Comprehensive Study Proposal for Procedures and Protocols

Closed Or Open after Source Control Laparotomy for Severe Complicated Intra-Abdominal Sepsis (the COOL trial): study protocol for a randomized controlled trial

Version 4.8 November 2018

Clinical Trials Registration at;

https://clinicaltrials.gov/ct2/show/NCT03163095

This Protocol has been written to comply with the Standard Protocol Items: Recommendations for Interventional Trials(1-4) and configured to document the World Health Organization Trial Registration Data Set information(5), and is registered with the National Institutes of Health

Signature Page

World Health Organization Trial Registration Data Set

1. **Primary Register: Clinical Trials Registration at;**
   https://clinicaltrials.gov/ct2/show/NCT03163095

2. **Date of Registration: May 22, 2017**

3. **Secondary identifying numbers:**

   a. **Provincial Research Administration Administrative Approval for Research to Proceed June 19, 2017; REB16-1588**
   b. **Conjoint Health Research Ethics Board (CHREB) Ethics ID: REB16-1588**
   c. **WSACS: The Abdominal Compartment Society Multi-Centre trial registration; WSACS 021**

4. **Sources of Monetary Support**
   a. **Unrestricted gift from the Acelity Corporation**
   b. **The Snyder Laboratory, University of Calgary**
   c. **Departments of Critical Care Medicine and Surgery, University of Calgary**
5. **Primary Sponsor: World Society of Emergency Surgery**
6. **Secondary Sponsor: The Abdominal Compartment Society**
7. **Contact for Public Queries:**

   a. **1) Professor Andrew W Kirkpatrick**
   Regional Trauma Services
   University of Calgary
   1403 29 St NW, Calgary, Alberta
   T2N 2T9
   403-944-2888
   403-944-8799 (fax)
   Andrew.kierkpatrick@ahs.ca

   b. **2) Ms Jessica L McKee BA MSc**
   Regional Trauma Services
   University of Calgary

1403 29 St NW, Calgary, Alberta
T2N 2T9
Jlb9@ualberta.ca

8. Contact for Scientific Queries
    a. **1) Professor Andrew W Kirkpatrick**
    Regional Trauma Services
    University of Calgary
    1404 29 St NW, Calgary, Alberta
    T2N 2T9
    403-944-2888
    403-944-8799 (fax)
    Andrew.kierkpatrick@ahs.ca

9. **Public Title; Closed Or Open after Source Control Laparotomy for Severe Complicated Intra-Abdominal Sepsis (the COOL trial): study protocol for a randomized controlled trial**

10. **Closed Or Open after Source Control Laparotomy for Severe Complicated Intra-Abdominal Sepsis (the COOL trial): study protocol for a randomized controlled trial**

11. **Countries of Recruitment: Canada, Italy, Brazil, Unites States of America, Israel, Ireland, Finland, Australia, Chile, China, New Zealand, Turkey, Bulgaria, Peru, Japan, United Arab Emirates, United Kingdom.**

12. **Health Condition Studied: Severe complicated Intra-abdominal sepsis**

13. **Interventions: Closing the fascia or not after the index source control laparotomy in cases of severe complicated intra-peritoneal sepsis. Not closing the fascia will involve the utilization of a temporary abdominal closure (TAC) device utilizing active negative pressure peritoneal pressure (AbThera)**

14. **Inclusion criteria: this study will enroll only those severely ill with intra-peritoneal sepsis. Those patients will be identified by;**

    a) **Hypotension requiring pressors for MAP > 65 AND**

Serum lactate > 2 mmol/litre after resuscitation

<u>OR</u>

b) PIRO 3 or more

<u>OR</u>

c) WSES Score 8 or more

AND

<u>Complicated 2º peritonitis as identified by:</u>

- **(uncontained or unconfined);**
- **Purulence**
- **Feculence**
- **Enteric spillage**

The Exclusion criteria will be;

a) pregnancy

b) confirmed or strongly suspected severe IAH (IAP > 20 mmHg) based on;

i) concerning rise in ventilator pressure assessed by the anesthetist;

ii) increase in IAP measured in the bladder greater than 20 mmHg;

iii) physical inability of the surgical team to close the fascia without "undue pressure";

iv) intra-operatively determined absolute requirement for "Damage Control" surgery including intra-peritoneal packing or non-anatomic post-surgical anatomy (ie surgically placed permanent packing or non-anastomosed bowel ends will not be purposefully closed within intact fascia.

c) there is no intentional of providing ongoing care (ie the treating team wishes to close the abdomen to leave the operating room with the sole

intention of withdrawing aggressive measures and providing only "comfort Care" in the ICU.

d) laparoscopic surgery

e) pancreatitis as the source of peritonitis

f) acute superior mesenteric artery occlusion is the primary pathology

g) current co-enrollment in another investigational study

h) peritoneal carcinomatosis

i) acute presentation with traumatic injury (within 24 hours of injury)

j) age < 18

k) uncontrolled bleeding

15. Study Type: Variable Block Intra-Operatively Randomized Single Blinded Analysis of two treatment arms

16. Date of First Enrollment: planned July 2018

17. Target Sample Size: 550 patients

18. Recruitment Status: Pending

19. Primary Outcomes: 90 Day Survival

20. Key Secondary Outcomes:

- **a. 30-day hospital free days**
- **b. 30-day ICU free days**
- **c. 30-day Ventilator free days**

d. **30-day renal replacement free days**

21. **Role of the Sponsor(s)**

a. **The Acelity Corporation (San Antonio, Texas) provided unrestricted funding for am Investigators Planning Meting in Parma, Italy on November 26 2017. The Acelity Corporation had no input into the design of the study and has no control of the analysis, interpretation, or dissemination of the trial data and results all of which remain under the sole control of the Academic Independent Investigators.**

b. **The Snyder Laboratory from the University of Calgary, will provide direct costs for the conduct of immunological assays including but not restricted to the performance of laboratory studies and the provision of reagents. The analysis, interpretation, or dissemination of the trial data and results of these investigations will remain under the sole control of the Academic Independent Investigators including the Snyder Laboratory.**

c. **The Departments of Critical Care Medicine and Surgery Medicine from the University of Calgary, will provide unrestricted academic funding to support the conduct of the randomized trial. The analysis, interpretation, or dissemination of the trial data and results of these investigations will remain under the sole control of the Academic Independent Investigators including the Department of Critical Care Medicine at the University of Calgary.**

Roles and Responsibilities

Principal Investigator: [1,2,3,4]**Andrew W. Kirkpatrick, MD, FRCSC**

International Steering Commitee

Andrew W Kirkpatrick (Canada)	**Andrew.kirkpatrick@ahs.ca**
Luca Ansaloni (Italy)	**lansaloni@asst-pg23.it**
Federico Coccolini (Italy)	**federico.coccolini@gmail.com**
Massimo Sartell (Italy)	**massimosartelli@gmail.com**
Ari Leppaniemi (Finland)	**Ari.Leppaniemi@hus.fi**
Matti Tolonen (Finland)	**matti.tolonen@hus.fi**
Jose Diaz (USA)	**jdiaz@umm.edu**
Paul Kubes (Canada)	**pkubes@ucalgary.ca**
Derek Roberts (Canada)	**derek.roberts01@gmail.com**
Yoram Kluger (Israel)	**y_kluger@rambam.health.gov.il**
Ernest Moore (USA)	**Ernest.Moore@dhha.org**
Fausto Catena (Italy)	**faustocatena@gmail.com**
Chad Ball (Canada)	**ball.chad@gmail.com**
Bruno Peireira (Brazil)	**drbrunompereira@gmail.com**

Data Safety Monitoring Board

John C Marshall (Toronto, Ontario, Canada)

Peter Faris, PhD, Calgary, Alberta, Canada)

Local Calgary Co-Investigators:

[4,5,6]Paul Kubes PhD
[4]Craig Jenne
[1,2,3,4]Paul McBeth
[2]Derek Roberts PhD
[2,3]Chad G. Ball, FRCSC, MD
[3]Elijah Dixon MD FRCSC
Anthony MaClean MD FRCSC
[2]Christopher Doig MD FRCSC

Data Analysis:

Derek Roberts PhD, Ottawa, Ontario, , Canada

Economic analyses:	**Braden Manns, Calgary, Alberta**
Immunological Analyses	**Craig Jenne, Calgary, Alberta**
Microbiological Analyses	**Federicco Coccolini, Bologna, Italy** **Massimo Sartelli, Italy**

Corresponding Author
AW Kirkpatrick, MD, MHSC, FRCSC, FACS
Department of Surgery
Foothills Medical Centre
1403 – 29th Street N.W.
Calgary, Alberta T2N 2T9
Phone (403) 944-4262
Fax (403) 944-1277

E-mail: Andrew.kirkpatrick@albertahealthservices.ca

Endorsing Scientific Societies

The Abdominal Compartment Society

https://www.wsacs.org

World Society of Emergency Surgery

https://www.wses.org.uk/

Trauma Association of Canada

http://www.traumacanada.org/

Canadian Association of General Surgeons

http://cags-accg.ca/

EXPANDED ABSTRACT

Introduction

Severe complicated intra-abdominal sepsis (SCIAS) is a World-Wide challenge, with high mortality rates, and ever-increasing incidence. Mortality rates range from over 10% to 40% when shock is present. According to the WISS study of the World Society of Emergency Surgery (WSES) patients treated for severe peritonitis with a WISS score ≥ 7 experienced a mortality of 41.7%. Most cases result from secondary peritonitis in which there is a physical disruption of the integrity of the gastrointestinal (GI) tract leading to contamination of the peritoneal cavity. Ultimately, however the resultant organ damage that frequently becomes progressive and self-perpetuating results from auto-amplifying biomediator generation and systemic inflammation. The key principles of treating SIAS are early antibiotic administration and the earliest possible operative intervention to provide source control of GI perforations/disruptions. A further potential therapeutic option may be to utilize open abdomen (OA) management with active negative peritoneal pressure therapy (ANPPT) to remove intra-peritoneal inflammatory ascites and to ameliorate the systemic damage from SCIAS. Recent data from a randomized controlled trial including either severe peritonitis or severe trauma, showed the 30-days mortality appeared different between the AbThera ANPPT open abdomen dressing and non-commercial techniques with a mean mortality between the two groups of 25-30%.

Although there is now a biologic rationale for such an intervention as well as non-standardized and erratic clinical utilization currently, this remains a novel therapy with potential side effects and much clinical equipoise. Thus, the Closed Or Open after Laparotomy (COOL) study will constitute a prospective controlled randomized trial to address this issue.

Significance:

ANPPT has been highly effective in animal models in reducing the local and systemic damage associated with SCIAS. Survival advantages have also been suggested in both

randomized and non-randomized human trials including SCIAS in the inception cohort. However, current guidelines and suggested standard of care recommend not utilizing OA with ANPPT in cases of SCIAS. Thus, high quality data to direct clinical decision making in this highly lethal condition is urgently required, a position espoused by both the Abdominal Compartment Society and the World Society of Emergency Surgery.

Intervention: The study intervention will comprise the randomized decision to either A) primarily close the fascia after laparotomy for SCIAS (CLOSED); or B) leave the fascia open after laparotomy for SCIAS and apply an AbThera temporary abdominal closure (TAC) device (OPEN).

Study Hypothesis:
ANPPT will reduce the mortality of patients with SCIAS undergoing laparotomy for source control from 42% to 30% and will reduce the degree of organ dysfunction in association with systemic reduction in Biomediator activation.

The trial will be pragmatic permitting any procedure leaving the fascia open with AbThera application versus any that technique that formally closes the fascia. For pragmatic reasons in the open abdomen with AbThera application may be supplemented with or without fascial traction at the clinician's discretion.

Primary Outcome: 90-Day survival after laparotomy for SCIAS.

Secondary Outcomes: Secondary outcomes will be considered logistical, physiologic, and economic. Logistical outcomes will include Days Free Of (DFO); ICU, ventilation, renal replacement therapy, and hospital at 30 days from the Index Laparotomy. The physiological secondary outcomes will include change in APACHE II, SOFA, RIFLE, ARDS scores after laparotomy. Biomediator outcomes for centres participating in COOL-Max will consist of the measurement of IL-6 and 10, Procalcitonin, Activated Protein C (APC), High-Mobility Group Box Protein 1, complement factors, and mitochondrial DNA. Economic secondary outcomes will

comprise standard costing for utilization of hospital resources.

Inclusion Criteria: Patients will be randomized intra-operatively once it is determined that severe complicated Severe Complicated Intra-Abdominal Sepsis (SCIAS) is present. Severe will be inferred by the presence of septic shock as defined by the Sepsis-3 definition of those requiring vasopressors to maintain mean blood pressure greater than 65 mmHg and having a serum lactate level > 2 mmol/l **OR** Predisposition-Infection-Response-Organ Dysfunction (PIRO) Score of 3 or more **OR** a WSES Score of 8 or more.
Eligible patients must also be COMPLICATED which will be defined as uncontained (non-abscess) presence of purulent, feculent, or enteric spillage identified at laparotomy

Exclusion Criteria:
Among those undergoing laparotomy for secondary causes of SCIAS patients will be excluded if; a) pancreatitis, b) they are pregnant, c) physical inability of the surgical team to close the fascia without “undue pressure”; d) absolute requirement for repeat laparotomy including intra-peritoneal packing or non-anatomic post-surgical anatomy, e) laparoscopic surgery, f) pancreatitis as the source of peritonitis, g) acute superior mesenteric artery occlusion is the primary pathology, h) current co-enrollment in another investigational study, i) peritoneal carcinomatosis, j) acute presentation with traumatic injury (within 24 hours of injury), k) age < 18, l) uncontrolled bleeding. It should be stated that there is an increasing use of the open abdomen technique after resection with delayed anastomosis for SCIAS, and therefore the screening log of non-eligible patients with this indication will constitute a third important (albeit non-randomized) study group.

Allocation Methodology:
Multicenter prospectively block randomized non-blinded controlled trial. Patients will be identified by the attending acute care surgeons of the participating centers as those undergoing urgent laparotomy for severe sepsis. Randomization will occur intra-operatively with either the preoperative signing of informed consent or under waiver of

consent depending on local Ethical Guidelines. Once COMPLICATED and SEVERE peritonitis is confirmed eligible patients will be randomized to OPEN or CLOSED through direct online randomization over the internet (www.coolstudy.ca). To ensure close balance of the numbers in each of the two treatment groups, permuted block randomization by site will be used. If the operating team is uncertain regarding the potential stratified severity according to either the WSESSSS or CPIRO methods, online decision support software will greatly simplify these calculations regarding any potential enrollment.

Sample size calculations

The COOL trial will overall be powered to detect a significant difference in the primary outcome, 90-day survival. While there is little solid data with which to integrate, the preceding peritoneal VAC study revealed an intention-to-treat 90-day mortality of 21.7% in the ABThera group versus 50.0% in the Barker's vacuum pack group [HR, 0.32; 95% confidence interval (CI), 0.11–0.93; P = 0.04] [60]. This 30% reduction in mortality is likely too dramatic to expect to be practically replicated, and thus, a more conservative effective of 10% reduction in mortality would be appropriate. Thus, given a mortality rate of 33% in the general population of those with severe intra-abdominal sepsis, and considering a power of 80% and an alpha of 0.05, the number needed to recruit in each arm is 275 patients.

Measurements:

Biomediators and standard hematological and chemical measurements to allow for APACHE II and SOFA scoring (WBC, lactate, ABGs, etc) will be measured every 6 hours for the first 24, every 12 hours until 48 hours, at 72 hours, , and at the conclusion of the first week.

The trial will be held on a secure web application for building and managing online surveys and databases (https://projectredcap.org/software/), which is a free, secure,

browser-based application designed to support Electronic Data Capture (EDC) for research studies. The Clinical Research Unit (CRU) in the Cumming School of Medicine at the University of Calgary is a local REDCap host and offers this to the investigators.

Anticipated Study Schedule:

The COOL investigators plan to begin enrollment in November 2018 and hope to complete patient accrual by July 2021 with initial expedited publication of results in January 2022.

COOL-Max versus **COOL-Lite**: The study will be powered to detect a mortality difference between the 2 allocated therapies. Thus, the critical determinant of a potential geographical site being able to participate is ethical approval and willingness to randomly allocate eligible patients to either study protocol. All sites will be requested to obtain serum and peritoneal fluid samples for Biomediator level determination (**COOL-Max**). If a site does not have the laboratory or financial resources however to collect and process study samples for Biomediator analysis they will be eligible to participate without the collection of the Biomediator samples (**COOL-Lite**). **COOL-Mic**: will also be considered regarding understanding the microbiology of secondary peritonitis in the OA arm of **COOL-Lite** and to follow the subsequent modifications in microbiologic flora including and patients in the CLOSED arm who require reoperation. **COOL-Costs** will use information on survival (which can be extrapolated to life expectancy), quality of life, and health-care costs to conduct a full economic evaluation. **COOL-QOL** will assess quality of life in survivors, which will be assessed using the SF-36 and Euroqol EQ-5D-5L at

90 days and 1-year post-enrollment in survivors, either by paper or by phone, which has been used extensively in ICU survivors.

Clinical Trials Registration at;

https://clinicaltrials.gov/ct2/show/NCT03163095

Table of Contents

LIST OF AMMENDMENTS

1) **Dec 2 2017 Inclusion Criteria Amended**

Inclusion Criteria was amended to constitute; a) Hypotension requiring pressors for MAP > 65 (AND) Serum lactate > 2 mmol/liter after resuscitation OR b) a PIRO 3 or more OR c) WSES Score 8 or more; IN ADDITION to Complicated 2° peritonitis (uncontained or unconfined) with Purulence, Feculence, or Enteric spillage.

2) **Dec 2 2017 Inclusion Criteria Amended**

The use of qSOFA as an inclusion criteria was removed as this criteria seems to be overly sensitive in other studies, but it is emphasized that a positive qSOFA is a marker of patients who should be screened for COOL eligibility(6).

3) **Dec 2 2017 Exclusion Criteria Expanded**

The Exclusion Criteria for the study was expanded to include the following list of exclusions;

Patient will need to be excluded from Enrollment and Randomization if;

a) they are pregnant,

b) they have confirmed or strongly suspected severe IAH (IAP > 20 mmHg) based on;

i) concerning rise in ventilator pressure assessed by the anesthetist;

ii) increase in IAP measured in the bladder greater than 20 mmHg;

iii) physical inability of the surgical team to close the fascia without "undue pressure";

iv) intra-operatively determined absolute requirement for "Damage Control" surgery including intra-peritoneal packing or non-anatomic post-surgical anatomy (ie surgically placed permanent packing or non-anastomosed bowel ends will not be purposefully closed within intact fascia.

c) there is no intentional of providing ongoing care (ie the treating team wishes to close the abdomen to leave the operating room with the sole intention of withdrawing aggressive measures and providing only "comfort Care" in the ICU.

d) laparoscopic surgery (no open laparotomy)

e) pancreatitis as the source of peritonitis

f) acute superior mesenteric artery occlusion

g) current co-enrollment in another investigational study

h) carcinomatosis

i) acute presentation with traumatic injury (within 24 hours of injury)

j) age < 18

k) uncontrolled bleeding

4) June 23 2018 AbThera as only ANPPT device

Clarification of AbThera as only acceptable ANPPT device permitted with the study protocol.

5) **June 23 2018 Removal of the requirement for a intra-peritoneal drain**

There will no longer be a requirement for an intra-peritoneal drain in the closed group

6) **June 23 2018 Intention to use the REDCap from the University of Calgary**

The trial will be held on a secure web application for building and managing online surveys and databases (https://projectredcap.org/software/), which is a free, secure, browser-based application designed to support Electronic Data Capture (EDC) for research studies. The Clinical Research Unit (CRU) in the Cumming School of Medicine at the University of Calgary is a local REDCap host and offers this to the investigators.

Amendments – Continued

Introduction

Sepsis is a global health problem that has defied all the technical advances of our time to become an ever-increasing cause of death through-out the world(7). International consensus has concurred that sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. In the most severe cases mortality rates approach 30-40%, and there are an ever-increasing estimated number of cases per year approaching 18 million worldwide per year(8-11). When the focus of infection is located within the abdominal cavity, a particularly severe form of sepsis may result in association with the particular anatomic and physiologic characteristics of the abdominal cavity and the viscera within.

Intra-abdominal sepsis (SCIAS) thus remains the 2nd most common cause of sepsis. The most recent Sepsis-3 Consensus Definitions from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine (12). These newest guidelines, which consider the importance of the pathobiology of sepsis), emphasize the life-threatening nature of organ dysfunction with the view that cellular defects underlie physiological and biochemical abnormalities within specific organ systems. Under this terminology "severe sepsis" becomes superfluous(12, 13). While greatly respecting this concept, surgeons making intra-operative decisions require practical decision making tools, and thus the concepts of severe espoused by the World Society of Emergency Surgery will be retained although interpreted within the newer Sepsis-3 Framework. From a functional clinical perspective, cases have been defined as severe when sepsis is associated with observed organ dysfunction(14-17).

Cases are also defined as complicated when the inflammation or contamination spreads beyond a single organ, causing either localized or diffuse peritonitis(14, 18). SCIAS requires aggressive surgical intervention requiring large inputs of resources from different hospital departments and disciplines. SCAIS typically resulting from secondary peritonitis may be distinguished from other causes of severe sepsis through a requirement for surgical abdominal exploration to surgically address the breech in the gastrointestinal (GI) tract. However, despite advances in diagnosis, surgery, and antimicrobial therapy, mortality rates associated with complicated intra-abdominal infections and intra-abdominal sepsis remain exceedingly high(17). Currently one third or more of patients afflicted with severe non-traumatic intra-peritoneal sepsis will succumb to this disease(19). As recommended by the World Society of Emergency Surgery (WSES), patients with severe sepsis or septic shock of abdominal origin require early hemodynamic support, source control, and antimicrobial therapy(18). Despite such practical recommendations however, SIAS may result in progression to septic shock and multiple organ dysfunction ultimately driven by excessive inflammation. There is great variability in the human immune response to an infectious focus, and some individuals will greatly over-react to an inciting infection with a massive Biomediator storm that propagates multi-system organ failure and death whereas other individuals have little or no response to the same stimuli. Alternatively, the failure to obtain adequate source control of the cause of SIAS has been identified as an independent predictor of mortality in SIAS(20). However, recognizing “failed source control”(21, 22), from a self-propagating Biomediator storm is often difficult or impossible without abdominal re-exploration (relaparotomy).

Given the severity of SCIAS with poor outcomes often controversial surgical therapies have been debated. Despite, the appeal of a single therapeutic "cure, relaparotomy may frequently be necessary to eliminate persistent peritonitis or new infectious foci(23-25). In those randomized to expectant management with fascial closure AFTER laparotomy for intra-abdominal sepsis, 42% still required relaparotomy for suspected or proven persistent peritonitis in a large Dutch multi-centre trial(23). Until recently, two debated surgical approaches to ensuring source control in the peritoneal cavity consisted of "laparotomy on demand – (LOD)" versus "planned re-laparotomy" (PRL)(23, 26, 27). In a planned re-laparotomy strategy, re-laparotomy was routinely performed every 36-48 hours in order to inspect, drain, and lavage the abdominal cavity until the intra-operative findings were negative for peritonitis(23). For the COOL trial this may be more simply designated Re-laparotomy on demand (ROD) offers repeat laparotomy only in those patients in whom the lack of clinical improvement or even clinical deterioration has suggested that on-going peritonitis has resulted from either persistent peritonitis or a new infectious focus(23). The relative merits of either approach have been widely debated for many years, but were best addressed by the large randomized controlled trial (RCT) conducted by Van Ruler et al(23)., which noted no difference in mortality between the two approaches, although the ROL strategy reduced direct medical costs by 23%(23). The equivalence in outcomes, coupled with an apparent cost-savings, has generated Consensus Guidelines that recommended that LOD after laparotomy for peritonitis be adopted as the standard of care(28). Upon critical review the mortality in this RCT of severe secondary peritonitis well illustrates the devastating nature of this

disease with the resultant mortality of approximately 1/3 of all afflicted patients. No matter which cohort is considered, such a dismal outcome demands alternate approaches to attempt to save more lives.

At present, pharmacologic approaches are not the answer. Despite the continuous general improvement in supportive critical care that has occurred over time, there has not been any seminal advances in addressing the central dysregulated inflammation that ultimately causes the organ damage that kills or maims patients with severe sepsis. Attempting to derive pharmacologic therapies for combating post-infective inflammation has proved to be an incredibly expensive and frustrating process so far. There have been literally 100's of failed anti-mediator trials and thus the developmental pipeline for novel therapeutics to treat sepsis has diminished to a trickle with repeated failures and even the one potential drug APC, being taken off the market(29). Over one hundred attempts at blocking single biological response mediators have failed examining the early cytokine storm of sepsis(30). It has become readily apparent from these failed anti-mediator trials, that attempt to neutralize, block, or promote a single biomediator(s) after they have been generated is not currently helpful(30).

Secondary peritonitis ultimately remains a surgical disease. Thus it appears that the only potential options to improve outcomes in SCIAS, are surgical in nature. A controversial, potentially morbid, potentially life-saving technique in surgery is the adoption of a Damage control approach to surgery especially when conducting laparotomy. The rationale and conduct of Damage Control derives from abbreviated, expedited surgical

approaches used in trauma, aiming to arrest hemorrhage, and to control enteric and other biological fluid contamination, using non-definitive, often non-anatomic techniques that require a follow-up operation to complete(31-33). One of the most common Damage-control techniques utilized is not closing the mid-line fascia post-operatively, which be definition constitutes an open abdomen technique(28, 34). The focused aim is to arrest the physiologic insult of severe trauma which most often includes hemorrhage and resultant progressive ischemia. Although not typically due to hemorrhage, SCIAS also induces progressive ischemia and tissue damage that must be reversed as soon as possible for patient survival. Ultimately this organ dysfunction is associated with a progressive oxygen deficit, ongoing organ failure, massive biomediator generation, in a progressive downward spiral. Non-trauma Damage Control surgery thus attempts to break this downward spiral, through emergent surgical intervention, aimed at controlling enteric leakage, removal of ischemic tissue, without regard to completing the formal laparotomy. It is increasingly being reported in uncontrolled series, as another potentially desirable option for the sickest SCIAS patents(14, 21, 22, 35-37).

Use of the OA in severe sepsis may thus allow early identification and increased drainage of any residual infection, control any persistent source of infection, more effectively remove biomediator rich peritoneal fluid, prophylaxis against the abdominal compartment syndrome, and allow for the safe deferral of gastrointestinal re-anastomosis(14). Compared to trauma patients however, patients undergoing OA management for intra-abdominal sepsis have greater risks subsequent to OA utilization, including entero-atmospheric fistula (EAF), intra-abdominal abscesses, and lower rates of

definitive fascial closure(14, 16, 38). Non-trauma patients especially with peritonitis seem to be more prone than trauma patients to develop complications of the OA(39, 40), especially the feared entero-atmospheric fistula (EAF)(40, 41).

Although, case series reporting the use of an OA strategy after non-trauma laparotomies have been reported there are no other contemporary randomized studies to address this critical issue. There has only been one other RCT conducted prior to 2006 that randomized patients to a closed or open strategy, but the techniques of OA management used were inadequate by today's standards noting that the management of an OA has undergone dramatic improvements I technology and technique in recent years. Robledo and colleagues randomized patients severe secondary peritonitis to open or closed strategies after laparotomy, using a non-absorbable polypropylene (Marlex) mesh in a interposed position between the open fascia, thus exposing the underlying bowel to great risk of enterocutaneous fistula(42). The study was stopped at the first interim analysis. Although the mortality differences between the two groups did not reach statistical significance, the relative risks and odds ratio for death were higher with an OA strategy(42). The OA Management technique used in this study(42) would appear to be clearly inadequate by today's standards. Although RCT data comparing techniques is badly needed, meta-analyses conducted by both ourselves(43) and the Amsterdam group(39) have concluded that NPWT treatment appears to be both safest and most effective open abdomen management technique currently available. The commercial NPPT therapy systems now available for OA have greatly reduced the risks of enterocutaneous fistula, and thus greatly increased the safety for the patient.

A more fundamental attribute to consider offering an OA is the fact that OA with newer active NPPT may facilitates the delivery of a new novel therapy to the peritoneal cavity; that of active Negative Peritoneal Pressure therapy (NPPT)(28, 43-45). Both animal(46) and in-silica modeling of these animal studies(47) have shown reduced plasma Biomediator levels with enhanced NPPT in a randomized trial comparing NPPT to passive peritoneal drainage. Systemic inflammation (TNF-α, IL-1β, IL-6) was significantly reduced in the NPPT group and was associated with significant improvement in intestine, lung, kidney, and liver histopathology(46). Although the mortality rate in the NPPT was 17% versus 50% in the control group, but this difference was not statistically significant (P = 0.1859) likely due to the smaller numbers. A larger prospective but non-randomized multi-centre cohort study in critically ill/injured patients requiring an open abdomen, enrolled 280 patients from 20 sites, in whom 168 underwent at least 48 hours of consistent OA therapy(48). The two types of OA therapy possible were enhanced or standard NPPT. Although Biomediator levels were not measured in this trial, the 30 day all-cause mortality rate was 14% in those treated with NPPT and 50% in those with the passive therapy and the OA(48).

Our research group has conducted the only prospective randomized controlled trial addressing this question; the Peritoneal VAC trial which compared a modified Barkers VAC Pac technique to AbThera utilization(49). This RCT, conducted in Calgary, enrolled 45 out of 63 potentially eligible patients over a 15-month period between Sept 2011 and Dec 2012. Patients were enrolled in the operating room after an attending surgeon made the

critical decision that an abbreviated laparotomy was required in critically ill/injured patients. In additional to numerous physiological variables, Biomediator levels were measured every 24 hours in the initial post-laparotomy phase of critical care(49, 50). Although standard Biomediator levels were not statistically different nor was peritoneal fluid drainage, the 90-day mortality rate was improved in the ANPPT group (hazard ratio, 0.32; 95% confidence interval, 0.11–0.93; P=0.04)(49). A valid critique of the Peritoneal VAC trial was that despite the fact that all patients were deemed to need OA therapy by the attending surgeon, there was still a heterogeneous mix of patients including trauma and non-trauma (although the only statistically significant difference in baseline criteria was more chronic disease in the ANPPT patients)(49). Thus, although unexplained, significantly improved survival with the AbThera ANPPT does warrant further exploration as a means of breaking the progression to wards MSOF and death in cases of severe SCIAS. The COOL Investigators thus feel that the potential life-saving potential of ANNPT after laparotomy for SCIAS coupled with global clinical equipoise warrants a carefully conducted randomized prospective study.

The Peritoneal Cavity as a Reservoir for Systemic Inflammation

There is a complex relationship between pressure, ischemia, and inflammation within the peritoneal cavity. Independently the damaged gut seems to act as a continued source of inflammation propagating SIRS and potentiating MODS(45, 51-53). Although

extremely complicated, visceral ischemia further characteristically generates multiple immunological mediators with the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), and interleukin six (IL-6), as well as inhibitive cytokines such as interleukin ten (IL-10)(54-57). Post-operative complications associate with increasing levels of systemic IL-6, and peritoneal TNF- α(56, 58). Jansson and colleagues believe that peritoneal cytokines in humans respond more extensively compared to systemic cytokines, and that a normal postoperative course is characterized by decreasing levels of peritoneal cytokines based on studies of both elective and emergency surgery(59). Overall, the peritoneal cytokine response is much higher than the systemic response in peritonitis(57, 60-62). In a series of rat studies, Hendriks and colleagues demonstrated that peritoneal cytokine levels (especially IL-6, TNF- α, (63)and IL-10) were dramatically different in rats who either survived or succumbed to an intra-peritoneal sepsis model in the 24 hours after cytokine determination(60). Finally, recent work suggests that blood filters designed to hemofiltrate blood endotoxins and cytokines may improve hemodynamics, organ dysfunction and even mortality in the critically ill(64-67).

We believe that if it can be done safely, it is logical to attempt to remove intra-peritoneal Biomediators to potentially ameliorate the local effects and to prevent their being absorbed systematically. Although early uncontrolled work suggested benefit to simple continuous peritoneal lavage after either gross peritoneal contamination in secondary peritonitis or in the setting of necrotizing pancreatitis(68, 69), more structured studies could not confirm such benefits(70-72). Thereafter work focused upon using

hemofiltration to remove inflammatory mediators from the blood which has been associated with decreased hypercytokinemia (as assessed by blood IL-6 levels), early improvements of hemodynamic state and decreased lactate levels(73-75). In an attempt to comprehensively increase efficiency, the potential utility of adding extra-corporeal mediator removal through hemofiltration in addition to continuous peritoneal lavage have been entertained and studied in early models(67).

ANNPT therapy may be a more direct and focused solution to this complicated problem, and one that will be complementary to the other benefits of OA use in the sickest patients. Whether improved post-operative courses can be obtained through this relatively simpler approach of actively removing peritoneal cytokines with a more efficient and comprehensive VAC therapy in humans is therefore a stated secondary but important objective of the COOL-MAX arm of this trial.

Another potential benefit of ANPTT after severe infection may be the attendant decompression of the abdominal compartment and prevention of even modest degrees of IAH. Patients with intra-abdominal infections are at risk of elevated IAP both as a result of the primary intra-peritoneal disease, as any large fluid resuscitation often required to maintain organ perfusion(76-78). Recent studies have demonstrated a high prevalence of IAH following aggressive resuscitation of septic patients. Intra-abdominal hypertension is present in as many as 80% of septic medical and surgical ICU patients(79, 80). Reintam also reported that septic patients with IAH had a 50% rate of mortality compared to 19% without IAH, making IAH a significant marker for an increased risk of death(81). Within

our own institution, rates of IAH were over 87% of septic ICU patients and further 61% of these patients had severe IAH at levels commensurate with ACS, despite the fact that IAP was only measured in 10% of the patients in whom guidelines recommend monitoring(82). Although direct translation to humans is uncertain, even modest degrees of IAH (often clinically ignored) have been found to have profound far reaching effects on propagating multiple organ failure in animals with ischemia/intra-peritoneal infections(83-85).

This proposed study will thus address critical issues concerning a disease process that currently kills more than one-third of those afflicted, answering an urgent need for randomized controlled trial raised by other authors after reviewing this problem(35, 86).

Intervention

Patients will be randomized intra-operatively once it is determined that complicated SCIAS is present. SIAS will be defined and denoted by the presence of **SEVERE** due to the presence of any organ dysfunction (septic shock) or identification by a World Society of Emergency Surgery Sepsis Severity Score ≥ 8, or a Calgary Predisposition-Infection-Response-Organ Dysfunction Score ≥ 3 AND **COMPLICATED** due to presence of uncontained purulent, feculent, or enteric spillage.

Once this eligibility is confirmed they will be randomized to either;

Re-Laparotomy on Demand (ROD) – primary closure of the fascia

OR

Open Abdomen with AbThera (**OA**) – the fascia will not be closed, and a AbThera ANPPT device will be utilized inside the peritoneal cavity.

Primary Closure and Re-Laparotomy on Demand after

This strategy will consist of primary closure of the fascia. There will be no formal requirement for relaparotomy. Post-operative diagnostic imaging, and all other aspects of post-operative care shall be at the discretion of the treating critical care/surgical teams. Any decision to perform a relaparotomy will be at the discretion of the treating critical care/surgical teams, and in no way mandated by this study, although this will constitute a study outcome. If at any subsequent laparotomy the attending and responsible surgeon selects an open abdominal strategy as being in the patient's best interest this will be

permitted and the outcomes will be analyzed considering the original intention to treat allocation at enrollment. Any application of any wound suction or negative pressure device to the soft tissue above the fascia will be permitted but will not change the understanding that the fascia has been formally closed and this is a CLOSED abdominal patient.

Open Abdomen with AbThera active Negative Pressure Peritoneal Therapy

The time that the AbThera TAC dressing will be left in place, will be left to the discretion of the attending surgeon, but revised practice guidelines (**Appendix C**) mandate either formal abdominal closure or dressing change at 24-72 hours from placement at the Foothills Medical Centre. This is congruent with International Guidelines for TAC changes, although it is understood there is little scientific evidence guiding these practices(14, 18, 87). The primary outcome of mortality will analyzed based on the initial allocated study arm regardless of the duration of TAC application, however, secondary outcomes involving Biomediator outcomes and intra-peritoneal drainage will be assessed on a Per-Protocol basis

Inclusion Criteria

This study will enroll only those most severely ill with intra-peritoneal sepsis who have septic shock on the basis of intra-peritoneal sepsis. Those patients will be identified by;

Septic Shock or Sepsis with adverse prognosticators identified by;

a) **Hypotension requiring pressors for MAP > 65 (AND) Serum lactate > 2 mmol/litre after resuscitation**

   OR

b) **Predisposition-Infection/Injury-Response-Organ Dysfunction (PIRO) Score 3 or more(88)**

   OR

c) **World Society of Emergency Surgery Sepsis Severity Score 8 or more(15-17)**

IN ADDITION TO

- **Complicated 2^{o} peritonitis (uncontained or unconfined) with Purulence, Feculence, or Enteric spillage.**

Rationale for Inclusion criteria

Deriving the ideal inclusion criteria to identify the study population at risk of adverse outcomes, but also most likely to potentially benefit from the trial intervention proved challenging. Thus the COOL investigators extensively reviewed the global literature and modelled outcomes on surrogate populations to derive an universally agreed-upon inclusion criteria that has been explained in detail in a separate manuscript(6).

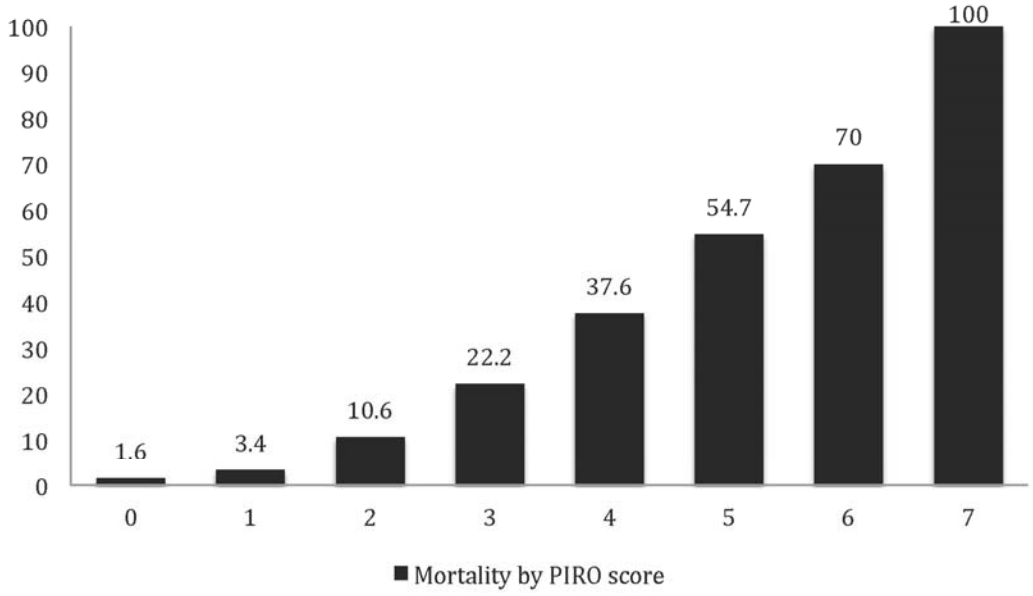
The combination of hypotension requiring vasopressor therapy and serum lactate greater than 2 mmol/l was found to have the best performance out of a number of different

combinations of variables and either indicator alone when extensively review by the Guidelines Task force who crate the new revised Third Consensus Definitions for Sepsis and Septic Shock. This combination of variables demonstrated a 42.3% mortality when evaluated using the Surviving Sepsis Guidelines(12, 13). These indicators will thus reliable indicate patients in septic shock who are at a high risk of death. It is relevant to note that vasopressor dependent hypotension equates to a cardiovascular SOFA component score of $\geq$ 2(89, 90). It is also pertinent that the new defined lactate threshold of 2 mmol/litre was found to perform as well as earlier cutoffs that were higher in identifying those at a high risk of death, recognizing the serum lactate is a proxy for cellular metabolic abnormalities(13).

The predisposition, infection, response and organ dysfunction (PIRO) staging system was designed as a stratification tool to deal with the inherent heterogeneity of septic patients(91). The concept of the predisposition, infection, response, and organ dysfunction (PIRO) scoring system was recommended at the 2001 International Sepsis Definitions Conference to improve the traditional classification of sepsis(92, 93). The PIRO system is an ideal staging system that incorporates assessment of premorbid baseline susceptibility (predisposition), the specific disorder responsible for illness (infection), the response of the host to infection, and the resulting degree of organ dysfunction. The four components of the PIRO system cover multiple known independent factors that may influence the onset, development, and outcome of sepsis(91). PIRO scores have been developed in patients with severe sepsis (94), community acquired pneumonia (CAP) (95) and ventilator associated pneumonia (VAP) (96). They were recently evaluated in a population of

septic patients (25% intra-abdominal sepsis) seen in the emergency department and the PIRO score had a significant improved area under the curve than both the APACEHE II and MEDS score(91). Most recently, a specific intra-abdominal sepsis PIRO score has been created in Calgary(88). In this population the PIRO score showed consistent mortality discrimination outperforming both APACHE II and SOFA(88). The mortality rate by PIRO score was 37.6% for a PIRO of 4 and 54.7% for a PIRO of 5. In a test population with SCIAS requiring source control laparotomies, combining the Sepsis-3 septic-shock definition and WSESSS ≥ 8 increased detection by screening tools to 80%, and including a CPIRO score ≥ 3 increased this to 82.8% (Sensitivity-SN; 83% Specificity-SP; 74%(6). Thus, patients will be recruited into the COOL study if they have a PIRO score of three or more as discussed in the Inclusion Criteria manuscript(6). Use of the PIRO Score is Fully Described in **Appendix A**

Figure 1. Mortality rate by PIRO score



The final criteria that may be used to identify patients with intra-abdominal sepsis at a high risk of death is a World Society of Emergency Surgery Sepsis Severity Score of 8 points or more, which also indicates a high risk of death. The World Society of Emergency Surgery (WSES) first derived a Sepsis Severity Score derived from data and experience obtained from a global prospective observational study (CIAOW Study)(16, 97). To derive this score, risk factors for death during hospitalization were evaluated and review by an expert international panel. The most significant variables, adjusted to clinical criteria, were used to create a severity score for patients with Complicated Intra-abdominal infections (cIAIs) including clinical conditions at admission (severe

sepsis/septic shock), the origin of the cIAIs, the delay in source control, the setting of acquisition and any risk factors such as age and immunosuppression.

Table 5 WSES sepsis severity score for patients with complicated Intra-abdominal infections (Range: 0–18)

Clinical condition at the admission	
• Severe sepsis (acute organ dysfunction) at the admission	3 score
• Septic shock (acute circulatory failure characterized by persistent arterial hypotension. It always requires vasopressor agents) at the admission	5 score
Setting of acquisition	
• Healthcare associated infection	2 score
Origin of the IAIs	
• Colonic non-diverticular perforation peritonitis	2 score
• Small bowel perforation peritonitis	3 score
• Diverticular diffuse peritonitis	2 score
• Post-operative diffuse peritonitis	2 score
Delay in source control	
• Delayed initial intervention [Preoperative duration of peritonitis (localized or diffuse) > 24 h)]	3 score
Risk factors	
• Age>70	2 score
• Immunosuppression (chronic glucocorticoids, immunosuppresant agents, chemotherapy, lymphatic diseases, virus)	3 score

This predictive system carries the advantage of having been derived in one population of critically ill septic patients and validated in another world-wide population, giving great generalizability to the scoring system. In general, a score above 5.5 was the best predictor of mortality, but scores of 8 or more had a 41.7% mortality(15), very comparable to other groups of patients presenting with septic shock. The WSESSS is further described in **Appendix B.**

Exclusion Criteria

Patient will need to be excluded from Enrollment and Randomization if;

a) they are pregnant,

b) they have confirmed or strongly suspected severe IAH (IAP > 20 mmHg) based on;

i) concerning rise in ventilator pressure assessed by the anesthetist;

ii) increase in IAP measured in the bladder greater than 20 mmHg;

iii) physical inability of the surgical team to close the fascia without "undue pressure";

iv) intra-operatively determined absolute requirement for "Damage Control" surgery including intra-peritoneal packing or non-anatomic post-surgical anatomy (ie surgically placed permanent packing or non-anastomosed bowel ends will not be purposefully closed within intact fascia.

c) there is no intentional of providing ongoing care (ie the treating team wishes to close the abdomen to leave the operating room with the sole intention of withdrawing aggressive measures and providing only "comfort Care" in the ICU.

d) laparoscopic surgery

e) pancreatitis as the source of peritonitis

f) acute superior mesenteric artery occlusion

g) current co-enrollment in another investigational study

h) carcinomatosis

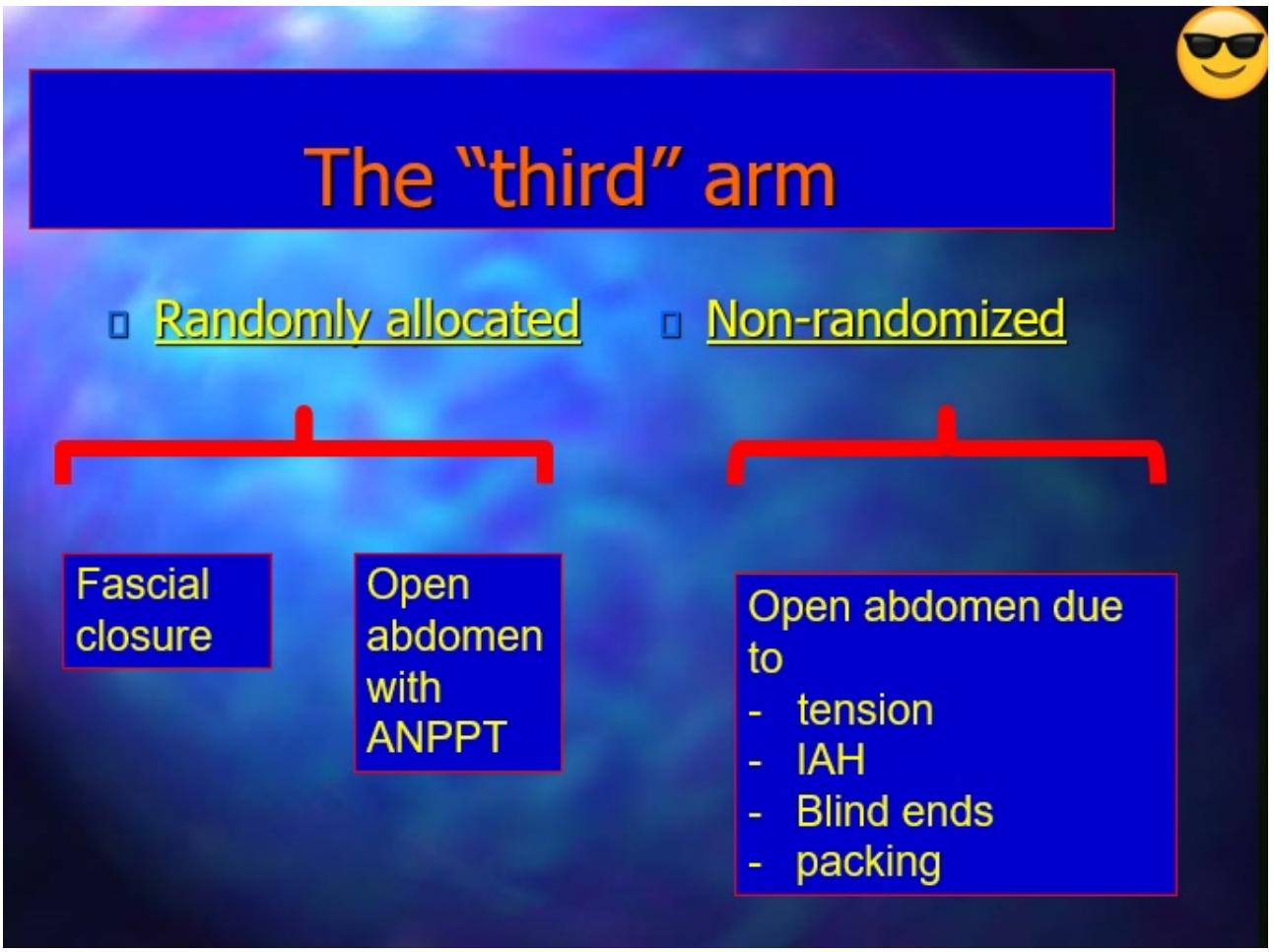
i) acute presentation with traumatic injury (within 24 hours of injury)

j) age < 18

k) uncontrolled bleeding

Study Recruitment Log and Non-Randomized Patients

In current world-wide clinical practice, it is likely that the most common reason for non-eligibility will be the surgeon-based decision to resect a hollow viscus and due to the perceived critical nature of the patient decide not to re-anastomose the bowel but to instead perform Damage Control and return the bowel ends into the peritoneal cavity without a diverting stoma. As this is an absolute indication for a future re-operation these patients will be ineligible for randomization. Although some influential authors are highly critical of this practice [81], others recognize or even recommend this approach(21, 35, 86, 87, 98, 99) . This group of patients will be expected to constitute a significant and important population of very sick patients who although non-randomized and excluded with constitute a "defacto third arm" requiring follow-up and outcome description. Participating COOL institutions will be expected to submit basic demographic and outcome data on all in-eligible patients study patients who had source control laparotomies for SCIAS and subsequently were managed with an open abdomen. The basic data variables required for these patients is outlined in **Appendix G Data variables for Ineligible Open Abdomen Cases with SCIAS**. Participating institutions will be encouraged to participate in the International Registry of the Open Abdomen (IROA - https://www.clinicalregisters.org/IROA/) which will facilitate collection of non-randomizable cases of OA for SCIAS to augment the COOL study results, but also to provide a global picture of OA management and outcomes.


The "third" arm
Randomly allocated
Non-randomized
Fascial closure
Open abdomen with ANPPT
Open abdomen due to
- tension
- IAH
- Blind ends
- packing

Biomediator Measurements

Summarized Biomediator Samples for COOL-MAX centres

- Will be drawn from the serum

Timings
- Enrollment in the OR
- 6 hours post enrollment
- 12 hours post enrollment
- 18 hours post enrollment
- 24 hours post enrollment
- 36 hours post enrollment
- 48 hours post enrollment
- 72 hours post enrollment
- 168 hours (7 days) post enrollment
- 336 hours (14 days) post enrollment
  720 (30 days) 18 hours post enrollment

After enrollment is confirmed blood will be drawn from an existing arterial or venous line in the OR (being designated the "enrollment sample"). Thereafter the same quantity of blood will be drawn every six hours for the first 24, every 12 hours threader till 48 hours, again at 72 hours, at one week, and finally at 30 days post enrollment. Fifty (50) ml of peritoneal fluid will also be collected from the abdomen at the same time as serum samples are obtained while the abdomen is either open or while an intra-peritoneal drain is present. Blood samples will be taken from existing vascular catheters and all fluids will essentially be "waste" fluids that would be discarded normally, so there will be of absolutely no discomfort or inconvenience to the patient.

Study Hypothesis

The Null hypothesis will be that there will be no difference in mortality when an Open Abdomen Management Strategy administering active negative pressure peritoneal therapy is utilized compared to a primary fascial closure strategy in patients suffering severe intra-peritoneal sepsis.

Study Setting

The study will be conducted in operating rooms around the world where critically ill patients with severe complicated intra-abdominal sepsis undergo source control laparotomies. The lead study Centre will be the Foothills Medical Centre, a Quaternary Care academic Medical Centre in Alberta, Canada serving a referral base of approximately 2 million people. Potential patients will be identified in the emergency departments, in-patients wards, and critical care units of this Academic referral Centre, but the true eligibility will only be confirmed in the operating room during the conduct and near completion of laparotomy. Other recruiting sites will be world-wide and will include academic centers as well as community hospitals willing to provide full clinical follow-up

Site Eligibility

Participating Institutions will be expected to be familiar with the proper utilization of the AbThera device, and to undergo an in-service with a content matter expert on AbThera device utilization prior to site participation. For both arms of the trial it will be expected that Attending surgeons are involved in either the direct supervision and/or inter-operative participation with either facial closure or temporary abdominal closure in order to be an acceptable participating Centre. Further criteria required of potential participating centers is presented below**. All**

participating surgeons will be required to view a short briefing video and thereafter pass a knowledge transfer-test of proper ABThera placement.

Minimal System Resources Required for Site Participation in COOL-LITE

- **Designated Primary Investigator** presumably with an Academic Affiliation willing to take overall medical/ethical/academic responsibility for the conduct of the study
- **Ethical Approval –** by the appropriate local ethics committee with oversight of the participating Institution
- **Site Investigators/willing local surgeons** with the responsibility of caring for those with SIAS and thus the ability to recruit patients
- **Internet Access –** either within or closely available to the operating theatre to allow on-line randomization of patients during laparotomy
- **AbThera Negative Peritoneal Pressure Therapy (NPPT) Dressing Availability** for those randomized to OPEN
- Familiarity with the application of the AbThera ANPPT device and a willingness to undergo training and in-service on the safe utilization of the AbThera ANPPT device
- **Study Personnel/Investigator** capable to record and compile case record and submit to the Central Study Registry
-

Full System Resources Required for Site Participation in COOL-MAX

- Above and also;
- Study Personnel capable of obtaining blood samples
- Laboratory capability to store blood at – 80 °C fluid till study completion and send to Calgary for analysis

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Full System Resources Required for Site Participation in COOL-MIC

- Medical Microbiology Laboratory capable of basic microbiology studies
- Medical Records and Information Processing capable of providing microbiology results for study analysis

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Full System Resources Required for Site Participation in COOL-Cells

- **Geographic proximity to Calgary**
- Ability to collect fresh peritoneal fluid and to rapidly ship to the Snyder Laboratory for time-of-flight mass spectrometer

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Full System Resources Required for Site Participation in COOL-Costs and COOL QOL

- Ability to provide administrative and microcosting data

Full system resources required for site participation in COOL-QOL

- Ability to administrator SF-36 and Euroqol EQ-5D-5L at 90 days and 1-year post enrollment in all survivors

Interventions

For those randomized to **CLOSED**, the fascia will be closed at the index source control laparotomy. CLOSED is defined as the primary approximation of the fascia using whatever suture desired in either interrupted or continuous fashion. There is no stipulation on any necessity to actually close the skin, or on whether a skin suction device is utilized, all of which will be at the discretion of the treating clinical team. There will be no prohibition preventing the treating clinical team from re-opening (Re-opening on Demand), if the patient's best interest is deemed to be served by re-laparotomy, although this decision will constitute a study outcome.

For those randomized to **OPEN**, the fascia will NOT be closed and an AbThera active pressure negative peritoneal pressure (ANPPT) device will be placed following Manufacturer's directions and/or Institutional protocols. Participating Institutions will be expected to be familiar with the proper utilization of the AbThera ANPPT device, and undergo an in-service with a content matter expert on the AbThera ANPPT utilization prior to site participation. The addition of any other fascial tension device such as mesh-mediated fascial closure(100-103), or other fascial tension devices(104) will be permitted as long as an AbThera ANPTT device is utilized within an abdominal cavity without fascial closure. There will be no requirement or stipulation on how long the abdomen must be left open for in the OPEN arm, other than good practice recommendations recommend attempts to close the abdomen as soon as safely possible(28), and ideally within the first one to two weeks of hospitalization(105, 106).

For both arms of the trial it will be expected that Attending surgeons are involved in either the direct supervision and/or inter-operative participation with either facial closure or temporary abdominal closure in order to be an acceptable participating Centre.

Concomitant Care

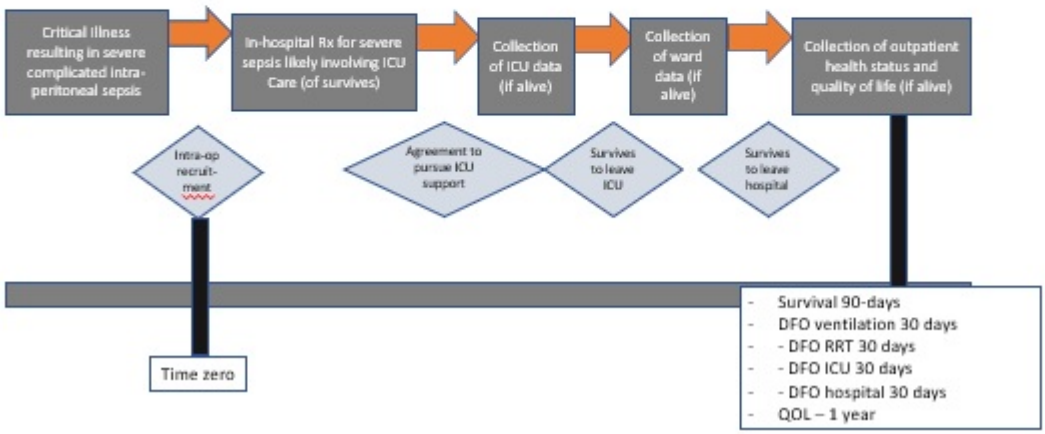
Other than the randomly allocated decision to either primary close or leave the abdomen open after source control laparotomy, there will be no mandated or enforced supportive care requirements for on-going clinical care of enrolled patients enrolled in the COOL trial recognizing the many and multiple controversial aspects of critical care support. It will therefore be assumed that the random nature of patient allocation will ensure patients are provided equivalent post-surgical care in either arm. Thus, while clinical care will not be rigidly mandated after intra-operative randomization, institutions requesting clinical guidance will be referred to the World Society of emergency Surgery's Consensus Management Guidelines on Open Abdomen Management(107).

Primary Outcome Measure

The primary outcome will be 90-day survival which will be measured using Cox proportional hazards models were used to calculate hazard ratios (HRs) for mortality.

Participant Time-line

Participant Time-line for COOL Recruitment



Participants will be recruited in the operating room when it is determined that they have complicated intra-peritoneal contamination in addition to severe sepsis. This will be time zero for study recruitment. For those centers participating in COOL-MAX involving the collection of serum and peritoneal fluid samples may potentially be collected at 6, 12, 18, 24, 36, 48, 72, 168, 336, and 720 hours after enrollment. A potential economic analysis of the costs involved in treating severe intra-abdominal sepsis may also collect resource-utilization data on each enrolled patient but no direct patient contact will be required for this other than a one-time ascertainment of ethical permission to access health care administrative data-bases for their costing data.

Sample Size Calculations

The peritoneal VAC study revealed an Intention-to-treat 90-day mortality of 21.7% in the ABThera group versus 50.0% in the Barker's vacuum pack group [HR, 0.32; 95% confidence interval (CI), 0.11– 0.93; P = 0.04]. This 30% reduction in mortality is likely too dramatic to expect to be practically replicated and thus a more conservative effective of 10% reduction in mortality would be appropriate. Thus, given a mortality rate of 33% in the general population of those with severe intra-abdominal sepsis N = 275/arm.

Intention to Treat

The analysis of the primary outcome, mortality will be on an intention to treat basis related to the allocation of initial intra-operative therapy.

Planned Sub-Group Analysis

There will be a planned subgroup analysis of the actuarial mortality stratifying patients into those with and without the presence of septic shock during the first 48 hours after onset of peritonitis (if known and 24 hours before and 24 hours after 1st laparotomy if not known), versus patients deemed eligible due to the CPIRO
and WSESSS score thresholds.

Statistical Analyses:

The effectiveness of randomization will be displayed through a detailed presentation of patient demographic characteristics. The analysis of the primary outcome, mortality, will be on an intention to treat basis related to the allocation of initial intra-operative therapy. There will be

a planned subgroup analysis of the actuarial mortality stratifying patients into those with and without the presence of septic shock (defined as Sepsis-3 Consensus Guidelines) during the first 48 hours after onset of peritonitis (if known and 24 hours before and 24 hours after 1st laparotomy if not known). Secondary Outcomes are described below. For the comparison of health care costs, we will use established methods to enable comparisons of mean costs, as these are easily interpretable and relevant to health care payer. We will include the full cost of the intervention, as well as the hospital costs for the cost categories noted above (for both groups) and will use non-parametric bootstrap estimates to derive 95% confidence interval (95% CI) and mean cost differences between the treatment arms. We will use 1000 bias-corrected bootstrap replications (including sampling with replacement from the original data) to estimate the distribution of a sampling statistic to derive 95% confidence intervals. In sensitivity analyses, we will also use generalized linear models to compare total costs across groups, considering three family distributions (Gaussian, inverse Gaussian and gamma) and specifying two link functions (identity and log).

Interim Analysis

There will be a single interim analysis planned after the recruitment of 275 patients, which will analyze the difference in 90 days mortality between allocated therapies. The COOL Investigators appreciate the general reluctance to stop randomized trials early due to benefit, due to the frequent over-estimating of treatment effects(108-110). Despite this, it is possible that the COOL trial will be great over-powered as although the Sample size calculations are based on the best outcome data from randomized trials of ANPPT, this is still inferential as there is no previous relevant data with which to accurately guide such calculations. Thus, if a profoundly

significant difference is found ($p < 0.01$) the trial will be stopped, otherwise it will continue to full recruitment.

Known Risks and Benefits

Patients who suffer from SCIAS are an extremely sick cohort of patients with a high chance of dying no matter what therapies are offered. With SCIAS mortality approaches 30-40% when shock is present (12, 15, 111), although this may be 80% in the developing world (7). Therefore, the greatest risk if no therapy is offered is death. After a source control laparotomy for SCIAS, if a closed abdominal strategy is chosen the primary risks to the patient are induction of the abdominal compartment syndrome which is a highly lethal condition regardless of whether rescue open abdomen therapy is utilized(82, 112, 113). Patients whose abdominal cavity is formally closed after source control laparotomies are also at risk for inadequate source control of intra-peritoneal sepsis which is perceived to be a key determinant of mortality in SCIAS(20). Further, if an abdominal cavity is formally closed in the presence of severe IAH, abdominal perfusion is compromised and late abdominal wall failure with massive ventral hernia is more common. In those patients treated with an open abdomen traditionally accepted risks include higher rates of enteric fistulae, intra-abdominal abscess, and anastomotic breakdown, although the newer TAC devices such as the AbThera selected for this research project have not demonstrated these traditional risks in the most contemporary reports(39, 49, 114).

The potential benefits of a closed abdominal strategy are an earlier definitive abdominal closure which if uncomplicated may allow patients to avoid critical care unit therapy solely due to the presence of an open abdomen. The potential benefits of an open abdomen strategy employing ANPPT are mitigation of progressive multi-system organ dysfunction, avoidance of the abdominal compartment syndrome, and reduced hospital and critical care unit stays due to overall better outcomes.

Ethical Concerns

The Hippocratic Oath requires physicians to "consider for the benefit of my patients and abstain from whatever is deleterious and mischievous" and to "give no deadly medicine to any one if asked, nor suggest any such counsel". Thus philosophically, as there is complete clinical equipoise concerning the treatment of SCIAS with or without the OA technique, the COOL Investigators feel a moral imperative to provide the best evidence to counsel bedside critical care physicians and surgeons(115). The COOL trial is currently approved by the Conjoint Research Ethics Board of the University of Calgary (REB-16-1588) to proceed with a delayed consent process given the time-sensitive critical nature of decision making. Research ethics will vary through-out the world and it is anticipated that various local policies concerning community consent, waiver of consent, or informed consent of significant patient proxies will vary among the local approaches to ensure the COOL trial is performed to the highest ethical standards on a Global basis. All participating Institutions will thus be required to obtain Ethical Approval appropriate and applicable to their Institutions. This paradigm will involve the minimum standard of formally recognizing that the COOL study will be conducted in accordance with Good Clinical Practice Guidelines and applicable regulatory requirements in all health care systems at all times.

Subject Withdrawal Criteria

All subjects recruited into the COOL trial will at all times be permitted to withdraw from the study without any impact on their clinical care. The exact mechanism for this will depend on the ethical procedures in each participating health region. For instance, in Calgary where patients will be recruited intra-operatively under a delayed consent mechanism the initial intra-

operative treatment allocation cannot be changed. However, patients can request a specific ongoing therapy if they regain capacity and ultimately have the absolute decision on whether to provide delayed consent to allow their own data to be included in the study outcomes or not.

Adverse event collection and procedures for reporting

All serious adverse patient events with any perception of being related to study allocation will be reported to an independent Data Safety Monitoring Board (DSMB) chaired by Professor John Marshall from the University of Toronto (**Appendix H**). While Investigators will be encouraged to report any events, they are concerned about mandatory reporting events will include unexpected deaths, enteroatmospheric fistulae, overt abdominal compartment syndrome, and relaparotomy in formally closed abdomens.

Accessing source data and both routine and random audits and inspections

It will be a requirement of all participating COOL centres that they permit both routine and random audits of their medical records, study procedures, and data handling if requested either from the University of Calgary as the Study Administrating Centre, or the sponsor if requested. Such audits will be at the cost of the requesting party and will endeavor not to prove an administrative burden on the participating centre.

Data Handling Procedures

All patient information will be treated with confidentially and no information will be released that will allow any individual patient identification. After consulting with the University of Calgary legal department the COOL investigators have been instructed that the uploading of

data for the COOL project must be performed on a University of Calgary server. This is required for data management issues and privacy agreements with data sharing. The main centre for the study (the University of Calgary, PI Professor Andrew W. Kirkpatrick), must remain in control of the data at all times. Understanding these issues means that COOL cannot have multiple sites upload data to servers that are not being monitored by the initiating site for the study. The COOL investigators have been informed that this is not only an issue for the University of Calgary, but would hinder ethics approval through most of the sites in North America, Europe, and Globally. The COOL investigators will address these concerns by using the REDCap. REDCap (Research Electronic Data Capture) is a secure web application for building and managing online surveys and databases (https://projectredcap.org/software/). It is a free, secure, browser-based application designed to support Electronic Data Capture (EDC) for research studies. The Clinical Research Unit (CRU) in the Cumming School of Medicine at the University of Calgary is a local REDCap host and offers the support and use of the service to CSM and AHS personnel. The COOL investigators will not only be able to create and design projects either online or offline. But this software also allows automated export procedures to Excel and common statistical packages (SPSS, SAS, Stata, R), as well as a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields. As discussed earlier data on the non-randomized excluded patients will be also be collected in the IROA database and shared in confidential non-identifiable manner with the COOL database stored on REDCap at the University of Calgary.

At all times the Industry sponsor will be able to inspect, verify, and audit the COOL data. After completion of the data collection the sponsor will be informed of the data and study

findings, however the decision to publish and final interpretation of the data will be at the full discretion of the authors.

Secondary Outcomes

There will be a number of secondary outcomes and potential COOL sub studies

Overview of Study Outcomes

	Indicator	Timeline
Primary Outcome	**Mortality**	90 days
Secondary Outcomes		
Logistical	Days free of ICU	30 days
	Days free of ventilation	30 days
	Days free of RRT[1]	30 days
	Days free of hospital	30 days
Physiological	APACHE II[2] scores	up to 30 days[3]
	SOFA[4] scores	up to 30 days[3]
	Pa02/Fi02[5] ratios	up to 30 days[3]
	ARDS[6] scores	up to 30 days[3]
Safety	enterocutaneous fistula	30 days
	ACS[7] and/or severe IAH[8]	30 days
	Intra-abdominal abscess	30 days
Biological	Il-6	up to 30 days[9]
	IL-10	up to 30 days[9]
	Procalcitonin	up to 30 days[9]
	Activated Protein C	up to 30 days[9]
	High Mobility Group Box Protein 1	up to 30 days[9]
	Mitochondrial DNA	up to 30 days[9]
	C3a and C5a	up to 30 days[9]
Microbiological	intra-abdominal microbiological cultures	up to 30 days[10]
Mass Cytometry	intra-peritoneal inflammatory cells	up to 30 days[11]
Economic	Micro-costed resource consumption	1 year
Quality of Life	Euroqol EQ-5D 5L	90 days and 1 year
	SF-36	90 days and 1 year

Legend: [2]RRT = Renal Replacement Therapy; [2]Acute Physiology and Chronic Health Evaluation Score; Measured daily using the worst value of that day; [4]SOFA = Sequential organ Failure Assessment; [5]$Pa0_2/Fi0_2$ = Partial pressure of oxygen over inspired fraction of oxygen; [6]ARDS = Acute Respiratory Distress Syndrome; [7]ACS = Abdominal Compartment Syndrome; [8]IAH = Intrabdominal Hypertension; [9]measured as per Table 3.; [10]measured as clinically

indicated by the treating team; [11]measured on intra-peritoneal fluid obtained in Calgary

Per-Protocol Biomediator Profile Outcomes

Analysis of Biomediator Profile Kinetics/Dynamics will be on a "per-protocol basis" with per-protocol considered the delivery of at least 24 continuous hours of ANNPT for those randomized to OPEN and at least 24 hours in the first 48 hours post enrolment of fascial closure in those randomized to CLOSED. In addition for those patients recruited in Calgary (and potentially other geographically close sites in Alberta) mass cytometry specimens will be collected from the peritoneal fluid when possible. Mass cytometry is a mass spectrometry technique based on inductively coupled plasma mass spectrometry and time of flight mass spectrometry used for the determination of the properties of cells (cytometry). In this approach, antibodies are conjugated with isotopically pure elements, and these antibodies are used to label cellular proteins. Cells are nebulized and sent through an argon plasma, which ionizes the metal-conjugated antibodies. The metal signals are then analyzed by a time-of-flight mass spectrometer. The approach overcomes limitations of spectral overlap in flow cytometry by utilizing discrete isotopes as a reporter system instead of traditional fluorophores which have broad emission spectra

i) Systemic inflammatory marker levels (e.g. TNF-α, IL-1β, IL-6, IL-10)

ii) Peritoneal fluid inflammatory marker levels (e.g. TNF-α, IL-1β, IL-6, IL-10)

iii) Determination of the type and activation status of inflammatory cells present in the

peritoneal fluid.

iv) Measurement of the activation potential of peritoneal fluid CyToff (Mass Cytometry)

v) Peritoneal fluid drainage volume

vi) Post-operative fluid balance

v) a) Mean 24-hour intra-abdominal pressure (IAP)

v) b) daily WSACS IAH grading classification

Intention to Treat Physiological Outcomes

vi) SOFA score and individual organ system components of the score

vii) PaO_2/FiO_2 ratio

viii) Oxygenation Index

ix) Vasopressor Requirements

x) RIFLE score

xi) Need for renal replacement therapy

xii) APACHE II score

xiii) Mean 24-hour lactate level

Intention to Treat Global Secondary Outcomes

i) Days with fascial closure for the month after admission

ii) Ventilator free days for the month after admission

iii) ICU free days from the month after admission

iv) Hospital free days from the month after admission

v) Days free of renal replacement therapy from the month after admission

Other Baseline and Follow-Up Variables

1) Demographic data: age, gender, pre-existing and co-morbid medical conditions including, but not limited to, respiratory, cardiac, endocrine, and neurological diseases, Sabadell modification of the McCabe score regarding underlying conditions and known comorbidities before the OA(116), and a modification of the Charlson Comorbidity Index(117, 118).

2) **Admission illness severity data:** APACHE 2, SOFA(12, 89), Quick-SOFA(12), and Manheim Peritonitis Score(119, 120)

3) **Physiologic and laboratory data:** mean arterial pressure, heart rate, white blood cell count, neutrophils count, platelets count, lactate levels, base deficit, type and site of infection and arterial blood gasses, requirements for inotropic support, requirements for mechanical ventilation.

4) Surgical Outcomes: anastomotic leakage, enteric fistulae and type, intra-abdominal abscess and requirements for any intervention.

Recruitment Strategies

Academic Medical Centers will be recruited primarily from the partner Academic Institutions of the World Society of Emergency Surgery, Abdominal Compartment Society, Canadian Association of General Surgeons, and the Trauma Association of Canada. All these

Societies are endorsing the trial, and the institutions involved with these Societies have a history and track record of successful research into intra-abdominal sepsis and open abdomen management research(14, 15, 19, 49, 121-129) as well as fair, equitable, and practical ethical oversight from their associated institutions. These institutions will be contacted through direct communications between the PI and site investigators, which has actually been an ongoing process recognizing that many renowned and established intra-abdominal sepsis researchers have attended the Protocol Refinement Meeting in Parma, Italy, November 26 2017(130).

In addition to the word of mouth, society communications, and direct emails, the study will also be publicized through the formal academic publication of a concise study protocol document published in the world Journal of Emergency Surgery(131). Finally, many academic presentations will be given by the academic investigators around the world and any interested institutions that are able to fulfill the requirements listed below will be invited to participate in this trial.

Recruitment Issues

Lead Hospital: Foothills Medical (FMC) Centre

The FMC is one of the largest single site hospitals in Canada. It is one of Canada's most recognized medical facilities as well as one of the leading hospitals in Canada, providing advanced healthcare services to over two million people from Calgary, North Western United States, Southern Alberta, southeastern British Columbia and southern Saskatchewan(132). At the FMC acutely ill emergency surgical patients are cared for by the Acute General Surgery Service, attended by staff surgeons on a weekly basis. Patients requiring laparotomy for source control will be taken to the operating room under the care of the Surgical attending who will be present for the operation. It will be the Attending surgeons role to recognize the patients eligibility for the study and to initiate the recruitment process which can all be completed on-line. After care in the ICU is conducted in a closed multi-disciplinary ICU during which time the care is under the direct care of the ICU attending with regular consultative care from the surgeon. The local investigators include both surgeons, and intensivist, as well as dually cross appointed surgical-intensivists. This group was extremely supportive of a similar recruitment process in the Peritoneal VAC trial, in which out of 63 potentially eligible patients, 45 (71%) were recruited over 15 months. Reasons for non-recruitment included patients undergoing gynecological procedures and rescue laparotomies outside of a regular operating room. In the Peritoneal VAC trial, 53% of patients were non-traumatic, and thus a similar range of

recruitment would be expected for this trial with thus at least 27 patients recruited per year as a conservative estimate. As the COOL study will extend the option of OA with ANPTT to a greater cohort of SCIAS, more than 27 patients per year may be expected.

Partner Hospitals in the Regional System

The Calgary Zone of the Alberta Health Services is Regionalized, such that many standards, protocols, and staff are shared between freely communicating and co-operating hospitals. The care of SIAS is provided at three other hospitals, the Peter Lougheed, the Rockyview, and the South Health Campus. These three institutions will all be invited to participate in the COOL study.

Partner Hospitals Globally

It is anticipated that members of both the Abdominal Compartment Society (www.wsacs.org) and the World Society of Emergency Surgery (https://www.wses.org.uk/) will engage their own hospitals as study sites. Although all such sites will be encouraged to participate in COOL-MAX, they may elect to participate in COOL-LITE, in regards to recruiting for the primary mortality outcome.

Learning from the Peritoneal VAC Trial

The investigators and the scientific community have extensively reviewed and critiqued the results of the preceding Peritoneal VAC trial(133). Methodologic concerns with the Peritoneal VAC trial were that it enrolled quite heterogeneous patients with a

wide range of ages and included traumatized patients with an exactly known time of injury and severe IAS patients in whom the timing of onset of severe disease was inexactly known. Thus, the COOL-MAX/LITE trial will focus on a more heterogeneous group of patients with intra-operatively confirmed SCIAS in order to increase the signal to noise ratio. IL-6 continues to be considered a critical mediator if systemic inflammation and was an appropriate primary endpoint for a trial not expected to show a mortality difference. However, IL-6 levels are rapidly dynamic and important changes (in IL-6 and other important Biomediators) may have occurred that were not captured by a 24 hour early sampling window and thus more samples will be determined earlier in the study.

Randomization and Data Collection

Randomization shall be through a treatment allocation generator hosted on the dedicated COOL study research page (www.coolstudy.ca) replicating the previously successful methodology from the Peritoneal VAC trial. This site is freely open to the public. The ability to enroll a patient however, can only be accessed with a Password by any member of the surgical/anesthesia/critical care medicine/nursing team, thus freeing the senior surgeon to concentrate on care. When an appropriate patient is recognized, the research website will be accessed, simple identifiers of the patient will be entered, and treatment allocation (CLOSED with fascial closure or OPEN with AbThera ANPPT placement associated with this entry will be generated. Prior to Allocation however, decision support software ensures that the patient meets the inclusion criteria for Complicated Intra-peritoneal Sepsis, and then assists the operative team to ensure that the case of intra-peritoneal sepsis is severe enough to meet one of the three inclusion

thresholds. Only at this point will the webpage permit the operating team to randomize the patient and generate the treatment allocation. It should be noted that as long as a non-scrubbed team member can access an intra-operative computer the operating surgeon can supervise the recruitment and randomization in a few minutes without breaking scrub. To ensure close balance of the numbers in each of the two treatment groups a variable block size randomization will be used.

At the lead site (FMC) full data collection and completion of the data forms will be collected and completed by the Research support staff of Regional Trauma Services with possible assistance of the Department of Critical Care Medicine. The Research Nurses of the Department of Critical Care Medicine may assist in this task while patients are being cared for in the ICU, but the Research Manager of Regional Trauma Services will be responsible for overseeing the complete data collection from all patients at FMC from admission to discharge/death.

The collection and completion of data forms at all other contributing sites will be an Institutional requirement with local solutions required. All completed case report forms will be uploaded to a central REDcap secure Database administered by the Global Research Manager. All contributing sites will be required to collect all appropriate blood samples if participating in COOL-MAX. All such samples will be sent to the Snyder Laboratory/Research Centre in Calgary for central processing.

Official Study Language

The official language for scientific communications and initial flagship publications for COOL will be English. However, accurate translations of all COOL documentation and consent forms will be considered if the Steering Committee feels it will be important to facilitate recruitment and conduct of COOL in non-English speaking health care settings. Thus, it will be intended to publish translations of the original COOL protocol document in the Journal of Peritoneum (http://www.jperitoneum.org/index.php/joper).

The Research Team and Prior Relevant Research

This research study project aims to take leverage the collective inputs of clinicians, scientists, and scholars worldwide to answer a difficult but fundamentally important question concerning severe intra-abdominal infection. The results are expected to have both great clinical as well as basic science importance. The two principal sponsoring Societies are the Abdominal Compartment Society (http://www.wsacs.org/) and the World Society of Emergency Surgery (https://www.wses.org.uk/). These are global medical societies interested in severe intra-abdominal infection and the pathophysiology and treatment of such within the abdominal compartment. Both societies and their memberships have authored numerous original scientific studies and consensus management guidelines on this topic(14, 16-18, 128, 134, 135), and both have identified this question as crucial to advancing care.

Locally, the lead hospital is ideally suited to leverage our previous work and to continue the tremendous cooperative relationship between clinical care and basic science. The basic science team of Dr. Paul Kubes, director of the Calvin, Phoebe and Joan Snyder Institute of Infection, Immunity and Inflammation (http://www.snyder.ucalgary.ca/) and Chair of the Snyder Translational Laboratory in Critical Care Medicine, is world famous for their work on leukocyte recruitment in sepsis, a critical step in the defense of the host against invading organisms. Dr. Kubes is also a founding member of the Alberta Sepsis Network, an Alberta Innovates Health Solutions funded team grant focusing on the development of new science and technology which will serve to uniquely understand this devastating disease and help in the design of successful clinical trials

The Intra-abdominal Hypertension/Abdominal Compartment Syndrome research team led by Dr Andrew Kirkpatrick, has also been active in researching this entity for over 15 years, and hopes to continue to leverage the elegant basic science of Dr Kubes team to assist with their practical surgical knowledge as was done with the Peritoneal VAC study(50, 82, 133). This surgical critical care group has previously studied/described methods of diagnosis and measurement of IAP(125-127, 136-142), studied it's bedside interpretation(143-146), as well as extensively reviewed the literature(44, 139, 147-163). Further, members of our research group sit on the Executive, including the position of the President of Abdominal Compartment Society and have co-authored Society-based consensus documents and statements(28, 41, 164-167).

Statistical analysis will be led by a dedicated world renowned biostatistician, Dr Peter Faris PhD, who is Director of Research Facilitation in the Department of Analytics in Alberta Health Services (AHS), and is an Adjunct Professor in Community Health Sciences at the University of Calgary where he is co-instructor for a unique graduate course on the analysis of administrative data. He will lead experienced surgical statisticians including Dr Derek Roberts PhD, Dr Fikri Abu-Zidan, and Dr Luca Ansaloni, and Dr Federico Coccolini. Further we have enlisted the assistance of another world browned health economist, Dr Braden Manns, who is the Braden Manns is the Svare Professor in Health Economics and a Nephrologist at the University of Calgary in the Departments of Medicine and Community Health Sciences and an Alberta Innovates – Health Solutions Health Scholar. Dr Manns and his team will allow the COOL investigators to further understand the health economic implications of any medical benefits arising from the COOL trial.

Finally, an international network of some of the worlds most engaged academic clinicians with interest and global experience in managing severe complicated intra-peritoneal sepsis has collaborated to devise and refine the COOL study protocol to have the greatest global appeal and generalizability.

Appendices

Appendices

Appendix A Calgary PIRO Score for predicting mortality of intra-abdominal sepsis

Table 4. PIRO Score.

Score	Variable	Point
Predisposition	Age > 65 years	1
	Comorbidities	1
Response	Leukopenia	1
	Hypothermia	1
Organ Dysfunction	Cardiovascular dysfunction	1
	Respiratory dysfunction	1
	Renal dysfunction	1
	CNS dysfunction	1
Total		8

Comorbidities are score as Yes or No based on these Chronic Health Problems:

1) Cirrhosis of the liver confirmed by biopsy

2) New York Heart Association Class IV

3) Severe COPD -- Hypercapnia, home O2 use, or pulmonary hypertension

4) On regular dialysis or

5) Immunocompromised

Organ Dysfunction is Based on the SOFA score values with $\geq$ 2 as scored using the standard SOFA criteria for cardiovascular, respiratory, renal, and central nervous system function.

Appendix B **World Society of Emergency Surgery Sepsis Severity Score for patients with complicated intra-abdominal sepsis**

Table 5 WSES sepsis severity score for patients with complicated Intra-abdominal infections (Range: 0–18)

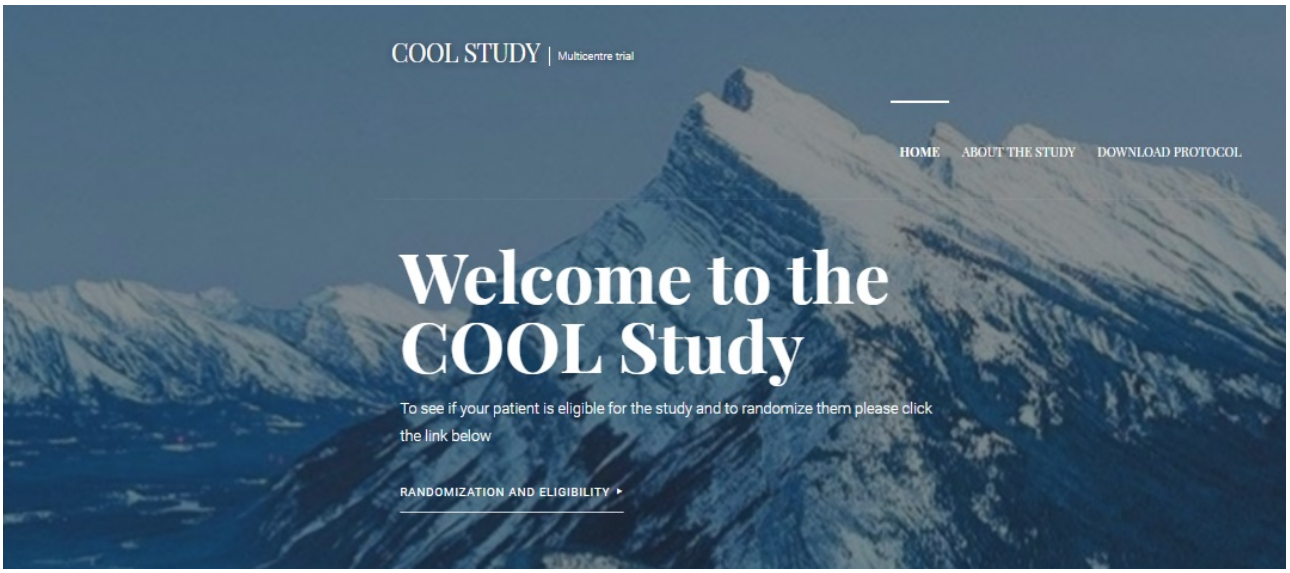
Clinical condition at the admission	
• Severe sepsis (acute organ dysfunction) at the admission	3 score
• Septic shock (acute circulatory failure characterized by persistent arterial hypotension. It always requires vasopressor agents) at the admission	5 score
Setting of acquisition	
• Healthcare associated infection	2 score
Origin of the IAIs	
• Colonic non-diverticular perforation peritonitis	2 score
• Small bowel perforation peritonitis	3 score
• Diverticular diffuse peritonitis	2 score
• Post-operative diffuse peritonitis	2 score
Delay in source control	
• Delayed initial intervention [Preoperative duration of peritonitis (localized or diffuse) > 24 h)]	3 score
Risk factors	
• Age>70	2 score
• Immunosuppression (chronic glucocorticoids, immunosuppresant agents, chemotherapy, lymphatic diseases, virus)	3 score

From Sartelli; World J Emerg Surg 2015(15)

Appendix C Recruitment and Treatment Allocation on the COOL Study website (coolstudy.ca)

COOL Study Webpage (www.coolstudy.ca)

The COOL webpage provides online assisted decision support to assess intra-operative patient eligibility and allows randomization of appropriate patients.



Home page (https://coolstudy.ca/)

Inclusion Criteria

Does your patient have complicated 2nd degree peritonitis?

- Including uncontained or unconfined
  - Purulence
  - Feculence
  - Enteric Spillage

YES **NO**

Eligibility criteria assessment – step 1 (Complicated intra-peritoneal sepsis)

https://coolstudy.ca/cool-study-eligibility-step-1/

Your Patient Has Complicated 2nd Degree Peritonitis

However, They Must Also Meet One of the Criteria Below Before Being Enrolled In the COOL Study:

- **Shock**
- **CPIRO >= 3**
- **WESESSS >=8**

Please click one of the links below to ensure your patients eligibility and proceed to randomization

Shock	CPIRO	WSESSSS
Click Here	Click Here	Click Here

Step 2 – does the patient have severe intra-peritoneal sepsis with each severity criteria opening a sub-menu

https://coolstudy.ca/about-copy/

If both Step 1 and Step 2 are appropriate the Randomization Page will be unlocked

Your patient is eligible for randomization click the link below

Online Randomization

Click Here

For Urgent Issues please contact Jessica Mckee at 780-906-4947 or at Jessica.Mckee@ualberta.ca

https://coolstudy.ca/randomization-2/

Appendix D

International Clinical/Methodological Committee for Trial Protocol Development

[AWK]Andrew W Kirkpatrick; Departments of Surgery, Critical Care Medicine, and the Trauma Program, University of Calgary, Calgary, Alberta, Canada.

[FC]Federico Coccolini; General, Emergency and Trauma Surgery Dept., Bufalini Hospital, Cesena, Italy.

[LA]Dr. Luca Ansaloni, Unit of General and Emergency Surgery, Bufalini Hospital of Cesena, Italy.

[DJR]Derek J Roberts; Department of Surgery, University of Calgary, Calgary, Alberta, Canada.

[MT]Matti Tolonen; Department of Abdominal Surgery, Abdominal Center, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland.

[JLK]Jessica L McKee; Regional Trauma Services, Foothills Medical Centre, Calgary, Canada.

[AL]Ari Leppaniemi; Department of Abdominal Surgery, Abdominal Center, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland.

[PF]Peter Faris; Research Facilitation Analytics (DIMR), University of Calgary, Calgary, Alberta, Canada.

[CJD]Christopher James Doig; Departments of Critical Care Medicine and Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Canada.

[FC]Fausto Catena; Emergency Surgery Department, Parma University Hospital, Italy.

[TF]Timothy Fabian; Professor of Surgery, University of Tennessee Health Sciences Center

Memphis, Tennessee, United States of America.

[CNJ]Craig N Jenne; Department Critical Care Medicine, University of Calgary, Calgary, Canada.

[OC]Osvaldo Chiara; General Surgery and Trauma Team Niguarda Hospital Milano, Milan, Italy.

[PK]Paul Kubes; Director Calvin, Phoebe and Joan Snyder Institute for Chronic Diseases, Professor Departments of Physiology and Pharmacology Cumming School of Medicine University of Calgary, Calgary, Canada.

[BM]Braden Manns; Departments of Medicine and Community Health Sciences; Libin Cardiovascular Institute and O'Brien Institute of Public Health, University of Calgary. Calgary, Alberta, Canada.

[YK]Yoram Kluger; Rambam Health Care Campus, Haifa, Israel.

[GPF]Gustavo P. Fraga; Division of Trauma Surgery, University of Campinas, Campinas, SP, Brazil.

[BP]Bruno M Pereira; Division of Trauma Surgery, University of Campinas, Campinas, SP, Brazil.

[JJD]Jose J. Diaz; Vice Chair Quality & Safety, Department of Surgery, Professor and Chief Acute Care Surgery, Program Director Acute Care Surgery Fellowship, R Adams Cowley Shock Trauma Center, University of Maryland School on Medicine, Baltimore, MD, United States of America.

[MS]Michael Sugrue; Letterkenny University Hospital, Donegal Clinical Research Academy, Donegal, Ireland.

[EEM]Ernest E. Moore; Vice Chair of Trauma and Critical Care Research, University of Colorado, Denver, Colorado, United States of America.

[JR]Jianan Ren; Department of Surgery, Jinling Hospital, Medical School of Nanjing University, China

[CGB]Chad G Ball; General, Acute Care, and Hepatobiliary Surgery, and Regional Trauma Services, University of Calgary, Calgary, Alberta, Canada.

[RC]Raul Coimbra; Surgeon-in-Chief, Riverside University Health System Medical Center

Professor of Surgery, Loma Linda University School of Medicine, Loma Linda, California, United States of America.

[ZJB]Zsolt J. Balogh, Director of Trauma, John Hunter Hospital and Hunter New England Health District. Professor of Surgery and Traumatology, University of Newcastle, Newcastle, NSW, Australia.

[FMAZ]Fikri M. Abu-Zidan, Professor; Department of Surgery, College of Medicine and Health Sciences, UAE University, Al-Ain, United Arab Emirates

[ED]Elijah Dixon; Professor of Surgery, Oncology, and Community Health Sciences

Chief - City Wide Section of General Surgery, University of Calgary, Calgary, Alberta, Canada

[WB]Walter Biffl; Medical Director of Trauma and Acute Care Surgery, Scripps Memorial Hospital La Jolla, La Jolla, California, United States of America

[AM]Anthony MacLean, Site Chief, Division of General Surgery Foothills Medical Centre;

Clinical Associate Professor Department of Surgery University of Calgary, Canada.

[IB]Ian Ball; Department of Medicine and Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada.

[JD]John Drover; Departments of Critical Care Medicine and Surgery, Queen's University, Kingston, Ontario, Canada.

[PBM]Paul B McBeth; Departments of Surgery, Critical Care Medicine, and the Trauma Program, University of Calgary, Calgary, Alberta, Canada.

[JGPC]Juan G Gabriel Posadas-Calleja; Department of Critical Care Medicine University of Calgary, Calgary, Alberta, Canada.

[NGP]Neil G Parry; Departments of Surgery and Critical Care, Western University, Victoria Hospital, London Health Sciences Centre, London, Ontario, Canada.

[SDS]Salomone Di Saverio; Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, United Kingdom.

[CAO]Carlos A Ordoñez; Department of Surgery, Fundación Valle del Lili and Universidad Del Valle, Cali, Colombia

[JX]Jimmy Xiao; Regional Trauma Services, Foothills Medical Centre, Calgary, Alberta, Canada.

[MS]Massimo Sartelli. Department of Surgery. Macerata Hospital, Macerata, Italy.

Appendix E Detailed Definitions of Physiological Outcomes Variables

Table E1

Systemic inflammatory marker levels (e.g. TNF-α, IL-1β, IL-6, IL-10) Inflammatory mediators present in blood that are released as a response of the body to infection or injury. In sepsis the level of these mediators are markedly higher than the nomal level. Reference - (168)	
Peritoneal fluid inflammatory marker levels (e.g. TNF-α, IL-1β, IL-6, IL-10) Inflammatory mediators present in the peritoneal fluid that are released as a response of the body to infection. The concentration of these markers in the peritoneal fluid is higher in the presence of peritoneal sepsis. Reference (168)	
APACHE II score	Acute Physiology and Chronic Health Evaluation score. Measure of the severity of disease for adult patients, based on 12 acute physiologic variables (Table D1), age (Table D2), and chronic health status (Table D3). The APACHE II score is determined by totaling points from these 3 sections, resulting in a total score between 0 and 71 points. APACHE II Score=Acute Physiologic Score+ Age Points+ Chronic Health Points. Points are assigned based on the most deranged physiological variables during the initial 24 hours in ICU. Higher scores imply a more severe disease and a higher risk of death . Reference - (169)
SOFA score	Sepsis related Organ Failure Assessment. Describes organ dysfunction/failure, computed based on respiratory, coagulation, cardiovascular, GCS, liver and renal variables (Table D4). Reference - (170)
FiO2/PaO2 ratio	Index to characterize the acute respiratory distress syndrome
Oxygenation Index	**(**FiO2 * Mean Airway Pressure) / PaO2
RIFLE score	Risk, Injury, Failure, Loss and End-stage renal failure score. Defines and stages acute kidney injury based on creatinine value increase and decrease in glomerular filtration rate (GFR) of urine output (Table D5). **Reference - (171-173)**
IAP	Intra-Abdominal Pressure. Pressure concealed within the abdominal cavity; expressed in mmHg. Normal IAP is ~ 5-7 mmHg in critically ill adults.
IAH	Intra-Abdominal Hypertension. Sustained or repeated pathologic elevation of IAP>=12 mmHg. IAH is graded as follows: Grade I: IAP 12-15 mmHg, Grade II: IAP 16-20 mmHg, Grade III: IAP 21-25 mmHg, Grade IV: IAP>25 mmHg. Reference - (164)

Table E2

Acute Physiologic Score (APS)

Physiologic Variable	Score	High Abnormal Range				Normal		Low Abnormal Range		
		+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (Rectal/Core) Oral: add 0.5ºC Axilla: add 1.0 ºC		**≥ 41**	**39-40.9**		**38.5-38.9**	**36-38.4**	**34-35.9**	**32-33.9**	**30-31.9**	**≤ 29.9**
Mean Arterial Pressure (mmHg)		**≥ 160**	**130-159**	**110-129**		**70-109**		**50-69**		**≤ 49**
Heart Rate		**≥ 180**	**140-179**	**110-139**		**70-109**		**55-69**	**40-54**	**≤ 39**
Respiratory Rate Non-ventilated or ventilated		**≥ 50**	**35-49**		**25-34**	**12-24**	**10-11**	**6-9**		**≤ 5**
Oxygenation a) $FiO_2 \geq .5$, record $AaDO_2$		**≥ 500**	**350-499**	**200-349**		**< 200**	AaDO2 : $[FiO_2 \times 713]-[PaCO_2 \div 0.8]- PaO_2$			
b) FiO2 < .5, record only PaO_2						**> 70**	**61-70**		**55-60**	**< 55**
Arterial pH		**≥7.7**	**7.6-7.69**		**7.5-7.59**	**7.33-7.49**		**7.25-7.32**	**7.15-7.24**	**<7.15**
Serum Sodium (mmol/L)		**≥180**	**160-179**	**155-159**	**150-154**	**130-149**		**120-129**	**111-119**	**<110**
Serum Potassium (mmol/L)		**≥7**	**6-6.9**		**5.5-5.9**	**3.5-5.4**	**3-3.4**	**2.5-2.9**		**<2.5**
Serum Creatinine (μmol/L)	*	**≥309**	**177 - 308**	**132-176**		**53-131**		**<53**		
		***DOUBLE SCORE FOR ARF**								
Hematocrit (%)		**≥60**		**50-59.9**	**46-49.9**	**30-45.9**		**20-29.9**		**<20**
WBC		**≥40**		**20-39.9**	**15-19.9**	**3-14.9**		**1-2.9**		**<1**
GCS (Score=15 minus actual GCS)		Enter Actual GCS here _____								
***HCO_3** (Venous mMol/L) (*Only if no ABG)		**≥52**	**41-51.9**		**32-40.9**	**22-31.9**		**18-21.9**	**15-17.9**	**<15**
TOTAL PHYSIOLOGIC SCORE										

Reference - (169, 174)

Table E3

Age Points	
Age (years)	Points
<=44	0
45-54	2
55-64	3
65-74	5
>=75	6

Table E4

Chronic Health Points	
Non-operative or emergency postoperative patients	5 points
Elective postoperative patients	2 points
No history of severe organ dysfunction or immune compromise	0 points

Table E5

SOFA score	**1**	**2**	**3**	**4**
Respiration PaO2/FiO2 mmHg	<400	<300	<200 ---with respiratory support----	<100
Coagulation Platelets X $10^3/mm^3$	<150	<100	<50	<20
Liver Bilirubin, mg/dl (umol/l)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (.>204)
Cardiovascular Hypertension	MAP<70 mmHg	Dopamine<=5 or dobutamine (any dose)	Dopamine>5 or epinephrine<=0.1 or norepinephrine<=0.1	Dopamine>15 or epinephrine>0.1 or norepinephrine>0.1
Central nervous system GCS	13-14	10-12	6-9	<6
Renal Creatinine, mg/dl (µmol/l) or urine output	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (>440)

Reference - (170)

Table E6

RIFLE Category	Glomerular Filtration Rate	Urine Output Criteria
Risk	Increased serum creatinine X 1.5 or decrease of GFR >25%	<0.5 mL/Kg/hr for 6 hrs
Injury	Increased serum creatinine X 2 or decrease of GFR >50%	<0.5 mL/kg/hr for 12 hrs
Failure	Increased serum creatinine X 3 or decrease of GFR >75% or serum creatinine >=4mg/dL	<0.3 mL/kg/hr for 12 hrs or anuria for 12 hrs
Loss	Complete loss of renal function for >4 wks	
End-stage kidney disease	Need for renal replacement therapy for >3 mos	

References - (171-173)

Appendix F Detailed Definitions of other baseline and follow-up data

Table F1

Demographic data	
Sabadell modification of the McCabe score	A predictive score that reflects a subjective prognosis of each patient at discharge, based on the subjective perception of the attending intensivist (Table E1). References – (67)
Admission injury severity data	
AIS	Abbreviated Injury Scale. Numerical method for comparing injuries by severity, allocated to one of six body regions (head, including cervical spine; face; chest, including thoracic spine; abdomen, including lumbar spine; extremities, including pelvis; and external). It is based on a 6-point ordinal severity scale ranging from AIS 1 (minor) to AIS 6 (maximum). The AIS doesn't assess the combination of multiple-injured patients. The Maximum AIS (MAIS), which is the highest single AIS score in a patient with multiple injuries, has been used to describe overall severity (Table E2). References - (175, 176)
ISS	Injury Severity Score. Anatomical scoring tool that provides an overall score for patients with single system or multiple system injuries. The ISS is the sum of the squares of the highest AIS score in each of the three most severely injured body regions. ISS scores range from 1 to 75, with higher ISS indicating more severe injuries (Table E3). References (177)
RTS	Revised Trauma Score. Physiological index of injury severity, calculated from GCS, systolic blood pressure (SBP) and respiratory rate (RR). These values are multiplies by weights determined by logistic regression of a baseline dataset S=0.9368(GCS)+0.7326(SBP)+0.2908(RR). RTS takes values between 0 and 7.8408; higher values are associated with improved prognoses. References - (178, 179)
GCS	Glasgow Coma Score. Standardized system for assessing the degree of conscious impairment, involving 3 determinants: eye opening response (E), verbal response (V), motor response (M). M is a 6-point scale varying from 'no response' to 'obeys verbal commands'. V is a 5-point scale varying from 'no response' to 'oriented' and E is a 4-point scale varying from 'none' to 'spontaneous'. GCS can range from 3 (lowest) to 15 (highest) (Table E4). References - (180-182)
Physiologic and laboratory data	
FiO2/PaO2 ratio	Index to characterize the acute respiratory distress syndrome.
IAP	Intra-Abdominal Pressure. Pressure concealed within the abdominal cavity; expressed in mmHg. Normal IAP is ~ 5-7 mmHg in critically ill adults.
IAH	Intra-Abdominal Hypertension. Sustained or repeated pathologic elevation of IAP>=12 mmHg. IAH is graded as follows: Grade I: IAP 12-15 mmHg, Grade II: IAP 16-20 mmHg, Grade III: IAP 21-25 mmHg, Grade IV: IAP>25 mmHg. Reference - (164)

Table F2

Sabadell score	**Prognosis**	**ICU readmission**
0	Good for >6 months survival	Unrestricted if needed

1	Poor for >6 months survival	Unrestricted if needed
2	Poor for <6 months survival	Debatable
3	Poor for hospital survival	Not recommended

Table F3

AIS Code	Description
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Maximum

Table F4

Total score of the GCS

Eye Opening Response	Motor Response	Verbal Response
Spontaneous=4	Obeys Commands=6	IF NOT INTUBATED:
To Voice=3	Localizes to Pain=5	Oriented=5
To Pain=2	Flexion/Withdrawal=4	Confused=4
None=1	Abnormal Flexion=3	Innapropriate=3
	Extension=2	Incomprehensible=2
	No Response=1	No Response=1
		IF INTUBATED:
		Appears to be able to converse=5
		Ability to converse questionable=3
		Unresponsive=1

Cardiovascular SOFA scoring

Cardiovascular system [edit]

Mean arterial pressure OR administration of vasopressors required	SOFA score
MAP ≥ 70 mm/Hg	0
MAP < 70 mm/Hg	1
dopamine ≤ 5 μg/kg/min or dobutamine (any dose)	2
dopamine > 5 μg/kg/min OR epinephrine ≤ 0.1 μg/kg/min OR norepinephrine ≤ 0.1 μg/kg/min	3
dopamine > 15 μg/kg/min OR epinephrine > 0.1 μg/kg/min OR norepinephrine > 0.1 μg/kg/min	4

Respiratory SOFA Scoring

Respiratory system [edit]

PaO_2/FiO_2 (mmHg)	SOFA score
≥ 400	0
< 400	1
< 300	2
< 200 **and** mechanically ventilated	3
< 100 **and** mechanically ventilated	4

Renal SOFA Scoring

Kidneys [edit]

Creatinine (mg/dl) [µmol/L] (or urine output)	SOFA score
< 1.2 [< 110]	0
1.2–1.9 [110-170]	1
2.0–3.4 [171-299]	2
3.5–4.9 [300-440] (or < 500 ml/d)	3
> 5.0 [> 440] (or < 200 ml/d)	4

Neurological SOFA Scoring

Nervous system [edit]

Glasgow coma scale	SOFA score
15	0
13–14	1
10–12	2
6–9	3
< 6	4

Appendix G Data variables for Ineligible Open Abdomen Cases with SCIAS

The core variables that will be required to understand the epidemiology and clinical outcomes of patients with SCIAS will be demographic to ensure the patients are comparable to other patients undergoing both surgical and non-surgical treatment of SCIAS, as well as key outcomes of interest. Although not mandated by the COOL trial, participating institutions are also encouraged to participate in the International Registry of the Open Abdomen (IROA)(https://www.clinicalregisters.org/IROA/). The key information points that will be of critical importance are to assess whether excluded OA patients due to damage control interventions are truly sicker than OA patients who are eligible to be enrolled in COOL. Based on the Peritoneal VAC trial, baselined demographic data for those excluded (and enrolled) will ideally consist of;

1) Demographic data: age, gender, pre-existing and co-morbid medical conditions including, but not limited to, respiratory, cardiac, endocrine, and neurological diseases, Sabadell modification of the McCabe score regarding underlying conditions and known comorbidities before the OA(116), and a modification of the Charlson Comorbidity Index(117, 118).

2) **Admission illness severity data:** APACHE 2, SOFA(12, 89), Quick-SOFA(12), and Manheim Peritonitis Score(119, 120)

3) **Physiologic and laboratory data:** mean arterial pressure, heart rate, white blood cell count, neutrophils count, platelets count, lactate levels, base deficit, type

and site of infection and arterial blood gasses, requirements for inotropic support, requirements for mechanical ventilation.

Key Outcome information that will ideally be collected for non-enrolled open abdomen patients will include;

1) **Survival**
    a. To hospital discharge
    b. 90 day survival
2) **Critical Care Outcomes**
    a. Days free of ICU at 30 days
    b. Days free of ventilation at 30 days
    c. Days free of Renal Replacement Therapy at 30 days
    d. Days free of hospital at 30 days
3) **Surgical Outcomes:**
    a. Days of fascial closure at 30 days
    b. anastomotic leakage
    c. enteric fistulae and type
    d. intra-abdominal abscess
        i. any requirements for any intervention.

Appendix H Data and Safety Monitoring Plan (DSMP) for the Closed Or Open after Source Control Laparotomy for Severe Complicated Intra-Abdominal Sepsis (the COOL trial)

Data and Safety Monitoring Plan (DSMP) for the Closed Or Open after Source Control Laparotomy for Severe Complicated Intra-Abdominal Sepsis (the COOL trial)

(https://clinicaltrials.gov/ct2/show/NCT03163095)

September 2018

PREFACE

The goal of this DSMP is to provide an expanded description of the role of the COOL trial Data Safety Monitoring Board (DSMB) that will further enhance the overall plans and protocols to maintain the highest standards of data and safety monitoring. This document should at all times be read in conjunction with the comprehensive COOL study protocol available at www.coolstudy.ca, the published concise protocol(183), and in discussion with the Study Steering Committee as appropriate. All attempts have been made to follow Good Clinical Practice as outlined in the E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm464506.pdf)

TABLE OF CONTENTS

1.0 PARTICIPANTS SAFETY

1.1 Potential Risks and Benefits for Participants

Patients meeting inclusion criteria to be enrolled in Closed versus Open Abdomen in the Surgical Treatment of Severe Secondary Peritonitis: A Randomized Controlled Clinical Trial will all by definition be critically ill with high changes of death and morbidity. This is due to the fact that severe complicated intra-abdominal sepsis (SCIAS), is a very severe condition with great risks to the patient no matter what is done and at this moment nobody in the world knows how to best treat this condition. Those with SCIAS are some of the sickest that surgeons are called to deal with and currently it is uncertain what the right treatment is especially in terms of closing the abdominal cavity after surgery. The sponsor of this trial will be the University of Calgary through which the PI Andrew W Kirkpatrick will be working on behalf of.

Serious Adverse Risks: Death

The greatest potential risk for any patient suffering from SCIAS will be death, which will be a concern regardless of whether such a patient is enrolled in COOL or not, and regardless as to which treatment arm they are enrolled in. Mortality approaches 30-40% when shock is present (7-9), although this may be 80% in the developing world (1). Intra-abdominal sepsis (IAS) constitutes the 2nd most common form of sepsis, which may be particularly severe because of the unique anatomic, physiologic, and microbiologic characteristics of the abdominal cavity and its contained hollow viscera (10). Thus, it has been reported that hospital mortality is highest for patients who have intra-abdominal infection secondary to ischemic bowel or disseminated infection (11).

Potentially Fatal Serious Adverse Risks:

Sepsis also affects the entire human body with the elaboration of toxic biomediators that adversely affect all organ systems(12, 13). There are thus many other expected adverse events that include;

a) Multiple organ dysfunction including
    a. Renal failure
    b. Cardiovascular failure

c. Respiratory failure
d. Gastrointestinal failure
e. Hematopoietic failure

b) Prolonged life support
c) Intra-abdominal abscesses
d) Entero-cutaneous fistulae
e) Pneumonia
f) Deep vein thrombosis
g) Pulmonary embolism
h) Wound infections
i) Wound dehiscence
j) Prolonged hospitalization
k) Loss of independent living capability after release from hospital
l) General debility

Potential Benefits: There are however many potential benefits to patients participating in the COOL trial which include;

a) Reduced risk of death
b) Reduced occurrence of Multiple organ dysfunction including
   a. Reduced Renal failure
   b. Reduced Cardiovascular failure
   c. Reduced Respiratory failure
   d. Reduced Gastrointestinal failure
   e. Reduced Hematopoietic failure
c) Shortened requirement for life support
d) Reduced Intra-abdominal abscesses
e) Reduced Entero-cutaneous fistulae
f) Reduced Pneumonia
g) Reduced Deep vein thrombosis

h) Reduced Pulmonary embolism
i) Reduced Wound infections
j) Reduced Wound dehiscence
k) shortened hospitalization
l) increased independent living capability after release from hospital
m) increased General robustness

1.2 Definition, Collection and Reporting of Adverse Events (AEs), Serious Adverse Events (SAEs) and Unanticipated Problems (UPs)

Definitions of Adverse Events shall conform to GCP standards;

Table 1. Definitions of Adverse Events and Serious Adverse Events Occurring in Clinical Research or After Marketing Approval	
Adverse event ICH GCP E6 (R2) 1.2 or ICH GCP E2A	Any untoward medical occurrence in a patient or clinical investigation participant given a pharmaceutical product; does not necessarily have a causal relationship with such treatment. Any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal (investigational) product; not necessarily related to the product.
Adverse drug reaction ICH GCP E6 (R2) 1.1	**Before market approval:** Any noxious and unintended response to a medicinal product related to any dose; causal relationship between the medicinal product and an AR is at least a reasonable possibility.

	After market approval: Any noxious and unintended response to a product that occurs at doses normally used in humans to prevent, diagnose, or treat disease or to modify physiological function.
Serious Adverse event ICH GCP E6 (R2) 1.50 or ICH GCP E2A	A **serious** adverse event (SAEs) or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; and/or causes other medically significant events.
Unexpected Adverse event ICH GCP E6 (R2) 1.60 or ICH GCP E2A	An **unexpected** adverse event is defined as: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product)

The severity of adverse reactions will be defined according to standard guidelines of Good Clinical Practice

Table 3. Grading of AEs Based on Signs and Symptoms	
None	No signs/symptoms or within normal limits
Mild	Minor signs/symptoms; no specific medical intervention required; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance
Moderate	Requiring minimal, local, or non-invasive intervention only
Severe	Significant symptoms requiring hospitalization or invasive intervention
Life-threatening or disabling	Complicated by acute, life-threatening metabolic or cardiovascular complications (such as circulatory failure, hemorrhage, sepsis); life-threatening physiological consequences; or need for intensive care or emergent invasive procedure
Fatal	Causing death

The relation between the AE and any study intervention will be defined by standard definitions reflecting Good Clinical Practice

Table 5. Relatedness of AEs to an Intervention (Product)	
Definite (must have all 4)	Has a reasonable temporal relationship to the intervention Could not have readily been produced by the participant's clinical state or have been due to environmental or other interventions Follows a known pattern of response to intervention Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure
Probable (must have 3)	Has a reasonable temporal relationship to the intervention Could not have readily been produced by the participant's clinical state or have been due to environmental or other interventions Follows a known pattern of response to intervention Disappears or decreases with reduction in dose or cessation of intervention
Possible (must have 2)	Has a reasonable temporal relationship to the intervention Could not have readily been produced by the participant's clinical state Could not readily have been due to environmental or other interventions Follows a known pattern of response to intervention
Unlikely	Does not have a temporal relationship to the

(must have 2)	intervention Could readily have been produced by the participant's clinical state Could have been due to environmental or other interventions Does not follow a known pattern of response to intervention Does not reappear or worsen with reintroduction of intervention

Reporting of events by Investigators

As per the ICH GCP which states: "*An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately*."

The industry standard is to report all SAEs within 24 hours of their identification. If the event is life-threatening or fatal, the event should be reported immediately. The sponsor should spell out clearly in the protocol what the reporting requirements are.

However, expedited reporting to regulatory agencies is **not required** for events that are either:

- Serious but expected
- Not reasonably related to the investigational product.

These latter events, if serious, still might need to be promptly reported to the sponsor and to the REB (ICH E6 (R2) 3.3.8.c), according to local requirements. The sponsor will outline in the protocol the criteria and process for reporting all AEs, including those that are serious. Since all SAEs are still adverse events,

they must be recorded on the relevant case report form (CRF) page unless otherwise directed by the sponsor.

As discussed, as the COOL trial will be studying very critically ill patients with many expected events occurring in all enrolled patients. The expected AEs and SAEs are described in Section 1.1 above and shall not require reporting except for enterocutaneous fistulae (EAF) or the occurrence is unexpected to constitute an **Suspected Unexpected Serious Adverse Reactions (SUSARs**). EAF is a specific theoretical concern regarding the use of active negative peritoneal pressure therapy (ANPPT), especially if ANPPT is utilized by in-experienced caregivers. Although recent experiences in high performing medical systems have NOT shown any increased risk of EAF with ANPPT, and despite the fact that EAF may occur spontaneously with SCIAS, the occurrence of EAF will be considered an immediately reported SAE (IRSAE). Further, although all the AEs and SAEs described in Section 1.1, will be expected through-out the course of the study all investigators and all study staff will be expected to report any unexpected or unusual SAE, as an **Suspected Unexpected Serious Adverse Reactions (SUSARs)**.

Table 6. Information to Include in SAE Reports	
Demographic data, patient details	May include: initials, study unique identifier number, sex, date of birth/age, height, weight (note privacy rules may limit use of identifiers)
Product information	Brand name, International Nonproprietary names, batch number, dosage form and strength, daily dose and regimen, route of administration, start and stop dates, total cumulative dose and/or duration of treatment, indication for use
Other treatments	The same information as for the suspected product for each concomitant drug (prescription, Over The Counter medication, supplements) that the participant was taking
Details of the suspected adverse event	Full description, including event (body site), severity, signs, symptoms. A specific diagnosis should be provided for the reaction. Include seriousness criteria, onset date/time of reaction, stop date/time or duration, dechallenge (withdrawal) and rechallenge data. Other observations and relevant information to aid in assessment of event include medical history, allergy history, substance abuse history, family

	history, history of current disease.
Treatment of event	Steps taken to treat the event, including withdrawal of the suspect product, interventions taken, drugs given, tests conducted and results, other treatment given.
Outcome	Recovery or after effects. If death is the outcome, cause of death, and autopsy or post-mortem findings if available.
Details of person submitting the report	Name, address, telephone number, profession.
Administrative and sponsor information	To be submitted by sponsor: source of report, date report received, country in which event occurred, type of report (initial or follow-up), name and address of sponsor/manufacturer, name/address of contact person, IND/IDE CTA or CTX number, manufacturer's identification number for the case.

Reporting by the Sponsor

As per GCP, the trial sponsors will be expected to report SAEs that are unexpected and associated with the use of an investigational product to regulatory agencies within specific time periods. These reports are called **Suspected Unexpected Serious Adverse Reactions (SUSARs) in**

Canada. Again, the objective of rapid notification is to protect participants in all trials of the investigational product (not just a specific protocol).

Once the sponsor files a SUSAR in Canada, the sponsor will notify all investigators participating in COOL. Investigators should then notify their Research Ethics Board (REB) or Independent Review Board (IRB). Certain events may require modification of the informed consent form and notification to research participants, although is not expected.

Reporting requirements are based on the definitions listed in Section 2 and are summarized in the Table 7 below ICH GCP and (*21 CFR 312.32*).

Table 7. Sponsor Reporting Requirements for IND Safety Reports (from time of Notification of Occurrence) and SUSARs

Type of SAE	Sponsor to Health Canada and/or FDA	Sponsor to Investigators
Unexpected SAEs associated with the drug but **not** fatal or life-threatening	15 calendar days	15 calendar days
Unexpected SAEs associated with the drug **and** fatal or life-threatening	ASAP, but within 7 calendar days (fax or phone acceptable) followed by a complete written report within 8	15 calendar day

	calendar days (total 15 calendar days)	

1.3 Protection against Study Risks

Informed Consent Process.

The COOL trial is being conducted in various institutions across the world, that are governed by a variety of different legal and medicolegal legislation. Thus, a variety of informed consent mechanism and processes will be appropriate to COOL. All are unified however, by attempting balance protection of the individual from harm with the rights and need to allow important research to be conducted in difficult circumstances and for potentially vulnerable populations not to be excluded from the benefits of research(184). Thus, research ethics will vary through-out the world and it is anticipated that various local policies concerning community consent, waiver of consent, or informed consent of significant patient proxies will vary among the local approaches to ensure the COOL trial is performed to the highest ethical standards on a Global basis. All participating Institutions will thus be required to obtain Ethical Approval appropriate and applicable to their Institutions.

Protection against Risks.

Both arms of the COOL trial are currently considered to be within the current standard of care throughout the world. As described the major risks to patients enrolled in COOL are those related to SCIAS. The primary mechanism of attempting to mitigate these many risks will be to conduct the trial in academic medical centers throughout the world, thus enhancing the chances that the clinical care provided will be of the highest standard. Although ANPPT is a standard of care world-wide it is possible for it to be technically misused. COOL will attempt to mitigate these risks by mandating that all participating investigators view an in-service on safe ANPPT use prior to enrolling patients.

2.0 INTERIM ANALYSIS & STOPPING RULES

There will be a single interim analysis planned after the recruitment of 275 patients, which will analyze the difference in 90 days mortality between allocated therapies. The COOL Investigators appreciate the general reluctance to stop randomized trials early due to benefit, due to the frequent over-estimating of treatment effects(108-110). Despite this, it is possible that the COOL trial will be great over-powered as although the Sample size calculations are based on the best outcome data from randomized trials of NPPT, this is still inferential as there is no previous relevant data with which to accurately guide such calculations. Thus, if a profoundly significant difference is found ($p < 0.01$) the trial will be stopped, otherwise it will continue to full recruitment.

3.0 DATA AND SAFETY MONITORING

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis and for reporting Serious Adverse Events and Unanticipated Problems to the sponsor. The sponsor will be responsible to report the events to the DSMB, and Health Canada as required. There will be one interim analysis at which time the study statistician will prepare a report that lists adverse events, serious adverse events, deaths, and disease-or treatment-specific events required for monitoring body review in order to ensure good clinical care and identify any emerging trends. In the event that obvious concerns regarding patient safety outcomes are raised, the DSMB may recommend protocol revisions, protocol suspension, or protocol termination in order to protect the best interests of trial participants. If no obvious concerns regarding patient safety outcomes are raised the trial will continue to completion unless there are unexpected SAEs that warrant immediate ad-hoc reviews and potential intervention by the DSMB.

3.1 Frequency of Data and Safety Monitoring

The PI will be informed of serious adverse events as soon as they occur by the study coordinator and will notify the sponsor within 48 hours of becoming aware of the event. The PI will report the Serious Adverse Events and Unanticipated Problems to his or her IRB within 5 business days of

becoming aware of the event, according to local IRB requirement. Specific triggers for an ad hoc review or initiation of the process of an ad hoc review will occur if there are unforeseen deaths or the threshold for SAE has been met. Collated safety reports will be sent by the sponsor to the DSMB on a yearly basis and will include a detailed analysis of study progress, data and safety issues.

3.2 Content of Data and Safety Monitoring Report

The content of the reports submitted by the sponsor to the DSMB will include;

- CONSORT diagram and actual versus expected enrollment figures that illustrate recruitment and participation status.[1]
- Data tables that summarize demographic and baseline clinical characteristics.
- Data quality tables that capture and missing case report forms.
- Safety assessments of aggregate tables of adverse events and serious adverse events.
- Listings of adverse events, serious adverse events, deaths, unanticipated problems and protocol deviations/violations.
- Aggregate tables of clinical laboratory values.

As COOL will be a multi-site study, Tables will be presented as aggregated data as well as data by site.

3.3 Data Safety Monitoring Body Membership and Affiliation

The DSMB will consist of the monitoring entity's name(s) and affiliation(s).
Name: **Dr John Marshall MD**
Professor of Surgery, University of Toronto

Name: **Dr Peter Farris PhD**
Title, University of Calgary

3.4 Conflict of Interest for Monitoring Bodies

Monitoring body members will have no direct involvement with the study investigators or intervention. Each member will sign a Conflict of Interest Statement which includes current affiliations, if any, with any steering committees or advisory councils associated with the study, pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial or non-commercial interests pertinent to study objectives.

3.5 Protection of Confidentiality

Only de-identified data will be presented during the open sessions of the DSMB. All data, whether in a report or discussed during a DSMB meeting are confidential. Participant identities will be kept confidential unless safety concerns necessitate unmasking some or all data.

3.6 Data Safety Monitoring Board Responsibilities

The following charter provides a detailed list of the DSMB responsibilities, which may include:

- Evaluating the progress of the study on an ongoing basis including an assessments of data quality, participant recruitment, accrual and retention, participant risk versus benefit, performance of study site(s), and other factors that can affect the outcome performed at the 50% recruitment mark.
- Reviewing the interim analyses and/or accumulating data at the specified interval(s), and as appropriate and make a recommendation to continue, terminate or modify the study based on observed benefit or harm in accordance with the planned stopping rules.
- Considering the impact of factors external to the study when new information, such as scientific or therapeutic developments becomes available that may affect safety of participants, their willingness to participate in the study or the ethics and conduct of the study.
- Reviewing Unanticipated Problems, Serious Adverse Event reports and inform the sponsor and PI whether there is an effect on participant safety.

- Reporting any problems with study conduct or performance to the sponsor, University of Calgary, or the PI as appropriate.
- Ensuring the measures to ensure the confidentiality of study data and results are appropriate.

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