Esmolol to Treat the Hemodynamic Effects of Septic Shock

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B1. PURPOSE OF PROTOCOL

We hypothesize that the provision of beta blockade to tachycardic patients in vasopressor-dependent septic shock will lower the heart rate, thereby improving diastolic filling time and improving cardiac output, resulting in a reduction in need for vasopressor support. To test our hypothesis, we propose a Phase II randomized trial to determine if esmolol decreases vasopressor requirements (primary endpoint) and alters the inflammatory cascade as well as oxygen consumption in patients with septic shock. Given that the compelling finding of a 30% reduction in mortality was the result of a single center European study, **we submit that a Phase II pilot study is needed in a U.S. critical care environment, to validate this concept, before a larger, multicenter U.S. trial could be justified**. If we find that esmolol does allow for more rapid decrease of vasopressor need over time, without evidence of harm, we will have the necessary and sufficient data upon which to design a larger Phase III investigation aimed at addressing clinical patient-related outcomes.

Specific Aim #1: To determine if continuous infusion of esmolol improves the hemodynamic profile in septic shock by decreasing the need for vasopressor support.
In order to achieve this Aim, we will perform a multi- center trial randomizing patients to receive a continuous infusion of esmolol compared to usual care (total of 104 patients) with the primary outcome of reduction in need for vasopressor support.
Specific Aim #2: To characterize the effects of esmolol infusion on the pathophysiology of septic shock.
Specific Aim #2a: To characterize the effects of esmolol infusion on total body oxygen consumption (VO_2) in patients with vasopressor-dependent septic shock.
In the Morelli *et al*.[6] study, there was significantly lower VO_2 in the esmolol group vs the control group at every time point measured (p=0.001). In that study, VO_2 was measured indirectly via pulmonary artery catheter measurements; we aim to validate the finding of decreased oxygen consumption in patients receiving esmolol by directly measuring VO_2 via the ventilator circuit in the subset of patients who are mechanically ventilated. Our hypothesis is that esmolol infusion, in part by decreasing the workload of the cardiac myocytes, will decrease overall oxygen demand, leading to lower VO_2 in septic shock.
Specific Aim #2b: To characterize the effects of esmolol on inflammatory markers in patients with vasopressor-dependent septic shock.

In previous human and animal studies, esmolol has been associated with decreased inflammation as represented by attenuation of inflammatory cytokines and biomarkers.[8-11] In this Aim, we will test the hypothesis that esmolol modifies the inflammatory response by measuring key biomarkers at 0, 6, 12, and 24 hours after enrollment.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Severe sepsis and septic shock are the cause of significant morbidity and mortality worldwide. **An estimated 751,000 cases (3.0 per 1,000 population) of severe sepsis occur in the U.S. each year, resulting in approximately 215,000 deaths**.[1] Septic shock is characterized by cardiovascular dysfunction (most typically systemic arterial hypotension), a hypermetabolic state, and lactic acidosis, potentially leading to death. In addition, the economic burden on the health care system for patients suffering from severe sepsis is striking. Weycker *et al*. report that patients suffering from severe sepsis will require an average of $45,000 dollars of medical care cost on their index admission

and up to $78,500 dollars in the first year post-diagnosis.[12] These figures rival such entities as acute myocardial infarction, trauma, and stroke.

Despite advances in critical care and increased awareness of the need for early identification and aggressive treatment of sepsis, morbidity and mortality for septic shock remains unacceptably high. The downstream cardiovascular effects of septic shock, beyond the shock period itself, are not trivial: myocardial depression, tachycardia-induced cardiomyopathy, and direct myocyte toxicity.[2-5] Novel therapies for septic shock are continually being sought, with a long history of agents which have failed to improve outcomes for these patients, and in some cases, have actually conferred harm.[13-18] Currently, there is no adjunctive therapy for the treatment of septic shock that has adequately demonstrated an ability to reduce morbidity and mortality. ***Furthermore, beyond the use of vasopressors and inotropes to support failing hemodynamics, there is currently no specific therapy targeted at the cardiovascular effects of septic shock.*** Identification of a therapy which could improve outcomes for patients with septic shock, specifically related to cardiovascular dysfunction, would be a major advancement in a field plagued by a history of therapeutic failures. While a recent single-center European trial has shown promise for the use of beta blockade in septic shock, further evaluation is necessary before widespread application of this therapy could be safely and responsibly advocated. However, there are reasonable existing data available to justify moving forward with this line of investigation, as outlined below.

2.1a. Esmolol is associated with reductions in heart rates in patients with septic shock Morelli *et al*.[6] conducted an open-label randomized Phase II trial of esmolol for patients with septic shock who had a heart rate >95/min and received high dose norepinephrine to maintain a mean arterial pressure (MAP) >65mmHg. The investigators randomly assigned 77 patients to esmolol and 77 to standard care, with a primary outcome of reduction of heart rate to 80-94/min for 96h. Secondary outcomes included organ dysfunction as well as mortality. They found that they were able to achieve heart rate control in all patients in the esmolol group without adverse effects. In what has received the most attention in the critical care community, 28 day mortality was 49.4% in the esmolol group vs 80.5% in the control group (hazard ratio, 0.39; 95% CI, 0.26 to 0.59; $P < .001$). *While these results appear promising, the study cohort may not represent a typical septic shock population in a United States ICU*. For example:
1) The control group had a 28-day mortality of 80.5% and an overall in-hospital mortality of 90.9% which is much higher than typical mortality related to septic shock seen in the U.S. (generally 25-50% in most U.S. ICUs).[19, 20]
2) All of these patients had pulmonary artery catheters (PACs) which are not routinely used in the care of septic shock patients in most ICUs
3) The study patients were receiving what would be considered high doses of norepinephrine in most U.S. ICUs (the median dose of norepinephrine in the study was 0.38 mcg/kg/min [0.21-0.87] in the esmolol group and 0.40 [0.18-0.71] in the control group)
4) All study patients received hydrocortisone (300mg/day) which is not routine for all cases of septic shock in most U.S. ICUs
5) Study patients who had a mixed venous oxygen saturation <65% or increasing arterial lactate concentration were treated with levosimendan, a non-adrenergic calcium

sensitizer aimed at improving systemic oxygen delivery which is not used clinically in the United States

For these reasons, *it is essential to reproduce this trial in a critical care environment in the United States before larger scale trials could be advocated.*

2.1b. Use of esmolol in septic shock appears to be safe and well-tolerated

Additionally, a group from the Czech Republic reported the results of a single center trial in which 10 septic shock patients were treated with esmolol infusion, demonstrating efficacy in terms of heart rate reduction as well as safety of this intervention (no change in norepinephrine infusion dosage, non-significant changes in stroke volume, oxygen delivery, VO_2, or lactate).[21] This study further contributes to the data that esmolol therapy can be safely administered in septic shock.

2.1c. Esmolol may modulate the inflammatory response. Previous animal study and small human trials suggest that esmolol may modulate the immune response. In an animal model of septic shock, mice were injected with lipopolysaccharides (LPS) intraperitoneally, and then randomized to either esmolol infusion or normal saline infusion. There was significantly higher survival at 120 hours in the esmolol group (34.9%) vs. the saline group (11.6%), p=0.01. Additionally, the investigators found that there was increased gene expression in immunologic and apoptotic pathways which may have a role in the survival difference.[9] Kim *et al*.[8] performed a trial of esmolol infusion in patients undergoing laparoscopic gastrectomy; patients were randomized to one of three groups (saline, a clinical dose of esmolol, and a subclinical dose of esmolol). They measured levels of IL-6, IL-4, IL-10, C-reactive protein (CRP), and found that post-operative levels of IL-4 were decreased significantly in the clinical dose group compared to the saline group (2.14 vs 21.91 pg/mL, p=0.022), as well as lower CRP levels on post-operative day 1 in the esmolol-treated groups in a dose-dependent manner.

2.1d. Beta-blocker improves survival of septic rats through preservation of gut barrier function. In this study, sepsis was induced via cecal ligation and perforation in 19 rats, with 9 randomized to control treatment and 10 randomized to treatment with esmolol. Investigators found that mean survival time in the esmolol group was significantly longer compared with the control group (69.5 +/- 26.8 vs. 28.6 +/- 11.0 h, p<0.01). Furthermore, intraperitoneal fluid TNF-alpha levels were elevated in the control group but significantly depressed in the esmolol group (16.8 +/- 10.7 versus 5.4 +/- 7.1 pg/mL, p<0.05), and the gut mucosal injury score was elevated (4.1 +/- 0.6 versus 2.8 +/- 0.6, p<0.01) suggesting that the esmolol infusion may have modified gut barrier function in this animal model of intra-abdominal sepsis.[10]

2.2 Significance

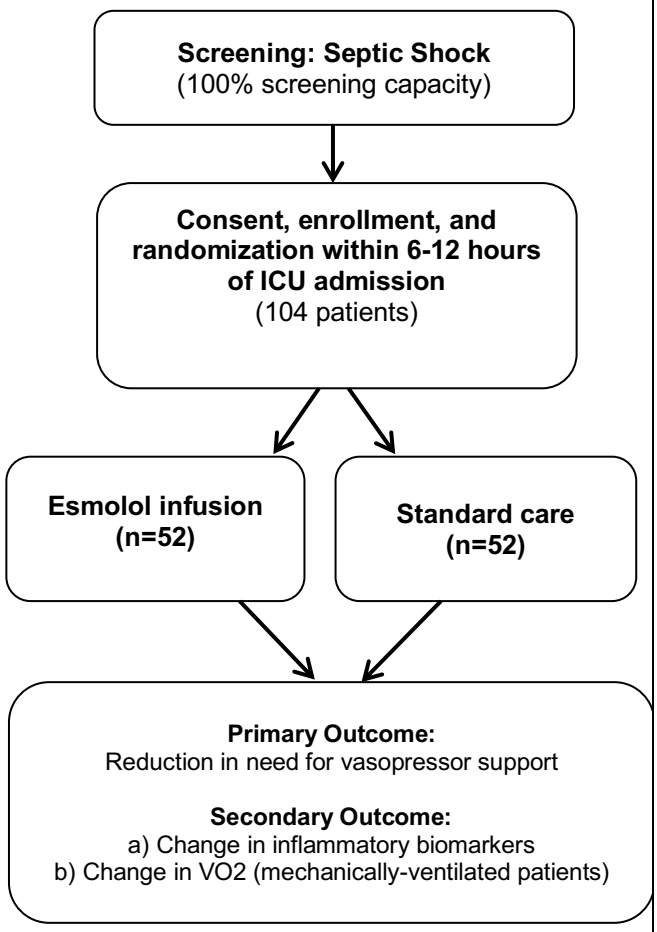
2.2a. Overall significance of the current proposal: Given the sheer numbers of patients afflicted with septic shock each year, and the current mortality rates despite advances in early aggressive treatment and sophisticated critical care, new targets are needed in the armamentarium against this disease. With the ageing of the U.S. population, it is anticipated that the incidence of sepsis and septic shock will only increase[1], adding to the urgency to identify an intervention to improve outcomes and reduce disease burden amongst survivors.

2.2b. Innovation: The current proposal is innovative in that it leverages an existing therapeutic agent for a new indication, building on existing data supporting the concept of beta-adrenergic antagonism in septic shock. If the promising findings reported in the recent single center study from Italy[6] could be confirmed in a pilot study in a septic shock cohort in a typical U.S. tertiary care medical center, the science of the resuscitation of septic shock could be considerably advanced. Esmolol, which is already used in practice in other clinical scenarios in critical care, could easily be incorporated into the treatment of patients with septic shock, if the balance of evidence ultimately indicates benefit in this population. In addition to evaluating the effects of esmolol on hemodynamics, our proposal is innovative in that we will also directly measure continuous VO_2 in the subset of patients who are mechanically-ventilated in order to better understand how beta blockade therapy will affect overall oxygen consumption in a septic shock population, which to our knowledge has not been previously examined in this way.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design: A Multi-center, open-label, randomized, phase II trial comparing esmolol to standard care (no esmolol) in septic shock patients with tachycardia.



Screening: All patients admitted to the ICU will be identified through electronic patient records and screened for possible enrollment by trained research assistants. Our research group employs multiple full-time research assistants responsible for screening and enrollment. With this staffing structure, we are able to enroll patients 24 hours per day/7 days per week.

Consent: If a patient meets all of the inclusion criteria and none of the exclusion criteria, a member of the research team will approach the patient for written informed consent. If the patient is unable to consent, a legally authorized surrogate may be approached per standard IRB procedures. Investigators will explain the study's background and significance, potential risks and benefits, and study protocol. In the event that a physician Investigator or a surrogate is not physically present in the hospital to perform the consent process, a non-physician study staff (research assistant or research coordinator) will coordinate a conference (i.e. FaceTime or Skype video conferencing or telephone) for the physician investigator / surrogate to join in the consent discussion. If consent is obtained, a signed copy will be given to the patient and another copy placed in the medical record. The original signed informed consent will be kept in our locked research office (see specifics in **Section B6 - Recruitment and Consent Procedures**).

Randomization: The randomization will be done in a 1:1 ratio between treatment and control groups in varying blocks of two to six using SAS software. This main list of group assignment will be maintained in the hospital research pharmacy.

Study Arms: After randomization as described above, patients will be assigned to one of the following two arms: esmolol for 24 hours or standard care (no esmolol).

1) Esmolol for 24 hours: Patients in this arm of the study will have Esmolol for 24 hours.

2) "Usual Care": Patients will receive 100 mL of normal saline over 5-10 minutes at the beginning of the study in addition to usual care. When patients are enrolled in a clinical trial there is a time period from consent to study drug administration that depends on the investigative team, the research pharmacy, and the available nursing staff. In order to guarantee that this time interval is similar between the two groups the control arm will receive a small bolus of saline at the beginning of the trial. This will ensure that "time zero" is similar between the two groups.

Blinding: The study will not be blinded as an esmolol infusion must be actively titrated to effect by clinicians and it will noticeably decrease heart rate.

Standard septic shock treatment: Patients, irrespective of treatment group, will be managed at the discretion of the clinical team. BIDMC has internal guidelines for the management of septic shock which reflect the most recent 2012 Surviving Sepsis Campaign guidelines and are incorporated into the care of patients with septic shock in the ICUs.[23]

Study medication preparation and administration: After consent and enrollment, a form will be faxed to the pharmacy confirming the consent, indicating the specific study, and supplying information on the location of the patient. An electronic order will be placed in the computer to initiate the study drug. Telephone contact will be made with the pharmacist to confirm receipt and execution of the study medication protocol. Enrolled patients will be randomized to either esmolol or standard care (see above). The study drug will then be sent to the ICU and will be administered to the patient by the treating nurse. Esmolol will be titrated to a heart rate of 80 - 94 per minute, starting at 10mcg/kg/min and subsequently increasing every 20 minutes in increments of 10 mcg/kg/min (or slower at the discretion of the team) until target is achieved. The maximum allowed dose will be 300mcg/kg/min. Esmolol will be continued for 24 hours.

If the patient is randomized to standard care, a one-time 100 mL saline placebo will be administered as a time stamp for the study protocol.

Rationale for dosage regimen: The dosing regimen chosen for this study is similar to that described in the study by Morelli *et al*.[6] In that study, the median esmolol dose was 100mg/hr (IQR 50-300), and they did not exceed a maximum of 2000mg/hr. At BIDMC, we administer esmolol via a weight-based protocol, and for an average 70kg patient, the mean dose would not be expected to exceed the maximum dose used in the Morelli *et al.* study, therefore helping to ensure safety. Since esmolol is titrated, we will have a titration protocol that will be utilized by the

bedside nurse in the ICU to adjust the infusion based on target heart rate parameters.

Safety considerations: In order to minimize the risk of causing a decrease in cardiac output and resultant worsening hypotension, we will only enroll patients after they have been adequately volume resuscitated such that preload is optimized. Furthermore, we will obtain a baseline measurement of CO/CI; study drug will only be administered if the CI >2.2 L/min/m^2. By using an ultra-short acting ($t_{1/2}$ approximately 9 minutes[24]) and titratable agent like esmolol, the infusion can be adjusted or even terminated without lingering effects of the medication if there are unintended hemodynamic effects such as hypotension or decrease in CI. We will ensure nurse comfort and competency by having the dedicated ICU Clinical Nurse Specialists (CNS) oversee the implementation as it pertains to frontline ICU nurses. We will also have a critical care pharmacist assist with the design of the titration protocol.

Measurements:

Hemodynamics: Heart rate and blood pressure will be measured hourly for all patients for the full study period. Cardiac index and stroke volume will be measured continuously with the use of the Non-invasive Cardiac Output Monitor (NICOM) (Cheetah Medical, Oregon, USA) which is a validated tool for hemodynamic measurements in the critically ill.[25]

Vasopressors: Vasopressor doses will be recorded hourly for the full study period.

Additional measurements: At baseline we will collect pertinent variables such as demographics and past medical history. At baseline, 6, 12 and 24 hours after, trained research assistants will collect information on laboratory values and interventions performed by the clinical team (including but not limited to fluid administration, procedures, pharmacological intervention etc.), ventilator settings, results of cultures, etc. Patients will be followed to hospital discharge and time on mechanical ventilation, length of ICU stay, length of hospital stay and mortality will be recorded. SOFA scores[26] will be calculated at all time points. In a subset of patients who are mechanically ventilated, we will also continuously measure oxygen consumption for these patients via continuous VO2 monitor connected to the ventilator circuit (see below for details).

Research Blood draws: At each of the four time point approximately 40 mL of blood will be obtained by venipuncture, or from an existing venous or arterial catheter for a total of 160 mLs of blood: (40ml x 4 draws =160ml)

1. Time zero (just before study drug administration)
2. T=6 hrs (+/- 4 hrs)
3. T=12 hrs (+/- 4 hrs)
4. T=24 hrs (+/- 4 hrs)

Data Collection:

Cytokine and biomarker analysis: Blood will be processed, aliquoted and frozen at -80ºC for later cytokine and potential other biomarker analyses. Measurements will include but not necessarily be limited to Interleukin (IL)-1β, IL-6, IL-8, IL-10, metabolomic profile, CRP, procalcitonin, and IL-6, IL-4, IL-10, TNF alpha at serial time points (0, 6, 12, 24 hours) after study drug delivery. The inflammatory cascade assays will be measured in the Center for Resuscitation Science Laboratory.

Oxygen metabolism analysis: Research blood will be used in the isolation of peripheral blood mononuclear cells (PBMCs) from blood: Plasma will be separated by centrifugation at 800g for 15min at 4°C and saved without disturbing the buffy coat. Then plasma will be replaced with the same volume of phosphate buffered saline (PBS). The cell pellets will then be mixed by gently pipetting up and down several times to disperse the cells. Next, PBMCs will be isolated from the PBS substitute blood samples using density gradient, Ficoll-Paque premium (GE Healthcare Bio-Sciences Corp).

The isolated PBMCs will be used in the cellular metabolism and mitochondrial function analysis. Using the XF24 Extracellular Flux Analyzer (Seahorse Bioscience) we will simultaneously measure the oxygen consumption rate (an indicator of mitochondrial respiration), and the extracellular acidification rate (an indicator of the lactate produced e.g. anaerobic metabolism). First, PBMCs will be re-suspended in Dulbecco's modified Eagle's medium and seeded in a 24-well assay plate pre-coated with CellTak (BD Biosciences) and incubated at 37°C for 30 min to allow cells to attach to the bottom of the plate. Then the wells will be washed and 675uL of fresh XF assay buffer will be added to each well. The plate will be incubated at 37°C without Carbon Dioxide (CO2) for 1 hour prior to assay start.

Lactate, ScVO2 measurements: Lactate and ScVO2 levels will be measured using whole blood collected in a standard blood gas syringe by the clinical nursing team with the assistance of our research staff at the bedside prior to drug delivery (baseline), and again at 0, 6, 12, 24 hours after enrollment. The sample will be sent to the hospital's clinical lab for immediate analysis.

VO2 measurements: The Compact Anesthesia Monitor by General Electric is a patient monitor with a built-in module for measuring spirometry and gas exchange. A respiratory therapist will be responsible for connecting/disconnecting the monitor. The gas exchange module measures the volume of inspired gas using a pneumotachograph, and the partial pressure of oxygen with inspiration and expiration using a rapid paramagnetic analyzer. Measurements are taken by a sensor placed in the ventilator tubing and connected to the gas analyzing module,[27] providing continuous readings with each patient breath. All data are downloaded onto a laptop used solely for research purposes. The Compact Anesthesia Monitor has been FDA approved for the measurement of VO_2 in

mechanically ventilated patients. The technology has been validated against indirect calorimetry, and is perhaps even more accurate at higher FiO_2.[27, 28]

Outcome measures and data management:

Primary endpoint: The primary endpoint will be improvement in the hemodynamic profile as measured by a decrease in the need for norepinephrine support. This will be defined as the difference in norepinephrine dose between groups at 6 hours after onset of study drug.

Justification: The initial trial showed that esmolol not only decreases heart but also decreases vasopressor requirements in patients with septic shock. While the reduction in heart rate might be considered expected from a beta blocker, the reduction in vasopressor dosage is not. However, the reduction in vasopressor dosage would be a significant clinical advancement for the treatment of septic shock and therefore we chose this as the primary clinical endpoint for the trial. We chose the 6 hour time point as the primary endpoint since we anticipate the effect of esmolol will be apparent by that time (rapid onset and effect based on previous study) and that the variance between groups (based on our control preliminary data) is minimal at that time point allowing for adequate power to detect a difference. We also will have secondary endpoints evaluating other time points as well as change over time (below).

Secondary endpoints:

Additional hemodynamic endpoints: While the primary endpoint will be difference in norepinephrine dose at 6h, we will also measure the difference in vasopressor dose between groups at 12h and over time using mixed linear model (see data analysis). We will also measure differences in heart rate at the 6 and 12h time points and over time (see data analysis). Other secondary hemodynamic endpoints will include time to shock reversal (cessation of all vasopressors for at least 12h) and change in lactate over time (0, 6, 12, 24 h).

Oxygen consumption: Aim #2a endpoint will consist of difference in oxygen consumption over time between esmolol and control groups. Based on findings in the Morelli *et al*. study, we anticipate a similar decrease in VO2 among those who receive esmolol. While Morelli *et al*. measured VO2 via PA catheter, we will measure VO2 directly via the ventilator.

Inflammatory endpoints: For Aim #2b, we will characterize the effects of esmolol infusion on the inflammatory cascade as measured by changes in select inflammatory biomarkers at time points 12 and 24 hours accounting for baseline measurements at time zero.

Clinical endpoints: Recognizing that we lack power to detect differences in mortality, we will still collect in-hospital mortality anticipating that if the overall study is positive, we can use these data to help power a future Phase III trial. In addition, we will measure the clinical endpoints of length of ICU stay, hospital length of stay, and organ dysfunction at 96 hours as defined with the SOFA score.

Data acquisition and management: Dr. Cocchi and the Center for Resuscitation Science have extensive experience in data collection, data entry, database development, and data management for both large-scale observational trials and randomized clinical trials. The Center for Resuscitation Science currently manages over 20

active databases with over 1 million data points from nearly 10 years of research. As such, we have honed an effective and reliable protocol for managing data as described below.

Data Entry and Quality:

Immediately following data collection, the paper data sheet will be entered directly into the electronic database REDCap (described below). Two trained research assistants will independently enter the data for primary and secondary endpoints to ensure transfer accuracy. Several measures are taken to assure data quality. They are as follows:

1) Database access is restricted to team members trained in data entry for this study.
2) The REDCap database is specifically designed to maintain data integrity by preventing unintentional changes or lost data.
3) The principal investigator and/or his designee will perform random data spot-checks and audits.
4) Designated database manager will be assigned to oversee the database and to maintain quality.

Database: The database application we will use is REDCap. REDCap is a professional database endorsed by the National Institutes of Health (through the clinical and translational science award) that provides a secure, user-friendly database with capacity for easy statistical analysis. To ensure confidentiality, all entries will be identified by a patient identification number rather than a name or hospital medical record number. The REDCap data management system is fully HIPAA-compliant and includes a complete audit-trail for data entry validation. We will maintain an electronic and paper copy of the master list with identifiers. The computer list will be maintained on the hard-drive of two separate computers in password-protected files.

Information security: All hard copies of study data will be kept in a locked filing cabinet to which only the PI and co-investigators will have access. All electronic data will be stored on the BIDMC secure server behind a firewall in a password protected database. We will also utilize the database application, REDCap. REDCap is a professional database endorsed by the National Institutes of Health (through the clinical and translational science award) that provides a secure, user-friendly database with capacity for easy statistical analysis.

Safety Monitoring:

In order to help ensure adequate protection of human subjects enrolled in this clinical study, we established an independent three-member panel with expertise in the areas of clinical trials, critical care and statistics. The Data Safety Monitoring Board (DSMB) will consist of: 1) Dr Peter Clardy MD (Pulmonary Critical Care at Mount Auburn Hospital and former MICU Director BIDMC, will serve as Chair of DSMB), 2) Dr. Marwa Sabe MD, MPH (Cardiovascular Disease and Advanced Heart Failure) and 3) Dr. Myles Boone MD (Anesthesia Critical Care).

The DSMB will be charged with reviewing all serious adverse event reports and will also perform interim analysis of the data. A statistician will prepare the data reports for review by the DSMB Committee. Data will be reviewed for safety after the initial 20 patients are enrolled and then every 40 patients thereafter; this schedule is subject to change depending on the recommendations of the DSMB. Any adverse events will be reported in real-time. The Chair of the DSMB can convene a meeting at more frequent interval if deemed necessary.

The site PIs at each collaborating institution will be responsible for reporting all adverse events (AEs), serious adverse events (SAEs) as well as any other adverse events or issues felt to be related to the study protocol to the coordinating center , Beth Israel Deaconess Medical Center. In addition to reporting all adverse events to the DSMB, all adverse events will be disseminated by BIDM to each participating institution's IRB for review according to their policies and guidelines.

POSSIBLE BENEFITS

There may be no benefits to patients participating in this study. This is a randomized interventional trial. Although we do not know whether the active medication will provide benefit it is possible that patients enrolled in this investigation and receive the active medication will have improved lactate clearance and better clinical outcome. The knowledge gained from the proposed study may help similar patients in the future.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Risks to patients involve the following main areas:

(1) ***Risk associated with hemodynamic effects of esmolol****: Esmolol is an FDA-approved medication that is already utilized in clinical practice but in this trial will be applied for the purpose of controlling heart rate in septic shock, which is not standard clinical practice. We have created procedures to ensure that patients have been adequately volume resuscitated and will be well-monitored in a critical care setting before receiving this infusion. All patients will have continuous monitoring of cardiac output during the study period.*

There are side effects associated with esmolol, which range from minor to serious:

More common: Blood pressure decreased, nausea, infusion site reaction

Less Common: Peripheral ischemia, dizziness, somnolence, confusion, headache, agitation, vomiting

Rare: Abdominal discomfort, abnormal thinking, angioedema, anorexia, anxiety, bradycardia, bronchospasm, cardiac arrest, constipation, coronary arteriospasm, decompensated heart failure, depression, dyspepsia, flushing, heart block, hyperkalemia, lightheadedness, pallor, paresthesia, psoriasis, renal tubular acidosis, seizure, severe bradycardia/asystole, syncope, urinary retention, urticaria, xerostomia

Esmolol is ultra-short acting and easily terminated if there are any untoward side effects like significant drop in cardiac output or hypotension. The low risk of esmolol administration and the potential increased understanding of the role of the cardiovascular system in septic shock, as well as identification of a new therapeutic target, make the risk/benefit ratio of this study beneficial. A three-physician panel along with a biostatistician will be convened a minimum of once a year to provide data safety and monitoring for the trial. Any adverse events will be reported in real-time. The Chair of the DSMB can convene a meeting at intervals more frequently if deemed necessary and all potential issues and concerns will be reported to both the Institutional Review Board (IRB) and the Chair of the DSMB in real-time. This study proposal will be reviewed by the IRB at BIDMC. All data will be kept confidential as detailed above.

(2) ***Risk associated with blood draws:*** *The majority of septic shock patients will have arterial and/or venous access at the time of the blood draws and phlebotomy will therefore not be necessary. There is a very small risk of infection associated with assessing venous or arterial lines. If patients do not have existing lines we will perform venipuncture the risks associated with venipuncture (for blood draws for biomarker analysis) include momentary pain during needle insertion and hematoma at the site of needle insertion. Infection, excess bleeding, clotting, and fainting also are possible, though unlikely. A qualified health care professional trained in accessing existing lines will do this thereby minimizing the already very low risk of infection. For those few patients requiring phlebotomy we will minimize the highly unlikely side effects of a blood draw by conforming with standard phlebotomy techniques including drawing blood while patients are supine, the site of the blood draw will be cleansed prior to the draw, and direct pressure will be held post-blood draw. All research assistants performing phlebotomy will have formalized training and oversight.*

(3) ***Risk associated with VO2 and cardiac index measurements:*** *Connecting the GE monitor requires a brief disconnection (less than 5 seconds) of the ventilator tubing. This will always be done by a respiratory therapist, and we have had no adverse effects from this in any of our pilot studies using similar equipment. Once the monitor is connected it confers no risk or discomfort to the patient. The NICOM is connected with four adhesive sensors similar to electrocardiography (ECG) or telemetry leads. All ICU patients already have telemetry leads*

attached to the chest, so we do not think the addition of four sensors will add significantly to patient discomfort.

(4) ***There is the risk of loss of confidentiality.*** *However, none of the participant's protected health information will be shared with any of the other sites. In addition, all measures will be taken to ensure that no confidential information is released. All data will be kept on password protected computers behind the BIDMC firewall. The data safety and monitoring board (DSMB) will provide a multidisciplinary, independent review of the study design, ethical and scientific conduct of the study, monitor interim results and make recommendations with respect to continuation, modification, termination of study. Each individual is an experienced academician and together will provide clinical, research, and statistical expertise. The DSMB will meet at planned interim analyses for safety, at completion, and at any other needed interval.*

We do not anticipate any psychological risks of participating in the study. There will be no financial risks associated with study participation.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Potential subjects will be evaluated for eligibility by the research team. Some of these patients may be critically ill and unable to provide informed consent. However, due to the severity of their illness, most of these patients will have family members or their health care proxy (HCP) in attendance. If the patient is unable to consent for themselves, consent may be obtained from a legally authorized representative (LAR).

Before the patient or surrogate is approached for consent, the case is reviewed by the study MD (PI or Co-investigator) to ensure that the patient is appropriate for inclusion in the trial. Additionally, the physician on the clinical team caring for the patient is contacted as well, to ensure that the clinical team authorizes approaching the patient/surrogate for consent.

Consent

Consent will be obtained by the Principal Investigator (Dr. Cocchi) or one of the physician co-investigators prior to performing any procedures solely for the purpose of research. If the patient is eligible, the Principal Investigator (PI) or physician co-investigator will review the consent with the patient/proxy, making sure to discuss the potential risks and benefits as well as all steps that will be required for the patient to participate. The consenting Investigator will specify that participation in the trial is optional, and that the patient's choice to participate or not participate in the study will not affect the care they receive. We rely on the independent assessment by the clinical team to determine the capacity of a subject to consent as this is routinely performed by clinicians who need consent for standard medical care and procedures. This methodology avoids bias from the research team and allows for expert clinician assessment of capacity. If the clinical team has deemed or deems a patient not to have capacity to consent, we will approach the legally authorized surrogate. If the patient agrees to

participate, he / she will sign and date (and a witness if applicable) the inform consent form. The name of the study investigator obtaining consent will be clearly documented, and this person will sign the informed consent document and provide the date of their signature and time. Signed copies of the consent form will be given to the participant/legally authorized representative (LAR), and the original consent document will be stored in the secure study file. A copy of the consent form will also be placed in the subject's medical record.

At times, the surrogate may not be in the immediate Boston-area and is unable to come to BIDMC within the protocol mandated window for the initiation of study treatment. In such a circumstance, the study staff will send the informed consent document to the subject's surrogate electronically (email, facsimile, etc.) and a licensed physician investigator, or a co-investigator will conduct the consent discussion by video or telephone. Once the surrogate has had time to review the consent form, if he/she agrees to participation he/she will sign the consent and return the signed document to the investigator electronically (email, facsimile, etc.).

All email correspondence will occur in accordance with BIDMC guidelines. Once the signed consent form has been received by the investigator, he/she will then sign, date, and time the form. No study procedures will occur before the consent form has been signed by both the surrogate and the investigator. The surrogate will be instructed to return the original signed consent form to BIDMC which will be kept in the subject's research record with the electronically transmitted copy and a detailed note to file.

In the rare event that a physician Investigator is not physically present in the hospital to perform the consent process (for example, overnight) and given the time-sensitive nature of this trial, a research assistant will coordinate a video conference (ie, FaceTime) between the physician investigator, the patient or LAR, and the research assistant; the physician investigator will perform the consent from a remote location. The physician investigator will subsequently sign the paper copy; in the interim, the research assistant will sign the consent, in addition to the patient or LAR, and that signed copy will be included in the patient's medical record and as well as be provided to the study subject.

Once the patient is enrolled in the trial, the study MD enters a note in the patient's medical record documenting the enrollment. Only after the consent form is signed by both the family/HCP and the investigator, will study procedures take place. In obtaining and documenting informed consent, each investigator will comply with the applicable regulatory requirements and adhere to the ethical and Good Clinical Practice principles that have their origin in the Declaration of Helsinki. The consent must be the Institutional Review Board (IRB)-approved version corresponding to the version of the protocol approved when the screening was initiated.

Subject Protection

There will be no undue influences on the potential study subjects to participate. No subjects will be vulnerable to coercion or undue influence. Patient information will be encrypted and stored on password protected computers, therefore minimizing the risk of their privacy being compromised.

Dr. Cocchi will also periodically review the data to evaluate subjects' safety and data integrity. The purpose is to determine whether study subjects are exposed to unreasonable risk because of study participation, and to monitor study progress and integrity. Dr. Cocchi will

review and report all adverse events to the Committee on Clinical Investigation (CCI) according to the adverse event reporting policy of the CCI.

All biological material will be stored in a locked refrigerator/freezer within a locked facility, which is under hospital security surveillance at all times. All electronic records will be maintained on BIDMC IS compliant computers.

B7. STUDY LOCATION

Privacy
In order to maintain privacy, the investigators will discuss the study and consent the subjects in a private area in-hospital. Standard clinical protocols regarding patient confidentiality will be followed during the course of the study. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research.

Physical Setting
The study will take place in the Emergency Department and ICUs at Beth Israel Deaconess Medical Center and Lahey Hospital & Medical Center in Burlington Massachussets.

B8. DATA SECURITY

All hard copies of study data will be kept in a locked filing cabinet to which only the PI and co-investigators will have access.

All electronic data will be stored on the BIDMC secure server behind a firewall in a password-protected database. We will also utilize the database application, REDCap. REDCap is a professional database endorsed by the National Institutes of Health (through the clinical and translational science award) that provides a secure, user-friendly database with capacity for easy statistical analysis. The program can support multiple research studies, is presently being used at dozens of major academic research centers to support numerous NIH and AHA funded projects and is available for free at our center.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☒ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☒ Yes ☐ No

Coordinating Center (BIDMC) Responsibilities: The trial will be directed by the Principal Investigator, who will have responsibility for receiving and analyzing data for the trial, and will oversee all functions. We will provide the other institutions with documents to use and communicate procedures.

As the coordinating center for this multicenter trial, Dr. Cocchi assumes full responsibility for ensuring all aspects of the study are conducted appropriately. This will be achieved via the following mechanisms, under the direction of Dr. Cocchi:

1. Coordinating center (the Center for Resuscitation Science – CRS) will receive a copy of the screening log from Lahey Hospital & Medical Center on a monthly basis

2. At a minimum, quarterly conference calls will be held with Lahey Hospital & Medical Center site PI/research coordinator to discuss study progress
3. Any questions or problems that arise during an enrollment will be addressed in real time through direct communication between Lahey Hospital & Medical Center staff and the CRS. The study PI will be available to Lahey Hospital & Medical Center site PI for consultation 24/7 via cell phone/email.
4. CRS staff will track and report all serious adverse events and unanticipated problems
5. CRS will provide periodic updates to affiliated investigators on participant enrollment, general study progress, and relevant scientific advances
6. CRS staff will ensure that all relevant IRB correspondence (continuing review amendments) and study status changes are communicated to Lahey Hospital & Medical Center
7. CRS staff will document receipt, shipment and storage of study specimens
8. Data management: Study enrollment data will be entered into RedCap directly by Lahey Hospital & Medical Center research staff. HPI (name, MRN, etc) will not be available to BIDMC staff. In order to ensure strict data integrity, CRS staff will perform data checks in the REDCap database.
9. The study PI will be personally notified within 24 hours of any serious adverse event and will receive a copy of the AE form submitted to Lahey Hospital & Medical Center IRB within a week of the event
10. PI will be personally notified within 24 hours of a protocol deviation and will receive a copy of the deviation form submitted to the Lahey Hospital & Medical Center IRB.
11. We will conduct an in-person site visit after every 20 enrollments or earlier on an as needed basis. During these site visits, we will assess research study progress and compliance with the IRB approved protocol and procedures. This will include review of source documents for key data elements.
12. As part of our on-site visit, we will include a Lahey Hospital & Medical Center Research Pharmacy review to assess the following: documentation of secure drug storage; drug accountability from receipt of drug through all dispensing and ultimately destruction on drug accountability logs; documentation of performance of regular inventory verification; confirmation that orders for research medication are written only by authorized prescribers on the 1572 form or delegation of authority log; confirmation that study drug must has continuous temperature monitoring and recorded at least daily on temperature logs (minimum, maximum, current); verification of drug destruction per Lahey Hospital & Medical Center internal policy. The BIDMC Research Pharmacy will be available to answer questions as they may arise from the Lahey Hospital & Medical Center Research Pharmacy.
13. A formal site monitoring report will be provided to Lahey Hospital & Medical Center and the CCI after each site visit. This report will include data on the number of charts reviewed, discuss any identified deficiencies and any corrective actions taken. The Lahey Hospital & Medical Center site PI will then provide this report to their local IRB in accordance with local IRB reporting requirements.

Database Management: The coordinating center (BIDMC) will be responsible for developing the online database (see section 4.4), including a shared database with common data definitions. All forms and data dictionary will be available online for all individuals who perform data entry.

All sites will enter de-identified data into the electronic database. Data entry will be done via REDCap. Discrepancies or missing data points will be identified through a data review process by the coordinating center resulting in queries sent to the participating sites for resolution. Changes will be made in REDCap by each participating site.

The coordinating center will oversee and instruct sites on specimen collection and separation. Sites will be provided with detailed instructions for laboratory processing. All sample types will be processed initially on site, separated by centrifugation if necessary, dispensed into aliquots if required, and kept frozen (preferable at -80°) until shipment to the Center for Resuscitation Lab .

All de-identified research samples will be shipped by commercial courier on dry ice to the Center for Resuscitation Lab where a study staff will accept, unpack and place samples in the freezer.

Laboratory analyses will be conducted at either the Center for Resuscitation or shipped off-site to a 3rd party vendor. Biological samples shipped to a 3rd party for analysis will occur through the Center for Resuscitation Lab. Study blood will only have the specimen ID # and will be devoid of any personal identifiers.

B10 Dissemination of Research Results

We will aim to publish the results of this study in a pertinent peer-reviewed journal within 6 months of completion of data collection.

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AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock		
CCI PROTOCOL # : 2014P-000415		
PRINCIPAL INVESTIGATOR: Michael Cocchi MD		
E-MAIL ADDRESS: mcocchi@bidmc.harvard.edu	STUDY COORDINATOR'S NAME: ELINITA ROSSETO	
P.I.'S TELEPHONE : 617-754-2388	P.I.'S PAGER #: 38983	FAX # :617-754-2350

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. ***Check all applicable items.***	
☐ Principal Investigator	☐ Study Type (e.g. Phase)
☐ Co-Investigators/Study Staff *(include Part Q if **adding** new staff)*	☐ Recruitment, Publicity Materials and/or procedures
☐ Study Title	☐ Consent Procedures
☐ Sponsor	☐ Duration of Subject Participation
☐ Application (CCI or sponsor protocol) Content/Version	☐ Patient Materials (e.g. diaries)
☐ Consent Form	☐ Questionnaires, or Investigator Brochure
☐ Local Site Enrollment # of Subjects	☐ Remuneration
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Research Related Use of Medical Records (*Part O)*
☐ Types of Subjects	☐ Use of Specimens
☐ Source of Subjects	☐ Research Related Use of Discarded Material (*Part N)*
☒ Other (specify): Part E	☐ *Study Status Change (*i.e.,* CTE, hold, suspension) **This refers to changes prior to Continuing Review*
Industry Sponsored Protocols only: Sponsor Amendment/Version #:	Revised Protocol Issue Date:

AMENDMENT ATTACHMENTS

Indicate study documents that have been modified as a result of this amendment and are appended to this application.	
☐ Revised Protocol (New Version) (*1 clean, 1 highlighted)*	☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*	☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☒ Other (specify): Part E	

AMENDMENT DESCRIPTION

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.

1. Addition of detail in Part E.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.

1. These changes were made to clarify operational details in drug preparation and dispensing.

This change does not affect the risk benefit ratio. This change does not necessitate a change in the consent form.

☐ PI Memo/Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

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CCI PROTOCOL # : 2014P-000415		
PRINCIPAL INVESTIGATOR: Michael Cocchi MD		
E-MAIL ADDRESS: mcocchi@bidmc.harvard.edu	STUDY COORDINATOR'S NAME: ELINITA ROSSETO	
P.I.'S TELEPHONE : 617-754-2388	P.I.'S PAGER #: 38983	FAX # :617-754-2350

AMENDMENT DETAILS

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☐ Principal Investigator	☐ Study Type (e.g. Phase)
☒ Co-Investigators/Study Staff *(include Part Q if **adding** new staff)*	☐ Recruitment, Publicity Materials and/or procedures
☐ Study Title	☐ Consent Procedures
☐ Sponsor	☐ Duration of Subject Participation
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☐ Consent Form	☐ Questionnaires, or Investigator Brochure
☐ Local Site Enrollment # of Subjects	☐ Remuneration
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Research Related Use of Medical Records (*Part O)*
☐ Types of Subjects	☐ Use of Specimens
☐ Source of Subjects	☐ Research Related Use of Discarded Material (*Part N)*
☒ Other (specify): Change in inclusion/exclusion criteria	☐ *Study Status Change (*i.e.,* CTE, hold, suspension) **This refers to changes prior to Continuing Review*
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☒ Other (specify): Part A, HIPAA, Part Q	

AMENDMENT DESCRIPTION

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1. Addition of Gabriel Verzino as co-investigator.
2. 15 cc of existing blood totals to Dr. Shapiro's "Markers" 2005P-000116 at 0 or 6 hours and 24 hour time points (no additional volume will be taken).
3. Add a placebo of 100 mL normal saline for patients randomized to standard care.
4. Inclusion criteria #3 removal of "and a central venous pressure".
5. Inclusion criteria #5 removal of "ICU" and the later limit of 24 hours.
6. Exclusion criteria #5 change "Do not resuscitate (DNR)' to "Comfort measure only (CMO)".
7. Exclusion criteria #6 removal of "dopamine, phenylephrine".
8. Exclusion criteria #7 addition of "that would preclude administration of a beta blocker medication; this would be determined by the clinical team caring for the patient so as to not create a conflict of interest. For example, a patient may have a history of COPD but is already on a beta blocker medication as an outpatient; that patient should not be excluded for consideration of enrollment in this trial."

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.

1. Gabriel Verzino is being added as co-investigator to increase productivity and enrollment.
2. For collaboration, we will provide blood sample at two time points to Dr Shapiro's biomarkers study. This will be deducted from the amount already being collected in the Esmolol study; no additional volume will be taken.
3. This will serve as a time stamp for the study start for those patients not receiving esmolol.
4. The reason for the removal of this criterion is that the standard of care around sepsis has changed and clinicians are not routinely checking CVP measurements. For consistency, we would use the more consistent clinical parameters already in place, which are a minimum fluid administration of 30mL/kg and the measurement of cardiac function via the NICOM. This should not result in any increased risk to the patient since most clinicians are already not using CVP to guide resuscitation; this amendment will reflect current clinical practice.
5. Elimination of "ICU" as some patients may board in the ED for prolonged periods of time. Elimination of the later limit of 24 hours as it is not necessary, for example if a patient was in the ICU for another reason and on day 3 developed septic shock it would be okay to enroll this patient.
6. A patient with a DNR order is acceptable to enroll in the study. We would not enroll a DNI patient as this is a more significant limitation on aggressive resuscitation, nor would be enroll a patient who is comfort measures only (CMO).
7. Removal of "dopamine, phenylephrine' as exclusions as some patients may be on these vasopressors, although the most common vasopressor used in septic shock is norepinephrine. This should not result in any increased risk to the patient.
8. The purpose of this exclusion was to avoid giving a beta blocker to a patient who is at high risk for respiratory distress, however many patients with asthma or COPD routinely receive beta blocker medications without side effects. For example, a patient may have a history of COPD but is already on a beta blocker medication as an outpatient; that patient should not be excluded for consideration of enrollment in this trial. Therefore, we would like to add the language that "that would preclude administration of a beta blocker medication; this would be determined by the clinical team caring for the patient so as to not create a conflict of interest.' This should not represent an increased risk to the patient as the clinical team would also be potentially administering this class of medication if clinically-indicated. If there were an unexpected reaction to the study drug, as with any patient enrolled in this study, they are being continuously monitored in a critical care setting and would be treated immediately, and the drug would be discontinued.

☐ PI Memo/Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Print Name Michael Cocchi

AMENDMENT FORM

STUDY INFORMATION

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1. Inclusion criteria #3 removal of "and a central venous pressure".
2. Inclusion criteria #5 removal of "ICU" and the later limit of 24 hours.
3. Exclusion criteria #5 change "Do not resuscitate (DNR)' to "Comfort measure only (CMO)".
4. Exclusion criteria #6 removal of "dopamine, phenylephrine".
5. Exclusion criteria #7 addition of "that would preclude administration of a beta blocker medication; this would be determined by the clinical team caring for the patient so as to not create a conflict of interest. For example, a patient may have a history of COPD but is already on a beta blocker medication as an outpatient; that patient should not be excluded for consideration of enrollment in this trial."

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.

1. The reason for the removal of this criterion is that the standard of care around sepsis has changed and clinicians are not routinely checking CVP measurements. For consistency, we would use the more consistent clinical parameters already in place, which are a minimum fluid administration of 30mL/kg and the measurement of cardiac function via the NICOM. This should not result in any increased risk to the patient since most clinicians are already not using CVP to guide resuscitation; this amendment will reflect current clinical practice.
2. Elimination of "ICU" as some patients may board in the ED for prolonged periods of time. Elimination of the later limit of 24 hours as it is not necessary, for example if a patient was in the ICU for another reason and on day 3 developed septic shock it would be okay to enroll this patient.
3. A patient with a DNR order is acceptable to enroll in the study. We would not enroll a DNI patient as this is a more significant limitation on aggressive resuscitation, nor would be enroll a patient who is comfort measures only (CMO).
4. Removal of "dopamine, phenylephrine' as exclusions as some patients may be on these vasopressors, although the most common vasopressor used in septic shock is norepinephrine. This should not result in any increased risk to the patient.
5. The purpose of this exclusion was to avoid giving a beta blocker to a patient who is at high risk for respiratory distress, however many patients with asthma or COPD routinely receive beta blocker medications without side effects. For example, a patient may have a history of COPD but is already on a beta blocker medication as an outpatient; that patient should not be excluded for consideration of enrollment in this trial. Therefore, we would like to add the language that "that would preclude administration of a beta blocker medication; this would be determined by the clinical team caring for the patient so as to not create a conflict of interest.' This should not represent an increased risk to the patient as the clinical team would also be potentially administering this class of medication if clinically-indicated. If there were an unexpected reaction to the study drug, as with any patient enrolled in this study, they are being continuously monitored in a critical care setting and would be treated immediately, and the drug would be discontinued.

These changes do not affect the risk/benefit ratio. These changes *do not* necessitate a revised written informed consent form.

☐ PI Memo/Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock		
CCI PROTOCOL # : 2014P-000415		
PRINCIPAL INVESTIGATOR: Michael Cocchi MD		
E-MAIL ADDRESS: mcocchi@bidmc.harvard.edu	STUDY COORDINATOR'S NAME: ELINITA ROSSETO	
P.I.'S TELEPHONE : 617-754-2388	P.I.'S PAGER #: 38983	FAX # :617-754-2350

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. ***Check all applicable items.***	
☐ Principal Investigator	☐ Study Type (e.g. Phase)
☒ Co-Investigators/Study Staff *(include Part Q if **adding** new staff)*	☐ Recruitment, Publicity Materials and/or procedures
☐ Study Title	☐ Consent Procedures
☐ Sponsor	☐ Duration of Subject Participation
☒ Application (CCI or sponsor protocol) Content/Version	☐ Patient Materials (e.g. diaries)
☒ Consent Form	☐ Questionnaires, or Investigator Brochure
☐ Local Site Enrollment # of Subjects	☐ Remuneration
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Research Related Use of Medical Records (*Part O)*
☐ Types of Subjects	☐ Use of Specimens
☐ Source of Subjects	☐ Research Related Use of Discarded Material (*Part N)*
☐ Other (specify):	☐ *Study Status Change (*i.e.,* CTE, hold, suspension) **This refers to changes prior to Continuing Review*
Industry Sponsored Protocols only: Sponsor Amendment/Version #:	Revised Protocol Issue Date:

AMENDMENT ATTACHMENTS

Indicate study documents that have been modified as a result of this amendment and are appended to this application.	
☒ Revised Protocol (New Version) (*1 clean, 1 highlighted)*	☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☒ Revised Consent Form (*1 clean, 1 highlighted)*	☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☐ Other (specify):	

AMENDMENT DESCRIPTION

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.

1. Addition of a placebo of 100 mL normal saline for patients randomized to standard care.
2. Addition of Gabriel Verzino and Alexander Wulff as co-investigators.
3. Removal of Michael Michalcyzk as co-investigator.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.

1. In order to clearly mark the start time of the study for patients who are randomized to standard care, a 100 mL saline placebo will be administered as a one-time time stamp. This will be provided by the Research Pharmacy and administered by the bedside nurse.
2. Gabriel and Alexander are being added as co-investigators to increase enrollment capacity and productivity.
3. Michael Michalcyzk is being removed as co-investigator as he is no longer with the insitition.

These changes do not affect the risk/benefit ratio. These changes *do* necessitate a revised written informed consent form.

☐ PI Memo/Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☒ Addition/Removal of Co-Investigator or Research Staff Member

For amendments limited to only the addition or removal of research staff in addition to this form the following is required:

- Research Staffing Form (1 clean, 1 highlighted)
- Revised Part E if amendment involves change in Authorized Prescribers for study medication
- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☒ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☒ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.	
1. Removal of two study staff. 2. Addition of one study staff.	
☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.	
1. Mary MacDonald and Mathias Holmberg are being removed as they are no longer involved with the protocol. 2. Mathias Karlsson Is being added as consenting co-investigator to increase productivity. These changes do not affect the risk/benefit ratio. This study is approved with written, informed consent.	
☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____
Signature of Principal Investigator Date

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☒ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☒ Addition/Removal of Co-Investigator or Research Staff Member

For amendments limited to only the addition or removal of research staff in addition to this form the following is required:

- Research Staffing Form (1 clean, 1 highlighted)
- Revised Part E if amendment involves change in Authorized Prescribers for study medication
- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☒ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.

1. Addition and removal of study staff members
2. Addition of alternate number for subjects to call besides the PI on the ICF, **WHOM TO CONTACT IF YOU HAVE QUESTIONS OR PROBLEMS.**

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☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.

1. Removal of Gabriel Verzino as he is no longer with the institution. Addition of 2 consenting co-investigators: Sarah Ganley John Paul Couce.
2. We are changing the contact number to a telephone number where subjects can easily reach someone and have their questions answered.

.

These changes do not affect the risk/benefit ratio. This study *DOES* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____

Signature of Principal Investigator Date

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☒ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☒ Addition/Removal of Co-Investigator or Research Staff Member

For amendments limited to only the addition or removal of research staff in addition to this form the following is required:

- Research Staffing Form (1 clean, 1 highlighted)
- Revised Part E if amendment involves change in Authorized Prescribers for study medication
- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☒ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify: Part E to add Ari Moskowitz MD as an authorized prescriber.

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.	
3. Addition of study staff member. .	
☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo. Ari Moskowitz is being added as a co-investigator and an authorized prescriber. These changes do not affect the risk/benefit ratio. This study *DOES* necessitate a change in the written, informed consent form.	
☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☒ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☐ Addition/Removal of Co-Investigator or Research Staff Member

For amendments limited to only the addition or removal of research staff in addition to this form the following is required:

- Research Staffing Form (1 clean, 1 highlighted)
- Revised Part E if amendment involves change in Authorized Prescribers for study medication
- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☒ Revised Part A (*1 clean, 1 highlighted)*
☒ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☐ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.	
1. One additional site is being added	
☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.	
1. Henry Ford Hospital in Detroit Michigan is being added to increase the enrollment speed. We will not be increasing the global number of enrollment. These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.	
☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____
Signature of Principal Investigator Date

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☒ Addition/Removal of Co-Investigator or Research Staff Member

For amendments limited to only the addition or removal of research staff in addition to this form the following is required:

- Research Staffing Form (1 clean, 1 highlighted)
- Revised Part E if amendment involves change in Authorized Prescribers for study medication
- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☒ Revised Part A (*1 clean, 1 highlighted)*
☒ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☐ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.	
Update study staff.	
☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo. 1. Removal of Josie Scheunemann, Julia Balkema, Chris Sulmonte and Alex Wulff as they are no longer with the institution. 2. Addition of Varun Konanki as co-investigator to increase enrollment capacity. These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.	
☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☒ Addition/Removal of Co-Investigator or Research Staff Member

For amendments limited to only the addition or removal of research staff in addition to this form the following is required:

- Research Staffing Form (1 clean, 1 highlighted)
- Revised Part E if amendment involves change in Authorized Prescribers for study medication
- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.	
Update study staff.	
☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.	
Addition of Anne Grossestreur Mathias Holmberg Michael McNaughton Jocelyn Portmann Nikola Stankovic Amy Ube and Jocelyn Portmann as co-investigators to increase enrollment capacity and assist with the protocol. Removal of John Paul Couce and Mathias Karlsson as they are no longer with the institution. These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.	
☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____
Signature of Principal Investigator Date

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☒ DSMB Reports/Monitoring Reports/Safety Reports - membership	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
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- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☒ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☐ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☒ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify: Part P- Data Safety Monitoring Plan

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

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Update DSMB member list.	
☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.

The DSMB is being modified due to prior members being unable to participate. Todd Sarge has been replaced by Dustin Boone (same division); Robb Kociol has been replaced by Marwa Sabe (same division). Due to difficulties with scheduling, we had to schedule the first DSMB meeting for Thursday December 15th/

These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____
Signature of Principal Investigator Date

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☒ DSMB Reports/Monitoring Reports/Safety Reports -	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
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☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

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AMENDMENT ATTACHMENTS:

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☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires
(1 clean, 1 highlighted)
☐ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☒ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify: DSMB letter dated 12/18/2016

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.	
The DSMB met on 12/15/2016	
☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.

The DSMB for the study met on 12/15/2016. There were no safety concerns and the board approved the study to continue.

Assessment of risk/benefit ratio: These changes do not alter the risk/benefit ratio of the study. These changes DO NOT necessitate a change in the consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____
Signature of Principal Investigator Date

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

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☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
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☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

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AMENDMENT ATTACHMENTS:

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☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
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☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

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Update study staff.	
☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

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☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

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☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
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☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

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AMENDMENT ATTACHMENTS:

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☐ Revised Part B (*1 clean, 1 highlighted)*
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☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

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Update study staff. Update in IRB correspondence status for Derek Guanaga.	
☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

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Addition of Deanna Lee and Eric Mubang as Research Students to increase enrollment capacity and assist with the protocol. Derek Guanaga is to receive IRB communications to better assist with the protocol. These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.	
☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Print Name Michael Cocchi MD

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
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☒ Addition/Removal of Co-Investigator or Research Staff Member

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AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
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Specify:

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Update study staff.	
☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	☒ No ☐ Yes, if yes, explain and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

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Update study staff: Removal of Sarah Ganley and Nikola Stankovic as they are no longer with the institution. Addition of Jacob Boise as co-investigator, Prachi Patel and Sierra Hagerty as Research Students to increase enrollment capacity and assist with the protocol.

These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Michael Cocchi MD
Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
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STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

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☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
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AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
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☐ Revised Part A (*1 clean, 1 highlighted)*
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Specify:

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A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.

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Administering the informed consent by telephone and email/fax: In the event that a patient does not have the capacity to consent and the surrogate is unable to come to BIDMC, we plan to contact the LAR over the phone following and send the informed consent document to the subject's surrogate electronically (email, facsimile, etc.) and a licensed physician investigator will conduct the consent discussion by video or telephone. Once the surrogate has had time to review the consent form, if he/she agrees to participation he/she will sign the consent and return the signed document to the investigator electronically (email, facsimile, etc.). All email correspondence will occur in accordance with BIDMC guidelines. Once the signed consent form has been received by the investigator, he/she will then sign, date, and time the form. No study procedures will occur before the consent form has been signed by both the surrogate and the investigator. The surrogate will be instructed to return the original signed consent form to BIDMC which will be kept in the subject's research record with the electronically transmitted copy and a detailed note to file.

As a result, Part B (Page 5 and Page 15) is updated

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.

Administering the informed consent by telephone and email/fax: Consenting over phone and email/fax will allow us to increase our enrollment capacity for those patients who get excluded for falling out of the protocol mandated window for the initiation of study treatment but are otherwise eligible to participate. No study procedures will occur before the consent form has been signed by both the surrogate and the investigator (as described above and in Part B). The surrogate will be instructed to return the original signed consent form to BIDMC which will be kept in the subject's research record with the electronically transmitted copy and a detailed note to file.

These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Michael Cocchi MD
Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☒ Addition/Removal of Co-Investigator or Research Staff Member

For amendments limited to only the addition or removal of research staff in addition to this form the following is required:

- Research Staffing Form (1 clean, 1 highlighted)
- Revised Part E if amendment involves change in Authorized Prescribers for study medication
- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires
(1 clean, 1 highlighted)
☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

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Update study staff.	
☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

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☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Michael Cocchi MD
Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

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☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☒ Revised Part A (*1 clean, 1 highlighted)*
☒ Revised Part B (*1 clean, 1 highlighted)*
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(1 clean, 1 highlighted)
☐ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
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Change in participating study sites: One study site (Henry Ford Hospital) is being removed and one additional study site (Lahey Hospital & Medical Center) is been added.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
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AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

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Change in participating study sites: Henry Ford Hospital in Detroit Michigan will no longer participate as a study site for our study. Lahey Hospital & Medical Center being added to increase the enrollment speed. We will not be increasing the global number of enrollment.

These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____
Signature of Principal Investigator Date

Michael Cocchi MD
Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

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☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
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☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
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☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
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Update study staff.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
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Update study staff: Addition of Thomas Leith as co-investigator to increase enrollment capacity and assist with the protocol.

These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Michael Cocchi MD
Print Name

AMENDMENT FORM

STUDY INFORMATION

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Update study staff.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
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AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

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Update study staff: Addition of Anthony Mahoney-Pacheco as research student to increase enrollment capacity and assist with the protocol.

These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____
Signature of Principal Investigator Date

Michael Cocchi MD
Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
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STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

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Update study staff.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

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AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

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Update study staff: Deanna Lee role's in the study is changed to Co-Investigator to assist with the protocol.

These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____
Signature of Principal Investigator Date

Michael Cocchi MD
Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
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STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

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Update study staff.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

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Update study staff: Addition of Tuyen Yankama as co-investigator to assist with the protocol. Removal of Michael McNaughton as he is no longer with the institution.

These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Michael Cocchi MD
Print Name

AMENDMENT FORM

STUDY INFORMATION

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CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☒ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☐ Addition/Removal of Co-Investigator or Research Staff Member

For amendments limited to only the addition or removal of research staff in addition to this form the following is required:

- Research Staffing Form (1 clean, 1 highlighted)
- Revised Part E if amendment involves change in Authorized Prescribers for study medication
- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☐ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☒ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify: Lahey Clinic, Inc. Institutional Review Board approval letter. (dated 04/03/2018)

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.

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Participating study site – Local IRB approval granted to Lahey Hospital & Medical Center study site: The CCI approved the addition of Lahey Hospital & Medical Center as a study site on 11/28/2017. Local IRB approval has been obtained at Lahey Hospital & Medical Center; we are submitting a copy of the Lahey Clinic, Inc. Institutional Review Board approval letter.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.

Participating study site – Local IRB approval granted to Lahey Hospital & Medical Center study site: The CCI approved the addition of Lahey Hospital & Medical Center as a study site on 11/28/2017. Local IRB approval has been obtained at Lahey Hospital & Medical Center; we are submitting a copy of the Lahey Clinic, Inc. Institutional Review Board approval letter.

This update does not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____

Signature of Principal Investigator Date

Michael Cocchi MD

Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☒ Addition/Removal of Co-Investigator or Research Staff Member

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AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
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☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

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Update study staff.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

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Update study staff: Addition of Shamsher Ali as coordinator to assist with the protocol. Removal of Amy Uber and Sierra Hagerty as they are no longer with the institution.

These changes do not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____

Signature of Principal Investigator Date

Michael Cocchi MD

Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Elinita Rosseto	STUDY COORDINATOR EMAIL ADDRESS: EROSSETO@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

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AMENDMENT ATTACHMENTS:

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☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
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Update study staff: Addition of Ying loo as co-investigator, Shivani Mehta and Evans Jabari as research students as to assist with the protocol.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

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☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____

Signature of Principal Investigator Date

Michael Cocchi MD

Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Shamsher Ali	STUDY COORDINATOR EMAIL ADDRESS: SALI11@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
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☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
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☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☒ Part Q(s) for addition of any non-BIDMC personnel
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- **Addition/Removal of Co-Investigator or Research Staff Member:** We are adding Amanda Frias-Howard as Administrator and changing the role of Shivani Mehta to co-investigator to assist with the protocol. We are removing Francesca as Administrator. We are removing Anthony Mahoney-Pacheco, Jabari Evans, Varun Konanki, Thomas Leith. They are no longer with the institution.
- **Requested Modifications:** Moved Lars Andersen from active staff to outside collaborator. He will work with de-identified data for analysis as needed. Adding Emma Hershey as co-investigator to assist with the study.
  Part Q included.

☐ PI Memo/Cover Letter Describing Changes is attached ☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

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- **Addition/Removal of Co-Investigator or Research Staff Member:** We are adding Amanda Frias-Howard as Administrator and changing the role of Shivani Mehta to co-investigator to assist with the protocol. We are removing Francesca as Administrator. We are removing Anthony Mahoney-Pacheco, Jabari Evans, Varun Konanki, Thomas Leith. They are no longer with the institution.
- **Requested Modifications:** Moved Lars Andersen from active staff to outside collaborator. He will work with de-identified data for analysis as needed. Adding Emma Hershey as co-investigator to assist with the study.
  Part Q included.

This change does not affect the risk/benefit ratio. This study *DOES NOT* necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached ☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Michael Cocchi MD
Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Deanna Lee	STUDY COORDINATOR EMAIL ADDRESS: DLEE19@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☒ Addition/Removal of Co-Investigator or Research Staff Member

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- Research Staffing Form (1 clean, 1 highlighted)
- Revised Part E if amendment involves change in Authorized Prescribers for study medication
- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

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- **Requested Modifications:** Moved Lars Andersen from active staff to outside collaborator. He will work with de-identified data for analysis as needed. Adding Emma Hershey as co-investigator to assist with the study.
  Part Q included.

☐ PI Memo/Cover Letter Describing Changes is attached | ☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
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- **Addition/Removal of Co-Investigator or Research Staff Member:** We are removing Shamsher Ali, Marcel Casasola, and Lise Witten as they are no longer with the institution.

This change does not affect the risk/benefit ratio. This study does not necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached | ☐ Sponsor Letter Describing Rationale is Attached

Signature of Principal Investigator _____ Date _____

Michael Cocchi MD
Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: Deanna Lee	STUDY COORDINATOR EMAIL ADDRESS: DLEE19@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
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AMENDMENT ATTACHMENTS:

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☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
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- **Addition/Removal of Co-Investigator or Research Staff Member:** We are adding Lakshman Balaji to the study protocol to assist with data monitoring.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
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and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

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_____ _____
Signature of Principal Investigator Date

Michael Cocchi MD
Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: AMANDA FRIAS-HOWARD	STUDY COORDINATOR EMAIL ADDRESS: AFHOWARD@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*	
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☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☒ Addition/Removal of Co-Investigator or Research Staff Member

For amendments limited to only the addition or removal of research staff in addition to this form the following is required:

- Research Staffing Form (1 clean, 1 highlighted)
- Revised Part E if amendment involves change in Authorized Prescribers for study medication
- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.

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Addition/Removal of Co-Investigator or Research Staff Member: We are adding removing Emma Hershey, Mathias Holmberg, Jocelyn Portmann, Deanna Lee, Ying, Loo, Lethu Ntshinga, Garrett Thompson, Lara Roessler as they are no longer with the group or working on this protocol.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.

Addition/Removal of Co-Investigator or Research Staff Member: We are adding removing Emma Hershey, Mathias Holmberg, Jocelyn Portmann, Deanna Lee, Ying, Loo, Lethu Ntshinga, Garrett Thompson, Lara Roessler as they are no longer with the group or working on this protocol.

This change does not affect the risk/benefit ratio. This study does not necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

_____ _____

Signature of Principal Investigator Date

Michael Cocchi MD

Print Name

AMENDMENT FORM

STUDY INFORMATION

TITLE OF PROTOCOL: Esmolol to treat the hemodynamic effects of septic shock	
CCI PROTOCOL # : 2014P-000415	
PRINCIPAL INVESTIGATOR: Michael Cocchi MD	
STUDY COORDINATOR: NATIA PERADZE	STUDY COORDINATOR EMAIL ADDRESS: NPERADZE@BIDMC.HARVARD.EDU

AMENDMENT DETAILS

Indicate which components(s) or element(s) of your protocol are being changed. *Check all applicable items.*

☐ Principal Investigator	☐ Change and/or New Recruitment or Publicity Materials
☐ DSMB Reports/Monitoring Reports/Safety Reports	☐ Recruitment, Publicity Materials and/or procedures
☐ Revised and/or New Consent Form	☐ Consent Procedures
☐ Change and/or Addition of Study Procedures	☐ Duration of Subject Participation
☐ Local Site Enrollment # of Subjects	☐ Revised and/or New Study Documents or Subject Materials (e.g. diaries, questionnaires)
☐ Total Enrollment # of Subjects (Multi-Center Trials)	☐ Investigator Brochure, Date/Version:
☐ Change in subject selection or subject population	☐ Change in Remuneration
☐ Change of Sponsor/Funding	☐ Research Related Use of Medical Records
☐ Study Status Change (*i.e.,* CTE, hold, re-open to enrollment)	☐ Use of Specimens
☐ ***Industry Sponsored Protocols only***: Sponsor Amendment/Version #:	☐ Research Related Use of Discarded Material
☐ Change related to pharmacy or study drug administration	☐ Revised Sponsor Protocol, Issue Date/Version:

☒ Addition/Removal of Co-Investigator or Research Staff Member

For amendments limited to only the addition or removal of research staff in addition to this form the following is required:

- Research Staffing Form (1 clean, 1 highlighted)
- Revised Part E if amendment involves change in Authorized Prescribers for study medication
- Part Q and CITI training documentation for any non-BIDMC research staff member.

AMENDMENT ATTACHMENTS:

☐ Revised Sponsor Protocol (New Version) (*1 clean, 1 highlighted)*
☐ New or Revised Advertisement (*1 clean, 1 highlighted)*
☐ Revised Part A (*1 clean, 1 highlighted)*
☐ Revised Part B (*1 clean, 1 highlighted)*
☐ Revised Consent Form (*1 clean, 1 highlighted)*
☐ Revised Research Participant Materials or Questionnaires *(1 clean, 1 highlighted)*
☒ Revised Research Staffing Form (*1 Clean, I highlighted*:)
☐ Part Q(s) for addition of any non-BIDMC personnel
☐ Revised/New Part E (Obtain pharmacy signature and detail change below)
☐ Other Revised Part/Form Document (*1 Clean, I highlighted*:)
Specify:

AMENDMENT DESCRIPTION- REQUIRED FOR ALL SUBMISSIONS

A detailed description of the amendment, in your own words, **MUST** be provided below. The PI may provide a summary of a lengthy sponsor amendment in an attached cover letter or memo, however this should not simply be a copy of the sponsors amendment and/or letter. Either list the current item followed by the new item, or attach a redlined version of the changed document. If the consent form is revised, attach one copy of the consent form in which the changes (including additions and deletions) are clearly highlighted, and one clean copy of the consent form.

Study staff update.

☐ PI Memo/Cover Letter Describing Changes is attached	☐ Sponsor Letter Describing Changes is Attached

Impact on Budget/Funding

Does this amendment affect the current budget for the study?	Does this amendment affect the current funding for the study?
☒ No	☒ No
☐ Yes, if yes, explain	☐ Yes, if yes, explain
and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources	and contact: - Clinical Trials Office for Industry Funded Studies - Office of Sponsored Programs for Other Funding Sources

AMENDMENT RATIONALE- REQUIRED FOR ALL SUBMISSIONS

The reason or justification for the changes ***must*** be discussed as well as how the change might affect the risk/benefit ratio. Please also address how or if a change in the risk/benefit ratio impacts the informed consent form, and if the change necessitates a change in the consent form. The rationale may be provided ***here*** or in an attached cover letter or memo.

Study staff update:
We are removing Amanda Frias-Howard as she is no longer working on this protocol.
We are removing Ting Sun as she is no longer part of BIDMC.
We are adding correspondence to Natia Peradze as she will be working on this protocol and communicating with the IRB.

This change does not affect the risk/benefit ratio. This study does not necessitate a change in the written, informed consent form.

☐ PI Memo /Cover letter Describing Rationale is Attached	☐ Sponsor Letter Describing Rationale is Attached

Michael Cocchi, MD
Signature of Principal Investigator

05/12/2021
Date

Michael Cocchi MD
Print Name