# The Unrestricted Global effort to complete the Closed Or Open after Source Control Laparotomy for Severe Complicated Intra-Abdominal Sepsis (COOL) Trial

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## Abstract

· **Background:** Severe complicated intra-abdominal sepsis (SCIAS) has an increasing incidence with mortality rates over 80% in some settings. Mortality typically results from disruption of the gastrointestinal tract, progressive and self-perpetuating bio-mediator generation, systemic inflammation, and multiple organ failure. A further therapeutic option may be open abdomen (OA) management with negative peritoneal pressure therapy (NPPT) to remove inflammatory ascites and attenuate the systemic damage from SCIAS, although there are definite risks of leaving the abdomen open whenever it might possibly be closed. This potential therapeutic paradigm is the rationale being assessed in the Closed Or Open after Laparotomy (COOL-trial) (**https://clinicaltrials.gov/ct2/show/NCT03163095**). Initially, the COOL-trial received Industry sponsorship; however, this funding mandated the use of a specific trademarked and expensive NPPT device in half of patients allocated to the intervention (open) arm. In August 2022, the 3M/Acelity Corporation without consultation but within the terms of the contract cancelled the financial support of the trial. Although creating financial difficulty, there is now no restriction on specific NPPT devices and removing a cost-prohibitive intervention creates an opportunity to expand the COOL trial to a truly global basis. This document describes the evolution of the COOL trial, with a focus on future opportunities for global growth of the study.

· **Methods:** The COOL trial is the largest prospective randomized controlled trial examining the random allocation of SCIAS patients intra-operatively to either formal closure of the fascia or use of the OA with application of an NPPT dressing. Patients are eligible if they have free uncontained intra-peritoneal contamination and physiologic derangements exemplified by septic shock OR severely adverse predicted clinical outcomes. The primary outcome is intended to definitively inform global practice by conclusively evaluating 90-day survival. Initial recruitment has been lower than hoped but satisfactory, and the COOL steering committee and trial investigators intend with increased global support to continue enrollment until recruitment ensures a definitive answer.

· **Discussion:** OA is mandated in many cases of SCIAS such as the risk of abdominal compartment syndrome associated with closure, or a planned second look as for example part of 'damage control', however improved source control (locally and systemically) is the most uncertain indication for an OA. The COOL-trial trial seeks to expand potential sites and proceed with evaluation of NPPT agnostic to device, to properly examine the hypothesis that this treatment attenuates systemic damage and improves survival. This approach will not affect internal validity and should improve the external validity of any observed results of the intervention.

· **Trial registration:** National Institutes of Health (**https://clinicaltrials.gov/ct2/show/NCT03163095**).


## Background

Sepsis is an increasing cause of death worldwide(2, 3), with an incidence estimated between 18 to 31 million cases worldwide per year(3-7). Sepsis mortality approaches 30-40% when shock is present(8-10), and may be higher in the developing world (2). The incidence and mortality of sepsis can be compared to other critical global health problems such as COVID-19 with 6.5 million deaths worldwide over more than 2 years(11), or 4.4 million deaths from trauma each year(12). Sepsis was the single most expensive medical condition in the United States in 2016, with 22.2 billion dollars spent just on in-hospital stays(13). Intra-abdominal sepsis (IAS) is the 2$^{nd}$ most common form of sepsis, and may be particularly severe because of the unique anatomic, physiologic, and microbiologic characteristics of hollow viscera within the abdominal cavity (14). IAS occurs within a semi-rigid anatomic container that is exquisitely affected by raised intra-compartmental pressure that quickly induces abdominal visceral malperfusion and ischemia (15, 16). Further, the extensive flora of the human microbiome is contained within the abdominal container exacerbating any pathology in a multitude of ways that are yet only minimally understood(17, 18). Thus, it has been reported that hospital mortality is highest for patients who have intra-abdominal infection secondary to ischemic bowel or disseminated infection(19).

Severe complicated intra-abdominal sepsis (SCIAS) represents a subset of IAS sepsis but is perhaps the most challenging clinical situation. Sartelli and the World Society of Emergency Surgery have defined IAS as severe when associated with organ dysfunction (9, 20-22), and as complicated when the inflammation or contamination spreads beyond a single organ, causing either localized or diffuse peritonitis (20, 23). SCIAS may be distinguished from other causes of severe sepsis through a requirement for surgical abdominal exploration to address disruption in the gastrointestinal (GI) tract and provide source control.

Patients with SCIAS require early hemodynamic support, source control, and antimicrobial therapy(23). Despite advances in diagnosis, surgery, and antimicrobial therapy, mortality rates associated with complicated intra-abdominal infections and IAS remain very high(22). Failure to obtain adequate source control is often considered the driving cause of SCIAS and has been identified as an independent predictor of mortality(24). Even with prompt appropriate therapy, SCIAS may progress to septic shock and multiple organ dysfunction, presumed as a consequence of peritoneal and systemic inflammation. There is significant variability in the human immune response to an infectious focus, whereas some individuals produce a massive bio-mediator storm propagating multi-system organ failure and death, whereas other individuals may be anergic with little or no response to the same stimuli.

In patients with SCIAS, repeat laparotomy may be necessary to eliminate persistent peritonitis or new infectious foci(25-27). Differentiating "failed source control"(28, 29) from a self-propagating bio-mediator storm is difficult or impossible without abdominal re-exploration. In a Dutch multicenter randomized controlled trial (RCT), 42% of those randomized to expectant management after laparotomy for IAS, underwent relaparotomy for suspected or proven persistent peritonitis (25). Interestingly, 31% of the repeat laparotomies were negative. The results of the Dutch study, concluded a previously long-standing debate concerning two closed surgical approaches to ensuring source control in the peritoneal cavity; that of "laparotomy on demand – (LOD)" versus "planned re-laparotomy" (PRL)(25, 30, 31). The relative merits of either approach were widely debated until the conduct of the above RCT (25). Although this trial noted no difference in mortality between the two methods, the LOD strategy reduced direct medical costs by 23%(25). This equivalence in outcomes, coupled with an apparent cost-savings, resulted in the generation of consensus guidelines recommending that LOD after laparotomy for SCIAS be adopted as the standard of care(32). However, neither LOD or PRL arm included an open abdomen or negative peritoneal pressure therapy (NPPT). The mortality in this

RCT of severe secondary peritonitis illustrates the devastating nature of this disease having a mortality of approximately 1/3 of all enrolled patients regardless of treatment allocation. This observed mortality rate call out for ongoing examination of alternative approaches to manage SCIAS.

Pharmacologic approaches do not currently offer hope in SCIAS as studies of promising agents directed to combat post-infective inflammation have not shown evidence of significantly improved patient outcomes, and when suggested as having a role, have been incredibly expensive(33, 34). Alternatively, OA is increasingly recommended as an option to control of intraperitoneal contamination, and to ameliorate the propagation of inflammatory bio-mediators in SCIAS (35-37).

The use of the OA for non-trauma general surgery is increasingly being reported in uncontrolled series as an option for patients with SCIAS (20, 28, 29, 38-40). The use of the OA approach in SCIAS may increase drainage of residual infection, allow early identification and control of persistent infection, increase removal of biomediator-rich peritoneal fluid, prophylaxis against the development of the abdominal compartment syndrome, and allow for deferral of gastrointestinal anastomoses, with a potentially safer exit at the index operation(20). However, compared to trauma patients, OA management for IAS patients has been reported to have greater risk of complications, including entero-atmospheric fistula (EAF), intra-abdominal abscess, and a lower rate of primary fascial closure (i.e., fascia-to-fascia closure within the index hospitalization)(20, 21, 41) (42, 43). Thus, there remains clinical equipoise in the regular use of the OA in SCIAS, with benefits and risks to adopting or avoiding its use.

**Metanalyses and Randomized Controlled Studies of the Open Abdomen in Trauma and Sepsis**

Although the use of Damage Control and an OA concept were once liberally embraced and assumed to be the ideal therapy for major trauma (44), sober critique has questioned the need for this approach and suggested that the treatment paradigm and actual intervention may be overused (45-47). These concerns are germane when discussing non-trauma emergency surgical patients subjected to OA therapy as in IAS patients' comorbidities are more common and more severe, closure rates are lower, and patients tend to be older and less able to withstand OA complications should they occur. Thus, it is important to have data unique to IAS patients to inform clinical decision-making.

Unfortunately, although case series on OA after non-trauma laparotomies have been reported, there are no contemporary RCTs. A recent meta-analysis on the use of Damage Control in perforated acute colonic diverticulitis(48), found no RCTs and ultimately the conclusions reverted back to opinions, the weakest level of Evidence in the World Society of Emergency Surgery Consensus Guidelines(49, 50). In 2022 Cheng published a Cochrane Review on the use of negative pressure wound therapy for the non-trauma open abdomen and concluded that no recommendations could be made as there was no meaningful data(51). Only one other RCT, conducted prior to 2006, has randomized 40 patients to a closed or open strategy, but the technique of OA management utilized then are inadequate according to current guidelines, as the NPPT apart from other aspects of OA management has evolved in technique and technology. This earlier RCT randomized patients with severe secondary peritonitis to an open or closed strategy after laparotomy, using a non-absorbable polypropylene (Marlex™) mesh in an interposed position between the open fascia, exposing the underlying bowel to risk of enterocutaneous or enteroatmospheric fistula formation(52). The study was stopped at the first interim analysis for futility. The risk of death was higher with the OA, but did not reach statistical significance, again leaving uncertainty as to how to treat patients(52). Otherwise, there is no prospective randomized data and results other than that which will be collected in the COOL trial.

**Negative Pressure Peritoneal Therapy (NPPT)**

Newer non-commercial and commercial negative pressure peritoneal therapy (NPPT) systems are now available for OA and may reduce the risks of enterocutaneous fistula and facilitate enhanced delivery of negative peritoneal pressure to the peritoneal cavity(32, 53, 54). In one of the largest contemporary OA databases no difference in enterocutaneous fistula rates were noted related to the type of temporary abdominal closure dressing used(55). However, there is a suggestion that more efficient peritoneal drainage may fundamentally impact the systemic complications of SCIAS. Animal studies(56) and in-silica modeling of these animal studies(57) demonstrates NNPT provides negative pressure and clearance of fluid throughout the peritoneum in contrast to simply leaving the fascia open with a temporary closure device. NPPT may reduce plasma bio-mediator levels compared to passive peritoneal drainage. Systemic inflammation (TNF-α, IL-1β, IL-6) in a single animal study was significantly reduced in the NPPT group and was associated with significant improvement in intestine, lung, kidney, and liver histopathology(56).

**Ugh – You want our advice? We don't really know!**

Many of the current investigators in the COOL trial also conducted the largest prospective randomized controlled trial addressing the question of differing NPPT in open abdomen management, the Intra-Peritoneal Vacuum Trial (35). Patients were enrolled in the operating room after an attending surgeon made the decision that an OA approach was required in critically ill/injured patients. Serum bio-mediator levels were measured every 24 hours in the initial post-laparotomy phase of critical care(35, 58). Although standard systemic bio-mediator levels were not statistically different nor was peritoneal fluid drainage, the 90-day survival rate was higher in the NPPT group (P=0.04)(35). A valid critique of this trial was the heterogeneous mix of trauma and non-trauma patients(35). A reasonable interpretation of this study's results is that the study's suggestion of a survivable benefit at minimum supports further investigation to therapeutic benefit in patients affected by severe SCIAS. In summary, great clinical equipoise remains as to whether the abdomen should be left open or closed after laparotomy in patients with SCIAS and warrants continuing to conduct the COOL Trial(38, 59).

**The Globalization of COOL**

The original intent of the COOL trial investigators was to examine an OA-NPPT technique that could be used anywhere(60). The vision is to provide clinical operative guidance to surgeons with severe complicated abdominal sepsis as to whether they should close or not when the abdominal cavity is physically closeable. At the Inaugural Investigators COOL trial Meeting in Parma, Italy the COOL trial Steering Committee endorsed the requirement to utilize an AbThera dressing (3M, 3M Center St. Paul, MN 55144-1000). This decision was quite controversial and was fundamentally tied to financial trial support/sponsorship from the device manufacturer. It is important to clarify that apart from use of the AbThera dressing, the sponsor was independent of the design or conduct of the study. The investigators assumed that the manufacturers of the AbThera would welcome the opportunity for an unbiased Global network of scientists to validate the efficacy of their proprietary device. This reflected the fact that the AbThera was only approved for use by the United States Food and Drug Administration, based on a so-called 510K "loophole" that recognizes a substantial equivalence of the AbThera to 1976 predicate technologies, and not that the AbThera has ever been validated in rigorous human trials. Thus, the initial COOL Protocol required the use of a 3M/Acelity AbThera dressing for any patient enrolled in the OA (intervention) arm of the Trial. This protocol stipulation was not without consequence as it precluded a 'global' approach as many centers could not participate as the device was either not available and/or affordable.

**The potential to utilize other non-commercial negative peritoneal pressure abdominal dressings in the COOL Trial**

On August 19, 2022, the 3M Company, who had acquired the Acelity Corporation cancelled support for the COOL trial(60). The sponsorship contract for the trial did permit the Corporate Sponsor to cancel support anytime without cause. While a major logistical problem for the COOL trial Investigators, an unanticipated benefit is removal of the requirement for use of the specific AbThera dressing in the OA arm. The COOL trial was always designed to be pragmatic, and the original protocol upon which ethics approval was obtained was generic regarding OA and NPPT management. The intervention arm of the trial has simply required NPPT administered to an OA defined by the fascia not being formally closed following all four intra-peritoneal quadrants washed until macroscopically clean(32). Thus, any manner of mechanical devices(61, 62), or potential instillation therapies(63), are permitted adjuncts as long as the primary requirement for an open fascia with NPPT is met.

## Methods/ Design

The current document is based upon the previously published COOL trial concise protocol(1), and outlines the evolution and lessons learned during the initial conduct of the COOL trial.

**Objective/Aims:**

The aim of the COOL trial is to test the null hypothesis that there will be no difference in survival when an OA management strategy administering NPPT is utilized compared to a primary fascial closure strategy in patients with SCIAS. The study is designed as a prospective, single-blinded, multi-center, international RCT. A SPIRIT Diagram overview of the trial is Presented in **Table 1**. The complete protocol as well as a rich library of study related documentation is available at www.coolstudy.ca.

**Setting**

The COOL trial is being conducted in operating rooms around the world where critically ill patients with SCIAS undergo source control laparotomy. The lead study center is the Foothills Medical Centre, a Quaternary Care Academic Medical Centre located in Calgary, Alberta, Canada. To date thirteen hospitals on four continents have enrolled patients in the COOL trial, although more centers are open for recruitment.

**Inclusion/Exclusion Criteria:**

Potential patients will first be identified in the emergency departments, in-patient ward, and critical care units of the participating centers. Eligibility can only be completely determined after the abdomen is explored in the operating room during the conduct of a laparotomy for source control. Patients will be eligible for inclusion if they have SCIAS, as operationally defined by the COOL trial (**Figure 1**).

The inclusion criteria are conceptually a two-part assessment to ascertain if patients clearly fulfill the definition of both severe and complicated IAS (SCIAS) while undergoing source control laparotomy. Thus, during the laparotomy it will become apparent to the operating surgical team that peritonitis is complicated, which will be reproducibly demonstrated by uncontained or unconfined purulent, feculent, or enteric spillage. In addition to being complicated, the inclusion criteria require that patients have severe IAS. For the purpose of the COOL trial, severe will be defined by any of: septic shock as defined by Sepsis 3 Consensus Guidelines (8), a World Society of Emergency Surgery Sepsis Severity Score $\geq$ 8(9), or a Calgary Predisposition-Infection-Response-Organ Dysfunction Score $\geq$ 3(64). An elaborated explanation of the thought processes and identification attributes of these criteria modelled on a trial population of SCIAS patients was previously published by the COOL trial Investigators(65).

The exclusion criteria for the COOL trial include: a) pregnancy, b) perceived physical inability to physically close the fascia primarily without undue tension or concerns for inducing severe IAH/ACS, c) intra-operatively determined absolute or relative requirement for "damage control" laparotomy including intra-peritoneal packing or non-anatomic post-surgical anatomy (ie, surgically placed permanent packing or bowel that the operating surgeon believes must be left in discontinuity after resection), d) the patient is expected to die shortly after operation because of their condition in the operating room and there is no intention 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; an example of where this could occur would be complete transmural midgut ischemia/necrosis), e) laparoscopic surgery (no laparotomy), f) pancreatitis as the source of peritonitis, g) acute superior mesenteric artery occlusion as the primary pathology, h) co-enrollment in another investigational study, i) peritoneal carcinomatosis, j) traumatic injury within 24 hours of the development of SCIAS, k) age < 18, or l) uncontrolled bleeding. It will be important for surgeons considering recruiting a patient to recognize before enrolling and randomizing a patient that fascial closure is not possible, as recognizing this after allocation to closure will constitute a protocol violation.

In current practice, it is likely that the most common reason for non-eligibility will be a 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.

**Randomization:**

Treatment arm allocation is randomly allocated from a central, password protected, randomization website (www.coolstudy.ca) (**Figure 2**). This can be done from any computer or smartphone and accessing the enrollment site for randomization need not be conducted by the attending surgeon. The ability to enroll a patient can be accessed with a password by any member of the surgical/anesthesia/critical care medicine/nursing team. 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 an NPPT TAC dressing being applied) associated with this entry will be generated. 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, on-line decision support software simplifies these calculations regarding any potential enrollment.

**Primary Closure – CLOSED allocation (Control arm)**

This strategy consists of primary closure of the fascia using any technique or suture material as chosen by the attending surgical team. Closure of the skin and the method for preventing surgical site infections is left to the discretion of the attending surgeon. There is no expectation for relaparotomy. Post-operative diagnostic imaging, and all other aspects of post-operative care including any decision to perform a relaparotomy shall be at the discretion of the treating critical care/surgical teams. A decision to perform a relaparotomy will constitute a study outcome. If at any subsequent laparotomy the attending and responsible surgeon selects an open abdominal strategy (cross-over to the intervention arm) the outcomes will be analyzed based on intention to treat allocation at the time of original enrollment. Any application of any wound suction or negative pressure device to the soft tissue above a closed fascia is permitted within the control arm (closed abdomen).

**Open Abdomen with Negative Pressure Peritoneal Therapy – OPEN allocation (Intervention arm)**

Once the patient has been allocated to an OA, the trial protocol does not mandate the interval until fascial closure although the intention is that closure will occur expeditiously once clinical determined safe by the treating surgeon. The COOL trial protocol does not mandate any length of OA therapy, although the principle of the earliest safe formal closure is expected. The time that the temporary abdominal closure dressing will be left in place, will be left to the discretion of the attending surgeon, but typical practice guidelines mandate either formal abdominal closure or dressing changes at 24-72 hours if formal abdominal closure cannot be completed(49). For both arms of the trial, it will be expected that attending surgeons are involved in either the direct supervision and/or intra-operative participation with either facial closure or temporary abdominal closure. The trial is considered pragmatic in allowing a variety of techniques as long as NPPT is being administered to an OA defined by the fascia not being formally closed and that all four intra-peritoneal quadrants have been washed until macroscopically clean(32). A suitable NPPT dressing must provide a complete viscero-protective layer, a means of the controlled egress of intra-peritoneal fluid, and negative pressure within the peritoneal cavity. Thus, any manner of mechanical traction devices(61, 62), or potential instillation therapies(63), will be permitted adjuncts as long as the primary requirement for an open fascia with NPPT is met. When the COOL trial was initiated, the commercial AbThera dressing was mandated, but this requirement was amended on August 2022 following 3M's termination of the contract and sponsorship. Thus, other centers from countries that choose to use any other negative pressure dressing will be permitted; the type of NPPT will be considered in a subgroup analysis.

**Outcomes**

The primary outcome will be survival at 90-days from enrollment. Secondary outcomes will be logistical and physiologic (**Table 2**.). Logistical outcomes will include Days Free Of (DFO); ICU, ventilation, renal replacement therapy, and hospital at 90 days from the Index Laparotomy. The physiological secondary outcomes will include change in APACHE II, SOFA, ARDS scores after laparotomy. The COOL trial inclusion criteria concerning intra-peritoneal contamination will be recorded, and the index source control laparotomy and every subsequent laparotomy will be graded according to the OA classification system from 2013 World Society of Abdominal Compartment Syndrome (WSACS) grading scale for OA(32, 66, 67). Surgical complications occurring after the index laparotomy will be graded according to Clavien-Dindo (Grade I = any deviation from normal postoperative course, including wound infections opened at the bedside but not treated with antibiotics; Grade II = requiring pharmacological treatment, e.g. antibiotic treatment, blood transfusion or parenteral nutrition; Grade IIIa = requiring surgical, endoscopic or radiologic intervention without general anesthesia and IIIb under general anesthesia; Grade IVa = life threatening complication requiring IC/ICU management with single organ dysfunction and IVb with multiorgan dysfunction; Grade V = death of patient)(68, 69).

All data are entered into a secure web application for building and managing online surveys and databases (REDCap) maintained by the University of Calgary. While the COOL Trial Case Report form is available in paper format (**Figure 3.**), investigators are encouraged to submit data directly into the online format securely hosted in REDCap (R esearch E lectronic D ata Cap ture). The Case Report Form (CRF) was also recently simplified to become more pragmatic in anticipation of an increasingly global participation with less dedicated research administration. Although an immensely detailed and exhaustive COOL trial database would facilitate future "spin-off" studies this should not be constructed at the expense of exhausting global collaborators dedicated to participate, but with limited research resources.

**The Evolution of COOL over COVID and other World Crises**

The initial protocol for the COOL trial envisioned multiple nested studies examining all aspects of OA management, of which an adequately powered trial of mortality was the centerpiece(1). Thus, any hospital providing emergency surgical services with intensive care support can participate if they are committed to recruit and randomize patients with SCIAS fulfilling the eligibility criteria during source control laparotomies. Contributing towards this main outcome will require only collection of the clinical outcome data. Prospective sub-studies that were envisioned to augment this main goal included COOL-Max (Biomediators), COOL-Mic (Microbiology), COOL-Cells (cellular defense mechanism), and COOL-Costs (economics). After the initiation of the clinical COOL trial, it became apparent that realistic operational demands and economic limitations precluded the conduct of these sub-studies, although a retrospective

COOL trial economic analysis of open versus closed treatment is still a practical future analysis(70). Thus, the dedicated focus of the current COOL trial efforts is completing the clinical outcome analysis powered on mortality.

**Sample Size Calculations**

The COOL trial is overall powered to detect a significant difference in the primary outcome, 90-day survival. Although imperfect, the preceding Intra-Peritoneal Vacuum Trial 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](71). This 30% reduction in mortality was considered too dramatic to be practically replicated and a more conservative effective 10% reduction in mortality was chosen. 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 was calculated as 275 patients in each arm.

**Statistical Analyses:**

The effectiveness of randomization will be displayed through a detailed presentation of patient demographic characteristics as outlined in **Table 3**. 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 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 1$^{st}$ laparotomy if not known). There will also be a planned subgroup analysis looking for any difference in outcomes within the intervention arm of the study between patients managed with the AbThera commercial dressing and any other NPPT dressing.

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 trial Investigators appreciate the general reluctance to stop randomized trials early due to benefit, due to the frequent over-estimating of treatment effects(72-74). Despite this, if a profoundly significant difference is found ($p < 0.01$) the trial will be stopped, otherwise it will continue to full recruitment.

**Ethical Concerns**

There is clinical equipoise concerning the operative management of SCIAS. Thus, the COOL trial Investigators feel a moral imperative to conduct this research to provide the best evidence to counsel bedside critical care physicians and surgeons(75). The COOL trial is currently approved by the Conjoint Health 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 may be considered. All participating Institutions will thus be required to obtain Ethical Approval appropriate and applicable to their Institutions.

Research in critically ill incapacitated patients is important to advance care. Conducting research among SCIAS is complicated due to the severity of illness, need for emergent interventions, diagnostic criteria confirmed only at laparotomy, and obtundation from anaesthesia. In other circumstances involving critically ill patients, clinical experts have worked closely with ethicists to apply principles that balance the rights of patients whilst simultaneously permitting inclusion in research. COOL Investigators have collaborated with both current and past Chairs of REB's to review and interpret the science and ethics for surgical investigators globally(76, 77). The ultimate goal is to balance respect for patient participants and to permit participation with a reasonable opportunity for improved outcome and minimal risk of harm.

## Discussion

Randomized surgical trials, especially those not supported by industry are notoriously few, hard to complete, and increasingly poorly supported by traditional granting agencies(78-80). Yet these trials are desperately required. In general, the overall quality of surgical research can be criticized as being grossly inadequate despite being the purported basis of surgeons making evidence informed decisions with an impact which may affect a patient's outcome including death or being permanently impaired (76, 77, 81, 82). One famous commentary compared surgical research to "comic opera"(83), lamenting the reliance on retrospective case-series as a methodology, and another referred to the typical retrospective case series (that constitute the near totality of research concerning SCIAS) as "research waste"(81). Unfortunately, retrospective case series predominate, potentially because they are vastly easier to conduct, are free of regulatory hurdles that accompany conducting an RCT, are publishable in journals and offer career advancement to investigators. However, why surgical RCTs are so few may also relate to fundamental differences in the regulatory approval process between medicines and medical devices. Whereas the level of confidence in pharmaceutical safety has risen substantially since the Thalidomide debacle(84), comparable changes in the safety bar to approve medical devices are less well developed. Thus, RCTs are often not required by device manufacturers or regulators to allow market entry(81), and thus research funding for devices demonstrating a beneficial effect on outcome are often lacking.

Nonetheless, the COOL trial has been designed to answer a critical clinical question that faces clinicians world-wide on a daily basis for which there is important clinical equipoise and potential severe consequences for patients in regards to outcomes(38, 59). Thus, this question has been identified as one requiring urgent study (49). The COOL trial has continued to be supported by not-for-profit Scientific Organizations with vested interest in the best care of the critically ill patient including the Abdominal Compartment Society and the World Society of Emergency Surgery. The trial design and vision follow directly from the preceding single-center study of differing modalities of NPPT conducted at the Foothills Medical Centre (58, 71). When the Intra-Peritoneal Vacuum Trial investigators considered following up the pilot study and enrolling more patients in a multi-center fashion, it became apparent after peer-to-peer discussion that any differing effectiveness of NPPT techniques was not the most relevant question concerning the OA(85). With a evolution in resuscitation practices involving balanced resuscitation, more and more trauma patients who previously become so edematous they required OA therapy, are no longer being overresuscitated with crystalloids, and can be primarily closed(86-88). This change in at least the trauma care paradigm has justified questions regarding the whole premise of damage control surgery for trauma(89), and IAS(45).

As over-resuscitation becomes less common(90, 91), it is intuitive that there will be more abdomens in non-trauma IAS patients which may be technically closed without inducing intra-abdominal hypertension (IAH). However, although these abdomens *may* be closed, *should* they be closed? As has been recently emphasized, there are profound differences in the basic science of sepsis and traumatic injury(92), with the previously unifying concepts of non-infectious Systemic Inflammatory Response Syndrome (SIRS) being effectively discarded as a clinically helpful construct(8, 93, 94). The one nebulous, poorly defined "holy-grail" of the optimal management of SCIAS is adequate "source control". It is suggested that even if an abdomen can be physically closed that there may be an advantage to leaving it open to allow better drainage of intra-peritoneal contamination, a concept that is supported by animal data suggesting the ability of NPPT to mitigate the elaboration of the inflammatory bio-mediator cascade(56, 57, 95), although this has not been demonstrated in humans(71).

### The Peritoneal Cavity as a Reservoir for Systemic Inflammation

There is a complex relationship between pressure, ischemia, and inflammation within the peritoneal cavity(14, 16). Independently the damaged gut seems to act as a continued source of inflammation propagating SIRS and potentiating MODS(96-100). Basic, predominantly animal lab research, from the last decade suggests an exciting potential. Visceral ischemia 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)(101-104). Post-operative complications are associated with increasing levels of systemic IL-6, and peritoneal TNF- α(103, 105). Jansson and colleagues thus postulated that peritoneal cytokines in humans respond more extensively compared to systemic cytokine, and that a normal postoperative course is characterized by decreasing levels of peritoneal cytokines based on studies of both elective and emergency surgery(106). Overall, the peritoneal cytokine response is much higher than the systemic response in peritonitis(104, 107-109). Hendriks and colleagues demonstrated that peritoneal cytokine levels (especially IL-6, TNF- α, (110)and IL-10) were dramatically different in rats who either survived or succumbed to an IAS model in the 24 hours after cytokine determination(107). 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(111-114).

The biologic rationale for COOL is that if safe, removing intra-peritoneal bio-mediators may mitigate their local effects and prevent their being absorbed systemically. Although early work suggested benefit to simple continuous peritoneal lavage after either gross peritoneal contamination in secondary peritonitis or in the setting of necrotizing pancreatitis(115, 116), subsequent studies could not confirm a benefit (117-119). Studies using hemofiltration to remove inflammatory mediators from the blood have been associated with reduced elevations of inflammatory cytokines (as assessed by blood IL-6 levels), early improvements of hemodynamic state and decreased lactate levels(120-122). However, it has not yet been demonstrated that extracorporeal filtration of inflammatory mediators improves clinical outcomes (123, 124). One possible explanation for this is that after the mediators have left the peritoneal cavity and become systemic the "horse is out of the barn".

NPPT therapy may be a more direct, earlier, and focused solution to this complicated problem, and one that will be complementary to the other benefits of OA. 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 part of the biologic rationale of the COOL trial.

Another potential benefit of NPPT after severe infection may be the attendant decompression of the abdominal compartment and prevention of even modest IAH. Patients with intra-abdominal infections are at risk of elevated IAP both as a result of the primary intra-peritoneal disease, and as a consequence of the use of large volume crystalloid resuscitation often used to maintain organ perfusion(125-127). Recent studies have demonstrated a high prevalence of IAH following aggressive volume resuscitation of septic patients. IAH is present in as many as 80% of septic medical and surgical ICU patients(128, 129). Reintam also reported that septic patients with IAH had a 50% mortality rate compared to 19% without IAH, making IAH a significant marker for an increased risk of death(130). Within the lead COOL 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(131). 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(132-134).

### COOL Trial Recruitment

Like many, especially investigator-initiated randomized trials, recruitment has lagged behind original predictions for the COOL trial. Poor participant recruitment is the most frequent cause for premature discontinuation of randomized clinical trials(135, 136). The COOL trial has competed with the COVID pandemic as a novel challenge apart from other established causes for poor trial enrollment such as inadequate funding, a narrow (but necessary) eligibility criteria, and a de-emphasis of research priorities even in University hospitals(135). The financial burden of Clinical Trial Insurance has been a particularly challenging burden to the COOL trial. The difficulty in financing was made worse by 3M cancelling its contract to support the COOL trial. However, recruitment is measured against an arbitrary predictions, so the true adequacy of recruitment will only be assessable when the outcome data is formally analyzed. Although this is not planned until 275 patients have been recruited, it is relevant that at this time COOL is nearly twice as large as the most relevant RCT previously reported(52). Thus, as new centers are added (as they have been monthly) the COOL trial will continue and should be successful in meeting its enrollment goals.

## Conclusions

The COOL trial is designed to examine if a mortality difference exists in this highly lethal and morbid condition, and to ensure critically ill patients are receiving the best care possible and not being harmed by inappropriate interventions or devices based on opinion only. The COOL trial Investigators now welcome truly global participation for all interested surgical scientists and their supporters.

## Abbreviations

**COOL** Closed Or Open after Laparotomy trial (https://clinicaltrials.gov/ct2/show/NCT03163095)

**SCIAS** Severe complicated intra-abdominal sepsis

**OA** Open Abdomen

**NPPT** Negative pressure peritoneal therapy

**IAS** Intra-Abdominal sepsis

**RCT** Randomized Controlled Trial

**LOD** Laparotomy on Demand

**PRL** Planned Re-Laparotomy

**EAF** Enteroatmospheric Fistula

**CPIRO** Calgary Predisposition Infection Response Organ Dysfunction

**APACHE** Acute Physiology and Chronic Health Evaluation

**SOFA** Sequential Organ Failure Assessment

**ARDS** Acute Respiratory Distress Syndrome

**MODS** Multiple Organ Dysfunction Score

**SIRS** Systemic Inflammatory Response Syndrome

**qSOFA** Quick SOFA score

**WSESSSS** World Society of Emergency Surgery Sepsis Severity Score

**APC** Activated Protein C

**mtDNA** Mitochondrial DNA

**C5a** Complement Factor 5 Activated

**C3a** Complement Factor 3 Activated

**REDCap** (R esearch E lectronic D ata Cap ture) database

**REB** Research Ethics Board

**TAC** Temporary Abdominal Closure

**IAH** Intra-Abdominal Hypertension

**IAP** Intra-Abdominal Pressure

**ACS** Abdominal Compartment Syndrome

## Declarations

**Authors Contributions:**

AWK, LA, both FCs, both MSs, MT, JLM, CD, and MH, as well as the General membership of the Abdominal Compartment Society and the World Society of Emergency Surgery conceptualized the study.

AWK drafted the initial manuscript.

CD, MH, AG, JLM, and DJR extensively re-wrote the initial manuscript.

All authors read and approved the final manuscript.

**Funding:**

No funding was received for the conduct of this analysis or the preparation of this Manuscript.

The COOL Investigators as an entity were supported to conduct a Protocol Development Meeting in Parma Italy on November 26 2017 through an unrestricted grant from the Acelity Corporation in which Inclusion Criteria for Closed Or Open after Laparotomy (COOL) for Source Control in Severe Complicated Intra-Abdominal Sepsis (https://clinicaltrials.gov/ct2/show/NCT03163095) trial was discussed. The 3M/Acelity Corporation provided limited financial support for the COOL trial under contract 032519-000/2050 until unilateral cancelation on August 19 2022.

The COOL trial has also received unrestricted support from the Abdominal Compartment Society and the Andrew W Kirkpatrick Professional Corporation.

**Ethics :** The COOL trial has been ethically approved at the lead and pilot center by the Conjoint Health Research Ethics Board (CHREB) of the University of Calgary (REB16-1588). The study has also been registered with the National Institutes of Health (ClinicalTrials.gov Identifier: NCT03163095).

**Consent for Publication:** Not Applicable.

**Availability of Data and Materials:** All results and data from the COOL trial will be available from Dr Andrew Kirkpatrick (andrew.kirkpatrick@albertahealthservices.ca) on reasonable request, as well as from the Study Website (www.coolstudy.ca).

**Competing Interests:**

[1]Andrew W Kirkpatrick serves as the PI of the COOL trial, as a member of the Canadian Forces Medical Services and has consulted for the 3m/Acelity Corporation, Zoll Medical, Innovative Trauma Care, CSL Behring, and the Statesman's Group.

[2]Federico Coccolini reported no declarations.

[3]Matti Tolonen reported no declarations.

[4]Samuel Minor reported receiving research support and speaking honoraria from COOK Biotech

[5] Emanual Gois reported no declarartions.

[6]Fausto Catena reported no declarations.

[7]Christopher J Doig reported no declarations.

[8]Michael D Hill reported no declarations.

[9]Luca Ansaloni reported no declarations.

[10]Massimo Chiurgi reported no declarations.

[11]Dario Tartaglia reported no declarations.

[12]Orestis Ioannidis reported no declarations.

[13]Michael Sugrue reported consultancy for 3M/Acelity and Novus Scientific

[14]Elif Colak reported no declarations.

[15]S Morad Hameed reported being the Founder of T6 Health Systems.

[16]Hanna Lampela reported no declarations.

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[18]Jessica L McKee reported consultancies with the Aceso, Innovative Trauma Care, Andrew W Kirkpatrick, and Zoll Corporations, as well as consulting with the Geneva Foundation and South Trail Psychology.

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[20]Massimo Sartelli reported no declarations.

[21]Chad G Ball reported no declarations.

[22]Neil G Parry reported being medical advisor for Front Line Medical Technologies – Cobra REBOA

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[25]Jenna Kroeker reported no declarations.

[26]Derek J Roberts reported no declarations.

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[28]Corina Tiruta reported no declarations.

[29]Ernest E Moore reported no declarations.

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[54]Walter L Biffl reported no declarations.

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[58]Luca Cardinali reported no declarations.

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[61]Maria Michela Chiarello reported no declarations.

[62]Gianluca Costa reported no declarations.

[63]Nicola de’Angelis reported no declarations.

[64]Nicolo de Manzini reported no declarations.

[65]Samir Delibegovic reported no declarations.

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[67]Belinda De Simone reported no declarations.

[68]Dr Vincent Dubuisson received grants from 3M-Acelity in 2021 for a conference about how to manage an OA, at the congress of the French Association of Surgery

[69]Pietro Fransvea reported no declarations.

[70]Luca Garulli reported no declarations.

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[78]Mansour Khan reported no declarations.

[79]Alfonso Palmieri Luna reported no declarations.

[80] Manu Malbrain reported he is co-founder, past-President and current Treasurer of WSACS (The Abdominal Compartment Society, http://www.wsacs.org). He is member of the medical advisory Board of Pulsion Medical Systems (part of Getinge group), Serenno Medical, Potrero Medical, Sentinel Medical and Baxter. He consults for BBraun, Becton Dickinson, ConvaTec, Spiegelberg, and Holtech Medical, and received speaker's fees from PeerVoice. He holds stock options for Serenno and Potrero.

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[107]Desmond Winter reported no declarations.

[108]Xiuwen Wu reported no declarations.

[109]Andeen Zakaria reported no declarations.

[110]Zaidia Zakaria reported no declarations.

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## Tables

Tables 1 to 3 are available in the Supplementary Files section.

## Figures

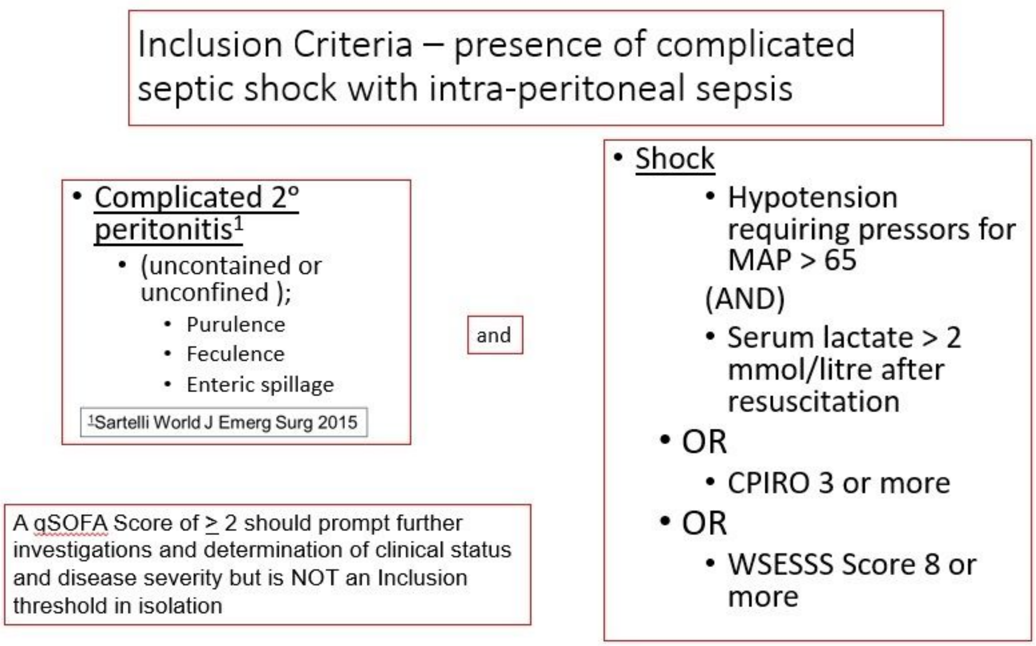


**Figure 1**

**Inclusion Criteria for COOL**

**Legend: CPIRO = Calgary Predisposition Infection Response Organ Dysfunction Score(137); WSESSS = World Society of Emergency Surgery Sepsis Severity Score(9)**

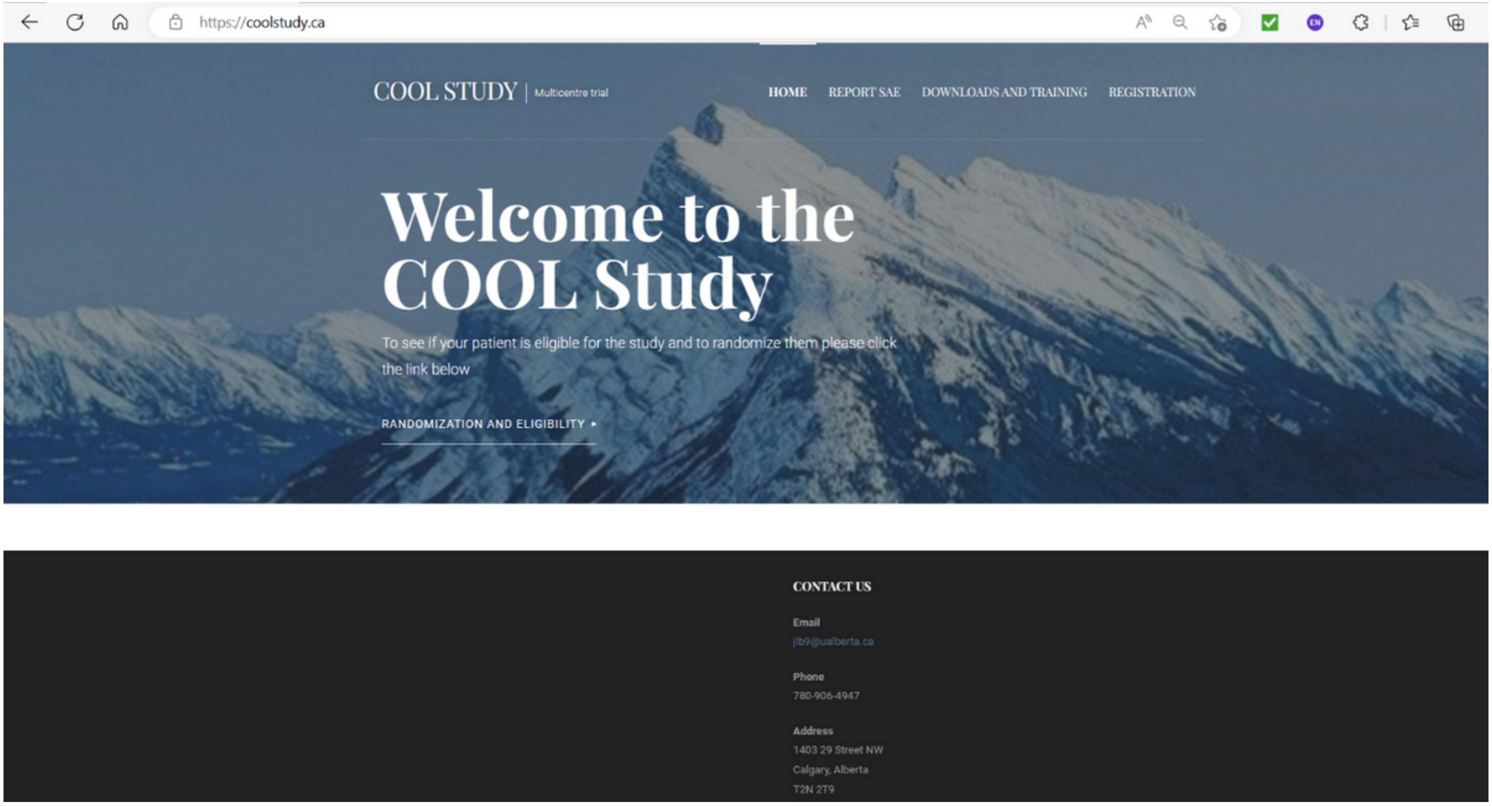


**Figure 2**

COOL Trial Enrollment Site

Legend: The COOL trial website (www.coolstudy.ca) provides central access to all study related documents as well as access to the password protected enrollment and randomization portal

COOL Study: CRF Version 3.2 Page | 1 Pt ID Number: ☐☐☐☐☐ - ☐☐☐ - ☐☐

| Demographics | |
|---|---|
| Age (years) | |
| Gender | ☐ M ☐ F |
| Height (cm) | . |
| Weight (kg) | . |

| Surgical History Data | Has the patient had any intra-abdominal surgery in the 30 days prior to the index laparotomy? Yes ☐ No ☐ **If yes**, please describe below* Date of Surgery (DD/MM/YYYY): |
|---|---|
| | |

*If there has been more than one intra-abdominal surgery in the 30 days prior to the index laparotomy, please use a separate surgical history data collection form for each. See Appendix A.

| Index ICU Admission Data (24 hrs of admission to ICU. Even if Prior to Index Laparotomy) | Admission Date (dd/mm/yyyy): | | Admission Time: __ : __ AM / PM |
|---|---|---|---|
| Vasopressors received: Yes ☐ No ☐ **If Yes**, please enter highest value below* | | Vitals and Laboratory Results. If not available enter 'NTA' | APACHE II: |
| Dopamine (ug/kg/min): | Dobutamine (ug/kg/min): | PaO2/FiO2** (mmHg) (Lowest): | GCS*** (Lowest): |
| Norepinephrine (ug/kg/min): | Milrinone (ug/kg/min): | Platelets x ($10^9$/L) (Lowest): | Bilirubin (μmol/L) (Highest): |
| Vasopressin (ug/kg/min): | Epinephrine (ug/kg/min): | MAP (mmHg) (Lowest): | Creatinine (μmol/L) (Highest): |
| Noesynephrine (Total ugs): | Ephedrine (Total ugs): | Respiratory Rate (BPM) (Highest): | Systolic BP (mmHg) (Lowest): |

*If a vasopressor was not given enter '0' in the field ** if no ABG, use SaO2/FiO2 Ratio ***If on sedatives or intubated estimate assumed GCS off sedation or extubated

| Study Enrollment Data / Shock | Yes | No |
|---|---|---|
| Did the patient have complicated secondary peritonitis at laparotomy including purulence, feculence and/or enteric spillage? | | |
| Did the patient have hypotension requiring pressors of MAP > 65 mmHg? | | |
| Did the patient have a serum lactate > 2 mmol/L after resuscitation? | | |
| CPIRO | | |
| Age > 65 years? | | |
| Any of the following comorbidities*: Liver Insufficiency, Cardiovascular, Respiratory, Renal, Immunosuppression? | | |
| Did they have a WBC <4000 | | |
| Did they have a temperature <36 degrees Celsius | | |
| Mean arterial pressure <90 OR administration of any vasopressor medications | | |
| PaO2/FiO2 (mmHg) <300 | | |
| Creatinine > 171 umol/L (2 mg/dl) OR < 500 ml urine day | | |
| Glasgow Coma Scale ≤ 12 | | |
| WSESSS | | |
| Did the patient have sepsis with organ dysfunction at admission* | | |
| **At admission** was the patient in acute septic shock requiring vasopressor agents* | | |
| Does/did the patient have health-care associated infection | | |
| Was Colonic non-diverticular perforation peritonitis the origin of intra-abdominal infection? | | |
| Was Small Bowel perforation peritonitis the origin of intra-abdominal infection? | | |
| Was Diverticular diffuse peritonitis the origin of intra-abdominal infection? | | |
| Was Post-operative diffuse peritonitis the origin of intra-abdominal infection? | | |
| Was there a delayed initial intervention of >24 hours for source control for your patient?* | | |
| Age > 70 years: | | |
| Does your patient have any of the following: Chronic glucocorticoids, immunosuppressive agents, chemotherapy, lymphatic disease, virus. Immunosuppression from chemotherapy, radiation therapy, long-term or recent high-dose steroids, immunodeficiency (eg, leukemia, lymphoma, AIDS)? | | |

*For further clarification on this question see Appendix B

| PRE- Operative Data* | Date (dd/mm/yyyy): | | Patient Location | Ward | ICU | ED | CVICU | Transferred from another Hospital | Step-down unit |
|---|---|---|---|---|---|---|---|---|---|

| Vasopressors received: Yes ☐ No ☐ **If Yes**, please enter highest value below* | | Vitals and Laboratory Results. If not available enter 'NTA' | |
|---|---|---|---|
| Dopamine (ug/kg/min): | Dobutamine (ug/kg/min): | PaO2/FiO2** (mmHg) (Lowest): | GCS*** (Lowest): |
| Norepinephrine (ug/kg/min): | Milrinone (ug/kg/min): | Platelets x ($10^9$/L) (Lowest): | Bilirubin (μmol/L) (Highest): |
| Vasopressin (ug/kg/min): | Epinephrine (ug/kg/min): | MAP (mmHg) (Lowest): | Creatinine (μmol/L) (Highest): |
| Noesynephrine (Total ugs): | Ephedrine (Total ugs): | Respiratory Rate (BPM) (Highest): | Systolic BP (mmHg) (Lowest): |

| Charlson Co-morbidity** | Yes | No | Charlson Comorbidity** | Yes | No | Randomization Data | |
|---|---|---|---|---|---|---|---|
| Myocardial infarct | | | Diabetics with end organ damage | | | | |
| Congestive heart failure | | | Cancer (without metastasis) | | | Randomization Date (dd/mm/yyyy) | |
| Cerebrovascular disease | | | Cancer with metastasis | | | | |
| Hemiplegia | | | Leukemia/lymphoma | | | Randomization Time (HH : MM) | __ __ : __ __ AM / PM |
| Peripheral vascular disease, AAA | | | Dementia | | | | |
| Connective tissue disease | | | Severe Organ Dysfunction, Kidney | | | Randomization: | Open / Closed |
| Immunosuppression/steroids use/chemotherapy | | | Severe organ dysfunction, Liver | | | | |
| Smoking | | | Presence of ostomy/incisional hernia | | | If Open, AbThera Product Number: | |
| Pulmonary disease mild | | | HIV infection | | | | |
| Pulmonary disease modern | | | HIV infection with complications | | | Notes: | |
| Pulmonary disease severe | | | Liver disease mild | | | | |

**Figure 3**

**COOL Study Case Report Form**

Notes: The Case Report Form is a extensive document that can be accessed online at Study Documents – COOL Study, but Investigators are encouraged to complete the form on-line where it will be securely entered into the University of Calgary REDCap (R esearch E lectronic D ata Cap ture) database.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables123.docx