0.37–0.83) and that MBP alone did not have an impact on reduction of SSIs compared to no bowel preparation (OR 1.31; 95% CI 1.00–1.72). Consequently, WHO has recommended that MBP/OAB combinations reduce SSIs, but MBP alone should not be used for the purpose of reducing SSIs. They acknowledge that there is a gap in the research comparing oral antibiotics with or without MBP with no bowel preparation at all. In addition, most of the studies in the literature evaluating MBP/OAB regimes are in predominantly open colorectal surgery, with less data and research available in the laparoscopic colorectal surgery which would be more relevant to current surgical practice.

3.14.1 Current Guidelines

NICE (NG125) guidelines: Do not use mechanical bowel preparation routinely to reduce the risk of surgical site infection (105).

WHO guidelines: The panel suggests that MBP/OAB combination should be used to reduce the risk of SSI in adult patients undergoing elective colorectal surgery. MBP alone (without administration of oral antibiotics) should not be used for the purpose of reducing SSI in adult patients undergoing elective colorectal surgery.(97).

CDC guidelines: No guidance (98).

Commentary: MBP/OAB combination reduces SSIs compared to MBP alone, and not at the risk of increased antibiotic related complications. However, there is a deficit in the current research about the role of OAB alone compared to MBP/OAB, and the role of intravenous prophylactic antibiotics in the presence of OAB. As such the guidance from NICE and WHO reflects that if MBP is to be used, it should only be used with OAB.

3.15 Compliance with standards

Despite the availability of evidence-based guidance for SSI prevention, there is variable compliance. Badia *et al.* (2020) conducted a survey of theatre nurses and surgeons in Spain to which 1105 responded (200). The awareness of the guidance in the specific domains and the actual practice varied from the respondents and demonstrated in Figure 2-3.
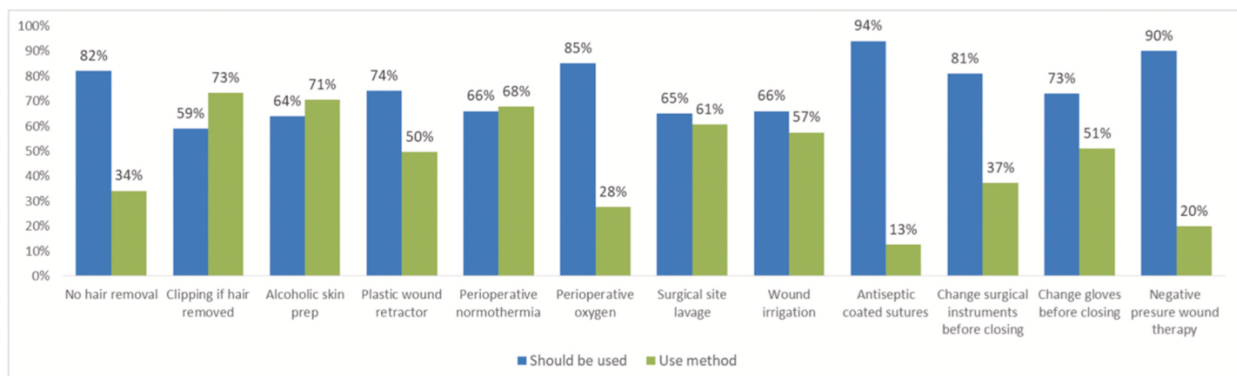
Figure 3-3 A comparison between respondents awareness of the guideline and the actual practice(200)

The biggest discrepancy was in hair removal, perioperative oxygen, the use of antiseptic coated sutures and the use of NPWT. Alcoholic CHG was used in only 57.2% of cases. Only 50% of the respondents received feedback on their personal SSI rates (200).

Within England, the 'Getting it Right First Time' programme reviewed many aspects of surgical departments across England, and as part of their findings found that there was a lack of awareness of SSI rates within their departments and of the current guidance on best practice for prevention of SSIs (201). Within UHW, a survey of consultant and trainee surgeon in 2018 demonstrated the following compliance (202):

- Ensuring patients showered the night before an operation: 29% compliance
- Antibiotic prophylaxis before the incision: 76% compliance
- Use of alcoholic CHG: 29% compliance
- Routine implementation of preoperative glycaemic control and use blood glucose target levels less than 200mg/dl (11.1mmol/L) in patients with OR without diabetes: 33% compliance - in both patients with and without diabetes
- Maintenance of Normothermia: 100% compliance

- Irrigation of wound before closure: 0% compliance

Section Two - Defining the Colorectal SSI Rate in Wales

4 Pilot study: A Single Institution Colorectal Surgical Site Infection Rate

4.1 Introduction

The baseline surgical site infection (SSI) rate for colorectal surgery within Wales is largely unknown, with independent units haphazardly monitoring individual departmental or consultant data but with no robust follow up methods. A collaboration between University Hospital of Wales (UHW) and Public Health Wales (PHW) was established to focus on the recording of colorectal SSI rates and the subsequent improvement of the SSI rates. Before a national Welsh prospective observational study could be designed to define this national baseline, a pilot study was conducted at a single site within Wales.

Despite a large successful project with caesarean patients (203), the colorectal patient cohort had different challenges particularly in the recording of SSIs diagnosed in primary care. Mothers, after caesareans, are visited frequently by health care professionals in the first few weeks post-delivery. These health care professionals were informed to direct patients back to obstetric units if there were wound problems but could also document any primary care input in the obstetric notes. Since 2006 it has been a requirement by the Welsh Government that all health boards with patients who undergo caesareans must participate in the national data collection to ensure an accurate number of SSIs. This has allowed for highly accurate collection of SSI rates (203).

However, with the colorectal patient cohort, these patients do not have follow up from healthcare professionals in their own home like caesarean patients. These patients, at present, will engage with primary care services primarily if there is a wound problem and the data are more difficult to obtain in a contemporaneous manner to be fed back to the operating team.

Before the undertaking of the prospective multicentre observation study, a pilot study was necessary to ensure that data could be accurately collected, which in this case was the diagnosis and treatment of SSIs in both secondary and primary care. The design of the pilot

study was to ensure that the data collection tool, via PHW's intranet, was easily accessible and contained the correct data fields. The observational study design could then be assessed for accuracy and ease of use before conducting the larger multi-centre study.

4.2   Aim

The aim of the pilot study was to evaluate the study design and assess if the primary care data can be accessed and used to obtain a more accurate number of SSIs diagnosed and their treatment. The pilot study would also provide an SSI rate that could be used as a reference point for the results of the main study.

4.2.1   Definition of Success

The pilot study will be assessed for success via the following paraments:

- Ease of data collection – did the data parameters collected provide adequate and useful data. Assessment will be via department evaluation of the data.
- Accuracy of SSI data collection – assessing the multi methods approach in providing consistent data.
- Provide a single unit colorectal SSI rate (within the time period) that is comparable to previous published data of 8.6% by Power et al. (44). This pilot SSI rate will be used as a reference for the future all Wales study.

4.3   Method

50 consecutive patients undergoing either an elective or emergency operation with an abdominal incision (laparoscopic and open surgery) under the care of any colorectal consultant and admitted to a single specified ward within a single institution, UHW, were prospectively included in the study. Each patient had demographic data collected including the date and type of operation (Figure 4-1). The patients were prospectively reviewed daily on the ward by a senior doctor (speciality trainee or a consultant surgeon) until discharge for the development of an SSI. The criteria for SSI diagnosis was based on the PHW criteria for superficial, deep and organ space SSIs, adopted from the CDC diagnostic criteria and is available as open access online reference (41,98). If the patient developed an SSI as an

inpatient, then a microbiology wound swab was taken and processed by the Hospital's microbiology laboratory as per standard NHS practice. Figure 4-1 is the data collection tool that was used, hosted on the NHS Wales Intranet by PHW.

The inclusion and exclusion criteria are shown in Table 4-1.

Inclusion	Exclusion
All patients on single colorectal ward	Patients not under the care of a colorectal consultant
Patients operated under the care of a colorectal consultant	Complex abdominal wall patients (Intestinal Failure/Multiple stoma or fistula)
Abdominal incision	Perianal incision only/Proctology

Table 4-1 Inclusion and Exclusion Criteria of patients within the pilot study

4.3.1   Follow Up

The patients underwent several aspects to the follow up for 30 days post operatively to identify those who developed an SSI. For those patients who were an inpatient for the full 30 days post-operatively they had a review on day 30 by the senior doctor. If the patient was discharged before 30 days, follow up was via interrogation of electronic GP records accessible in secondary care, via outpatient clinic attendances, or via a phone call to the patient. If at 30 days post-operatively there was no diagnosis of an SSI, the patient was be deemed as having a healed wound.

4.3.2   Primary Care Diagnostic Criteria

An early difficulty in this study that was identified was defining an SSI diagnosis in the community due to the limited access to the primary care records, particularly that of the GP notes made in the clinical assessment. The data that was readily available was acute prescriptions and broad reason for doctor/nurse interactions. For the pilot study, the patients that were treated for an SSI in the community through antibiotic prescription or

wound care interactions were presumed as a positive SSI diagnosis, with confirmation via the telephone call to the patient.

Figure 4-1 Data Collection Tool via the NHS Wales Intranet, created by Public Health Wales

4.4 Results

4.4.1 Patient Demographics

50 patients had abdominal colorectal surgery between 22nd October 2018 to 3rd December 2018 on a single ward in UHW, with 41 elective procedures and 9 emergency procedures. There was an equal number of males to females, who were aged 16-92 (Table 4-2) and the 'unknown' patient was due to a computer error. An assessment was made of their surgical wound through a mixture of daily ward reviews, outpatient clinic appointments, GP online records and telephone calls. Every patient in the pilot study received a phone call to

correlate the patient's post-operative pathway was correct when compared to the recorded clinical data.

Demographic	Number of Procedures	Number of SSIs	SSI Rate	95% CI
SEX				
Male	24	6	25.0%	9.8-46.7%
Female	25	4	16.0%	4.5-36.1%
Unknown	1	0	0.0%	0.00-97.5%
AGE GROUPS				
16-47 _(1st Quintile)_	10	2	20.0%	2.5-55.6%
48-59 _(2nd Quintile)_	8	1	12.5%	0.3-52.7%
60-68 _(3rd Quintile)_	11	4	36.4%	10.9-69.2%
69-74 _(4th Quintile)_	9	2	22.2%	2.8-60.0%
75-92 _(5th Quintile)_	12	1	8.3%	0.2-38.5%
URGENCY				
Elective	41	8	19.5%	8.8-34.9%
Emergency	9	2	22.2%	2.8-60.0%

PROCEDURE GROUP				
Duodenum	1	0	0.0%	0.0-97.5%
Small Bowel/Ileum	4	1	25.0%	0.6-80.6%
Appendix	4	1	25.0%	0.6-80.6
Colon	23	3	13.0%	2.8-33.6%
Rectum	14	5	35.7%	12.8-64.9%
Hernia Repair	4	0	0.0%	0.0-60.2%

Table 4-2 Demographics and SSI rate for 50 patients

4.4.2   SSI Rate

The overall SSI rate was 20%, which equates to 10 patients who developed an SSI following their colorectal surgery. Notable results included colonic surgery having an SSI rate of 13% and rectal surgery having an SSI rate of 35.7%

4.4.3   Follow Up Methods

As a pilot study, the main aim was to evaluate the follow up methods of the 50 patients in the primary care setting to ensure accuracy of SSI documentation. The follow up method combined four different approaches – daily ward reviews as inpatient, accessing GP records online, outpatient clinic appointments and patient telephone calls. From the follow up that happened post discharge, 2 patients were recorded as having an SSI which is 20% of the total number of SSIs diagnosed. The patient telephone calls did not add any further diagnostic information compared to all information that was collected from electronic records and outpatient clinics.

4.4.4   Assessment of Study Design

The pilot study highlighted that there needed to be some minor changes to the data collection tool to ensure more thorough data collection of the main study. The tool was amended as seen in Figure 4-2. There was the addition of an elective and emergency selection, a laparoscopic or open surgery selection and there were amendments to the procedure names to ensure that it was clear what operation was being selected.

Figure 4-2 - Amendments to the Data Collection Tool created by Public Health Wales as seen in Figure 3-1

4.5   Discussion

The pilot study was assessed for success, and subsequent limitations, in each of the domains defined pre-study.

4.5.1   Ease of Data Collection

The pilot study demonstrated that the methods of following up patients in the primary care setting, and prospectively on the ward can facilitate the collection of SSI data in the post-

operative period. Within UHW, I was the lead clinician for assessing wounds, but this was done with support from nursing staff and other clinicians.

Each patient had their hospital records interrogated for outpatient or GP attendances, and readmissions with complications from the wounds. All the patients received a telephone call to ensure that their post-operative pathway was the same as the clinical details recorded. This also ensured there were no missed SSIs.

The intranet tool was well designed and captured most of the data required for the study. However, there were some data fields that were identified as being important but not included within the tool. These included the type of operation – elective or emergency and whether the operation was laparoscopic or open. The names of the procedures were refined and edited to increase usability.

4.5.2   Accuracy of Data Collection and Single Centre SSI Rate

The overall SSI rate recorded in this small data set was 20%, which is much higher than the previously published rate of 8.6% (44). However, the SSI rate of 20% within this cohort of patients is also comparable to the wider literature further demonstrating reliability of the data collection methods. The patient cohort was a wide spread of ages, type of operations, length of hospital stays and included both elective and emergency operations. The operation spread was reflective of the normal mix of cases that are part of a colorectal surgeons practice within the UK.

As 20% of the total SSIs were diagnosed in primary care it further confirms that many SSIs are diagnosed and managed in the primary care setting. This is likely to be in part the explanation for the difference in SSI rate in the same unit during this small study and the previous published rate of 8.6% (44). This rate is lower than that found by Tanner *et al*., but still a significant portion of SSIs are diagnosed in the community (68). It is important to ensure that these post-discharge SSIs are captured and documented as a post-operative complication and included in any SSI surveillance project or SSI research.

However, the accuracy of the SSI diagnosis within the primary care setting is difficult to assess. Primary care physicians are less experienced in diagnosing and treating surgical

wound problems in comparison to the operating surgical teams. There are subtle differences between diagnosing a wound as being dehisced with slow healing, versus those which are infected. The pilot study demonstrated that a pragmatic approach needed to be adopted when assessing SSI diagnosis in the community – if the primary care physician diagnoses and treats the patient for an SSI, then they were assumed to have the correct diagnosis. As most SSIs are treated with antibiotics, and with increasing antibiotic resistance, it is necessary to understand the prevalence of those treated for an SSI so that any future projects can be multi-faceted in their approach to reducing SSI occurrence, from improving surgical care but also in improving diagnostics. However, it will be accepted that a limitation of the larger multi-centre study will be that it will not be possible to assess the accuracy of the GP diagnosis of an SSI.

Further to this, the telephone call was utilised to ensure that all clinical data for the patient (primary and secondary) was a true reflection of the patient pathway and experience. As no further SSIs were identified from these telephone calls, there is some confidence that the data obtained has good reliability.

4.5.3 Limitations of the Pilot Study

There are some limitations of the pilot study, further to the primary care diagnostic accuracy. The small patient cohort size, only allowed for limited assessment of the aims and markers of success. The changes to the data collection tool were identified early in the data collection due to the data collection tool (figure 4-1) had been designed for orthopaedics and was not representative of the different aspect of colorectal surgery including surgical approach and urgency. However, these changes perhaps did not go far enough, and did not include the broad classification of 'Colorectal vs General Surgery' selection, to separate the data more easily in the future studies.

An assessment of the accuracy of the data collected could not be confidently performed. Although the telephone call did not reveal any further additional SSIs not captured via interrogation of available clinical nots, with only 50 patients, this would be a strong presumption of accuracy. It is likely that as the primary assessor of the inpatients, I was very thorough in the data collection of a study of my design. However when the study is to be

rolled out across many centres, with many assessors, it is difficult to assess the reliability and accuracy of the pilot studies methods in that situation. In addition, the SSI rate was much higher than the previously published SSI rate of 8.6% which brings doubt onto the long-term accuracy of an SSI rate from this small date set.

These limitations do not take away from the successes of the pilot study in demonstrating that SSI surveillance within each colorectal unit could be undertaken by one (or small number) staff member, with a low time burden with reasonable accuracy and reliability. The accuracy of future data collection will have to be carefully scrutinised, but if the UHW SSI rate in the all Wales study is similar to the pilot study it will further add to the reliability of the data.

4.5.4   Impact on All Wales Data Collection

Overall, the pilot study demonstrated that a pragmatic approach could be used to ensure that an SSI rate could be recorded for up to 30 days post-operatively in colorectal surgical patients with a reasonable confidence in accuracy. The main change was in the intranet data collection tool with an increase to the data variables that would be collected.

The pilot study was presented at a National Meeting to representatives of the Welsh Colorectal Consultants and departments to disseminate the work and invite suggestions on improving the project before an all Wales project began. There was a collective agreement on the study design, and it was planned to conduct a snapshot study for one month to determine the SSI rate for patients under the care of a colorectal consultant.

5 All Wales Colorectal Surgical Site Infection Rate (WICS) – Defining the Baseline SSI Rate

5.1 Introduction

Following on from the pilot study conducted in UHW from October to December 2018, a much larger data collection project was planned to encompass the whole of Wales and to accurately assess the SSI rate of colorectal surgical patients. This was conceived as a project that would be undertaken through the general surgical research collaborative known as the 'Welsh Barbers', in partnership with PHW. The Welsh Barbers is a research group led by general surgical trainees, consisting of both core surgical trainees and higher surgical trainees, with an aim to design and deliver trainee led research through Wales and the UK. The collaborative style of the group ensures that all hospitals with a general surgical department have a trainee who is aware of and participating in Welsh Barber research projects.

Figure 5-1 - Logo for the All Wales Wound Infection in Colorectal Surgery Study

5.2 Aims and Objectives

Primary Aim

To establish the all Wales 30-day SSI rate from both primary and secondary care as based on the CDC recommendations for post-operative wound follow up (98). A GP diagnosis of SSI within primary care was considered to fulfil the CDC diagnostic criteria as these patients were treated as presumed SSI (limitations of this discussed in Chapter 4).

Secondary Outcomes

    a. To define the colorectal SSI rate compared to the previous published standard of 8.6% and comparison of the colorectal SSI rate with emergency general surgery performed under the care of the same consultants.

    b. To assess systemic factors influencing the prevalence of SSIs including geographical location, type of colorectal operation and elective operations in comparison to emergency operations.

    c. To define the percentage of SSIs diagnosed in primary care.

    d. To review microbiology results across Wales.

5.3   Method

5.3.1   Study Design

The WICS study was a national multicentre prospective surveillance study run in partnership between PHW and the Welsh Barbers (Figure 5-1). All hospitals that provided a colorectal surgical service were invited to participate in the study with a general surgical trainee or surgical nurse practitioner leading the study at each participating site. A total of 12 sites participated out of an eligible 13, covering the majority of the Welsh 3.06 million population. As the study was a prospective cohort study with no change in care there was no ethical requirements, but the study was registered as a service evaluation in each individual hospital.

Between 1st March- 31st March 2019, all consecutive elective and emergency operations performed under the care of each colorectal consultant (defined by membership of the Association of Coloproctology of Great Britain and Ireland (ACPGBI)) were prospectively recorded via the electronic data collection tool designed by PHW (Figure 4-2) and hosted securely by the PHW intranet. The colorectal consultant was either performing the

operation, supervising a trainee surgeon performing operation or had responsibility for the patient who had an operation performed solely by a trainee surgeon. Patient data collected included name, age, hospital site, date of operation, operation performed, surgical approach, surgical urgency, and date of discharge/death. Patient demographics and medical history, including ASA, co-morbidities and medications, were not collected as patient specific risk factors for SSIs have been well studied and defined (204). Patient data were anonymised prior to statistical analysis.

Operations were considered laparoscopic if they had an extraction site for the specimen and were considered open if the procedure was started as an open procedure or converted to open at any point. As the main focus was colorectal procedures the operations were grouped, as shown in Table 5-1. Other operations consisted of any operation that did not belong to the other groups, for example a laparotomy for small bowel obstruction with no resection. Inclusion of non-colorectal, general surgery procedures was to create a comparable data set to the colorectal group of patients. This was included on the request of the consultant cohort who were involved in the design of the study following presentation of the pilot data (see section 4.5.4). The inclusion of the general surgery data does make the group heterogeneous, but there will be analysis of date based on the whole cohort and further sub analysis of the colorectal cohort.

During the 30-day follow up the SSI diagnosis date, type of SSI, treatment received, and any positive microbiology results (wound cultures) were collected. If there was patient mortality after 48 hours but before the 30 day follow up was complete then they were considered to have an SSI if one developed before death.

Duodenum	Ileum	Appendix	Colon	Rectum	Hernia	Other Operations
Peptic ulcer perforation	Small Bowel Resection

Reversal of Ileostomy

Defunctioning Ileostomy | Emergency Appendicectomy

Elective Appendicectomy | Right/extended right/left hemicolectomy

ileo-colic resection

Sigmoid colectomy

Colostomy Reversal

Defunctioning colostomy

Subtotal Colectomy

Panproctocolectomy | Anterior Resection (low/high/TATME)

Proctectomy

Hartmanns

Abdomino - Perineal Excision of Rectum (APER)

Rectal Prolapse Surgery | Inguinal

Femoral

Umbilical

Incisional

Abdominal Wall Repair | Small Bowel Obstruction (no resection)

Wash out of Intra-abdominal collections (no resections) |

Table 5-1 Procedures categorised by Wales Hospital Coding definitions

The inclusion criteria were:

- Patients over the age of 16
- All elective and emergency operations under the care of a colorectal surgeon (including both laparoscopic and open operations)
- All operations that included an abdominal and/or groin incision
- Only wounds healing by primary intention

The exclusion criteria were:

- Patient mortality within 48 hours of operation
- Patients having their operation undertaken under the care of another specialty consultant – not a colorectal consultant
- Incisions which were to heal via secondary intention.
- Perineal incisions or Proctology only during the operation
- Laparostomy patients

- Patients undergoing Laparoscopic Cholecystectomy (there is a wide variability in this service across the hospitals and in the numbers of these performed by colorectal consultants in Wales)

The inclusion and exclusion criteria were refined compared to the pilot study criteria (Table 4-1).

5.3.2   Follow Up

To ensure that all SSIs that developed within the 30-day post-operative period were identified, several methods were used to follow up the patients – this was the same as the pilot study. This included prospectively reviewing daily medical and nursing notes during the weekdays to identify all SSIs that were diagnosed before discharge from hospital. Hospital microbiology results for wound swab cultures were used as a prompt to review any wounds with positive cultures but were not solely used for diagnosis of SSIs. Post discharge, electronic case notes were interrogated for diagnosis of SSIs from either outpatient appointments or primary care interactions particularly with their GPs. Within Wales, the inpatient electronic case note system is linked to the patient's GP notes, however details of GP clinical assessment are lacking from the online GP notes.

Each hospital department used their discretion to follow up patients with a telephone call dependent on their normal practice. In the main, the patients that did not have secondary care follow up within the 30 days post-operatively were telephoned on day 30 post operatively (+2 days) to ask specifically if they had had interactions with primary care about their surgical wounds post discharge via a non-scripted interview. The focus of the telephone call was to correlate the GP record with the patient which included discussing if the patient had had any specific wound treatment including dressings or antimicrobial therapy. If at 30-days there were no surgical wound problems or infections, patients were deemed as not having developed an SSI.

SSI infections were classified as either superficial, deep or organ space, and were diagnosed as per CDC criteria (98) (which PHW had adapted into guidelines (41,98)) whilst an inpatient. Organ space SSIs were included if they were intra-abdominal collections that were not caused by a surgical complication, for example an anastomotic leak. The inclusion of organ

space SSIs was to allow comparison with other data sets including obstetrics. Once the patient was discharged any GP positive diagnosis and/or commencement of treatment of an SSI was considered to fulfil the SSI diagnostic criteria. The limitations of GP diagnosis were accepted within the remit of this study.

5.3.3   Study Sites

Throughout Wales there are 13 hospitals over 6 University Health Boards (UHB) that provide an acute general surgical service with an elective colorectal surgical service. All hospitals were invited to take part in the study; however, one hospital did not have the staff resources to ensure the commitment required to collect accurate follow up data on the patient group. Therefore, a total of 12 hospitals agreed to participate in the national data collection (Table 5-2).

University Health Board	Participating Hospitals
Aneurin Bevan	Nevill Hall Hospital, Abergavenny
	Royal Gwent Hospital, Newport
Betsi Cadwaladr	Glan Clwyd Hospital, Bodelwyddan
	Wrexham Maelor Hospital, Wrexham
	Ysbyty Gwynedd, Bangor
Cardiff and Vale	University Hospital of Wales, Cardiff.
Cwm Taf Morgannwg	Prince Charles Hospital, Merthyr Tydfil
	Princess of Wales Hospital, Bridgend
	Royal Glamorgan Hospital, Llantrisant
Hywel Dda	Glangwili General Hospital, Carmarthen
	Withybush General Hospital, Haverfordwest
Swansea Bay	Morriston Hospital, Morriston

Table 5-2 List of the Welsh Health Boards and participating hospitals that collected data for the National SSI Snapshot Study.

5.3.4 Data and Statistical Analysis

Descriptive analysis of the number of SSIs that were diagnosed was performed with further subgroup analysis of gender, age, surgical approach, urgency, and procedure group with a focus on colorectal surgical procedures. The 12 sites were part of 6 Health Boards, and the analysis of SSI rates was conducted by Health Board due to small numbers at some individual sites. The data from this study were analysed to identify the number of SSIs that were diagnosed pre- and post-discharge and number of readmissions.

The statistical analysis was mainly descriptive with means and CI presented. Chi square tests were used to compare groups as appropriate, with the Mann Whitney U test used to compare primary and secondary care diagnosis of SSIs and time to discharge. Data analysis was performed in IBM SPSS statistics version 26. Statistical significance was accepted at $p<0.05$. Graphing was performed within GraphPad Prism version 8.3.1 (GraphPad Software, California USA).

5.4 Results

Between 1st- 31st March 2019, 545 patients had abdominal operations under the care of a colorectal consultant surgeon within 12 hospitals (6 local health boards), with no patient mortality. Seventy-one patients had an SSI diagnosed during the 30-day follow up, which resulted in a national SSI rate of 13.0% (71/545) for surgeries under the care of a colorectal surgeon. From the follow-up methods, no patient reported an SSI during a telephone consultation that was not electronically documented in the GP case notes. The demographics of the patient group and the associated SSI rate for these groups are shown within Table 5-3.

Demographic	Number of Patients	Number of SSIs	SSI Rate	95% CI	p-Value
GENDER					
Male	306	35	11.4%	8.1-15.5%	p= 0.247
Female	231	36	15.6%	11.2-20.9%	
Unknown	8	0	0.0%	NA	
AGE GROUPS (YEARS)					
16-42 (*1st Quartile*)	127	13	10.2%	5.6-16.9%	
43-60 (*2nd Quartile*)	141	17	12.1%	7.2-18.6%	p=0.555
61-72 (*3rd Quartile*)	132	20	15.2%	9.5-22.4%	
73-104 (*4th Quartile*)	136	21	15.4%	9.8-22.6%	
Unknown	9	0	0.0%	NA	
SURGICAL URGENCY					
Elective	280	40	14.3%	10.4-18.9%	p = 0.377
Emergency	265	31	11.7%	8.1-16.2%	

SURGICAL APPROACH					
Open	321	52	16.2%	12.3-20.7%	
Laparoscopic	220	19	8.6%	5.3-13.2%	$p = 0.028^*$
Unknown	4	0	0%	NA	
PROCEDURE GROUP					
Duodenum	3	1	33.3%	0.8-90.6%	
Ileum	29	3	10.3%	2.2-27.4%	
Appendix	136	14	10.3%	5.7-16.7%	
Colon	141	31	22.0%	15.5-29.7%	N/A
Rectum	53	10	18.9%	9.4-32.0%	
Hernia repair	146	7	4.8%	1.9-9.6%	
Other Operations	37	5	13.5%	4.5-28.8%	

Table 5-3 - Demographics and SSI rate for the 545 patients

The SSI rate for gender, age and urgency was similar with no significant differences between the groups. However, there was increasing trend of SSI rates with increasing age, with a greater than 15% rate of SSIs in those over the age of 60. With increased age there tends to be increased comorbidities (205) and increased co-morbidities is a risk factor for surgical complications, thus patients of increased age tend towards higher prevalence of SSIs. The rate of SSIs was significantly higher in open cases compared to the laparoscopic cases (p=0.028). There was no statistical comparison of the SSIs between the procedure groups due to the small numbers in some of the groups, however it is noted that there were a higher rate of SSIs in the colonic group followed by rectal procedures.

	Open		Laparoscopic		
	Number SSI/ Number Patients	SSI Rate	Number SSI/ Number Patients	SSI Rate	*Open vs Laparoscopic*
URGENCY					
Elective	30/185	16.2%	10/92	10.9%	*p*=0.278
Emergency	22/136	16.2%	9/128	7.0%	*p*=0.023
Elective vs emergency	*p*=1.000		*p*=0.449		
PROCEDURE (SELECTED)					
Appendix	5/18	27.8%	9/118	7.6%	
Colon	25/86	29.1%	6/54	11.1%	
Rectum	6/24	25.0%	4/29	13.8%	N/A
Hernia	7/133	5.3%	0/11	0.0%	

Table 5-4 Comparison of SSI Rates between Open and Laparoscopic Procedures.   Comparisons performed of elective vs emergency procedures with the χ2 test.

5.4.1   Open and Laparoscopic SSI Rates

As laparoscopic surgery is becoming more common in surgical practice, it was important to consider the differences in SSI rate between the two groups. Table 5-4 further illustrates the higher SSI rates in the open procedure groups in comparison to the laparoscopic groups. In both the appendix and colon procedures there was a greater difference between the open and laparoscopic procedures. Laparoscopic procedures had an SSI rate approximately half that of open procedures overall (8.6% vs 16.2%; p=0.023 – Table 5-3). It is further noted that there was a greater difference between the laparoscopic and open approach in emergency surgery that elective surgery. This is likely due to the degree of contamination of the emergency procedures, being higher in the open group.

5.4.2   Colorectal Procedures SSI Rates

Table 5-3 highlights the differences in the number of SSIs between the different procedure groups. Both colonic and rectal operations had a higher number of SSIs diagnosed, 22.0% (31/141) and 18.9% (10/53), respectively, in comparison to other groups of patients.

The overall colorectal SSI rate was 21.1% (41/194), with similar rates in both the elective and emergency group as seen in Table 5-5. Within this group of patients there was a larger difference between the open and laparoscopic SSI rate, with patients who had an open operation having an SSI rate of 28.2% (31/110) compared to 12.0% (10/83) for patients who had laparoscopic procedures.

	Number of Procedures	Number of SSIs	SSI Rate
URGENCY			
Elective	146	30	20.5%
Emergency	48	12	25.0%
APPROACH			
Open	110	31	28.2%
Laparoscopic	83	10	12.0%
Unknown	1	0	0%

Table 5-5 Colorectal Procedure SSI rates

5.4.3   Type of SSI

The SSIs were diagnosed as either superficial, deep or organ space according the CDC guidelines (98). There were 41 superficial, 18 deep and 12 organ space SSIs affecting 71 patients, a total of 13% (71/545) of patients. There were 59 patients with wound only SSIs (superficial or deep), a total of 10.8% (59/545) of patients. Of the 71 SSIs, 22.5% (16/71) required treatment with interventions including 5 patients requiring theatre for wound revision/washouts and debridement, and 11 patients requiring wound drainage and washout. These patients also required more complex dressings including negative pressure therapy. 77.5% (55/71) of the SSIs were managed by nurse led wound care including simple dressings; and/or antimicrobial therapy.

5.4.4   Variability across Wales

5.4.4.1   Independent Sites

SSI rates for each site were calculated to evaluate any differences. Table 5-6 shows the difference in the SSI prevalence at each site along with the percentage of the 545 cases that were completed at that site. The SSI rate ranged from 0% to 30.4% between the sites however the sample sizes were variable, some very small, with wide CI. Consequently, there needs to be caution when interpreting the results from individual centres. Across Wales there are high volume surgical centres and lower volume surgical centres, which can be seen from the site variability in the number of cases completed during the study period. Further to this there is variability in the case mix at each site.

5.4.4.2   Health Board

Each individual site is part of a local health board, which makes SSI rates more comparable. The variance between the 6 local health boards was 9.6% to 23.6%. Figure 5-2 shows the pooled SSI incidence at each local health board of the three procedures in which SSIs were most prevalent (colon, rectum and appendix). Comparison of the incidence of SSIs, represented in black diamonds, with the number of operations performed, demonstrates that SSI rates are higher in two of the three Health Boards in which the operations are performed less often.

Hospital	Health Board	Number of Patients	Number of SSIs	SSI Rate	C.I
Morriston	Swansea Bay UHB	49	7	14.3%	4.9-25.5%
Nevile Hall	Aneurin Bevan UHB	28	4	14.3%	2.8-28.0%
Royal Gwent	Aneurin Bevan UHB	74	6	8.1%	2.6-15.3%
Glan Clwyd	Betsi Cadwaladr UHB	62	4	6.5%	1.5-13.5%
Ysbyty Gwynedd	Betsi Cadwaladr UHB	72	9	12.5%	5.1-20.9%
Wrexham Maelor	Betsi Cadwaladr UHB	64	6	9.4%	2.8-17.1%
University Hospital of Wales	Cardiff and Vale UHB	72	17	23.6%	13.5-33.8%
Prince Charles	Cwm Taf Morgannwg UHB	40	7	17.5%	6.7-28.9%
Princess of Wales	Cwm Taf Morgannwg UHB	23	7	30.4%	12.5-50.0%

Royal Glamorgan	Cwm Taf Morgannwg UHB	31	1	3.2%	0.0-11.1%
Glangwilli	Hywel Dda UHB	18	3	16.7%	0.0-37.5%
Withybush	Hywel Dda UHB	12	0	0.0%	0.0-26.5%

Table 5-6 SSI Rate of each of the 12 hospitals in Wales
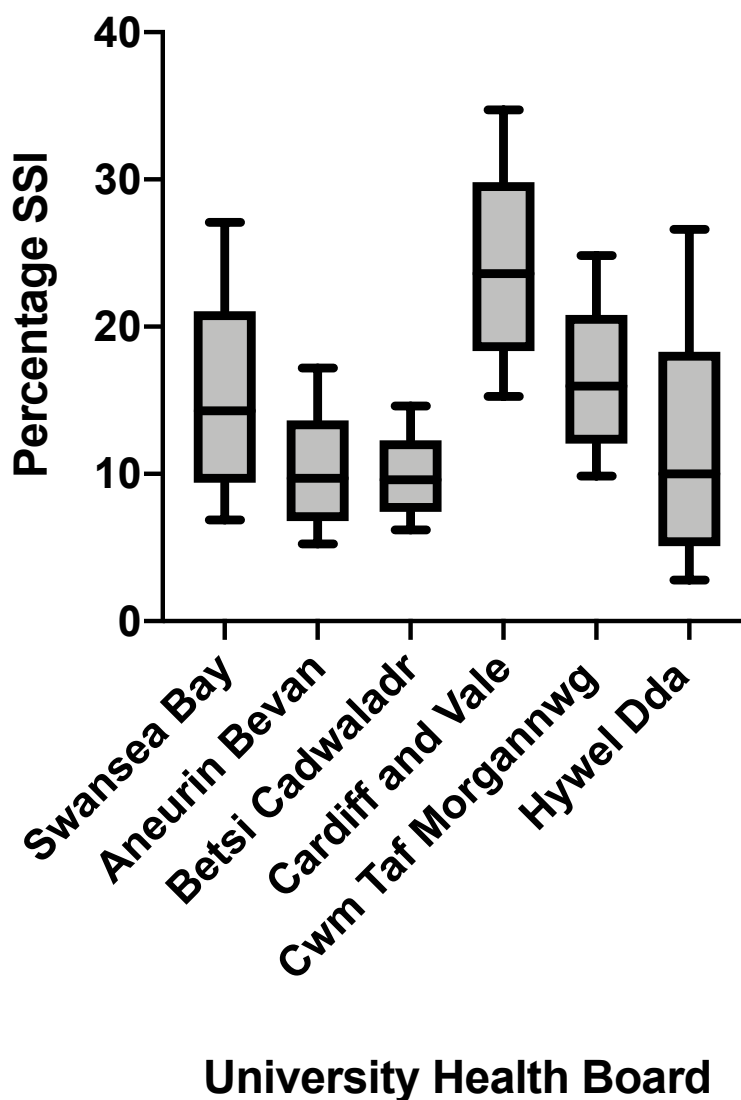
Figure 5-2 - SSI incidence at the six local health boards in Wales, shown as a 25-75th box plot and CI.

5.4.5 Time of SSI Diagnosis

Figure 5-3 illustrates the time to SSI diagnosis post-operatively in the patient cohort. There were two peaks of detection of SSIs, one at day 5-7 (early) and one at day 22-28 (late). This appears to be a mixed model of two peaks/curves of diagnosis. Figure 5-4 shows the time to SSI development between the procedure groups; the early and late SSI diagnosis were seen in the Appendix, Colon and Rectal procedure groups.

5.4.6 Primary Care Vs Secondary Care Diagnosis of SSIs

49.3% (35/71) of SSIs were diagnosed in the primary care setting with 28.2% (20/71) of all SSIs managed exclusively in the community. There were 15/71 (21.2%) patients readmitted with an SSI. The patients diagnosed with SSIs in primary care were discharged earlier than those diagnosed during their index admission in secondary care (p<0.001). SSIs diagnosed in primary care occur before day 20 post operatively, with those diagnosed in secondary care later, accounting for the second late peak.

5.4.7 Microbiology

For each SSI diagnosed, any positive microbiology results from wound cultures were recorded. Of the 71 patients with SSIs, there were 50 wounds with positive wound cultures. There were 36 wounds with 1 causative organisms, 10 with 2 causative organisms and 4 wounds with 3 causative organisms. The full list of cultured organisms from the SSIs and their frequencies are within Figure 5-5.
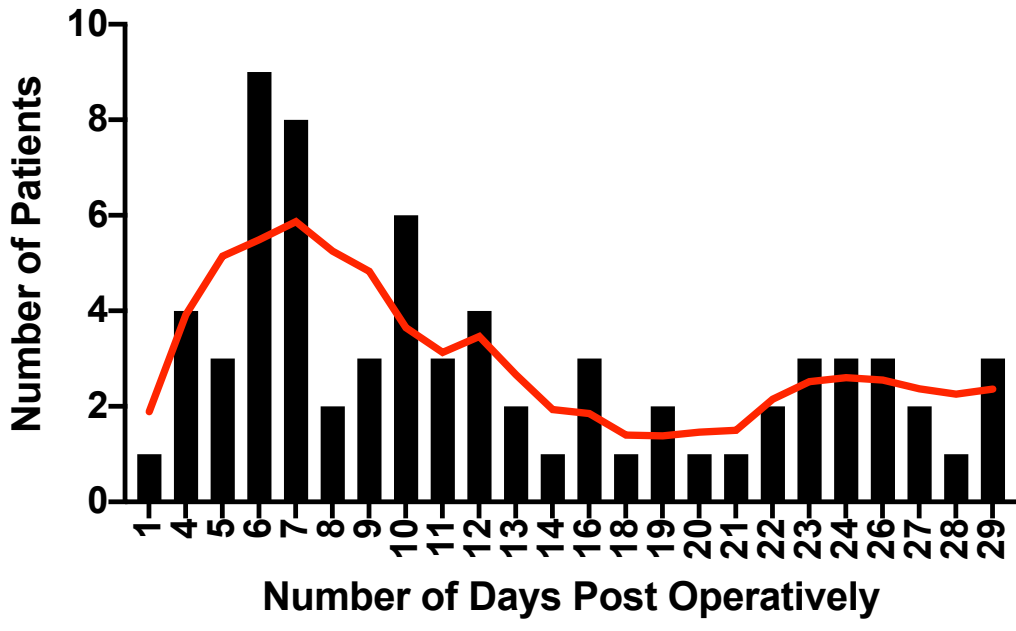
Figure 5-3 – Days to post-operative diagnosis of SSIs with a rolling average in red
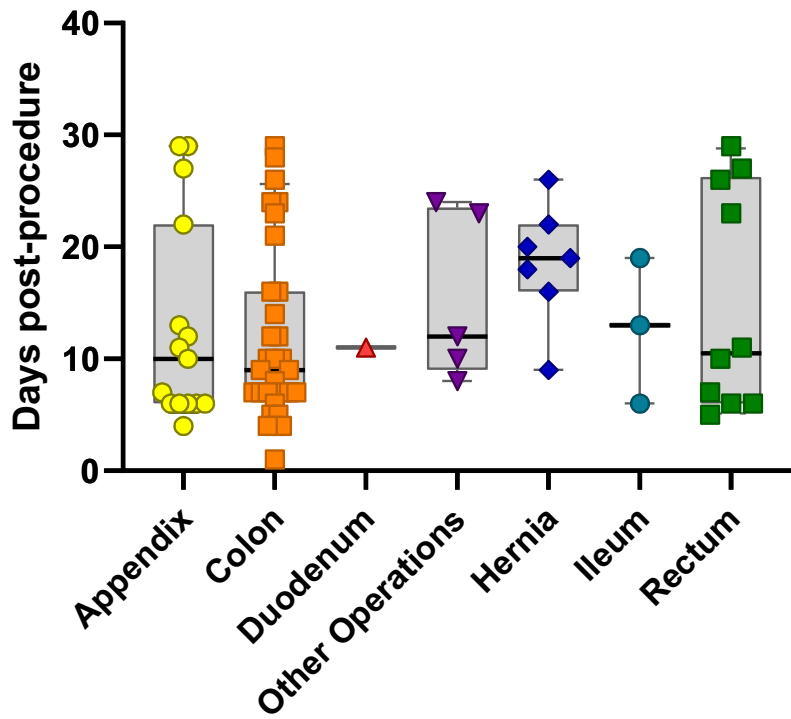
Figure 5-4 Time to SSI diagnosis (days) in each procedure group
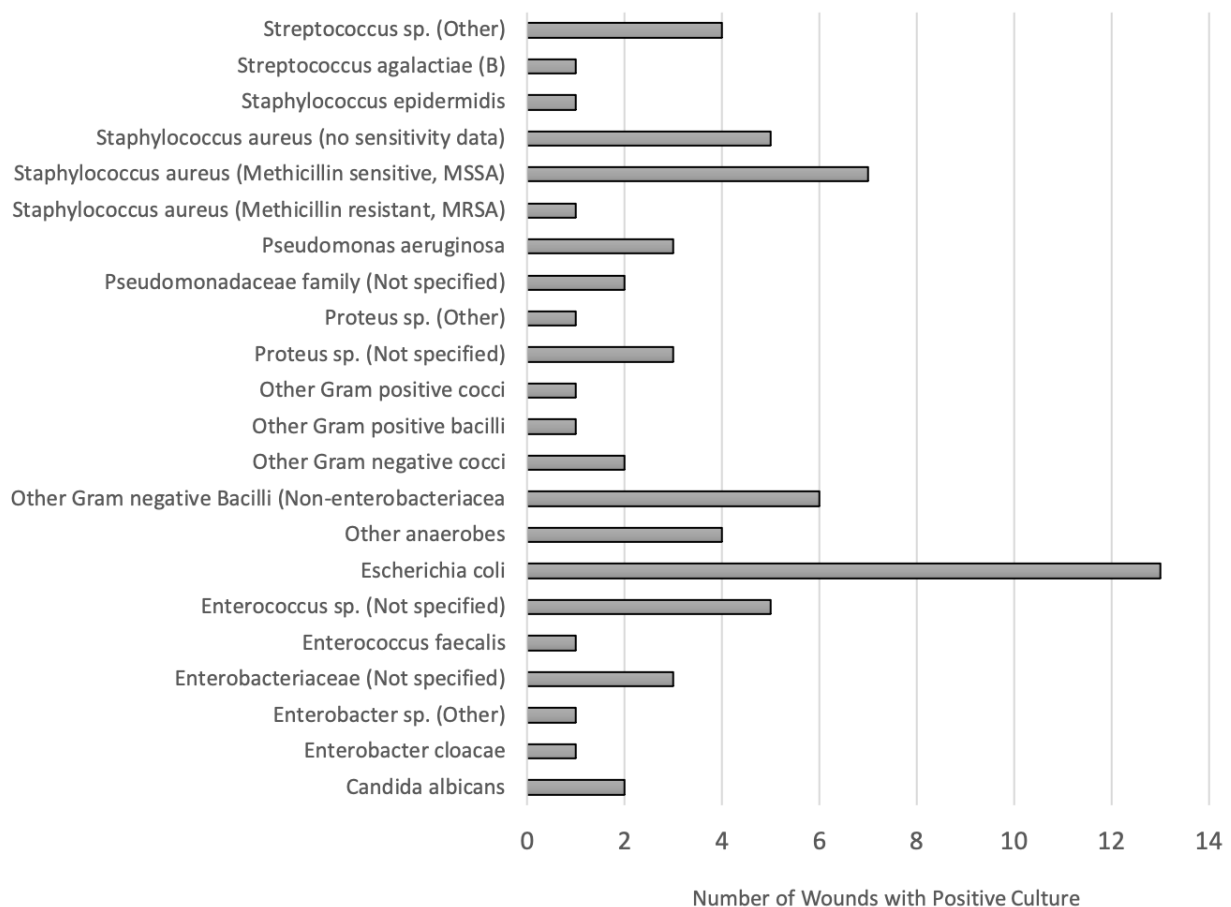
Figure 5-5 Number of Wounds infected with each Organism

5.5 Discussion

WICS, the Welsh national SSI project, resulted in a large consecutive data set providing a prospective review of colorectal (emergency and elective) SSI prevalence. Of the 545 patients operated under the care of a colorectal consultant in March 2019, there were 71 patients with SSIs diagnosed and treated with an overall rate of 13.0%. When considering procedures involving the colon or rectum (colorectal procedures), this rate was even higher at 21.1%, which equated to more than 1 in 5 patients developing an SSI. Of the 71 SSIs diagnosed, 49.3% were diagnosed post discharge in the primary care setting with 21.13% readmission rate. This meant that 20 patients were treated for wound infections exclusively in the primary care setting.

This data set is the largest prospectively collected data set across Wales, and when compared with the 2011 published SSI rate of 8.6% for UHW from 647 emergency and elective surgical patients, it is much higher at 14.7% (44). Power *et al*. found that 15% of their rectal patients developed an SSI, which is lower than the 18.9% found in the present study. As the 2011 study only included inpatient SSI diagnosis and readmissions from SSIs, the primary care diagnosis of SSIs in their study was unknown. Although the SSIs diagnosed in the community are mainly superficial SSIs, they still have an important economic and patient impact, and often result in antibiotic prescribing.

The all-Wales SSI rate of 13% is comparable to the literature in both registries and SSI trials. Known colorectal SSI rates include Hawaii with 12.08% SSI rate (89); New South Wales Australia with 9.64% SSI rate (85); and Switzerland with a national SSI rate of 17.9% for colon surgeries exclusively (86). Both the studies from Switzerland and Hawaii used similar follow up methods including telephone calls to ensure that all SSIs were captured even if the patient had been discharged into the community. When comparing WICS to the results of the ROSSINI study, 2013, their SSI rate was 25.4% in the control arm, which is similar to the open colonic procedures included in this study at 29.1% (73). However, the ROSSINI study only considered superficial SSIs, thus has a higher superficial SSI rate than WICS. Within the ROSSINI trial, each patient was reviewed at 30 days by a trainer assessor to ensure accurate SSI diagnosis and this is comparable to this data set including the primary care diagnosis.

When comparing this Welsh data set to England, it does appear that England has a lower SSI rate for colorectal surgery in accordance with the SSI rate of 8.7% as published by PHE (87). PHE data is not robust due to non-compliance with submission of complete data sets, and only 40% of English hospitals partake in PHE surveillance data (90). The variance of SSI rates between the English hospitals ranged from 1.6 to 20.7%, in agreement with the variance in SSI rates between hospitals across Wales (87).

When interpreting SSIs rates from other studies and national data collection, the method of data collection and the aim of the study is important to be considered as it impacts on the final SSI rate published. Although the PHE SSI rate of 8.7% is widely quoted, it does not include primary care diagnosed SSIs and thus it is an underestimate when evaluating impact to patients (post-operative complications and loss of work days), cost to primary care (which

includes nursing time and dressings cost (68)) and the total number of patients who are prescribed antibiotics for surgical wound infective complications. It mirrors the published UHW rate of 8.6% from 2011 which did not include the primary care diagnosed SSIs. Published SSI rates should be interpreted based on inclusion or exclusion of primary care diagnosed SSIs. If PHE data is compared to this data set, it would be reasonable to assume that the SSI rate could be as much as doubled if primary care diagnosis were taken into account.

5.5.1   Higher Risk Procedures

The data collected throughout the month of March 2019 highlighted that there are certain procedures that are associated with a higher SSI rate. The colorectal procedures had a higher SSI rate which included all rectal operations (SSI rate 18.9%) and colonic operations (SSI rate 22.0%) irrespective of whether performed in the emergency or elective setting, or whether the rectal surgical approach was open or laparoscopic. By including all operation by the colorectal surgeon – both general and colorectal; it was able to define that colorectal surgery did have a higher SSI rate even in comparison to the often more contaminated emergency general surgery. This was an important comparison as the same surgeons were performing both surgeries and thus it is likely that colorectal surgery is an independent risk factor for SSIs – although could not be statistically proven in this cohort with small sample size that was not powered.

Open procedures had a higher SSI rate, particularly open colonic operations (SSI rate 29.1%) and open appendicectomies (SSI rate 27.8%). In these two groups, operations are often open because of the increased difficulty of the operation, patient factors or if the septic burden is increased (purulent peritonitis due to appendicitis). As the open operation is often a reflection of the difficulty of the procedure, it is not unsurprising that the SSI rate was higher in this group of patients. However, the patients undergoing a rectal operation had a higher SSI rate across the different surgical factors and these patients, in the future, need to be considered as a cohort that are at a high risk for developing an SSI.

According to the present data set the procedures that had low rates of SSIs were abdominal wall hernia repairs, laparoscopic appendicectomies and emergency laparoscopic

procedures. These patients tended to have a shorter procedure with smaller incisions, particularly if completely laparoscopic.

5.5.2   Economic Impact

If 71 patients developed an SSI during March 2019, these data can be broadly extrapolated to give an approximate number of 852 SSIs per year in Wales for colorectal patients. It has been suggested that each SSI costs the NHS on average £10,523 in extra bed days, doctor and nursing time and resources (dressings and medications), which is the cost shared by both primary and secondary care (68,82). Based on the present findings it can be estimated that a colorectal SSI rate of 13.0% costs NHS Wales approximately £9 million. A program of change that were able to reduce the SSI rate by half would therefore generate savings more than £4 million per year. This is a significant saving that is spread across many departments throughout primary and secondary care.

Although the economic burden of SSIs is significant there needs to be a consideration of the other savings and gains from reducing the SSI rate including nursing time, as each SSI requires on average 19 visits from a District Nurse in the primary care setting (68). If each visit was approximately 30 minutes long, this equates to approximately 8000 hours of district nursing care, which is equivalent to 4 full time district nurses over a year in Wales. This is only one example of the other non-financial costs of SSIs to the NHS. The costs to the patient are very difficult to measure but include the loss of working days, travel to hospital, time with family, the psychological impact of a surgical complication (42) and ultimately the effect on patient quality of life post-operatively.

5.5.3   Primary Care Diagnosis of SSIs

The implementation of ERAS has reduced length of stay and resulted in earlier discharge of patients (26). One impact of earlier discharge is that post-operative complications are increasingly being diagnosed and managed in the primary care setting by primary care physicians and not by the operating team (206). This increases the workload for primary care, and increases the demands on resources, including district and practice nurse time and cost of treatment for the complications.

This study has demonstrated that up to 50% of SSIs are diagnosed in the primary care setting and this is likely to have increased since the implementation of ERAS in 2005. The two peaks of diagnosis, days 5-7 and days 22-28, raise a further important consideration of the limitations of measuring only 30-day SSI rates. It is, therefore, important that any measure of success of SSI reduction programmes include thorough 30-day follow up to ensure that all SSIs are recorded, with a robust methodology. The two time points of maximal diagnosis raised further discussions about the pathophysiology of SSI development. The first peak was SSIs mainly diagnosed in the primary care setting; thus, these patients are those who have been discharged earlier in part through the successful ERAS programmes. The second peak at day 22-28 was of both diagnosis location, primary and secondary care, which may indicate a different reason for the development, for example post-operative complications requiring longer hospital stays.

5.5.4   Limitations

The WICS study has provided an accurate prospective data set on the development of SSIs in colorectal patients, in both the elective and emergency setting. There has been a comprehensive follow up to ensure that all SSI diagnosis were recorded, with emphasis on the primary care diagnosis. A potential limitation of the follow up methodology was the telephone consultation, however no patient that was telephoned reported differences to their GP electronic records. The telephone call was not conducted using a validated tool such as the Bluebell Wound Healing Questionnaire (70), and thus its role was limited as a diagnostic method and primarily clarified primary care interactions. Any future work with SSI diagnosis in primary care in Wales would need to utilise a validate patient self-assessment tool.

A significant limitation of the WICS study was the small sample size collected over a small time period of one month, which was heterogenous in nature. The reason that a time period for collection was implemented was due to a pragmatic study design. As the study was performed as a collaborative project with minimal financial support, it was designed to ensure that the trainee collecting the data were able to do so with enthusiasm to ensure completeness of the data. If the study time was increased to ensure that a larger cohort was collected and thus allow a sample size to be established, then it would have been very

difficult to perform this with no funding via the trainee collaborative. It was decided that a smaller, more accurate data set would be more useful in setting a baseline SSI rate for colorectal surgery in Wales, allowing future research to be conducted from these results whilst accepting the limitation of the small sample size. In addition to maximise the data that was collected, the decision was made to include both emergency and elective colorectal procedures, but also to include all general surgical procedures performed by the colorectal surgeon during the same time period. This maximised the data collected and hence facilitated two subgroups – general and colorectal, which raised its own notable results, but allowed a comparison between the groups. In hindsight, a better study design would have been to collect data on a more limited set of procedures (colonic and rectal cancer resections) with an appropriate sample size calculation performed to allow comparison between procedure groups, but then also between hospital sites. Future data collection on SSIs in Wales should be for a longer time period, of exclusively colorectal surgery to provide more robust data that is reflective of practice over several months.

Further to the overall small sample size limitations as a collective data set, reviewing and comparing data from each hospital or health board has its own limitations. The wide CI demonstrated that the data was likely to have a widespread and was not a true reflection due to the small sample size. Also, each hospital covers a different patient demographic and size, with different numbers of procedures each month and with each hospital offering different surgery profiles, with some providing complex tertiary centre procedures. Again due to the small sample sizes, this could not be further explored with a statistical analysis

Although the decision-making process and diagnostic criteria used by primary care physicians was not evaluated, the aim of this study was to ensure that anyone presumed to have an SSI and treated in the community was included as this provides details on antimicrobial usage and current diagnostic practice. It is a limitation that there was no check on diagnostic accuracy based on CDC guidelines, however the data collected is comparable to other PHW SSI initiatives within obstetrics and orthopaedics. Further limitations included no detailed recording of comorbidities or on whether the operations were clean, clean-contaminated or contaminated as per CDC guidelines (98). There was also a lack of recording on stoma formation, and therefore the analysis of multiple patient risk factors on the development of SSIs within this cohort of patients has not been possible. The study was

designed to obtain a baseline level of SSIs which could be analysed based on a geographical location, operation type and primary care diagnosis but not to identify individual patient risk factors. In retrospect a colorectal only study for a period of six months (at least and dependent on sample size) should have been performed, but there was no funding for this.

5.6   Conclusions

WICS is the first all Wales prospective study looking at SSI rates in the 30-day post-operative period after emergency or elective surgery in patients under the care of a colorectal surgeon. The overall SSI rate was 13.0% and the colorectal SSI rate was 21.1%. The collection of these data ensured that both the inpatient SSI rate was collected but also any diagnosis of SSIs in primary care. 50% of SSIs in the colorectal cohort were diagnosed following discharge from hospital in the primary care setting. This data collection has provided a baseline SSI rate that can be used to measure any impact interventions may have in the future on this group of patients in the aim of reducing the total number of SSIs within this patient cohort.

6 Development of an SSI bundle to improve Colorectal Surgical Site Infection Rate

6.1 Development of the SSI bundle

6.1.1 SSI Bundle Evidence

There has been much research into the differing aspects of SSI reduction, which can be broadly divided into interventions (dressings and skin preparation) and improvements in patient care (showering and normothermia). However, some units have introduced multiple aspects of the guidance as a 'bundle' approach, mirroring the implementation of ERAS (28). The SSI bundles have different components which often include aspects and combinations that are unique to the centre implemented. There are published examples of individual centre and multicentre implementation of bundles that have consequently reduced the SSI rate within those centres. The Hawaii project demonstrated a reduction in SSI rates in colorectal surgery from 12.08% to 4.63% over 2.5 years from the implementation of an SSI bundle across its hospitals (89). Within that study each unit was free to uptake whichever aspects of the bundle it felt most appropriate with the use of chlorhexidine and correct antibiotic dosing and administration being the most common parts of the bundle adopted (89).

In the literature there have been three systematic reviews and meta-analyses looking at SSI bundles and their effectiveness within colorectal surgery (207–209). Each review found that the bundles reduced the risk of SSIs significantly, but that the studies included in their analysis were heterogenous in nature.

Tanner *et al.* looked at 8,515 patients from 16 studies and found that the SSI rate in the bundle group was 7.0%, whereas the SSI rate in the standard care group was 15.1% (207). Interestingly, none of the studies had identical bundles and the authors concluded that it was the act of implementing a bundle that was the main factor in reducing the SSI rate rather than the individual elements of that specific bundle (207).

Zywot *et al.* found that 30 of the 35 included studies had a reduction in SSI rates post implementation of a bundle. The meta-analysis of 23 studies found a 40.2% reduction in risk of developing an SSI after implementation of a bundle (RR=0.598; CI = 0.496–0.722; p<0.001). As before, there was wide heterogeneity between the trials (208). They found that the bundles that included a new sterile instrument tray (58.6 vs 33.1%, p = 0.019), oral antibiotics with mechanical bowel prep (55.4 vs 31.8%, p = 0.015) and pre-closure glove change (56.9 vs 28.5%, p = 0.002) had the biggest reduction in SSI rates (208).

Finally, Pop-Vicas *et al.*, in the most recent systematic review, found an overall risk reduction in SSIs of 44% with the introduction of a bundle (209). Within the types of SSIs, the meta-analysis found a reduction in superficial SSIs of 44% (RR, 0.56; 95% CI, 0.42–0.75); deep SSIs of 33% (RR, 0.67; 95% CI, 0.46–0.98); and organ-space SSIs of 37% (RR, 0.63; 95% CI, 0.50–0.81) (209). A meta-regression analysis found that bundles that contained more than 11 elements had the largest reduction in SSI rate of 59% and that the bundles contained a mixture of standard care principles and interventions (209).

The research into colorectal surgery SSI reduction by the implementation of bundles has been mirrored in obstetrics, with the introduction of SSI bundles during a caesarean delivery reducing SSI rates from 6.2% to 2.0% (R 0.33, 95% CI 0.25–0.43) (210). These reviews clearly evidence that the introduction of an SSI bundle reduces the rates of SSI.

6.2   Trial of SSI Bundle within one Colorectal Unit

6.2.1   *Design of the SSI Bundle*

From the WICS data it was evident that colorectal surgery, mainly elective colon and rectal surgery, had a high rate of SSIs, and thus an intervention was required to reduce this and improve patient outcomes. There was a decision to implement an SSI bundle type approach to reduce SSIs in colorectal surgery within Wales. From the WHO, CDC and NICE guidelines, a bundle was designed by me in collaboration with trainee surgeons, nursing staff and colorectal consultants to be trialled first within UHW to evaluate if the bundle was effective and feasible. The decision process between the multidisciplinary team on which elements of the bundle were included are summarised in Table 6-1. The final bundle design is shown in Figure 6-1 with the focus on improvements in peri-operative care parameters and two

interventions – NPWT dressings prophylactically in high-risk patients (rectal surgery and laparotomies) and the use of 2% chlorhexidine (Chloraprep™) in every patient. The decision to introduce these two interventions was based on the evidence in the literature and NICE guidelines (105).

Intervention	NICE / WHO Guidance	Main Discussion Points	Included?
Antibiotic Prophylaxis	NICE: Prophylactic Antibiotics 60 mins prior to incision and redoes at 4 hours. WHO: Prophylactic antibiotics within 120min of incision.	For all colorectal procedures the antibiotics should be given in accordance with Microbiology guidance prior to the decisions. *Action Points – Intraoperative antibiotics to be written on Drug Chart on admission, and checked given prior to incision*	Yes
Patient Hair Removal	NICE: Hair removal, if necessary, with a clipper WHO: Hair removal, if necessary, with a clipper	Team stated should already be standard practice. *Action Point: Preassessment nurses will encourage patients not to shave prior to admission*	Yes
Skin Preparation	NICE: Alcohol based CHG is first choice unless contraindicated, and only ChloraPrep was licensed. WHO: Alcohol based CHG, but no specific concentration of CHG.	In light of NICE guidance, there was consensus that ChloraPrep would be used for all patients unless contraindicated. *Action Point: ChloraPrep 1st Choice*	Yes
Perioperative Oxygenation	NICE: Maintain optimal oxygenation to aim a saturation of 95%.	There was debate between the anaesthetists and surgeons on this intervention, and the anaesthetists	No

	WHO: Recommends 80% FiO$_2$ intraoperatively and 2-6 hourly postoperatively	felt there was not enough strong evidence to support this.	
Normothermia	NICE: Patient temperature should be above 36°C, and active warming methods 30 mins prior to surgery and intraoperatively

WHO: Recommends warming devices in operating room | Consensus that normothermia should be maintained, however anaesthetists felt this was already the case. Decision to audit temperatures at time points to evaluate incidence of hypothermia.

Action Point: Temperature checks at specific time points to evaluate the number of patients that are hypothermic | Partially |
| **Intensive Perioperative Blood Glucose Control** | NICE: Do not give insulin routinely to those without diabetes to optimise blood glucose

WHO: Recommends the use of intensive perioperative blood glucose control protocols | Anaesthetists felt they should follow the NICE guidance on this point, unless the patients are within a RCT. There was agreement on at measuring all patients blood glucose during the anaesthesia to evaluate number of patients with hyperglycaemia

Action Point: Measure blood glucose on all patients prior to incision | Partially |
| **Incision Drapes** | NICE: Do not use an incision drape as routine

WHO: Do not use an incision drape as routine | Consensus agreement that incision drapes will not be used | No |
| **Wound Protector Devices** | NICE: No guidance | As the ROSINNI study had not demonstrated a significant reduction in SSIs with the wound protectors and | No |

	WHO: consider the use of wound protector devices in contaminated surgery to reduce SSIs.	no guidance from NICE, decision not to routinely use wound protectors to solely reduce SSIs	
Incisional Wound Irrigation	NICE: Do not use wound irrigation to reduce SSIs WHO: Insufficient evidence to recomment wound irrigation, but if used the irrigation with aqueous PVP-I solution could reduce SSIs	Wound irrigation was already in use by some of the consultant body. After discussion based on experience versus the poor-quality studies forming the systematic reviews, it was decided to use the wound wash as standard across the department with preference of using aqueous PVP-I *Action Point: Wound washes as standard with aqueous PVP-I*	Yes
Prophylactic NPWT	NICE: Recommends use of PICO dressings in High Risk patients WHO: Recommends NPWT in primarily closed surgical incision in high risk wounds.	NPWT dressings will be trialled with patients considered high risk to evaluate the use – Financial, Ease of Use, Patient and Nursing thoughts, wound healing/SSIs. Due to the high cost they will be used for patients who had a colonic or rectal resection – open or laparoscopic extraction site. *Action Point: Patients to be assessed pre-operatively for PICO dressings and applied intra-operatively. Sister of Ward will conduct an evaluation of dressings to find back to department.*	Yes
Surgical Gloves	NICE: Consider 2 pair of gloves if high risk of glove perforation	Despite the lack of evidence, the department already had a policy of glove change after the opening of bowel and contamination of gloves. It	Yes

	WHO: No recommendation on double gloving or changing gloves during the operation	was felt that this should be a standardised approach for the SSI bundle but would be re-evaluated after the Bundle implementation. *Action Point: Glove change only if contaminated from bowel opening during surgery (i.e. forming an anastomosis).*	
Antimicrobial Coated-Sutures	NICE: Consider the use of antimicrobial triclosan coated sutures to reduce SSIs WHO: Use triclosan coated sutures to reduce SSIs	There was a consensus that Triclosan coated sutures should be used. When this was investigated further, there was currently a large scale value based procurement project being conducted on triclosan coated sutures, and as such the sutures would not be available for the bundle.	No
MBP and Oral Antibiotics	NICE: Do not use MBP to reduce SSIs WHO: MBP and oral antibiotics should be used to reduce SSIs in colorectal surgery.	The colorectal consultants wanted to implement oral antibiotics with MBP due to the evidence. However, the microbiology consultants felt that the evidence was not strong enough, and would not allow the implementation of Oral antibiotics in this situation.	No

Table 6-1 The decision-making process for the design of the SSI bundle and the interventions included. The meeting was attended by Colorectal Consultants and Trainee Surgeons, Nursing Staff, Colorectal Anaesthetist, Microbiologist, Theatre Staff.

The bundle was split into areas and time-points to aid implementation. The first of these was the pre-operative phase which was mainly undertaken during the pre-admission assessment and in nursing care on the pre-operative ward. At this stage, the nursing staff were responsible for ensuring the patient had showered before theatre, and that the patient was normothermic. The clinical team was then responsible for ensuring that there had been the correct prophylactic antibiotics prescribed and a senior clinician or nurse

would assess the patient for a NPWT dressing (this was documented as PICO dressing on the checklist which was the brand of NPWT dressing to avoid confusion).

The anaesthetic team, including the anaesthetist and operating department practitioner (ODP), were responsible for ensuring antibiotics were administered within 60 minutes of the incision, and for recording patient temperature. This act of recording the temperature, instead of formulating normothermic methods was decided upon with discussion with the anaesthetists. It was felt that increasing the recording of temperature could act as a prompt for use of normothermic adjuncts.

The surgical team had the main responsibility for preparing the patient for the incision with hair clipping and use of chlorhexidine skin preparation. Additionally, the surgical team would then wash the wound and change gloves if appropriate. The surgical team consisted of the operating surgeon and their assistants, and the scrub nurses. The scrub nurse was empowered to remind the surgeons that the skin preparation of choice was chlorhexidine. Additionally, the scrub nurses were trained in the application of NPWT dressing to ensure that it was applied correctly to achieve the desired skin seal before the patient left the operating room.

The final aspect of the bundle that was not on the operative checklist was the maintenance of the NPWT dressing on the ward and patient education. This was part of the post-operative ward nursing responsibility.

Patient SSI Improvement Checklist

Pre-Operative

Prescribe Intra-Operative Antibiotics on Drug Chart ------------ ☐

Assess for PICO dressings (incision>5cm)---------------------------- ☐

Check patient has showered -- ☐

Temperature before leaving Ward _____°C (Time_____)

Anaesthetic

Administer Antibiotics (1hour before incision+after 4hrs op) ☐

Check BM   BM:_____ (Time_____)---------------------- ☐

Temperature at entry to theatre _____°C (Time_____)

Temperature at end of operation _____°C (Time_____)

Intra-Operative

Hair Clipping only --- ☐

Chlorhexidine Prep, let dry--- ☐

Change Gloves before wound closure (If Contaminated)-------- ☐

Wash Wound before closure -- ☐

Post-Operative

Apply PICO dressing --- ☐

Temperature when leaving Recovery _____°C ------------------- ☐

SPR/Consultant to diagnose SSI if develops

Figure 6-1 SSI Bundle. First design and implementation at UHW Cardiff November 2019

6.2.2 Method

50 consecutive patients undergoing an elective colorectal operation with an abdominal incision (laparoscopic and open surgery) under the care of a colorectal consultant and admitted to a single ward within a single institute, UHW, were prospectively included in the study. Each patient had the same demographic data collected as per the WICS study - age, hospital site, date of operation, operation performed, surgical approach, surgical urgency and date of discharge/death. The patients were prospectively reviewed daily on the ward by a senior doctor (registrar or a consultant surgeon) until discharge for the development of an SSI. The criteria for SSI diagnosis were based on the PHW criteria for superficial, deep and organ space SSIs (41,98). If the patient developed an SSI as an inpatient, then a microbiology wound swab was taken and processed by the Hospital's microbiology laboratory as per standard NHS practice. The inclusion and exclusion criteria, as with the overall method, were as per the WICS study, however only elective colorectal procedures were included.

The follow up of the patients was the same as the WICS study and included outpatient reviews and interrogation of electronic notes for GP interactions. These patients also had a phone call at day 30 to ensure that there had been no medical interventions with their surgical wounds.

6.2.2.1 Implementation of the SSI Bundle

Before the implementation of the SSI bundle, education and training about the different aspects of the bundle were delivered. The training was delivered to the following staff – consultant surgeons, trainee surgeons, ward level doctors, nursing staff on the wards, theatre staff, anaesthetic consultants, and anaesthetic staff (including ODPs). The colorectal department had a meeting based on the results of the WICS data, highlighting the overall rate of SSIs of 23.6% within Cardiff and Vale UHB compared to the national SSI rate of 13.0%. The SSI bundle (Figure 6-1) was introduced to the department, with explanation of the evidence for each step and the time point in the patient pathway that each step would be implemented - pre-operatively, during the anaesthetic, intra-operatively and post-operatively.

Training was administered to all staff about the two interventions. With the NPWT dressings there was training about application, method of action, dressing care and dressing removal. There was training in the correct administration of the chlorhexidine skin preparation, which was administered as Chloraprep™, and how to prepare the surgical field. There was also nurse led training to ward nursing staff on the preparation of patients for theatre (i.e., showering) and the correct wound advice for patients in the post-operative period.

6.2.2.2   Data and Statistical Analysis

Firstly, the SSI rates from the operations that had the SSI bundle implemented were calculated as percentages, and the data grouped into age, surgical approach and procedure groups (colon, rectum and all other). These results were compared to the SSI rates from the elective operations from Cardiff and Vale as part of the WICS study. The results are compared as percentages with statistical analysis by Fisher's Exact Test.

The compliance with the SSI bundle with a focus on individual aspects was analysed using descriptive statistics. A more detailed review of the individual SSIs was performed to identify the aspects of the bundle that were not implemented.

6.3   Results of SSI Bundle Implementation

6.3.1   SSI Rates

From the 1st November to the 19th December 2019 there were 50 elective operations performed by the colorectal surgeons. One patient was excluded from the analysis as they had more than one stoma/mucous fistula formed in the procedure. The overall SSI rate in this cohort that had the bundle implemented was 10.2% compared to the WICS Cardiff and Vale elective SSI rate of 24.3% (Table 6-2). The reduction in SSIs was mirrored in colonic operations (17.6% to 9.1%) and rectal operations (36.4% to 18.8%), with a reduction in open procedures and no SSIs in Laparoscopic procedures. The study was a feasibility study and not powered to detect statistical significance.

Demographic	WICS SSI Rate	SSI Bundle SSI Rate
Overall SSI Rate	24.3% (9/37)	10.2% (5/49)
AGE		
20-48(1st Quartile WICS)	44.4% (4/9)	10% (1/10)
49-60(2nd Quartile WICS)	22.2% (2/9)	20% (3/15)
61-71(3rd Quartile WICS)	22.2% (2/9)	18.2% (1/11)
72-92(4th Quartile WICS)	10% (1/10)	0% (0/13)
SURGICAL APPROACH		
Open	53.8% (7/13)	38.5 (5/13)
Laparoscopic	8.3% (2/24)	0% (0/31)
COLORECTAL PROCEEDURES		
Colon	17.6% (3/17)	9.1% (2/22)
Rectum	36.4% (4/11)	18.8% (3/16)
Other Operations	22.2% (2/9)	0% (0/11)

Table 6-2 Comparison of SSI Rates between the Cardiff and Vale Elective WICS date and the SSI rates from the SSI Bundle Implementation. Results displayed as Percentage and Number of SSIs.

Individual Bundle Component		Percentage Compliance
Pre-Incision Antibiotics	Correct Antibiotics	95.9% (47/49)
	Prescribed on Drug Chart	89.8% (44/49)
	Dosed <60 minutes before incision	95.9% (47/49)
	Re-Dosed at 4 hours intra-operatively	55.6% (5/9)
Check Blood Glucose		8.2% (4/49)
Patient Temperatures	>36°C at time of Anaesthetic	84.4% (38/45*)
	>36°C at time of knife to skin	48.8% (21/43**)
	>36°C at end of surgery	79.1% (34/43)
Hair Clipping		100% (30/30†)
Alcoholic Chlorhexidine		93.9% (46/49)
Wound Wash		79.6% (39/49)
NPWT Dressing	Assessed	100% (49/49)
	Applied	86.4% (19/22)

6.3.2 Analysis of Bundle Implementation

There were 49 patients who were part of the SSI bundle implementation project during the time period. Table 6-3 shows the percentage compliance with the different aspects of the bundle. There was more than 75% compliance in 10 aspects, with high compliance with pre-incision antibiotic prescribing and administration, and pre-operative patient preparation with hair clipping and skin preparation. These areas were a focus of the education of the surgical doctors and scrub team, which demonstrates a successful educational aspect of the intervention. There were some areas that were not implemented as successfully including 4 hourly re-dosing of antibiotics (55.6%), monitoring of blood glucose and maintenance of normothermia.

6.3.2.1 Patient Temperature Control – Normothermia.

Despite there being a high percentage of patients being normothermic prior to anaesthetic and at the end of the operation, 84.4% and 79.1% respectively, more than half the patients were hypothermic at the time of knife to skin. Also, there was a portion of patients did not have their temperature monitoring recorded during the operation. In terms of active warming adjuncts, all patients had a forced air warmer used, and over half of the patients had a further adjunct of either a fluid warmer and/or a heated under-mattress.

24 patients (of the 43 with documented temperatures) were hypothermic for some or all of their operative time. This ranged from 30 minutes to 5 hours 35 minutes. As a portion of the operation, 8 patients were hypothermic for their entire operative time, and a further 9 were hypothermic for at least half of their operative time. Only 3 of these 24 patients started their operation normothermic, whilst 15 were normothermic at the end of the procedure.

6.3.2.2 NPWT dressing

Each patient was assessed for the application of NPWT dressing and 19 of 22 patients had the NPWT dressing applied. The reasons that the other three patients did not have the NPWT applied were that one patient had multiple scars from previous abdominal surgery

and the seal could not be achieved, and in 2 further patients there was not the right sized NPWT dressing available. Of the 5 patients who developed SSIs, 3 had the NPWT dressing applied whilst the other 16 with the NPWT dressing did not have SSIs (an SSI rate of 15.8%). In comparison to the WICS dataset, 20/34 were suitable for a NPWT dressing of whom 7 developed SSIs (an SSI rate of 35%).

An added positive finding from the use of the NPWT dressing was that they remained in place for 7 days post-operatively. This meant that some patients were discharged with the dressing in-situ. Some of the claimed benefits of the dressing are the reduction in dressing changes and possible contamination of the incision by skin flora. Also, the mild erythema that normally happens in the healing process was masked by the dressing. It is unclear if this impacted on the reduced interaction with primary care on discharge from patients worried about 'red' wounds, and thus the reduction in primary care diagnosis to 20%.

6.3.3   Review of Each Individual SSI

Case 1

A 59-year-old male who underwent an open reversal of a Hartman's procedure. All parts of the SSI bundle were followed except the incorrect skin preparation with Betadine and maintenance of normothermia. The patient was hypothermic at start of the operation at 35.2°C and was then hypothermic for 78.6% of the operation (2:45 hours of 3:30 hours of the operation). The patient developed an anastomotic leak and a deep wound infection, which required complex dressings.

Case 2

A 39-year-old female who underwent a completion proctectomy for Crohn's disease. All parts of the SSI bundle were followed except the application of a NPWT dressing and maintenance of normothermia. The patient had previously had multiple surgeries, so it was not possible to achieve a good seal on the dressing. The patient was hypothermic at start of the operation at 35.5°C and was then hypothermic for 71.4% of the operation (2:30 hours of 3:30 hours of the operation). The patient developed a superficial SSI before discharge requiring simple dressings.

Case 3

A 68-year-old male who underwent an open right hemicolectomy. He had multiple cardiac comorbidities and alcohol excess. All parts of the SSI bundle were followed except the application of the NPWT dressing due to the lack of availability. This patient developed a deep SSI that required complex dressings.

Case 4

A 47-year-old male who underwent an open reversal of Hartman's procedure. All parts of the SSI bundle were followed except maintenance of normothermia. The patient was hypothermic at start of the operation at 35.4°C and was then hypothermic for 60% of the operation (2:15 hours of 3:45 hours of the operation). The patient developed a deep wound infection requiring a return to theatre for a wound wash out and complex dressings.

Case 5

A 51-year-old female who underwent an open ileocolic resection due to Crohn's disease. All parts of the bundle were followed successfully. However, the patient developed a superficial SSI after discharge in the community.

Overall

The main notes from the above case reviews are that the SSIs happened in 3 patients who were hypothermic and only one (20%) developed an SSI post discharge, which was lower than the number diagnosed from the WICS dataset of 49.3%.

6.4   Discussion

6.4.1   Improved Colorectal Surgery SSIs Rate

Overall, this study demonstrated that the implementation of the SSI bundle is feasible largely accepted by the entire perioperative team demonstrated by the compliance shown in table 6-3. There was only poor compliance with two new standards – measuring all patient's blood glucose and redosing of antibiotics at 4 hours. During this cohort of patients there was a decreased number of SSIs within a single centre, UHW. There was reduction

from 24.3% to 10.2% which was a greater than 50% reduction, however, this study was not a large cohort or powered to detect statistical difference, so the overall impact needs to be interpreted cautiously. From this first implementation of a SSI bundle, there was an enthusiasm from the wider multidisciplinary team to act to reduce SSIs. It is difficult from the small numbers in this cohort to identify the individual factors within the bundle that have had the greatest impact. However, it is likely that the cause of the reduction was similar to the conclusions of the systematic review by Tanner *et al.* which suggested that the act of implementing the bundle itself was the main reason for the reduction in the SSI rates.

Within medicine, there have been multiple checklists and bundles implemented with aim of targeted improvement in a specific aspect of patient care. Two such checklists are the WHO surgical safety checklist and the Sepsis 6 checklist. The WHO surgical safety checklist was a 19-item checklist that was designed to improve surgical outcomes and reduce morbidity and mortality (211). After its first implementation in 2007-2008, it reduced mortality to 0.8% from 1.5% and complications from 11% to 7% of patients (211). It has since become standard practice in the UK and many other countries worldwide to use the WHO surgical safety checklist. The Sepsis 6 bundle was designed from the international guidelines on management of sepsis in patients and involved 6 aspects that the junior clinicians should complete when sepsis is initially suspected (212). Since its implementation in 2006, there has been a 50% reduction in the mortality from sepsis due to the early implementation of key interventions (213). Overall, there are many examples of these checklists that aim to standardise care and improve outcomes within the health care setting.

Despite the criticism of medicine becoming a series of checklists that hinder independent thought and development, it would be difficult to criticise the attempts to standardise care of patients to reduce adverse outcomes (214,215). An SSI bundle allows the whole clinical and nursing team to focus on preventing an SSI, sharing the responsibility from the consultant surgeon in care of the patient to the wider team. This is particularly important when that surgeon may have just completed a long and complex operation, and thus the greater team is empowered to take some responsibility for SSI prevention. The SSI bundle implemented here distributed the responsibility of different aspects to different members of the team – ward nurses, junior doctors, anaesthetists, scrub nurses. Anecdotally, the nursing staff based on the elective ward fully embraced the SSI bundle, particularly the

patient education, showering and management of the NPWT dressings. A positive aspect of checklists/bundles is the ability to fully engage the wider team to work towards improving patient care.

6.4.2   Areas of Improvement

Within the bundle implementation, there were some areas with low compliance. These included re-dosing of antibiotics at 4 hours intra-operative time, checking patient blood glucose levels, and normothermic maintenance. With the NICE guidance stipulating that insulin should not be given intraoperatively to manage hyperglycaemia in non-diabetic patients, the practice in the UK generally does not require blood glucose monitoring in patients who are not diabetic (105,157). The growing evidence for intensive blood glucose control is still lacking a robust RCT demonstrating a clear benefit in the absence of adverse outcomes. Until that occurs it is unlikely that NICE will change its guidance and thus will be difficult to implement change of practice within the UK.

Despite education of surgeons and anaesthetists about the redosing of antibiotics at 4 hours, only 55.6% had a further intraoperative dose of antibiotics. Of the 4 patients (of 9 patients) who did not receive the 4 hourly antibiotics, 2 had operations that were 15 minutes longer than the 4 hours and it is likely in this instance that the act of closing the abdomen was in progress. Despite this, 2 patients had operations longer than 5 hours and thus ideally should have had the re-dose.

Maintenance of normothermia had poor compliance. Before the start of anaesthesia, 15% were hypothermic, increasing to 51% at knife to skin and 21% by the end of the operation. Of the 5 patients who developed SSIs, 3 were hypothermic during their operation. This is an area which can be improved, and although there is the use of forced air active warming as standard, addition adjuncts may need to become standard practice, including the use of warmed fluids and warming mattresses. With the understanding of redistribution hypothermia that occurs with anaesthesia, and an increasingly aging cohort of patients who are at greater risk of hypothermia, more active warming is needed to prevent the longer episodes of cooling.

6.5   Limitations

The limitations of reviewing the effectiveness of the bundle are the small group of patients it was trialled upon. Although improvements in the number of SSIs is seen in all areas, statistical significance could not be demonstrated as the study was not powered for this. The original aim was to implement the SSI bundle across the 13 hospitals within Wales, and this was planned for spring 2020. However, this was not possible due to the COVID-19 pandemic. The larger scale implementation would have allowed a more detailed analysis on the aspects of the bundle that had a significant impact on SSI prevention.

6.6   Conclusions

Overall, the implementation of the SSI bundle had a successful uptake, with good compliance. There was a reduced number of SSIs in this cohort, likely in part due to the standardisation of peri-operative care. Consequently, many aspects of the bundle are now standard care within UHW. The bundle highlighted the multi-disciplinary approach to preventing wound infections in the post-operative patient. However, there are some areas that need to be improved, and these are areas that require input from both the surgical team and the anaesthetic team particularly the dosing of antibiotics and the prevention of hypothermia.

Section Three: Hypothermia in Perioperative Patients

7 Hypothermia and the Impact on SSI

7.1 Background

7.1.1 Patient Core Body Temperature and SSI Rates

Intraoperative hypothermia can influence the patient's normal physiology and increase the risk of postoperative complications, including increased wound infections (141,142). The 2016 Cochrane review demonstrated that there is an increased risk of SSIs if patients are hypothermic during surgery, and as such it has become part of standard care and the ERAS bundle to maintain intraoperative hypothermia (148). However, the maintenance of normothermia can be difficult due to the body's normal physiological response to general anaesthesia with redistribution hypothermia.

During the introduction of the SSI bundle in Cardiff and Vale UHB in November 2019, 51% of the patients were hypothermic at the time of the operative incision. Seventeen patients of the 49 included patients were hypothermic for at least half of their operation. Of the 5 patients who developed SSIs, 3 spent time being hypothermic during their operation. The decision to further research hypothermia and an additional method for warming aside from the standard active warming methods, was due to the high rate of SSIs in colorectal patients and the high rate of hypothermia demonstrated in the SSI bundle, but anecdotally by consultant surgeons and ward nursing staff. Hypothermia is not a new phenomenon and has been researched previously, but much of the research has been in the context of open abdominal surgery where insensible losses and temperature reduction is more evident. However with increasing prevalence of laparoscopic surgery, it is important to consider hypothermia in a new way, particularly due to the effects of the laparoscopic insufflation on the abdominal environment.

Further to the technical challenges of laparoscopic surgery on hypothermia, it was noted during the implementation of the SSI bundle, that the maintenance of normothermia was a multidisciplinary task, with surgeons, anaesthetists and ODPs involved. A research study into hypothermia would unite all team members into re-evaluating current practices with particular focus on laparoscopic surgery. However, with many different health professionals

involved, brings its own challenges particularly in changing pre-existing mind sets. A study which demonstrates the extent of the hypothermic incidence and a potential new intervention to combat this would in part help to challenge pre-set ideas.

7.1.2 Pathophysiology of Hypothermia and SSIs

The induction of general anaesthesia, via most methods, may induce a loss in core body temperature of 0.5-1.5°C during the first hour of anaesthesia and cause hypothermia (141,216,217). Patients who are not anaesthetised do not become hypothermic when exposed to cool operating rooms, unwarmed fluids or surgical incisions. Anaesthesia impairs the normal human thermoregulatory mechanisms via its effects on the hypothalamus, impairing peripheral vasoconstriction and the ability to shiver to raise body temperature (218). Therefore, there is an imbalance between heat production and loss. This is emphasised within the first hour of anaesthesia, when there is vasodilation and redistribution of heat to the limbs and peripheries but without the compensatory thermoregulation mechanisms. This results in the initial reduction in core temperature by 0.5-1.5°C (216), which then leads to a slower, more linear reduction in core temperature until a plateau is reached after several hours (217,218).

The resultant hypothermia in patients has an impact on their morbidity from the procedure. In the short-term, patients can experience more discomfort in the immediate post-operative, recovery phase due to an increase in shivering, and this can be particularly difficult for elderly, frail patients (217,219,220). It also increases the chance of coagulopathy and there is increased blood loss with hypothermia (221,222). Hypothermia affects platelet function, through the impairment of platelet aggregation via reduced release of Thromboxane A_2 (223), although this is reversible with return to normothermia. There is also an effect on the function of several enzymes in the coagulation cascade which can impair clot formation (149). The result of impaired coagulation from hypothermia can be increased blood loss intraoperatively. A study of total hip arthroplasties demonstrated a significantly greater blood loss in hypothermic patients of 500 millilitres (p<0.001) (221). A further meta-analysis demonstrated that hypothermia of 1°C significantly increased blood loss by 16% (CI 4–26%) and increased the relative risk for transfusion by 22% (CI 3–37%) (222).

The pathophysiology of how hypothermia contributes to SSI formation is multifactorial. The main contributory factor is the effect of vasoconstriction from the autonomic response to hypothermia in the immediate peri-operative recovery stage of surgery. Vasoconstriction reduces the delivery of oxygen to the tissues and decreases the subcutaneous tissue oxygen tension (224). This has an impact on the immune response, with reduced migration and activation of leukocytes and lymphocytes at the wound edge (218,224). Reduced tissue oxygenation inhibits migration, production of oxygen free radicals and impairs the neutrophil oxidative killing of bacteria (225,226). It is hypothesised that contamination of the wound occurs at the time of surgery and that the intraoperative hypothermia may impair the immune response that would normally prevent infection by these organisms (226).

Hypothermic tissue can also have delayed healing due to the impact of temperature on collagen deposition. Hypothermia and reduced oxygen perfusion reduces collagen deposition (227) through the reduction of hydroxylation of collagen cross-links, including proline and lysine residues (220). Hypoxia also suppresses collagen and elastin repair mechanisms (224,228).

It is believed that the combination of reduced tissue oxygen perfusion, impaired immune response and delayed collagen deposition allows disruption of the wound environment which facilitates SSI development (224,228).

7.1.3   Current methods of Preventing Hypothermia

Once a patient has become hypothermic, it can be difficult for the anaesthetist and operating team to warm the patient due to the loss of the normal autonomic thermoregulatory mechanisms. Several methods can be used intraoperatively to actively warm a patient. These include forced air warming, heated mattresses or blankets and warming of intravenous fluid (148). Despite these methods, many patients remain hypothermic during surgery and 53% will be hypothermic in the post-operative phase (143,144). There has been some research into the use of pre-operative warming of peripheries (limbs) prior to anaesthesia to combat intra-operative hypothermia via the

reduction of redistribution hypothermia (149), as demonstrated by a 2020 meta-analysis which also showed it reduced SSIs (RR 0.60, 95% CI 0.42–0.87, P = 0.072) (150).

7.1.4 Challenges posed by Laparoscopic Surgery and Temperature Regulation

During laparoscopic surgery the abdominal cavity is filled with carbon dioxide (CO_2) gas to create a pneumoperitoneum within which surgery can be performed. The majority of laparoscopic operations is performed with dry, unwarmed CO_2. Despite the benefits of laparoscopic surgery with reduced pain and quicker recovery times, the use of dry, unwarmed CO_2 can cause hypothermia and tissue desiccation. Bessel *et al*. demonstrated that during laparoscopic surgery there was a temperature reduction of 1.3-1.7°C (229). As the abdominal cavity is subjected to cooling laparoscopic air, the body core temperature is further impacted during the initial hour of surgery. Patients undergoing colorectal surgery are particularly at risk of hypothermia due to the increased length of procedures that can be performed laparoscopically including anterior resections and subtotal colectomies. Aside from the influence on management of normothermia, the use of dry, unwarmed CO_2 can affect the tissues in the operative field through a drying effect, particularly affecting peritoneal tissues. A study of porcine models demonstrated that the dry, unwarmed CO_2 can induce peritoneal damage through mesothelial bulging, cellular microvilli damage and cellular hypoxia (230).

The impact of dry, unwarmed CO_2 has not gone unnoticed by industry, who have tried to combat this with the development of devices that warm and humidify CO_2 for laparoscopic surgery. One such device is HumiGard (Fisher and Paykel Healthcare), a CE marked medical device designed to humidify and heat CO_2 for insufflation. Dean *et al*. (2017) conducted a meta-analysis of 13 studies (796 patients) to compare patient core temperatures when using warmed, humidified CO_2 insufflation compared to unwarmed, dry CO_2 over a range of procedures (231). The patients had a significant difference in mean core temperature change, and an effect size of +0.3°C (95% CI 0.1–0.6). Further analysis demonstrated a more pronounced effect in studies that included procedure longer than 80 minutes (231).

A further meta-analysis by Balayssac *et al*. (2017) 15 studies (1,026 patients) evaluated the use of warmed, humidified CO_2 in relation to immediate post-operative pain, and only

showed a small beneficial effect (142). The other outcomes included post-operative temperatures, analgesic use, length of stay and procedure duration. Both meta-analyses included RCTS that were heterogenous and of poor quality. Furthermore, there was no in-depth analysis of the impact that warmed, humidified CO_2 had on post-operative complications included wound infections (142).

As there is a significant prevalence of hypothermia within the colorectal surgical cohort, the use of warmed, humidified CO_2 could minimise the hypothermic effects of using standard dry, unwarmed CO_2. A feasibility study was designed by myself with the support of Professor Torkington and a trials unit (CEDAR) and completed within UHW to evaluate any potential benefits that the use of warmed, humidified CO_2 could have on patient recovery, on maintenance of normothermia and reduction in post-operative complications.

7.2   Quality of recovery and perioperative Hypothermia in Elective colectomy patients: A feasibility study of a blinded randomised controlled trial – The HEAT Study

The use of HumiGard to deliver warmed, humidified CO_2 has demonstrated a benefit within the literature in increasing patient core temperature which can combat the effects of redistribution hypothermia and contribute to the maintenance of normothermia. However, there is a lack of robust RCT data using a patient reported primary outcome to compare the use of warmed, humidified CO_2 to standard care of dry, unwarmed CO_2. Consequently, it has been difficult to measure the impact of using warmed, humidified CO_2 on patient recovery and subsequent complications, particularly SSIs.

A blinded RCT has been designed by a trials team (myself, Professor Torkington and a trials unit (CEDAR)) to evaluate these outcomes – quality of recovery, intra-operative temperatures and post-operative complications including SSIs - The *Quality of Recovery and Perioperative Hypothermia in Elective Colectomy Patients* (HEAT study). Funding was achieved via an educational grant to conduct a feasibility study of 40 patients to evaluate if the larger blinded RCT could be successfully completed. The protocol for the main RCT has been published (232) and the feasibility study was an adaptation of this protocol to evaluate key aspects of the larger trial.

The main aims of the feasibility study were to evaluate:

- Acceptability of study to patients, measured by recruitment timeline
- the appropriateness of the Quality of Recovery – 40 (QoR-40) patient questionnaires, and if the questionnaire is sensitive measure of patient recovery in laparoscopic colorectal surgery
- The impact of warmed, humidified CO_2 on core body temperature and intra-abdominal temperature
- Impact of warmed, humidified CO_2 on post-operative complications.

Definitions of success for this feasibility study would be to recruit 40 patients over an appropriate time, whilst being able to measure all the variables indicated – QoR-40 scores, temperature measurements and post-operative complications. Additional information on the trends of temperatures from the small cohort and number/type of post-operative complications would be useful in designing future studies on hypothermia via study design and power calculations.

7.2.1 Feasibility Study Method

7.2.1.1 Study Design

This was a feasibility, equally randomised (1:1), triple-blind, parallel-group, sham device-controlled RCT of 40 patients undergoing laparoscopic colorectal resection surgery at UHW. The management of the RCT was led by myself in conjunction with CEDAR, which is a trials unit that is part of UHW There were two arms in the study, HumiGard plus standard care or a sham HumiGard plus standard care, with 20 patients in each arm. The sham HumiGard was a HumiGard device that was set up correctly but was turned off resulting in dry, unwarmed CO_2. Figure 7-1 is an overview of the study as a flow diagram, and the study protocol is Appendix 1. The main outcome of the larger RCT was to compare the QoR-40 scores post-operatively to evaluate the patient experience of recovery post-operatively.

7.2.1.2 Ethics

The feasibility study, including the trial protocol and patient documentation, was approved by the South East Wales Research Ethics Committee (19/WA/0266), IRAS number 271720

and was registered with Clinicaltrails.gov NCT04164706. The Chief Investigator was Professor Jared Torkington, and the Principal Investigator was myself (Nicola Reeves).
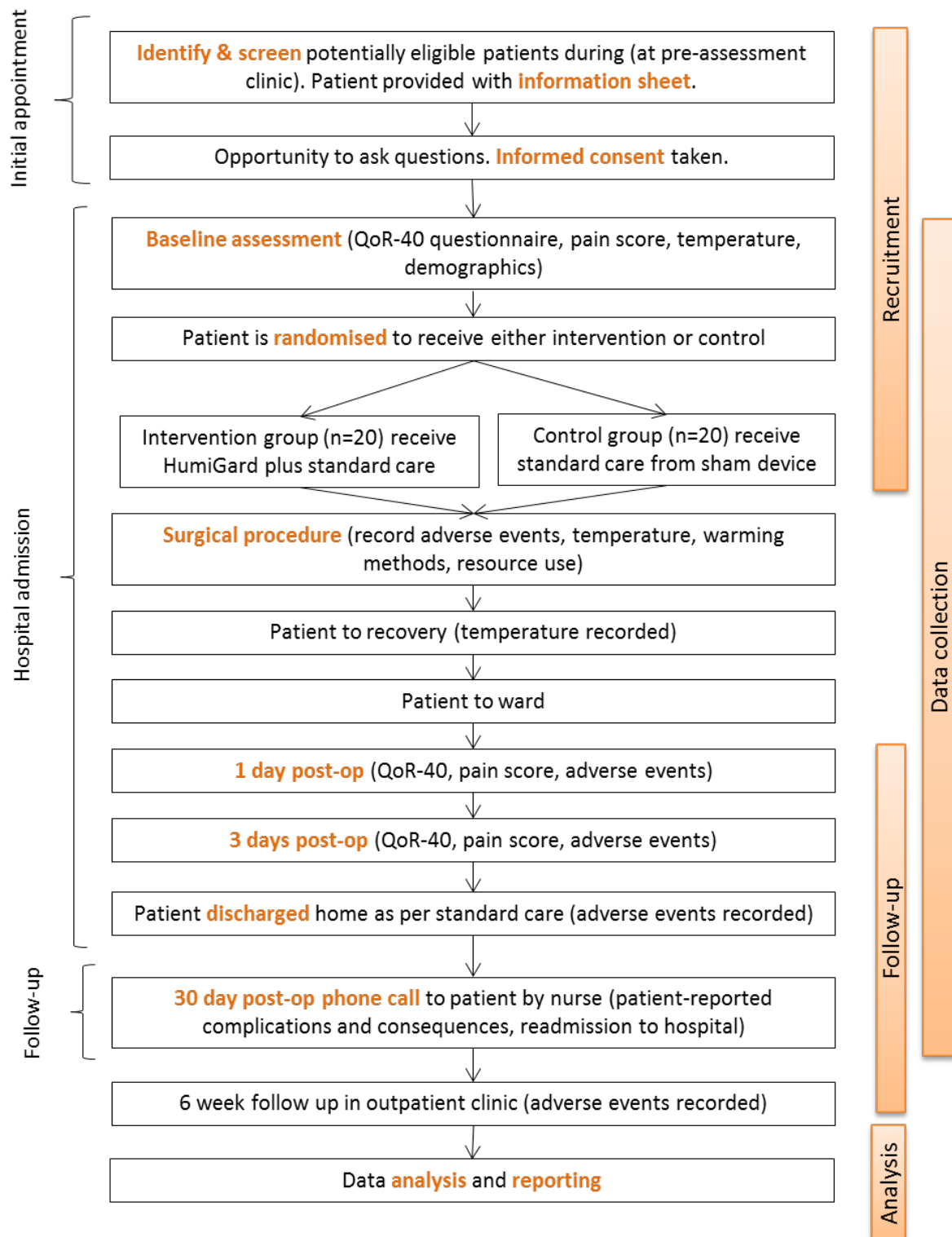
Figure 7-1 A flowchart demonstrating the study process; from the study protocol

7.2.1.3 Participants

The study recruited patients over 18 years of age undergoing laparoscopic colorectal resections.

Inclusion Criteria

- ≥18 years of age
- Participant able to give informed consent
- Scheduled for elective laparoscopic, segmental, or total colectomy

Exclusion Criteria

- Unable to complete study documentation
- Lack of capacity or not willing to give consent
- Open procedure planned

Consent

Patients were identified by the clinical research team and provided with a patient information sheet (PIS) (Appendix 2). Patients had 24 hours to consider the PIS before written consent was taken by the clinical research team. The patient personally signed and dated the consent form (Appendix 3) once the patient had chance to ask questions and discuss the study with the clinical research team. The consent form had 3 copies, one for the patient, one for the medical notes and one (original copy) for the site file.

Between March 2020 and June 2020 recruitment was paused due to the COVID-19 pandemic. The centre successfully established an operating pathway which allowed safe resumption of elective colorectal resections and research studies.

7.2.1.4 Randomisation

The randomisation of the patients was co-ordinated by CEDAR. A single member of the clinical research team telephoned CEDAR to perform the randomisation which happened between the consent process and before knife to skin. This member was then unblinded and was not able to interact with the patient post-operatively including the collection of

post-operative data. A minimisation randomisation method was utilised to ensure even distribution of key variables between the two arms. A bespoke minimisation package (CedarMin) which runs in R was used to assign patients to either group with a randomness element of 20%. The minimisation was based on three variables – Age, Pathology (benign/malignant) and the ASA grade.

Once the randomisation was performed, one member of the theatre staff who was not scrubbed set up the HumiGard device as being on for warmed, humidified CO_2 or turned off for the sham device.

7.2.1.5 Interventions

HumiGard is a Class IIa CE marked medical device indicated for use in laparoscopic or open abdominal surgery when carbon dioxide insufflation gas is used. The device comprises a surgical humidifier and a single use humidified insufflation kit. It humidifies and warms the carbon dioxide by passing the gas over a reservoir of water. The heated, humidified gas is then passed along a sterile tube for delivery into the abdominal cavity through a laparoscopic port. HumiGard is designed to be used both independently and in addition to other intra-operative warming measures.

Patients in the treatment arm received humidified and heated carbon dioxide insufflation gas into the peritoneal cavity using the HumiGard device. These patients also received standard intraoperative warming methods, including warmed intravenous fluids, and the use of a forced-air warming device or a warmed mattress at the anaesthetist's discretion. The intra-operative warming methods were not standardised for two main reasons:

1. For a study to be a pragmatic study it would have to involve all variables in warming methods. This would allow the RCT, which would be adequately powered, to evaluate the impact of warmed, humidified CO_2 in the presence of other warming adjuncts. This will allow a more complete resource analysis to be performed.

2. There was difficulty in establishing a standardised anaesthetic protocol amougnst the UHW anaesthetic department for the cohort of patients. The anaesthetists felt that they needed evidence that HumiGard provided adequate warming with or without certain warming adjuncts before standardising these. Further more, they

wanted the ability to increase their use of warming adjuncts if a patient was hypothermic.

As a feasibility study, it was decided that the use of warming adjuncts would be evaluated over the study with the hope that analysis of the adjuncts would allow future standardisation over majority use.

Patients in the control arm were treated with a sham device plus additional standard intraoperative warming methods. The sham device used in the standard care arm was the same HumiGard device as in the intervention arm; however, the sham device was turned "off" so that the gas delivered to the peritoneal cavity for insufflation was not heated or humidified. The sham device looked and sounded the same as the active intervention device.

7.2.1.6   Surgical procedures

Procedures were performed by the consultant surgeon or by a trainee under the direct supervision of the consultant. Intra-operatively, all patients underwent a standardised set up as per the WHO checklist. The general anaesthetic was administered as per the anaesthetist's choice, including any intra-operative warming methods (intravenous fluid warmers and forced-air warmers) and the post-operative analgesic regime. All patients received antibiotic prophylaxis as per the local microbiology guidance.

Intra-operatively, the pneumoperitoneum was established using the Hassan technique with a 10 mm trocar. Insufflation of the abdomen was via the HumiGard device, either turned on, or turned off as a sham device. The flow rate and insufflation pressure were determined by the operating surgeon. Specimen extraction was via a small midline incision or a Pfannenstiel incision. Post-operatively patients were managed on a dedicated surgical high dependency unit or a dedicated colorectal surgical ward and were recovered following the ERAS principles.

7.2.1.7   Blinding

The design of the study resulted in the patient, surgeon, anaesthetist, surgical scrub staff (except one member) and the post-operative clinical team (nurses, doctors,

physiotherapists etc.) being blinded to the arm allocation and intervention the patient received. Within theatre, the HumiGard device was positioned so that the operating team was not aware if it was turned on or off. The successful blinding of the surgeon was assessed as part of the trial outcomes.

7.2.1.8 Primary Outcome

The primary outcome of the study was the feasibility of patient recruitment timeline.

7.2.1.9 Secondary Outcomes

The secondary outcomes were:

- the evaluate the distribution of the demographics between the arms,
- the appropriateness of the QoR-40 patient questionnaires, and if the questionnaire is sensitive measure of patient recovery in laparoscopic colorectal surgery
- The impact of warmed, humidified CO_2 on core body temperature and intra-abdominal temperature
- Impact of warmed, humidified CO_2 on post-operative complications.

7.2.1.10 Assessments

Baseline Assessments – collected pre-operatively

- Age
- Sex
- BMI
- Smoking status
- Cardiac/respiratory disease
- ASA grade
- Primary diagnosis
- Presence of malignancy
- Other significant comorbidities
- Previous abdominal surgery

QoR-40 – completed at 4 time points: pre-operatively, post operatively day 1,3 and 30.

The QoR-40 is a validated and widely-used, patient-reported global measure of overall health status after surgery and anaesthesia (233). The QoR-40 questionnaire is a 40-item patient-reported questionnaire that provides a global score and separate scores across five dimensions: patient support, comfort, emotions, physical independence, pain (Appendix 4). The QoR-40 questionnaire has been used in main studies as a patient reported measure of quality of recovery and it has excellent validity, reliability, responsiveness and clinical utility whilst being highly sensitive to clinical change (234).

Temperature Monitoring – Day of Surgery and Intra-operatively

Baseline temperature measurements were taken using a tympanic thermometer pre-operatively on arrival into the anaesthetic room pre- and post-anaesthesia, and on entry to the recovery area post-surgery. Continuous temperature measurements were obtained using a urinary catheter thermistor. The anaesthetist measured core temperature as per their standard practice using an oesophageal temperature probe.

Post-Operative Complications – collected up to 6 weeks follow up post-operatively

All post-operative complications were collected until 6 weeks post-operatively. The complications were determined and defined by the clinical team and validated by the research team. The patients also recorded any complications in a patient diary, which was reviewed by the research team at 6 weeks post-operatively.

7.2.1.11 Data analysis and statistics

For primary outcome of recruitment rates, data were reported as frequencies. Other continuous variables (length of stay, length of procedure, readmission rates, and adverse events) were reported as means or medians with interquartile ranges (IQR). QoR-40 questionnaires were scored as per the authors' instructions (Myles *et al*. 2000). To maximise the partially completed questionnaires the following imputation rules were applied: i) if 50% or more of the domain was complete the mean of the remaining values in that domain was imputed ii) if more than 50% of the domain was missing then the mean from remainder of that patient's questionnaire was imputed.

Temperature data was analysed as two groups, core temperatures and urinary temperatures. These were graphically represented to demonstrate the two arms of the study, but also the patients which then developed infectious post-operative complications (SSIs and anastomotic leaks). The mean and standard deviations of the core and urinary temperatures were calculated at 30-minute intervals and compared. Finally, the difference between the urinary and core temperatures in each group were compared at 15-minute intervals using their mean and standard deviations.

7.2.2   Results of Feasibility Study

The study recruited 41 patients between 14/11/19 – 10/11/20, but the study was paused during 19/03/20 - 12/06/20 due to the COVID-19 pandemic suspending non COVID-19 research. The flow diagram in Figure 7-2 shows the patient pathway. Of the 39 patients included in the study analysis, none were lost to follow up. In one case, a patient in the HumiGard arm had their procedure started but the device was stopped due to issues with steaming of the camera (the remainder of procedure was carried out as per standard care). This patient was included in the HumiGard arm for analysis as per the intention to treat protocol.
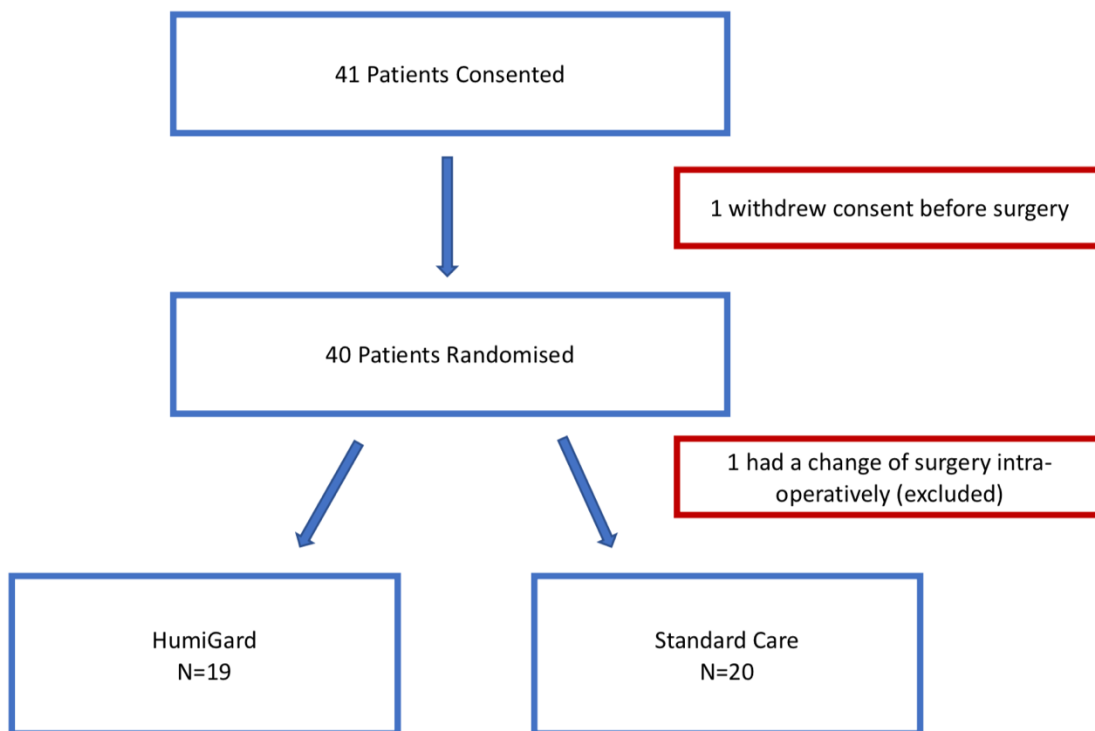
Figure 7-2 Patient Recruitment Flow Diagram

7.2.2.1   Patient Demographics

The patient groups were evenly matched in terms of the main variables: age, sex, BMI, ASA and presence of malignancy (Table 7-1). However, the distribution of operation types within the groups were not evenly matched and this was in part due to the type of operation not being part of the minimisation strategy. There were more right hemicolectomies in the HumiGard group, whilst there were more anterior resections, subtotal colectomies and abdominoperineal resections in the standard care group. There was no significant difference between the length of stay (p=0.27 Mann Whitney U Test) and length of operation (p=0.112 t-test) between the groups, although both were shorter in the HumiGard group.

	Standard Care group (n=20)	HumiGard group (n=19)
Age (Median (IQR))	69.5 (52.3-72.5)	72.0 (56.0-77.0)
Sex (male/female)	10/10	10/9
BMI (Median (IQR))	27.9 (23.8-30.6)	27.1 (25.4-29.5)
ASA GRADE		
ASA 1	2 (10%)	2 (11%)
ASA 2	12 (60%)	11 (58%)
ASA 3	6 (30%)	6 (32%)
Presence of malignancy	15/20 (75%)	17/19 (89%)
TYPE OF OPERATION		
Anterior resection	7 (35%)	5 (26%)
Right hemicolectomy	5 (25%)	11 (58%)
Left hemicolectomy	0 (0%)	0 (0%)
Subtotal colectomy	3 (15%)	0 (0%)

Abdominoperineal resection/excision	3 (15%)	1 (5%)
Other	2 (10%)	1 (5%)
MODE OF OPERATION		
Laparoscopic	18 (90%)	19 (100%)
Laparoscopic converted to open	2 (10%)	0 (0%)
Length of operation (minutes)	Mean 194 (SD 86)	Mean 151 (SD 74)
Hospital length of stay (days)	Median 5.5 (IQR 4.0-8.5) Min 3, Max 34	Median 4.0 (IQR 3.0-6.0) Min 2, Max 21

Table 7-1 Patient Demographics and Operative Details

	Pre-op		POD1		POD3		POD30	
	SC	HumiGard	SC	HumiGard	SC	HumiGard	SC	HumiGard
Total QoR-40 score								
Total QoR-40 score (max score 200)	n=19 Median 190.2 (IQR 16)	n=18 Median 190.5 (IQR 12)	n=17 Median 178.0 (IQR 15)	n=17 Median 185.0 (IQR 10)	n=16 Median 188.5 (IQR 10)	n=13 Median 187.0 (IQR 24)	n=16 Median 191.0 (IQR 18)	n=16 Median 193.5 (IQR 13)
Change in total QoR-40 score from pre-op	N/A	N/A	n=17 Mean -13.4 (SD 12.1)	n=16 Mean -7.7 (SD 17.3)	n=16 Mean -2.6 (SD 11.3)	n=12 Mean -10.3 (SD 22.0)	n=15 Mean -2.4 (SD 12.4)	n=15 Mean +2.6 (SD 12.5)

Table 7-2 The QoR-40 Scores at the different time points (SC = Standard Care)

7.2.2.2 Patient Quality of Recovery – 40 Scores

Overall, the majority of patients completed the QoR-40 questionnaire in the postoperative period, with the following completion rates:

- Pre-operatively: 97% response rate
- Post-operative day (POD) 1: 90%
- POD 3: 74%
- POD 30: 100%

The QoR-40 had a maximum score of 200. Table 7-2 summarises the main results from the QoR-40 questionnaire. On POD 1 there was an overall higher QoR-40 score, with a smaller change from the baseline, and this was reversed on POD 3 but neither of these were significantly different. However, the study was a feasibility study, and it was not powered to detect a significant difference between the two arms of the study.

7.2.2.3 Impact on Intra-operative patient temperatures

Each patient underwent temperature measurement in two methods, continuously via a urinary thermistor and simultaneously by the anaesthetist as per their usual practice using an oesophageal temperature probe. There were urinary thermistor measurements in 32 patients and more than two oesophageal temperature measurements in 32 patients. The two different temperature measurements are shown in Figure 7-3 and Figure 7-4. There were no significant differences between the two arms of the study. The core temperature readings via the oesophageal probe demonstrate the physiological process of redistribution hypothermia (Figure 7-3) with an initial period of hypothermia, which then increases towards normothermia after 60 minutes. However, with the urinary temperatures, they remained static between 35 and 36.5°C (Figure 7-4). This reflects that despite the patient core temperature increasing throughout the operation to normothermic limits, the urinary temperature did not show the same phenomenon further illustrated by matched temperatures in Figure 7-5. These differences were subtle and were not powered to reach significance.

When considering the differences between the patient matched core and urinary temperatures (Figure 7-6) the urinary temperature was up to 1°C lower than the core temperatures on average but needs to be interpreted with caution as the CIs overlap. Figure 7-6 does indicate some trends of temperature over time in both the standard care and HumiGard group. As the operation increased in length, this difference between the matched temperatures became greater as seen in the standard care group. However, in the HumiGard group, the difference between urinary and core was much less and stayed similar until length of operation exceeded 210 minutes. Again, these trends seen on the graph need to be interpreted with caution as they had overlapping Cis and was not powered to reach statistical significance. These early trends would be worth exploring further in a larger study to identify if these findings are accurate

Core Temperatures
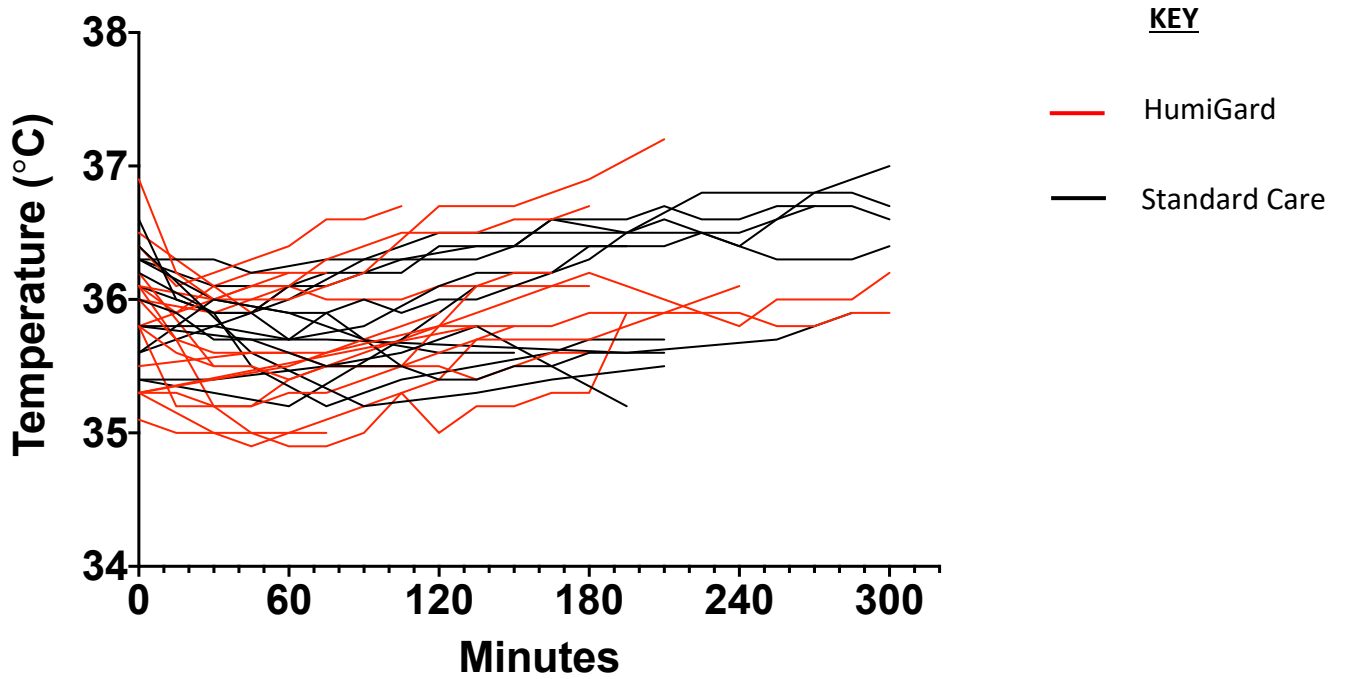
Figure 7-3 Graphical representation of the Core Temperature (oesophageal temperature probe)

Urinary Temperatures
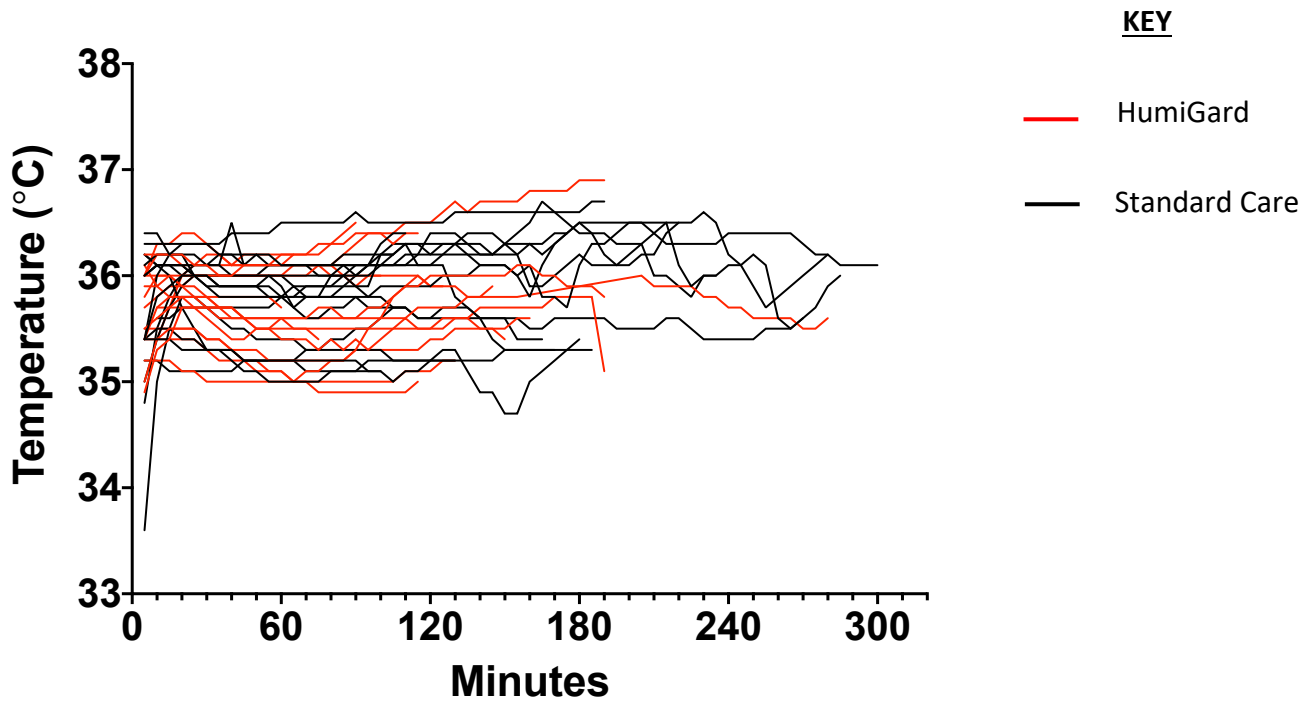
Figure 7-4 Graphical representation of the Urinary Thermistor temperatures
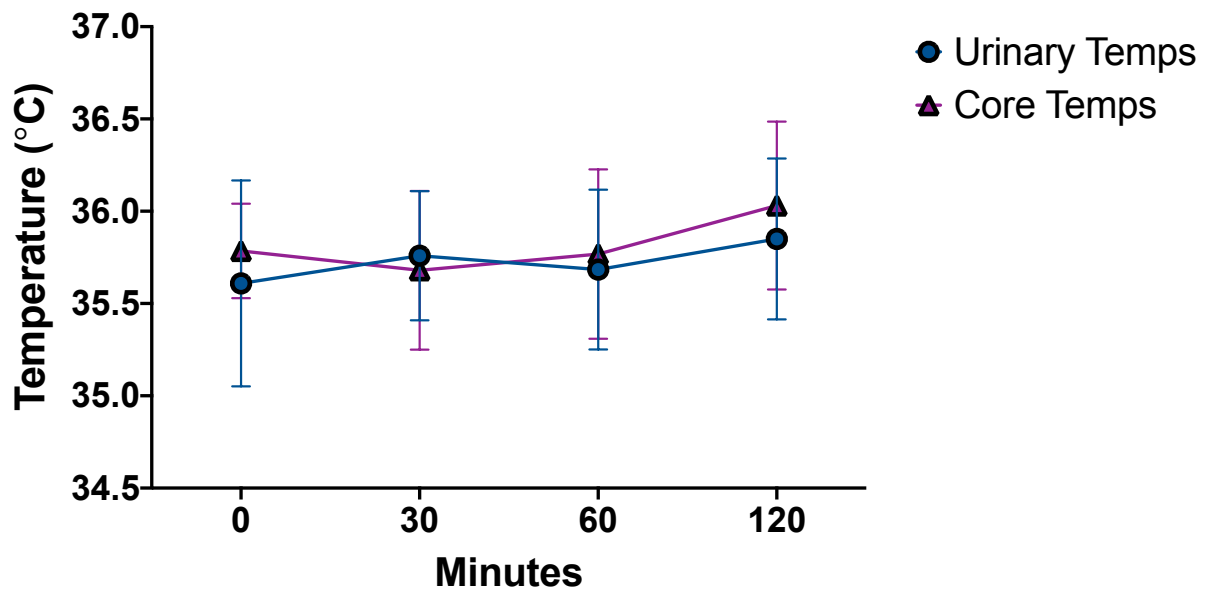
Figure 7-5 The mean and standard deviation of the core temperatures and urinary temperatures
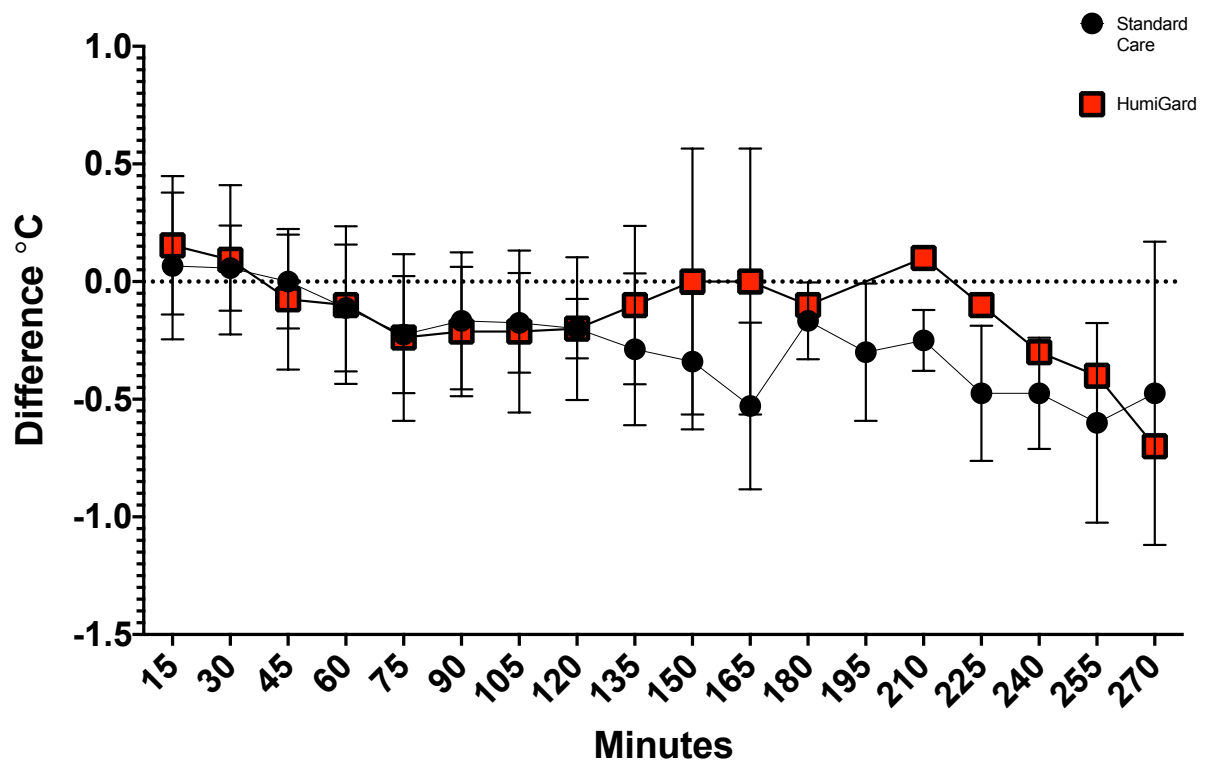
Figure 7-6 The difference between the matched urinary temperatures and the core temperatures

7.2.2.4 Adverse Events including SSIs

Adverse Events

There was no significant statistical difference between the number of adverse events (AE) recorded in the two arms of the trial (Table 7-3). However, the total number of AE was lower in the HumiGard group.

Nausea and Vomiting

The percentage of patients experiencing nausea and vomiting was lower in the HumiGard group on POD 1 (53% v 65%) and much so on POD 3 (37% v 60%). This was not significantly different on either day using Chi-Squared test – POD1 p = 0.433; POD3 p= 0.075.

SSI and Anastomotic Leaks

The overall SSI rate was 10.3% which included 3 superficial SSIs (7.7%) and 1 deep SSI (2.6%). There were 2 superficial SSIs in the SC arm, and the 1 superficial SSI and 1 deep SSI was in the HumiGard arm. There were 2 anastomotic leaks (5.1%). One anastomotic leak was in the SC arm and 1 was in the HumiGard arm. The deep SSI was in the patient who also had an anastomotic leak who was in the HumiGard arm. Overall, there were 5 patients who had infectious post-operative complications, 2 in the HumiGard arm and 3 in SC arm.

Figures 7-7 and 7-8 shows the available temperature data for the patients with SSIs or anastomotic leaks. It was noted that the patients with anastomotic leaks were not hypothermic in either temperature measurements, however those patients who developed superficial SSIs had core and urinary temperatures that remained below 36°C. The numbers were too small to perform any statistical analysis but were similar to the findings of the SSI bundle results.

Item	Standard Care group	HumiGard group
TOTAL ADVERSE EVENTS (AE)		
Total number of AEs	**Total: 70** Grade I: 61 Grade II: 1 Grade IIIa/b: 2 No grade: 6	**Total: 52** Grade I: 46 Grade II: 1 Grade IIIa/b: 2 No grade: 3
Device related AEs	0	0
Serious adverse events	2	2
Comprehensive complication index	Median 16.15	Median 15.00
POST-OPERATIVE DAY 1 (POD1)		
Total number of AE	36	28
Patient experienced pain	85%	79%
Patient experienced nausea and/or vomiting	65%	53%
Post-Operative Day 3 (POD3)		

Total number of AE	27	20
Patient experienced pain	70%	68%
Patient experienced nausea and/or vomiting	60%	37%

Table 7-3 Table of Adverse Events (Total, POD 1 and POD 3)

Urinary Temperatures
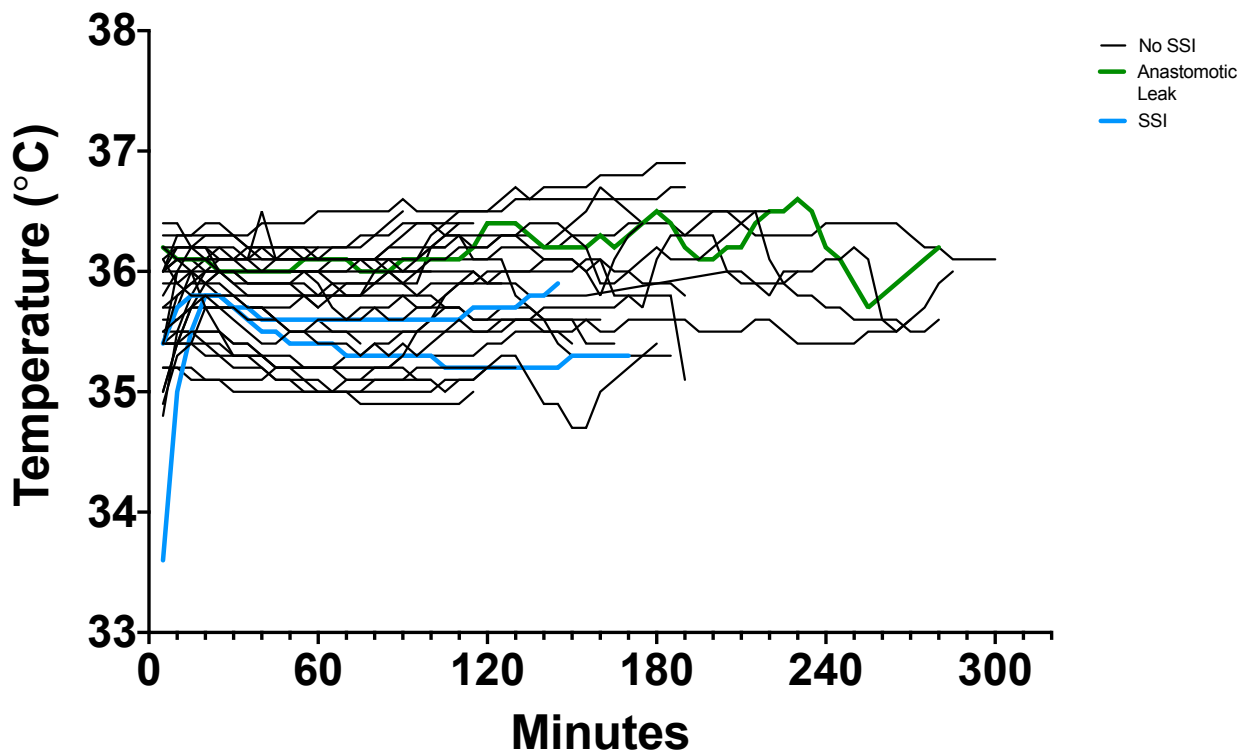
Figure 7-7 Patients with SSIs and Anastomotic Leaks within the Urinary Thermistor temperatures
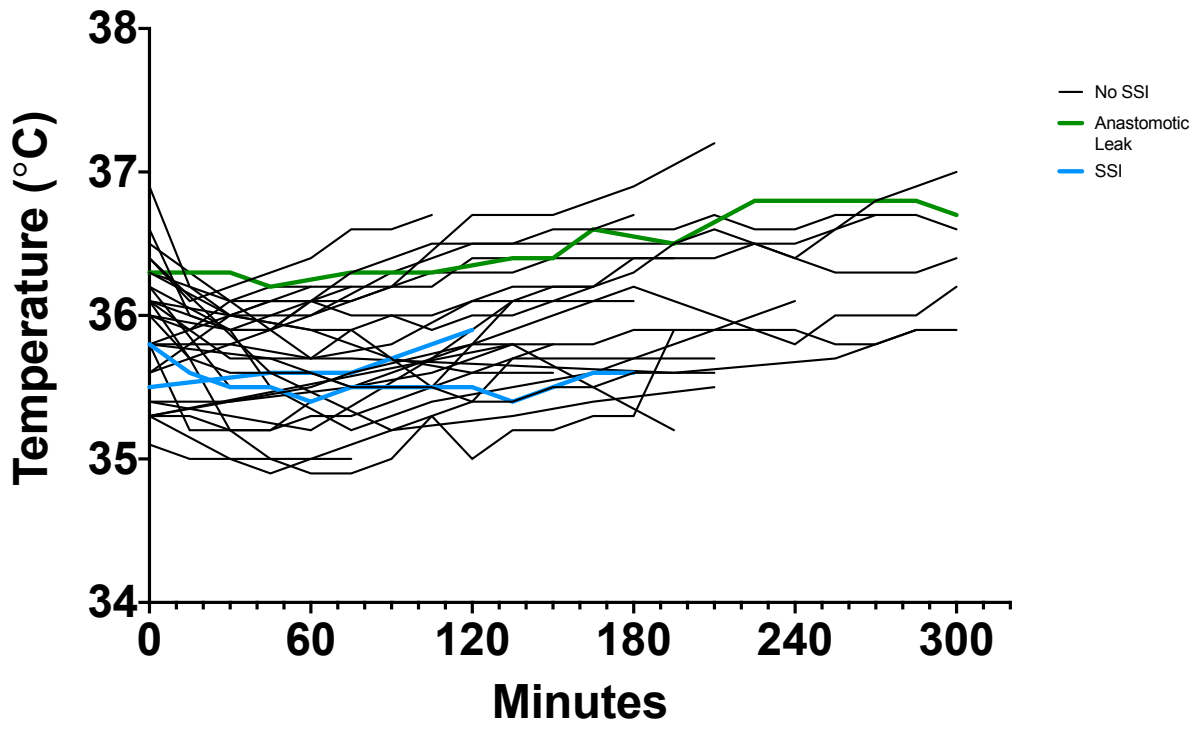
Figure 7-8 Patients with SSIs and Anastomotic Leaks with the Core Temperatures (oesophageal temperature probe)

7.3   Discussion

The HEAT study was a feasibility study which aimed to evaluate several aspects of a proposed larger RCT. Firstly, its main aim was the acceptability of the study to patients, and this was achieved. The study recruited well over a short period of time, and half of the patients were recruited during the COVID-19 pandemic period, which demonstrates positive patient attitudes towards to the study and the ease of the study conduct amongst the research team. Secondly, the QoR-40 questionnaire had a good response rate with 90% completion on POD1. However, the study identified that the QoR-40 questionnaire is unlikely to be sensitive enough to detect the differences between using HumiGard vs SC in any future RCTs. This is due to the QoR-40's strong ceiling effect conferring a measurement limitation which reduces the likelihood of detecting a real change in patient's quality of recovery, hence the little difference between the pre-operative score and the post-operative scores.

The main differences between the arms were in three different outcomes – length of stay, length of operation and percentage of patients experiencing nausea and vomiting. These three outcomes were all improved in the HumiGard arm with reduced length of stay and operating time, and almost half the prevalence of nausea and vomiting at POD 3 compared to SC. An important consideration is the demographics of the group which may explain these differences. There was a larger percentage of patients undergoing a right hemicolectomy in the HumiGard arm, and more patients undergoing anterior resections and complex operations in the SC arm. Right hemicolectomies are typically shorter operations, with reduced length of stay. Due to the uneven distribution of operation types between the arms, the full impact of HumiGard may not be appreciated in this study.

The other aim of the HEAT study was to explore the impact of HumiGard on improving the laparoscopic operating conditions with a focus on temperature regulation. Several interesting trends have been identified within the study, which are considered and discussed further, particularly when considering SSIs.

7.3.1 Patient Temperature regulation

The temperature measurements taken during the HEAT study were from both oesophageal and urinary thermistors. The oesophageal probe measured the core temperature of patients and is the main temperature measurements used by anaesthetists to guide their management of normothermia. The core temperature measurements in this study illustrated the concept of redistribution hypothermia that occurs within the first hour of anaesthetic as seen in Figure 7-3. This contrasts with the urinary temperatures which remained largely static throughout the operation, which means that if the urinary temperature was below 36°C, it remained hypothermic for the majority, if not all, of the operation.

When considering the two arms of the study there was little difference between the core and urinary temperature measurements between the two arms as seen in Figures 7-3 and 7-4. However, Figure 7-6 shows that the use of HumiGard does reduce the difference between the urinary and core temperatures in comparison to standard care. The use of warmed, humidified CO_2 via the HumiGard device reduced the variability between the two temperatures. This could be in part due to warming action of the HumiGard device keeping the abdominal cavity at a closer temperature to the core temperature with less temperature variability.

7.3.2 Concept of Intra-Abdominal Hypothermia

The use of the urinary thermistor was as a proxy measure of the abdominal cavity operating temperature. When considering the standard care arm in Figure 7-6, the difference between the abdominal temperature and the core temperature increased as the operation time increased, with the operating environment having lower temperatures than the core temperature. This is of importance because the anaesthetist who is the primary physician managing patient temperature does so based on the core temperature measurements. If the core temperatures are greater than 36.5°C, then the abdominal temperature is also likely to be normothermic. However, when the core temperature is 35.5-36.5°C then the abdominal cavity is hypothermic to a greater degree. As the operating area temperature is not routinely measured it is difficult for the anaesthetist to implement any interventions to

raise the temperature to normothermic. Alongside the temperature, as the standard care laparoscopic gas is not humidified this can result in the tissues becoming cool and dry which could impact the healing process.

This concept of intra-abdominal temperature is one that should be considered by the operating team during longer operations, with every effort to maintain core normothermia to prevent the operating field becoming hypothermic. This phenomenon has been reported by one study, Groene *et al.* (2020), which demonstrated a similar result with a reduction in abdominal temperatures in comparison to the core temperatures with an average difference of 0.4°C (235). The use of warmed humidified laparoscopic CO_2 via HumiGard may help to combat this difference in temperature as seen in Figure 7-6.

7.3.3   Impact of temperature on SSIs, including anastomotic leaks

Although there were no differences in the number of infectious complications (SSIs and anastomotic leaks) between the two arms, the study was not powered to identify a significant difference in SSIs. Within this study cohort of 39 patients there was an SSI rate of 10.3%, which was slightly lower than the WICS colorectal laparoscopic SSI rate of 12%. Further to this, the SSIs occurred in patients that were hypothermic, which correlates with the results from the SSI bundle implementation.

An interesting observation from Figure 7-7 and 7-8 is that the SSIs occurred only in patients who were hypothermic in both core and urinary/abdominal, whereas the anastomotic leaks happened in patients who were normothermic. It is difficult to postulate as to reasons for this with the small sample size and even smaller complication numbers, but it may be that the intra-abdominal temperature had a smaller impact on anastomotic healing whilst for skin wound healing, hypothermia cools the subcutaneous tissues disrupting the normal healing mechanisms to a greater extent.

7.4   Limitations of the study

The main limitation of the study is that it was a feasibility study, of a sample size that was chosen to measure recruitment and assess the acceptability of the study to patients. As such the outcomes based on temperature regulation and differences, patient recovery and

number of infectious complications have not shown statistical differences due to an underpowered small sample size. Also, the other consideration for interpreting the results of the study is the impact of the distribution of operation types between the two arms.

The lack of standardisation of patient warming adjuncts, analgesic use, and anaesthetic regimes, is a significant limitation of the study. There was difficulty in agreement with standardisation across the anaesthetic consultant body, and therefore an aim of the feasibility study in part was to assess the variability of specific regimes. However, it was found during the analysis that there was little consistency in the anaesthetic regimes and analgesic use, which individual anaesthetic consultants using their preferred individual regimes. Most patients had the warming mattress and forced air warmer, with some patients receiving the warmed IV fluids. This was something that could be standardised in future studies. These all added to confounders which have an impact on the validity of the results, however the feasibility study has identified these and thus can be addressed in the design of fully powered future RCT.

7.5 Conclusions

The HEAT study has further explored the effect of hypothermia on patient recovery post-operatively and the impact of using warmed humidified laparoscopic insufflation to minimise the effects of using unwarmed, dry laparoscopic insufflation within laparoscopic surgery. The increased use of laparoscopic surgery within colorectal surgery, alongside the implementation of ERAS has improved patient outcomes by reducing post-operative complications and facilitating earlier discharge. However, there are still elements of laparoscopic surgery that could be improved upon, and maintenance of normothermia and SSIs are two such areas.

8 Summary and Future Work

8.1 Summary

SSIs continue to affect up to 25% of patients undergoing colorectal procedures despite the use of laparoscopic surgery and ERAS (26,73,89,188,206). The likely reason for the higher SSI rate in colorectal surgery is due to its clean-contaminated nature for the opening of bowel viscus. Despite this, there are practices that can reduce the SSI rate which have been summarise in chapter 3 literature review. By standardising and improving care delivered the patients, the SSI rate should reduce and be similar across hospitals. One of the biggest difficulties in SSI management is the accurate diagnosis, and timely feedback to the operating surgeon. There can be slight differences in appearances between a healing wound and one with an early superficial infection. As such, the SSIs can be wrongly diagnosed and wounds overtreated. This body of work has aimed to define the SSI problem in colorectal surgery in Wales, demonstrated the feasibility of a SSI bundle in reducing the SSI rate and explored in more depth the role of hypothermia in SSI risk via an analysis of a feasibility study of the use of warmed humidified laparoscopic insufflation has on reducing the incidence of hypothermia and improving patient outcomes.

The all-Wales, prospective observational study, the WICS study, has demonstrated that colorectal procedures have an SSI rate 21.1% within Wales. This is the first study to define the Welsh colorectal SSI rate.

There were three aims and a main hypothesis that were constructed prior to the work commencing. It has been able to provide evidence to address these and as such further recommendations, and future work has been suggested to further reduce colorectal SSIs.

8.2 Conclusion of Aims

8.2.1 Study Aims

1.   A literature review of the evidence for the current SSI prevention recommendations - Chapter 3

2.   To determine the Colorectal Surgery SSI rate in Wales, with an evaluation on plans to reduce the SSI rates – Chapters 4-6. This will contain the following objectives:

   a. An All-Wales prospective observational study to establish the SSI incidence in colorectal patients – The Wound Infection in Colorectal Surgery (WICS) study

   b. The development and introduction of a standardised approach, 'An SSI Bundle', to reduce SSIs

   c. An Evaluation of the SSI Bundle – Compliance, strengths, and limitations

3.   Assessing the Impact of Hypothermia on SSIs – investigating the concept of intra-abdominal temperatures during laparoscopic surgery and methods to counteract this – a novel way to reduce SSIs – Chapter 7.

8.2.2   Main Findings and Interpretation

8.2.2.1   *A literature review of the evidence for the current SSI prevention recommendations*

The first aim was to comprehensively review the evidence within the literature for current strategies for SSI prevention. Chapter 3 summarises this evidence and has been the basis for guidance and practices within many hospitals. WHO, CDC and NICE have published guidance on the recommendations for SSI prevention, but within this guidance there are some areas with different recommendations. The literature review established the basis for the SSI bundle that was implemented with UHW.

8.2.2.2   *To determine the Colorectal Surgery SSI rate in Wales, with an assessment of the feasibility of an SSI bundle to reduce the SSI rates*

All Wales prospective observational study to establish the SSI incidence in colorectal patients – The WICS study

Before any improvement in the number of colorectal SSIs within Wales, the baseline SSI rate had to be defined. The only available data for the colorectal SSI data within Wales was from individual department retrospective case series, including the study by Power *et al.* from UHW (44). The WICS study was the first prospective observational study to define the Welsh colorectal SSI rate. The overall SSI rate for all operations (emergency and elective general

and colorectal surgery) under the care of a colorectal consultant surgeon was 13%. However, when considering colorectal surgery (both emergency and elective) this rate was 21.1%. Further to this 50% of the SSIs were diagnosed in primary care, which is an important consideration when designing any future studies to evaluate SSI prevention methods.

Development and introduction of a standardised approach, 'An SSI Bundle', to reduce SSIs

Following on from the literature review, an evidence-based SSI bundle was introduced to try and reduce the colorectal SSI rate. The bundle was introduced in one hospital initially, UHW, which had an SSI rate of 24.3%. There was education of staff and 2 interventions introduced – the use of 2% alcoholic chlorhexidine for intra-operative skin preparation and the use of prophylactic NPWT dressings.

Evaluation of the effectiveness of the SSI Bundle including compliance

The SSI bundle was successfully implemented and shown to be feasible within UHW. The SSI rate reduced from 24.3% to 10.2%, with SSI rates in colonic and rectal surgery reducing by up to a half (9.1% and 18.8%). There was more than 75% compliance in 10 aspects of the bundle, including the correct antibiotic and time administered, the use of 2% alcoholic chlorhexidine and hair clipping in patient intra-operative skin preparation. The main areas of poor compliance were the measurements of blood glucose, likely due to the NICE guidance, and the maintenance of normothermia. The majority of SSIs occurring in patients who were hypothermic, with 51% hypothermic at the time of operative incision with some patients remaining hypothermic for the majority of their operation. The main result of the implementation of the SSI bundle was that it allowed the multi-disciplinary team to become empowered and invested in the reduction of SSIs.

8.2.2.3 *Impact of Hypothermia on SSIs – investigating the concept of intra-abdominal temperatures during laparoscopic surgery and methods to counteract this.*

The HEAT feasibility study investigated the use of HumiGard to warm and humidify the laparoscopic insufflation gas to try improving patient recovery, reduce hypothermia and reduce the number of post-operative complications. The feasibility study demonstrated that there are early trends that intra-abdominal temperature during laparoscopic surgery is

often cooler that the core temperature. This hypothermia may contribute to SSIs as the SSIs that occurred during this study were in those patients which were hypothermic from both core and urinary temperature measurements. However further research via an appropriately powered study would further evaluate this.

8.3   Conclusion of Hypothesis

The hypothesis was '*that the implementation of targeted improvement in intraoperative variables will reduce the incidence of SSIs in colorectal patients in Wales.*'

Overall, this body of work has started to demonstrate that the colorectal SSI rate in Wales of 21.1% could be reduced through targeting interventions including the use of an SSI bundle, and the warming and humidifying laparoscopic insufflation gas as indicated by the included feasibility studies. This is the first all Wales study to define the colorectal SSI rate. This thesis has highlighted areas for future studies and work, particularly with the effects of hypothermia on SSIs.

8.4   Research Limitations

8.4.1   Impact of COVID-19 Pandemic

During this work of research, In March 2020, the UK began a nationwide lockdown in response to the exponential rise in the number of COVID-19 (SARS-CoV-2) cases (236). To mitigate against the significant risk that the NHS would be overwhelmed, all non-urgent care was temporarily suspended with redeployment of the surgical workforce, and this had a large impact on elective operations. As a consequence, two elements of the thesis were directly impacted. The first was that the SSI bundle was intended to be introduced to the 13 hospitals that contributed data to the WICS study, allowing a much larger evaluation of the impact of the bundle on the welsh SSI rate. Secondly, the HEAT feasibility study was intended to be completed as a fully powered RCT to evaluate whether warmed, humidified laparoscopic insufflation improved patient post-operative recovery including the impact of post-operative SSIs. As all non COVID-19 research was also suspended from March 2020, the study temporarily stopped recruiting for 3 months, which impacted the timeline of the full RCT and applications for further funding.

The personal impact of the COVID-19 pandemic was that for a period of time (March 2020 to August 2020) I was redeployed from dedicated research time to full time clinical duties to support the pandemic effort. During this there was limited time spent on research which also impacted on the recruitment to the HEAT study and the progression of the SSI bundle.

8.4.2 Other Limitations

Each aspect of the thesis had some limitations which are addressed in each chapter. A summary of these limitations are:

- WICS study
    - Lack of detail on the diagnostic accuracy of SSIs, particularly in the primary care setting.
    - Stoma formation and impact on SSIs was not evaluated
    - Lack of validated tool to conduct the telephone call
- SSI Bundle implementation
    - Small sample size
- HEAT Feasibility Study
    - Small sample size
    - Distribution of operations within the arms was uneven.

8.5 Future Work

The thesis has raised further questions that require further research. These include:

8.5.1 Could an all-Wales SSI bundle standardise peri-operative care with the aim to reduce Colorectal SSIs?

The implementation of the SSI bundle within UHW demonstrated its effectiveness on reducing SSIs with colorectal surgery, however this was a single site study. Implementing a standardised care bundle across Wales would allow a more detailed statistical analysis of the effects, and which elements are useful in the reduction of SSIs. Further to this, there would require further research into the improvement of colorectal SSIs even further than the initial results of a 50% reduction in SSIs.

8.5.2 Further robust RCTs to provide further evidence on intra-operative management of normoglycaemia and normothermia.

Both areas of normoglycaemia management and normothermic maintenance require further, appropriately powered, robust RCTs to define the impact of these factors on SSIs, but also on any adverse outcomes from intensive control of blood glucose and patient temperatures. The use of insulin in non-diabetics is a contentious issue and one that needs a carefully controlled study, with the input of endocrinologists, anaesthetists, and surgeons. Although maintenance of normothermia is a recognised minimum standard within surgery, it can at times be difficult due to patient factors and anaesthetic choice. Both require further research to define the peri-operative guidance.

8.5.3 Defining the abdominal intra-operative environment and the effect of laparoscopic surgery on the intra-abdominal temperature and peritoneum.

During a major abdominal operation, the body's core temperature is measured by the anaesthetist generally using an oesophageal probe. This is accepted as the core temperature for the patients, however the HEAT study and Groene *et al.* have shown that the intra-abdominal temperature is often different to the core temperature that is measured by the anaesthetist (235). The full effects of this difference, which is often that the intra-abdominal temperature is cooler, has yet to be fully explored although early work has demonstrated that there could be increased peritoneal inflammation and desiccation (229,230). Furthermore, the relationship of intra-abdominal hypothermia to SSIs is unclear as is the possible effects on anastomotic leaks.

8.5.4 Does warmed, humidified laparoscopic insufflation improve patient's post-operative recovery and reduce complications including SSIs?

The current evidence base for the use of warmed, humidified laparoscopic insufflation is based on temperature control, but there is a lack of patient reported outcomes on the impact of using such technology on improving patient's recovery. The HEAT Feasibility study has provided the basis for the design of a fully powered RCT that could add to this evidence, with a particular focus on the impact of HumiGard on patient reported nausea and vomiting, and the impact of HumiGard in longer operations on core and intra-abdominal

temperatures and the overall hypothermia impact for patients. A further larger, powered RCT would allow this to be further explored and a definitive answer for the impact of HumiGard on patient recovery.

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Quality of recovery and perioperative Hypothermia in Elective colectomy patients: A feasibility study of a blinded randomised controlled trial

Study Protocol

Protocol version number and date:
Version 1.0 Date 18/08/19

Full study title: Quality of recovery and perioperative Hypothermia in Elective colectomy patients: A feasibility study of a blinded randomised controlled trial

Short title: HEat: HumiGard Evaluation Study

Sponsor: Cardiff and Vale University Health Board, University Hospital of Wales, Heath Park, Cardiff , CF14 4XW Tel. 029 2074 7747

Study Coordination Centre: Cedar, Cardiff and Vale University Health Board

Funder: Fisher and Paykel Healthcare

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R&D ref: 19/MAR/7616

REC ref: 271720

IRAS ref: Not yet applied

This protocol has been authorised by:

Name:	Role	Signature	Date
Professor Jared Torkington	Chief Investigator		**18/08/19**

Name	Role	Signature	Date

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1. GENERAL INFORMATION

1.1. Study Summary

Study Title	Quality of recovery and perioperative <u>H</u>ypothermia in <u>E</u>lective colectomy patients: A feasibility study of a blinded randomised controlled trial.
Internal ref. no. / short title	HEat study
Study Design	Feasibility study of a blinded randomised controlled trial
Planned Sample Size	40 patients
Planned Study Duration	12 months
Primary Objectives	To assess if a recruitment target of at least 6 eligible patients per month is achievable and identify any barriers to recruitment
Secondary Objectives	- Assess the suitability of the Quality of Recovery (QoR-40) questionnaire as a primary outcome - Assess completion rates of the visual analogue scale (VAS) pain score - Assess if surgeons can be blinded adequately - Assess if continuous temperature measurements intra-operatively can be achieved and appropriate methods for analysis - Assess the variability in analgesia use and how best to analyse this outcome - Assess how discharge decision making can be recorded and analysed

Statistical Methodology and Analysis	Descriptive statistics of numerical outcome data including measurements of precision will be reported. Simple statistical comparisons between groups will be carried out where appropriate. The study is to evaluate if a larger, adequately powered randomised controlled study can be conducted to compare outcomes between groups.

1.2 Funding and Support in kind

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
Fisher and Paykel Healthcare (FPH)	Educational grant of £50,000 and provision of HumiGard devices and consumables

1.3 Role of Study Sponsor and Funder

The study sponsor will be Cardiff and Vale University Health Board (C&V UHB) who will also host the study within the single site at University Hospital of Wales (Cardiff), fulfilling this role according to the principles of Good Clinical Practice (GCP). Cardiff and Vale UHB will retain all Sponsor responsibilities, but many of these responsibilities will be delegated as per study agreements and delegation logs.

Prof Jared Torkington (JT) is an experienced Chief Investigator (CI) who will take overall responsibility for the study.

Miss Nicola Reeves (NR) will be responsible for managing the day-to-day clinical work including patient recruitment, medical history taking and study eligibility assessment, patient consent, data recording, adverse event (AE) management and recording.

Dr Judith White (JW) (Cedar, Cardiff & Vale UHB) will be responsible for management of the study on a day-to-day basis including governance, documentation, data collection and monitoring, data analysis, report writing, and financial management.

Prof Grace Carolan-Rees (GCR) (Cedar, Cardiff & Vale UHB) will have overall responsibility for Cedar's component of this study.

If any of the study team leave, they will be replaced with a new study team member of suitable grade and experience.

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study.

Fisher and Paykel Healthcare (FPH) have provided an educational grant and support in kind (provision of HumiGard devices and consumables) to fund the feasibility study. The study will be run independently of the device manufacturer. FPH will review the final publication to ensure correct use of HumiGard (and associated technical) terminology, only. FPH will not have access to any patient identifiable data (PID).

1.4 Protocol Contributors

The study has been designed by JT, NR, JW, and GCR. All are employed by Cardiff & Vale UHB and work at University of Wales, Cardiff.

The main contributors to the protocol have been JT, NR, and JC, from the colorectal surgery department of UHW, and JW and GCR from Cedar.

A PPI (patient public involvement) representative has been involved in reviewing the design of the study, providing an overview of the acceptability of the study to patients.

2. ABBREVIATIONS

AE	Adverse Event
ASA	American Society Anaesthiology
BMI	Body Mass Index
C&V UHB	Cardiff and Vale University Health Board
CCI	Comprehensive Complication Index
CI	Chief Investigator
CO2	Carbon Dioxide Gas
CRF	Case Report Form
ERAS	Enhanced Recovery after Surgery

GCP	Good Clinical Practice
GP	General Practitioner
HCRW	Health Care Research Wales
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
MDT	Multi-Disciplinary Team
MHRA	Medicines & Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PID	Patient identifiable data
PIS	Participant/ Patient Information Sheet
POD	Post-Operative Day
QALY	Quality Adjusted Life Year
QoR-40	Quality of Recovery – 40 Questionnaire
R&D	NHS R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Effect
SMG	Study Management Group
SOP	Standard Operating Procedure
VAS	Visual Analogue Scale

3. BACKGROUND AND RATIONALE

The Clinical Problem

Laparoscopic surgery involves filling the peritoneal cavity with carbon dioxide (CO2) gas (insufflation) to increase the working and viewing space in the abdomen. It is standard care in the UK to use dry, unwarmed CO2. There is evidence that dry, unwarmed insufflation is associated with tissue desiccation and intraoperative hypothermia as demonstrated by Bessel et al. (1999) showing that insufflation of cool dry gas resulted in a temperature drop of 1.3-1.7°C. Despite active warming methods, perioperative hypothermia is common. One study demonstrated that nearly half of patients had continuous core temperatures of 36°C for more than an hour (Sun et al. 2015). In Lavies et al. (2011), implementing active warming methods led to fewer patients with hypothermia, but 53% of patients were still hypothermic in the postoperative phase. Patients undergoing colorectal surgery are particularly at risk of hypothermia due to the long length of procedures.

Warmed, Humidified CO2 for Insufflation

HumiGard (Fisher and Paykel Healthcare) is a CE marked medical device designed to humidify and heat CO2 for insufflation. A meta-analysis by Dean et al. (2017) included 13 studies (total of 796 patients) comparing warmed, humidified CO2 insufflation compared to unwarmed, dry CO2 in patients having a range of procedures. There was a significant difference in mean core temperature change, and an effect size of +0.3°C (95% confidence interval [CI]: 0.1–0.6). This was more pronounced in studies of long procedures (80 min).

The Balayssac et al. (2017) meta-analysis of 15 studies (1026 patients) demonstrated a small beneficial effect on immediate post-operative pain but not at day 1 or 2. Warmed, humidified CO2 reduced the risk of intraoperative hypothermia (p=0.004) but postoperative core temperatures were not significantly different (10 studies, 718 patients). No differences were observed in analgesic consumption, length of stay, or procedure duration. The included randomised controlled trials (RCTs) however, were heterogenous and of poor quality. Matsuzaki et al. (2017) analysed the outcomes of HumiGard on gene expression for inflammation, in 40 patients undergoing a gynaecological operation. There was a significant reduction in inflammatory gene expression in the HumiGard arm. Few complications were reported. Low statistical power may have been responsible for no change in Quality of Recovery scores (QOR-40) before and after surgery.

The literature on the benefits of using of HumiGard shows that there is some benefit for the patient, however the studies are of low quality and underpowered. There is no strong evidence that the use of HumiGard has a positive impact on patients and their recovery in the post-operative period.

Intraoperative Hypothermia

General anaesthesia can cause hypothermia (defined as a temperature measurement of less than 36°C) during and after surgery by interfering with the patients' own regulatory responses to maintain normothermia (normal body temperature). In National Institute for Health and Care Excellence's (NICE's) clinical guidelines (CG65), an evidence review on the consequences of hypothermia were conducted. There was evidence that perioperative hypothermia increases:

- The risk of medical complications
- The risk of both morbid cardiac events and surgical wound infections
- The risk of requiring postoperative mechanical ventilation
- The length of stay in hospital
- The risk of requiring a blood transfusion
- Recovery time in post anaesthetic care unit which has an negative effect on surgical list management

The need to closely monitor patients' temperature perioperatively is widely recognised and it is standard care to warm surgical patients. NICE's recommendations on prevention and management of hypothermia in adults having surgery (CG65; 2016) include:

- Monitoring patient temperature intraoperatively every 30 mins
- Delay induction of anaesthesia until the patient's temperature is 36°C
- Warming of intravenous fluids and blood products to 37°C
- Warm patients intraoperatively using a forced-air warming device [warming blankets] for procedures of 30 mins
- Monitoring the patient's temperature every 15 mins on admission to the recovery room
- Delay ward transfer until the patient's temperature is 36°C

Maintenance of normothermia pre- and intraoperatively is part of Enhanced Recovery After Surgery (ERAS) intraoperative care bundle from 1000 lives plus in the Welsh NHS, with the aim of reducing harm to patients, reducing length of stay, and improving efficiency in the NHS.

NICE research recommendation

NICE have produced guidance on HumiGard for preventing inadvertent perioperative hypothermia. The committee recommended that research should be undertaken on HumiGard compared with standard insufflation gases in patients having laparoscopic or open surgery.

Cost Implications

With any device that is used within the National Health Service (NHS), it is important that it is cost effective. A cost-utility analysis by Jenks et al. (2017) demonstrated a cost saving to the NHS of £345 per patient and incremental Quality Adjusted Life Year's (QALYs) of 0.001 when HumiGard was used with laparoscopic colorectal surgery.

Patient Reported Outcome Measures

QoR-40 is a validated and widely-used, patient-reported global measure of overall health status after surgery and anaesthesia (Myles et al. 2000). QoR-40 is a 40-item patient-reported questionnaire that provides a global score and separate scores across five dimensions: patient support, comfort, emotions, physical independence, pain. QoR-40 is the most widely reported measure of patient-assessed quality of recovery after surgery. It has excellent validity, reliability, responsiveness and clinical utility in a broad range of clinical settings and is highly sensitive to clinical change (Gornall et al. 2013).

Matsuzaki et al. (2017) primary outcome was expression of inflammatory genes, however the study also evaluated patient reported evaluation of recovery via the QoR-40 questionnaire. As a secondary outcome, the study was not adequately powered and thus limited the conclusions that could be drawn from the results. It is important that any new medical device or treatment is evaluated fully on the effect of patient outcomes. If the feasibility study demonstrates that the QoR-40 questionnaire is acceptable to patients, the feasibility results will be used to help power the main RCT adequately to show if there is a difference in patient's recovery via the QoR-40 questionnaire.

A small-scale service evaluation of laparoscopic colorectal resections was performed at University Hospital of Wales during September 2018. A total of 7 from 8 patients (from 4 of 8 consultants) agreed to and were able to successfully complete the QoR-40 questionnaire. The QoR-40 scores showed differences between pre-operatively and post-operatively questionnaires. This small data collection positively indicates recruitment ability and that the QoR-40 questionnaire is able to be completed by patients.

Evidence explaining why this research is needed now

Despite the importance of avoiding perioperative hypothermia and the widespread introduction of Enhanced Recovery after Surgery (ERAS) in the NHS, there is evidence that many patients' temperature drops below 36°C during long surgeries. NICE recognised that HumiGard shows promise but that there is insufficient evidence to recommend routine adoption. Our study is designed to assess the feasibility of carrying out a RCT which will directly address the deficiencies of previous studies.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Objectives	Outcome Measures/Endpoints
Primary Objective	

To assess if a recruitment target of at least 6 patients per month in a tertiary centre is achievable and identify any barriers to recruitment	*Recruitment timeline of patients and reasons for non-recruitment recorded in screening log*

Secondary Objectives
   1. To assess if the QoR-40 questionnaire can be completed successfully by patients on post-operative days 1,3,30.
 	
   2. To assess if the VAS pain score can be recorded successfully by patients on post-operative days 1,3,30.
 	
   3. To demonstrate that urinary temperature probes are able to provide continuous intra-operative temperature readings
 	
   4. To assess whether blinding of the treating surgeons within the study can be achieved (HumiGard vs sham device).
 	
   5. To evaluate methods for recording and analysing post-operative analgesia use.
 	
   6. To assess methods for recording and analysing additional intraoperative patient warming techniques.
	1. Number of patients who successfully complete the QoR-40 questionnaire
	
	2. Number of patients who successfully complete VAS pain score
	
	3. Use of urinary thermistors to produce continuous data in comparison to the standard temperature monitoring used in current practice by the anaesthestists.
	
	4. Ability of treating surgeons and anaesthetist to predict whether device is HumiGard or sham device.
	
	5. Post operative analgesia will be delivered in line with standard care and will be recorded and analysis techniques applied.
	
	6. Additional intraoperative patient warming techniques to be recorded and analysis techniques applied.

Outcomes and time points	Parameters to measure
Preoperative data (day of admission)	Age, Sex, BMI, Cardiac/respiratory disease, ASA grade, other significant

	comorbidities, previous abdominal surgery, QoR-40 questionnaire and VAS pain score.
Intraoperative Patient Temperatures	• Urinary temperature probe – continuous measurements • Standard temperature measurements used by anaesthetists in theatre
Intraoperative Warming Methods	• Use (frequency and duration) of intraoperative warming blanket • Use (frequency and duration) of intraoperative warmed fluids
Intraoperative surgical and recovery data	• Type of operation performed • Length of surgery (minutes) • Surgeon blinded – successful • Temperature in recovery
Postoperative (post-operative day (POD) 1, POD 3, and POD 30)	• QoR-40 • Analgesia use (drug chart) • VAS pain score • Complication severity (Clavien-Dindo scale and Comprehensive Complication Index) • Date of discharge

5. STUDY DESIGN

This is a blinded, randomised controlled feasibility study on 40 patients receiving laparoscopic colorectal resectional surgery at a single site (University Hospital of Wales) and treated with either the HumiGard device plus standard care (20 patients) or a sham HumiGard device plus standard care (20 patients).

This study will assess various aspects of a proposed larger pragmatic blinded, RCT evaluating whether HumiGard insufflation device, when used with standard care, can improve patients' quality of recovery after laparoscopic colectomy surgery.

The feasibility study will aim to highlight the most appropriate outcomes to be measured in a main RCT, particularly looking at the role of QoR-40 or continuous temperature measurements. We will assess whether the outcomes of the study are suitable, achievable and measurable. The study will assess recruitment, ability to blind operating surgeon with a sham HumiGard device, use of urinary temperature probe compared to standard temperature monitoring in theatre, use of QoR-40 and VAS pain score by patients preoperatively (for a baseline score) and on POD 1, 3 and 30, analgesia use, and intraoperative patient warming techniques. Length of stay in hospital from procedure to discharge (or until medically fit for discharge) will also be recorded and reported.

Furthermore, methods for analysing the postoperative complication rate will be evaluated. Complications will be recorded at POD1, POD3, upon discharge and POD30. Their severity will be graded using the Clavien-Dindo scale, a widely used and valid method for grading severity of surgical complications which helps to reduce subjectivity (Clavien et al, 2009). The Comprehensive Complication Index (CCI) will then be used to create a composite score (0-100) for each patient (Slankamenac et al. 2013).

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

The study will recruit patients undergoing an elective laparoscopic colorectal resection operation for any pathology. The patients will be over 18, and able to provide informed consent.

6.2. Inclusion Criteria

- ≥18 years of age
- Participant is willing and able to give informed consent
- Scheduled for elective laparoscopic, segmental or total colectomy

6.3. Exclusion Criteria

- Unable to complete study documentation
- Lack of capacity or not willing to give consent
- Open procedure planned
- Emergency procedures

7. SCHEDULE OF STUDY PROCEDURES

The following table and the sections below describe the study procedures and assessments

Procedures	Visits						
	Screening	Baseline	Intra-Op	POD 1	POD 3	POD 30 (+/- 2 days)	Follow up clinic 6 weeks
Eligibility Check	x	x					
Informed Consent		x					
Demographics		x					
Medical history		x					
QoR-40		x		x	x	x	
VAS Pain Score		x		x	x	x	
Urinary Thermistor measurements			x				
Standard temperature measurements			x				
Analgesia Use			x	x	x	x	
Adverse Events and complications			x	x	x	x	x
Surgeon Blinding			x				
Warming Methods			x				
Operation Details			x				
Date of Discharge						x	

The following flowchart described the study procedures.

Initial appointment

Identify & screen potentially eligible patients during (at pre-assessment clinic). Patient provided with **information sheet**.

Opportunity to ask questions. **Informed consent** taken.

Hospital admission

Baseline assessment (QoR-40 questionnaire, pain score, temperature, demographics)

Patient is **randomised** to receive either intervention or control

Intervention group (n=20) receive HumiGard plus standard care

Control group (n=20) receive standard care from sham device

Surgical procedure (record adverse events, temperature, warming methods, resource use)

Patient to recovery (temperature recorded)

Patient to ward

1 day post-op (QoR-40, pain score, adverse events)

3 days post-op (QoR-40, pain score, adverse events)

Patient **discharged** home as per standard care (adverse events recorded)

Follow-up

30 day post-op phone call to patient by nurse (patient-reported complications and consequences, readmission to hospital)

6 week follow up in outpatient clinic (adverse events recorded)

Data **analysis** and **reporting**

Recruitment

Data collection

Follow-up

Analysis

7.1. Recruitment

Patients will be identified in the colorectal Multi-Disciplinary Team (MDT) and colorectal clinic by the Chief Investigator (CI) or other clinicians delegated this task on the study delegation log. Patients will first be approached by a clinician who is part of their care team.

Potential patients will receive the Patient Information Sheet (PIS) from a research officer prior to surgery in the outpatient clinic or pre-assessment visit by the research officer/nurse. Patients will have at least 24 hours to consider the PIS and will be consented by a clinician (on the delegation log) either pre-operatively in clinic or on the day of surgery.

7.2. Screening and eligibility assessment

Potential patients will be screened against the inclusion and exclusion criteria described in section 6. Eligibility assessment will be made by the CI, consultant surgeon, or research doctor (on the delegation log). A screening log will be kept by the research team to assess the number of eligible patients and the number recruited to the study.

7.3. Informed Consent

The participant must personally sign and date the latest approved version of the informed consent form (ICF) before any study specific procedures are performed.

Written and verbal versions of the PIS and ICF will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their General Practitioner (GP) or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent will be suitably qualified and experienced and have been authorised to do so by the CI. A copy of the signed ICF will be given to the participant to keep along with a copy of the PIS. The original signed form will be retained at the study site and a further copy will be kept in the patients' medical notes.

7.4. Randomisation, blinding and unblinding

Randomisation programme

The randomisation method will be minimisation using software called MINIM

(Altman & Bland 2005) to aid even distribution of important prognostic factors across the two treatment groups (e.g. ASA grade, body mass index (BMI), gender, benign/malignant procedure type). Minimisation will also ensure roughly equal numbers of participants allocated to each study arm (although not exactly equal as this would remove the random allocation element). The minimisation programme will be saved on a C&V UHB computer.

Randomisation procedure

A member of the research team will telephone Cedar (part of C&V UHW) on a specified telephone line when a new participant has given signed informed consent to take part in the study to allow randomisation to occur. This will occur on Day 0 of the study (usually in the morning of surgery). Randomisation will happen after the patient is consented but before entry into the operating theatre. This member of the research team will become unblinded to the allocation of that patient and will not be involved in data collection for that particular patient from the point of randomisation onwards.

The research team member will provide the required information to the Cedar staff member over the phone, including: date, patient ID and initials, name of research nurse, confirmation that the patient is eligible and has provided informed consent, and any prognostic factors required for the minimisation process.

Cedar staff (all of whom are located in Cardiff Medicentre and not involved in recruiting participants to the study) will be trained in the process of providing random allocation and will be available between the hours of 8.00am-5.00pm on Mondays to Fridays.

Cedar staff will then input the prognostic factors into the minimisation programme which will output the allocation result. This will be recorded in the randomisation log at Cedar and will be communicated to research team member over the phone.

Blinding

Once Cedar has revealed the patient's allocation to the unblinded research team member over the phone, the research team member will inform one member of the theatre staff who will then set up the HumiGard device in its on (actual device) or off (sham device) setting. This will happen before the patient enters the anaesthetic room to allow time to set up the HumiGard Device (actual or sham). The theatre staff member will be unblinded to allow operation of the HumiGard device, however they will endeavour to ensure blinding of surgeons and anaesthetists continues. Details of how the sham device works are described in section 8.

All theatre staff will be trained in setting HumiGard up but the operating team will not be informed of allocation.

Unblinding

The nature of the study device (low risk CE marked medical device used for its intended purpose alongside standard care for a finite period in theatre) means that there are no circumstances we can envisage where urgent patient unblinding is required. However, Cedar will hold an anonymised randomised database which will enable unblinding in office hours (8am-5pm) in the highly unlikely event that patient safety is at risk. If the clinical team need to find out which group a patient is allocated to, they will telephone the study manager (or other delegated individuals at Cedar) who will access the anonymised randomisation log. The patient study ID will be used to identify the patient in the randomisation log, and the Cedar study manager will inform the clinical team which group the patient was assigned to. The Cedar study manager will not inform the clinical team about the assignment of any other patients therefore allocation of the remaining patients will remain blinded. The unblinded patient can remain in the study and their data will be included.

7.5. Baseline Assessments

The baseline assessment will be carried out when the patient is in hospital for their surgery. This will usually be on the day of surgery or the day before. During the baseline assessment (Day 0 or -1) the research team will collect demographic data and a medical history. This will include the following:
- Age
- Sex
- BMI
- Smoking status
- Cardiac/respiratory disease
- ASA grade
- Primary diagnosis
- Presence of malignancy
- Other significant comorbidities
- Previous abdominal surgery

The patient will be given a paper copy of the QoR-40 questionnaire and VAS pain score sheet to complete. Any issues with completing these will be recorded by the research nurse.

7.6. Study Visits and follow up

Study assessment	Data collected

1) Intraoperative and recovery assessments (Day 0)	The following data will be recorded during surgery and in recovery by the research team (surgeons/research nurse)(day 0): • Temperature will be measured upon arrival to the anaesthetic room • Continuous temperature measurement during surgery using a urinary temperature probe • Standard temperature measurements currently used by anaesthetists will be captured • Type, frequency and duration of patient warming (or cooling) methods such as warming blankets or warmed fluids. • Volume of insufflation gas used • Type of operation performed • Length of surgery (minutes) • Surgeon asked to predict patient allocation • Temperature upon arrival and departure to recovery • Time when patient ready to leave recovery • Time spent in recovery • Intraoperative complications • Analgesia use (type, dose, frequency)
2) Postoperative day 1 (POD 1)	Approximately 12-24 hours after surgery the following data will be collected in hospital by Research Nurse (day 1): • The patient will be given a paper copy of the QoR-40 questionnaire and VAS pain score sheet to complete. • Analgesia use (type, dose, frequency)* • Adverse events/complications
3) Postoperative day 3 (POD 3)	Approximately 72 hours days after surgery the following data will be collected in hospital by Research Nurse (day 3): • The patient will be given a paper copy of the QoR-40 questionnaire and VAS pain score sheet to complete. • Analgesia use (type, dose, frequency)* • Adverse events/complications

4) Postoperative day 30 (POD 30+/- 2 days)	Approximately 30 days after surgery the following data will be collected via a telephone call to the patient from the blinded research team member (day 30): • A nurse will read the QoR-40 questionnaire and VAS pain score sheet aloud and record the patient's response. • Patient-reported adverse events including re-admittance (patients will be given an adverse event diary as a memory prompt)
5) Follow-up at 6 weeks	Approximately 6 weeks after surgery the following data will be collected during patients' routine postoperative outpatient clinic appointment: • Adverse events/complications (patients will be given an adverse event diary as a memory prompt)

* analgesia provision will be in line with standard care; type, dose, frequency will be captured and analysed.

No laboratory tests on patient samples will be taken for the purposes of this study.

7.7. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the CI may discontinue a participant from the study at any time if the CI considers it necessary for any reason including:
- Pregnancy
- Ineligibility (either arising during the study or if, during the study, previously unknown issues come to light which would make the participant ineligible)
- Significant protocol deviation as decided by the CI
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of consent
- Loss to follow up

Patients who are withdrawn from the study prior to completing the QoR-40 questionnaire at post-operative day 1 will be replaced. If a patient does not continue with the study, his/her data up to the point of withdrawal will be included in the analysis.

7.8. Study Amendments

It is the sponsor's responsibility to classify amendments as being non substantial or substantial. The CI will seek advice from C&V UHB R&D office prior to submission to the relevant bodies. The CI will follow Health Research Authority (HRA) processes for any amendments to the protocol or other study documents.

The NHS R&D Office will need to confirm capacity and capability prior to implementation. Amendments to the protocol or other study documents will not be implemented prior to appropriate approvals being granted.

7.9. Definition of End of Study

The end of the study is POD 30 of the 40th patient in the feasibility study.

8. PRODUCTS, DEVICES, TECHNIQUES AND TOOLS

HumiGard Device

HumiGard (Fisher and Paykel Healthcare) is a Class IIa CE marked medical device indicated for use in laparoscopic or open abdominal surgery when CO_2 insufflation gas is used. The device comprises a surgical humidifier and a single use humidified insufflation kit. It humidifies and warms the CO_2 by passing the gas over a reservoir of water. The heated, humidified gas is then passed along a sterile tube for delivery into the abdominal cavity through a cannula. HumiGard is designed to be used both independently and in addition to other warming measures that are applied to the external body surfaces and extremities, such as forced air warming.

There have been no identified contraindications to use of the system in safety checks.

Fisher and Paykel will provide the training required for using this device to theatre staff and operating consultants during the month preceding the start of the study. They will provide continued support during the study to ensure correct usage of the device. Fisher and Paykel will also create an SOP for theatre staff to use as reference during the study. Dates and details of this training, and the attendees, will be documented in a training log, and kept in the Trial Master File (TMF). The trainer/CI will confirm the competency of those trained, and all attendees must sign to indicate they are happy and feel confident/competent to use the device, as trained.

The device and consumables required for both the training and study will be provided by Fisher and Paykel free of charge.

Sham device

Following discussions with FPH, they advised that the HumiGard device could be used as a sham device in order to blind the treating surgeon and anaesthetists to the allocation of the patient. The sham device used in the standard care arm will be the same HumiGard device as is in the intervention arm. However, the sham device will be turned "off" so that the gas delivered to the peritoneal cavity for insufflation is not heated or humidified. The sham device will deliver CO_2 (as is the case for current standard practice in the hospital) through the HumiGard tubing. The sham device will look and sound the same as the active intervention arm where the HumiGard device is switched "on" and is delivering warm, humidified CO_2 to the peritoneal cavity. The main risk of inadvertent unblinding of theatre staff is that the tubing may feel warm if touched. It is not possible to conceal the tube with a sheath.

Training in using the device as a sham will also be provided by Fisher and Paykel.

9. SAFETY REPORTING

This study is a non-CTIMP study of a Class IIa CE marked medical device as such it poses a low risk.

9.1. Definitions of adverse events, serious adverse events, and relatedness

Adverse Events (AEs): any untoward medical occurrence in a clinical trial participant to whom a study intervention has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom or disease.

Serious Adverse Event (SAE): Adverse events are classified as serious or non–serious. A serious adverse event (SAE) is an adverse event which results in any of the following:

- Results in death;
- Is life-threatening, in the sense that the patient was at risk of death at the time of the event (but not if the event could have caused death if more severe);
- Requires hospitalisation (or prolongation of existing hospitalisation) defined as an unplanned admission of any length, even if precautionary for continued observation; however pre-planned hospitalisation (e.g. for an elective procedure or a pre-existing condition which has not worsened does not constitute an adverse event);
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect; or
- Is otherwise considered medically significant by the investigator

Relatedness: Whether the reporting investigator considers the adverse event to be related to **any of the study procedures** can be classed as follows:

- Definite

- Probable
- Possible
- Unlikely
- Not related

9.2. Identifying AEs

Intra-operative and post-operative AEs will be identified by the teams caring for study participants whilst they are in hospital. Events observed by the participant will also be recorded. Upon discharge, patients will be given an AE diary. Once participants are discharged from hospital they will be telephoned by a research nurse at 30 days post procedure. During this phone call the nurse will ask patients to report any problems using the AE diary as a memory prompt. The patient will return the AE diary at the 6 week outpatient appointment.

9.3. Expected AEs

Below are listed AEs that are considered expected for patients undergoing colorectal surgery. However, if the following events lead to death, that would be considered unexpected.

- Lower Respiratory Tract infection
- Urinary Tract infection
- Intra-abdominal sepsis Deep vein thrombosis
- Pulmonary embolus
- Bleeding
- Myocardial infarction (not leading to death)
- Stoma complications – prolapsed, retraction, dehiscence or hernia

The following are adverse events of special interest:

- Hypothermia
- Surgical Site Infections
- Anastomotic Leak
- Wound Infection
- Wound Breakdown

The manufacturer's Instructions for Use for the HumiGard device do not report any expected device-related AEs.

9.4. Recording AEs

All subjects experiencing AEs will be monitored until symptoms subside or until there is a satisfactory explanation for the changes observed. Details of all AEs (not just those thought to be device related) will be recorded on the AEs form in the participant's Case Report Form (CRF) and in their medical notes. Subjects experiencing AEs may be withdrawn from the evaluation at the discretion of the clinical investigator.

The following information regarding each AE will be obtained:

- Date and time of onset and resolution (duration)
- Severity (including whether the AE is serious)
- Any treatment required or action taken
- Outcome
- Relatedness to study device
- Whether the adverse caused withdrawal from the study

If an AE is considered to be serious (see definition above) then the reporting procedure for SAEs described below must be followed.

9.5. Reporting SAEs

When a SAE is observed the clinical staff or research nurses will complete a SAE form and contact Cedar by telephone. A Cedar staff member will then collect the SAE form from UHW within the following 24 hours. Cedar will escalate SAEs to Prof Jared Torkington (CI) or Miss Nicola Reeves (PI).

When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious. Hospitalisation for elective surgery or routine clinical procedures, which are not the result of an AE need not be considered AEs.

A SAE which has been classified by the CI as **RELATED and UNEXPECTED** (see definitions above) must be reported to both the Research Ethics Committee (REC) that gave a favourable opinion of the study and C&V R&D office. Reports of related and unexpected SAEs should be submitted within 15 working days of the CI becoming aware of the event, using the HRA report of SAE form. Reports of SAEs in double-blind trials should be unblinded.

Unrelated and expected SAEs do not require reporting to C&V R&D but a copy of the SAE report should be retained in the Investigator Site File for monitoring/audit.

Contact details for reporting SAEs

Tel: 02921 848612 or 02920744771 (Mon to Fri 09.00 – 17.00)

Cedar study manager will then collect the SAE form from the clinical team at UHW

9.6. Reporting adverse incidents involving medical devices

An adverse incident is an event that causes, or has the potential to cause, unexpected or unwanted effects involving the safety of device users (including patients) or other persons.

The following will be notified by the Cedar Study Manager to the Medicines & Healthcare products Regulatory Agency (MHRA) via the Yellow Card Scheme (https://yellowcard.mhra.gov.uk/):

- AEs or SAEs considered to be related to the HumiGard device
- Safety incidents (or near misses) for users of HumiGard device
- Delays or interruptions to a participant's treatment due to a faulty device

These and any reported usability issues with the HumiGard device will also be reported to the manufacturer (Fisher & Paykel Healthcare).

The following contact details should be used to inform FPH of any device-related adverse incidents:

Name: Jessica Fogarin (Clinical Research Manager)

Address: Fisher and Paykel Healthcare, 15 Maurice Paykel Place, East Tamaki, Auckland 2013

Phone: +64 9 574 0123 Ext: 7327

Email: Jess.Fogarin@fphcare.co.nz

9.7. Urgent Safety Measures and Serious Breaches of GCP

The CI and PI may take immediate safety measures to protect research participants against any hazard to their health or safety without prior authorisation from the REC or sponsor. However they must alert the sponsor as soon as possible of any such urgent measures by contacting the C&VUHB R&D Office and CI. The CI will notify the REC of the presenting issue within 3 days of the urgent measure setting out the reasons for the urgent measure and the plan for further action.

In the event that a serious breach of GCP or the Protocol is suspected, this will be reported to the sponsor immediately in accordance with C&V UHB SOP 235

Managing Breaches Of Good Clinical Practice Or The Study Protocol. The incident in question will be investigated by the sponsor who will determine whether the breach constitutes a serious breach. Any corrective action required will be undertaken by the

CI and REC informed if required. If necessary a protocol amendment will be submitted for review.

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

Sample size

This study is a feasibility study to assess recruitment targets and the appropriateness of selected outcome measures, particularly use of the QoR-40 tool and the use of a urinary thermistor for continuous intraoperative temperature recording. As such, a sample size calculation has not been used. Instead, the sample size has been selected to assess the feasibility of recruiting 6 patients per month for 12 months. A conservative sample size of 40 patients has been selected. The information from this study will be used to inform further studies for a future pilot/RCT study.

Statistical methods

The primary outcome of recruitment rates will be reported as frequencies.

QoR-40 questionnaires will be scored as per the authors' instructions. Means/medians with precision estimates will be reported. Analysis of covariance (ANCOVA) will be used to compare the change in QoR-40 between groups whilst controlling for the baseline (the covariate), assuming the data are normally distributed. However, results will be interpreted cautiously because the study has not been powered to detect this change.

Incidence of hypothermia (binary outcome) and duration and depth of hypothermia are outcomes of interest and we will explore analysis techniques. For instance, incidence of hypothermia may be compared between groups using logistic modelling for incidence rates, and continuous temperature measurement data will be evaluated using area under the curve (AUC) analysis.

During patients' time in hospital their complications (including surgical site infections) will be reported and scored by their treating clinical team. Complications will be recorded at POD1, POD3, upon discharge and POD30. Their severity will be graded using the Clavien-Dindo scale, a widely used and valid method for grading severity of surgical complications which helps to reduce subjectivity (Clavien et al, 2009). The feasibility of using the Comprehensive Complication Index (CCI) to create a composite score (0-100) for each patient (Slankamenac et al. 2013) will be assessed. Comprehensive Complication Index scores will be compared between groups using ANCOVA.

Other outcomes such as length of stay, length of procedure, readmission rates will be analysed using descriptive statistics.

Levels of missing data are expected to be low because most outcomes are measured whilst the patient is still in hospital and easily accessible by research nurses. Where outcome data cannot be collected from patients this will be recorded with reasons. Proportions of patients with missing data will be reported in full

11.   DATA MANAGEMENT

11.1.   Access to Data

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Direct access will be granted to authorised representatives from the Sponsor for monitoring and/or audit of the study to ensure compliance with regulations.

Cedar will perform the analyses of all study data. Procedures will be in place to enable transfer of study data as follows:
- From Surgery to Cedar (anonymous data) for the purposes of random allocation, analysis of outcome data and archiving.
- From Surgery to Cedar to enable Cedar to verify CRF data against the patient medical records, requiring access to personal identifiable data

All access to personal identifiable data by the investigators will be with documented consent by the participant.

The device manufacturer will not have access to any patient identifiable data. Fully anonymised data may be made publically available following publication of the study results.

11.2.   Data Recording and Record Keeping

Study data will be collected by the clinical team. Study outcomes will be recorded by the clinical research team on trial CRF which will be a paper document. A blinded member of the research team will be responsible for recording of data into the study CRFs (see sections 9.5 and 9.6).

Patients will be asked to complete a paper copy of the QoR-40 questionnaire and VAS pain score at baseline, POD 1, and 3. The QoR-40 and VAS score will be administered to patients via telephone call at 30 days post-operatively.

Cedar will be managing the feasibility study and thus will be responsible for data recording and record keeping. Judith White will be responsible for data entry to the study database, data quality and analysis.

All paper and electronic documents will be stored securely at UHW (paper) or on Cardiff & Vale UHB servers (electronic) and only accessible by study staff and authorised personnel. No PID will be transferred outside of Cardiff & Vale UHB.

Paper CRFs and questionnaires will be kept at the study site during the study period and when completed on Day 30 the CRFs will be signed-off by the study CI. Completed and signed-off CRFs will be transferred to Cedar (in person) as each patient completes the study period.

Two researchers from Cedar will input data independently from paper CRFs to an electronic Microsoft Access database to enable cross validation and ensure accurate data entry. The Access database will be stored on Cedar's secure server (part of Cardiff and Value UHB server) which is backed-up every 24 hours. All changes to raw data will be auditable.

SPSS will be used for data analysis.

There is permission from Professor Myles to the free use of the QoR questionnaire, where the research staff (officers/nurses) will assist in distributing and completion.

Cedar will undertake source data verification for 100% of CRFs. This will require Cedar to access personal identifiable data in the study recruitment and in patients' medical notes.

11.3. Participant Confidentiality and Data Protection

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

The data custodian in this study is Judith White (Cedar) and the data will be held on Cedar's secure server.

Study CRFs will be kept in secure locations (locked cupboard) at the study site and at Cedar. The study database at Cedar (part of Cardiff and Vale UHB) will be accessible only by Cedar personnel directly involved in the study (password protected files on Cedar secure NHS servers).

The device manufacturer will not have access to any patient identifiable data.

11.4. Record Storage and Retention

The TMF and Investigator Site File (ISF) containing essential documents will be kept for a minimum of 5 years after completion of study. Documents (paper and electronic) will be retained in a secure location during. Cedar will archive study documentation at the end of the study. A label stating the required retention time should be placed on the inside front cover of the medical records for study participants.

Essential documents pertaining to the study shall not be destroyed without permission from the sponsor.

12. QUALITY ASSURANCE PROCEDURES

The study may be subject to inspection and audit by C&V UHB R&D office under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research 2017.

A study management group (SMG) will meet at a total of 3 times over the duration of the study and its role is to develop the study documentation, determine the study activities and undertake the study activities. NR represents the clinical team who will recruit participants and collect the study data. The SMG will ensure the study is running to time and that recruitment is on target. It will also ensure that blinding and randomisation processes are working effectively. SAE's will be reviewed by the SMG.

Name	Role	Organisation
Prof Jared Torkington	Chief Investigator	Surgery, Cardiff & Vale UHB
Miss Nicola Reeves	Principal Investigator	Surgery, Cardiff & Vale UHB
Mrs Julie Cornish	Co-Investigator	Surgery, Cardiff & Vale UHB
Dr Judith White	Study manager	Cedar, Cardiff & Vale UHB
Prof Grace Carolan-Rees	Cedar Director	Cedar, Cardiff & Vale UHB

| Gail Williams | Research Nurse | Surgery, Cardiff & Vale UHB |
| Fiona Brennan | Anaesthetist | Anaesthetics, Cardiff & Vale UHB |

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and SOPs.

Cedar's role is to perform the following activities:
- Safety reporting (incl. reporting to REC, C&V UHB R&D and MHRA as necessary)
- Annual reporting and final report to REC (following sign off by CI)
- Coordinate the study, seeking input from members of the SMG as necessary.
- Monitor recruitment rates.
- Perform independent randomisation of study participants.
- Undertake site monitoring visits to validate the study data and ensure conduct is in compliance with the protocol and principles of GCP.
- Analyse the study data.
- Write the study report in collaboration with the clinical team and submit for publication in a peer-reviewed scientific journal.

13. ETHICAL AND REGULATORY CONSIDERATIONS

This study complies with the World Medical Association Declaration of Helsinki (2013) and GCP. The study will respect the rights of participating patients and ensure confidentiality of patient information. Patients undergoing surgery for colorectal cancer have an excellent support system through the specialist cancer nurses and the clinical team, as well as several charities and voluntary organizations. Patients undergoing surgery for non-cancer diagnosis will have support through the clinical team. Should participants have additional questions about the trial, advice will be available from both within the research team and outside the research team in the form of websites such as the NHS website page: http://www.nhs.uk/Conditions/Clinical-trials/Pages/Takingpart.aspx.

13.1. Review and Approvals

Ethical Approval and HRA/HCRW approval

- Before the start of the study, approval will be sought from Health Care Research Wales (HCRW) and REC for the protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.
- Amendments that require review by HCRW and REC will not be implemented until approval is granted. The CI (or delegate) should submit any amendments to the Sponsor, in the first instance, and their National Coordinating Unit, HCRW). The HCRW Permissions Service will assess and approve the amendment.
- All correspondence with the REC will be retained in the TMF/ISF.
- A progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the CI's responsibility to produce the annual reports as required.
- The CI will notify the REC of the end of the study
- If the study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

Peer Review

The protocol has undergone scientific review by two people independent of the study and with relevant experience. Furthermore, the protocol has been reviewed by C&V UHB as part of the Sponsor Assessment Meeting.

The PIS and ICF have also been reviewed by a Patient and Public Involvement (PPI) representative.

Governance Review

The study will be assessed for governance and legal compliance by HCRW. Once all checks are satisfied HCRW will issue HRA/HCRW approval. The study should not commence until local confirmation of capacity and capability is also received via email by the CI/ PI.

13.2. Reporting

The CI shall submit once a year throughout the study or on request, a progress report to the REC and sponsor. In addition, an end of study notification and final report will be submitted to the same parties and the funder. Cedar will send these reports to REC following sign off from the CI.

13.3. Expenses and Benefits

Patients will not receive any payments for their participation in the study.

14. INDEMNITY AND FINANCE

14.1. Indemnity

This is an NHS-sponsored research study, and the NHS indemnity scheme therefore applies. If there is negligent harm during the study when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. The NHS indemnity scheme does not cover non-negligent harm.

14.2. Financial and other competing interests

This study is supported by an educational grant of £50,000 from FPH. FPH will also supply HumiGard required devices and consumables to complete the study free of charge. FPH interviewed sites through a competitive process to select the most appropriate recipient of the educational grant.

Cedar's work on study design and protocol development was originally awarded to Cedar as a "research facilitation" project from NICE through open competition with other external assessment centres (although NICE now has no role in funding this feasibility study). Cedar will manage the study grant and has created an analysis code to control and account for all income and expenditure in the study.

Study contributors, JT, NR, JC, JW, and GCR report no competing interests that might influence trial design, conduct or reporting, including ownership interests, commercial ties, and non-commercial conflicts.

15. PUBLICATION AND REGISTRATION POLICY

15.1. Trial registration

The study will be registered on clinicaltrials.gov.

15.2. Dissemination plan

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared. Authors will acknowledge that the study was funded by Fisher and Paykel and other contributors will be acknowledged.

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

Study results will be published in a high quality scientific journal on an 'Open Access' basis so that they are freely available to anybody with internet access. Any publication would be in a journal that is peer reviewed and included in major evidence databases such as MEDLINE. The study report will follow the journal's authorship criteria and will acknowledge the contributions made by everyone related to the study.

A lay language report of the study will be made publicly available on the Cedar website.

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Appendix 2: HEAT Patient Information Sheet

Study Number: 19/MAR/7616

PATIENT INFORMATION SHEET

Title of Project: Quality of recovery and perioperative Hypothermia in Elective colectomy patients: A feasibility study of a blinded randomised controlled trial (HEAT study)

We'd like to invite you to take part in our research study. Joining the study is entirely up to you, and before you decide, we would like you to understand why the research is being done and what it would involve for you. We want you to have all of the information you need to help you decide whether or not you would like to take part in the research study and answer any questions you may have.

Please read this information carefully. Please feel free to talk to others about the research study if you wish. The research team are available to answer any questions you have.

The first part of this Participant Information Sheet tells you the purpose of the research study and what will happen to you if you take part.

Then we give you more detailed information about what the research study involves.

You will be given at least 24 hours to go home and to think about whether or not you want to take part in the research study. If you would like to go ahead and take part in the study we will ask you to sign a consent form.

What's involved?

What is the purpose of the research study?

During long surgical procedures under general anaesthetic, patients' body temperatures sometimes drop below 36°C. This is classified as hypothermia. These low temperatures are associated with an increased risk of problems after surgery, such as pain, wound infections, and heart problems. To prevent this, the team caring for a patient in theatre closely monitor his/her temperature and may use techniques to keep the patient warm such as warmed blankets and warmed fluids if needed.

We want to find out whether the HumiGard device used with other usual ways of warming patients, gives better outcomes for patients, compared to standard care alone. To do this, we first need to work out if such a study would be feasible to do. This study aims to look at the feasibility of carrying out a larger study on more patients.

HumiGard device

During keyhole (laparoscopic) surgery, surgeons use carbon dioxide gas to inflate your abdomen so that they can have a better view of your organs. HumiGard is a device which warms and moistens the gas used to inflate the abdomen during surgery to keep patients warm and to prevent the tissues from drying out. It is used together with other standard methods of keeping patients warm. Other studies suggest that the HumiGard device helps patients recover more quickly and wilth fewer problems after surgery. However, we want to study this in more detail.

Why have I been invited to take part in this research study?

You have been invited to take part in this research study because you are due to undergo a keyhole (laparoscopic) operation to remove all or part of your large bowel (colectomy) under general anaesthetic.

Do I have to take part?

It is up to you to decide whether or not to take part in the research study. You do not have to take part. If you do decide to take part you will be given this participant information sheet to keep and be asked to sign a consent form. If you decide to take part you are free to withdraw from the study at any time and without giving a reason. We will keep any data we have collected from you up until the point you decide to withdraw from the study. This will not affect the standard of care you receive. If you decide not to take part, your standard medical care will not be affected.

What will happen to me if I take part?

<u>Before your surgery</u>

If you consent to taking part in this study a doctor will take your medical history before your operation. You will then be asked to fill in a questionnaire about how you are feeling physically and emotionally, and you will be asked to tell us how much pain you are feeling. The questionnaire is called the Quality of Recovery 40 (QoR-40) questionnaire and a Visual Analogue Scale (VAS) pain questionnaire and will take around 5 minutes to fill in.

Before your operation you will be put in one of two groups. To do this, a member of the team caring for you will telephone a department within Cardiff & Vale University Health Board (called Cedar) with some of your details (which cannot be used to identify you). NHS staff at Cedar will use your details to run a computer programme which will put you into one or two groups using random chance.

1) Half of the patients in the study will have an operation using HumiGard (in addition to standard care).

2) Half will have an operation using a standard care only (a HumiGard device will be connected but turned off when you have your operation).

You cannot choose which group you go into and you will not be told which group you are in, but you will have an equal chance of receiving the possible advantages or

disadvantages. The team caring for you in theatre and afterwards will also not know which group you have been put in.

<u>During your surgery</u>

When the surgeon is ready to start your operation, you will be brought to Theatre and given drugs to put you to sleep (anaesthetised). While you are asleep, the staff caring for you in theatre will put a special type of catheter into your bladder through the tube that carries urine out of the bladder. This catheter has a temperature sensor in the tip which will enable staff to measure your temperature more closely for the whole time you are having your operation. The catheter will also drain urine from your bladder. This catheter is similar to the catheter which would be put in place to drain urine from your bladder even if you were not taking part in this research study. Because you will be asleep when the catheter is inserted, you will not feel anything. The catheter will be taken out before you wake up or in the days after the operation which is normal care after surgery.

Once your operation begins, and depending on which group you have been put in, the HumiGard machine then be switched on or will remain switched off.

Other than using the HumiGard device and the special catheter to measure your temperature, your operation will happen in exactly the same way as if you were not taking part in this research study. The theatre team will monitor your temperature at regular time points before, during and after surgery. If needed, you will get warmed fluids and blood products, and you may be warmed in theatre using a forced air warming device or warmed blankets.

<u>After your surgery</u>

After your surgery you will go to a recovery ward and be cared for in the same way as if you were not taking part in this research study.

The day after your surgery a nurse will ask you to fill in a questionnaire about how you are recovering from your surgery and how much pain you are feeling (the same questionnaire as before). The nurse will ask you to fill in the same questionnaire again three days after your surgery. You can talk to the nurse if you feel unable to fill

in the questionnaire or if you have any questions. During your recovery in hospital, the nurses and doctors will record any problems (complications) you experience.

Your doctor will speak to you and decide when you are well enough to go home. Before you go home, you will be given a patient diary to record any problems you may have during the first 6 weeks after your operation and a nurse will arrange to telephone you at home 30 days after your operation. During this telephone call, the nurse will ask you the questions in the questionnaire again and ask if you have experienced any problems and ask you to give your answers over the phone.

At 6 weeks after your operation, your will be called back to hospital to have a routine outpatient clinic appointment with your doctor to see how you are doing and whether you have experienced any problems since your operation. You will be asked to return the patient diary at this point. This appointment would happen even if you were not taking part in this research study.

After this clinic appointment at 6 weeks after your surgery, you will not be asked to do anything else for this research study.

What are the risks of taking part in the research study?

We believe that taking part in this study poses minimal, if any, increased risk to you because HumiGard is approved for use in the UK and is used routinely in some other NHS hospitals. The use of HumiGard is used in addition to standard care.

We will ask you some personal questions about how you are feeling. The inconveniences associated with this research study are related to the time needed to complete questionnaires.

What are the possible benefits of taking part in the research study?

We hope that the HumiGard device will make your recovery more comfortable and safer. However, this cannot be guaranteed. The information collected in the research study will help researchers to decide whether a larger study is possible which may help the NHS to decide whether HumiGard should be used more widely. If we show that HumiGard works, it may have important benefits to patients because they will feel better after surgery and avoid serious complications. It may also have

advantages to the NHS in Wales because patients will be able to go home sooner and less money will be spent treating complications and pain.

What happens if new information becomes available?

Sometimes during the course of a research study, new information becomes available about the treatment or drug that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

What if something goes wrong?

If you are harmed by taking part in this research study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints system will be available to you.

Will my taking part in this research study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the research site will have your name and address removed so that you cannot be identified. If you consent to take part in the research study, your medical records may be inspected by researchers from Cedar (Cardiff & Vale University Health Board), the Sponsor organisation (Cardiff & Vale University Health Board), or by people from regulatory authorities, to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

Information collected about you may be shared with other researchers in the future to support further research, but we will make sure that it does not contain any information which can be used to identify you. It is intended that the results of this

study will be presented at medical conferences, and published in medical journals. Any information which is made public will be completely anonymous and you will not be identified.

How will we protect your data?

Cardiff and Vale UHB is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Cardiff and Vale UHB will keep identifiable information about you 12 months after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information by contacting cav.ig.dept@wales.nhs.uk .

Researchers from Cardiff and Vale UHB will collect information from you and your medical records for this research study in accordance with our instructions. Cardiff and Vale UHB will use your name, NHS number, and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Cardiff and Vale UHB and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in Cardiff and Vale UHB who will have access to information that identifies you will be the team providing your care and people who need to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number, or contact details. Cardiff and Vale UHB will keep identifiable information about you from this study for 12 months after the study has finished.

What will happen to the results of the research study?

The information that we collect from people taking part in this research study (without any personal information which could be used to identify you) will be used decide whether it is possible to carry out a larger study on HumiGard. We will write a report which shows the findings of the study, and we will publish this. We will also put a summary of the results on the Cedar website (http://www.cedar.wales.nhs.uk/).

Who is organising and funding this research study?

The money to enable this research study to take place has come from the company that manufactures the HumiGard device, called Fisher and Paykel Healthcare. The company will not be able to find out who took part in this study. No one involved in your care is being paid personally for including you in this study.

Who has reviewed this research study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed by and given favourable opinion by [XX insert name of REC].

Further information and contact details

If you have any questions, comments or problems regarding this research study please feel free to contact the following individuals:

<u>Advice as to whether you should participate in the research study</u>

If you wish, please feel free to discuss your possible involvement with your GP, family members and friends or any person you feel would give you impartial advice and support.

<u>Who to approach with any questions about this research study</u>

If you have any questions or concerns about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions:

The Chief Investigator for this study in Cardiff is:

Professor Jared Torkington (Consultant Colorectal Surgeon)

University of Wales, Cardiff

Telephone: 02920747747

Email: jared.torkington@wales.nhs.uk

The Principal Investigator for this study in Cardiff is:

Dr Nicola Reeves (Surgical Registrar)

University Hospital of Wales, Cardiff.

Telephone: 02920747747

Email: Nicola.reeves@wales.nhs.uk

The Trial Manager for this study in Cardiff is:

Dr Judith White (Senior Evaluation Scientist)

Cedar, Cardiff & Vale UHB, Cardiff Medicentre

Telephone: 02921 848612

Email: Judith.White3@wales.nhs.uk

If you remain unhappy and wish to complain formally, you can do this through:

Cardiff & Vale University Health Board Concerns Office

Address: Chief Executive, Cardiff and Vale University Health Board Headquarters, University Hospital of Wales (UHW), Heath Park, Cardiff CF14 4XW

Telephone: 029 2074 3301 or 029 2074 4095

Email: concerns@wales.nhs.uk

You will be given a copy of this Information Sheet and your signed consent form to keep.

Thank you for considering taking part and taking time to read this patient information sheet.

Appendix 3: HEAT Consent For

Study Number: 19/MAR/7616

Participant identification number for this trial: _____

CONSENT FORM

Title of Project: Quality of recovery and perioperative Hypothermia in Elective colectomy patients: A feasibility study of a blinded randomised controlled trial (HEAT study)

Please initial box

1) I confirm that I have read the information sheet dated................... (version............) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2) I understand that my participation is voluntary and that I am free to decline to participate or withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3) I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Cardiff & Vale University Health Board or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4) I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.

5) I understand that all staff involved in this study must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information.

6) If I decide to withdraw, or am withdrawn from the study, I agree that the information collected about me up to the point of my withdrawal will be used in the data analysis for this study.

7) I agree to take part in the above study.

Name of Participant (capitals)	Date	Signature
Name of person taking consent	Date	Signature

Appendix 4: Quality of Recovery - 40

Patient Survey (QoR-40)

PART A

How have you been feeling __in the last 24 hours__?

(1 to 5, where : 1 = None of the time and 5 = All of the time)

For example: If you have been able to breathe easily all of the time, you should indicate this by circling the response 5 = ***all of the time*** as shown below:					
	None of the time	**Some of the time**	**Usually**	**Most of the time**	**All of the time**
Able to breathe easily	1	2	3	4	(5)

	None of the time	**Some of the time**	**Usually**	**Most of the time**	**All of the time**
Comfort					
Able to breathe easily	1	2	3	4	5
Have had a good sleep	1	2	3	4	5
Able to enjoy food	1	2	3	4	5
Feeling rested	1	2	3	4	5
Emotions					
Having a feeling of general well-being	1	2	3	4	5
Feeling in control	1	2	3	4	5
Feeling comfortable	1	2	3	4	5

How have you been feeling <u>in the last 24 hours</u>?

(1 to 5, where : 1 = None of the time and 5 = All of the time)

	None of the time	Some of the time	Usually	Most of the time	All of the time
Physical Independence					
Having normal speech	1	2	3	4	5
Able to wash, brush teeth or shave	1	2	3	4	5
Able to look after your own appearance	1	2	3	4	5
Able to write	1	2	3	4	5
Able to return to work or usual home activities	1	2	3	4	5
Patient Support					
Able to communicate with hospital staff (if/when in hospital)	1	2	3	4	5
Able to communicate with family or friends	1	2	3	4	5
Getting support from hospital doctors (if/when in hospital)	1	2	3	4	5
Getting support from hospital nurses (if/when in hospital)	1	2	3	4	5
Having support from family or friends	1	2	3	4	5
Able to understand instructions and advice	1	2	3	4	5

PART B

Have you had any of the following <u>in the last 24 hours</u>?

(5 to 1, where : 5 = None of the time   and 1 = All of the time)

	None of the time	Some of the time	Usually	Most of the time	All of the time
Comfort					
Nausea	5	4	3	2	1
Vomiting	5	4	3	2	1
Dry-retching	5	4	3	2	1
Feeling restless	5	4	3	2	1
Shaking or twitching	5	4	3	2	1
Shivering	5	4	3	2	1
Feeling too cold	5	4	3	2	1
Feeling dizzy	5	4	3	2	1
Emotions					
Bad dreams	5	4	3	2	1
Feeling anxious	5	4	3	2	1
Feeling angry	5	4	3	2	1
Feeling depressed	5	4	3	2	1
Feeling alone	5	4	3	2	1
Difficulty falling asleep	5	4	3	2	1

Have you had any of the following <u>in the last 24 hours</u>?

(5 to 1, where : 5 = None of the time   and 1 = All of the time)

	None of the time	Some of the time	Usually	Most of the time	All of the time
Patient Support					
Feeling confused	5	4	3	2	1
Pain					
Moderate pain	5	4	3	2	1
Severe pain	5	4	3	2	1
Headache	5	4	3	2	1
Muscle pains	5	4	3	2	1
Backache	5	4	3	2	1
Sore throat	5	4	3	2	1
Sore mouth	5	4	3	2	1

Thank you for your assistance.

Please check that all questions have been answered.

Appendix 5: Publications