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# The LIPid Intensive Drug therapy for Sepsis Phase II (LIPIDS-P) Trial

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**Title: The LIPid Intensive Drug therapy for Sepsis ¬Pilot (LIPIDS-P) Phase I/II Trial**

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**Abstract**

Sepsis is a life-threatening disease for which there are no effective treatments. It results from metabolic and immunologic derangements that lead to organ dysfunction, shock and sometimes death. Both "good" (high density lipoprotein, HDL-C) and "bad" (low density lipoprotein, LDL-C) cholesterol should protect against sepsis by clearing bacterial toxins from the blood and providing substrate for endogenous corticosteroids (protective in shock). However, for partially unknown reasons, cholesterol levels drop to critically low levels in early sepsis (first 48 hours), leaving the body defenseless against sepsis via these mechanisms. A fish-oil lipid injectable emulsion is FDA-approved for septic and critically ill patients that may be capable of elevating serum cholesterol levels. **We hypothesize that fish oil lipid injectable emulsion administration to critically ill septic patients will improve quantitative and qualitative lipid measures, provide substrate for bacterial toxin clearance and steroid synthesis, and lead to improvements in early organ function and mortality.** This phase II randomized pilot clinical trial, proposes to assess the drug's ability to optimally, transiently elevate cholesterol and preliminary measures of biological activity and clinical outcomes. **This novel LIPid Intensive Drug therapy for Sepsis Pilot (LIPIDS-P) clinical trial is the first study to attempt to transiently elevate cholesterol levels as a treatment modality in critically ill septic patients and will form the basis of a future Phase III randomized, controlled trial.**

**1.0 Aims**

Sepsis is a common, costly, and deadly condition for which there are no effective treatments. Although early interventions have improved short-term in-hospital mortality, persistent immunologic and metabolic derangements may lead to long-term organ dysfunction and late mortality.(Guirgis et al., 2014) In addition, early organ failure predicts death and subsequent chronic critical illness.(Levy et al., 2005; Shapiro et al., 2006) Novel early treatments for sepsis are needed to improve long-term outcomes.

Circulating lipoproteins play an important role in sepsis. Cholesterol plays an important role in sepsis and levels of both LDL-C and HDL-C are dynamically regulated in sepsis. Cholesterol is considered protective for its ability to bind and clear bacterial toxins, its anti-inflammatory properties, and is needed for steroid synthesis in stressful conditions. However, our research team has observed that *lipid dysregulation occurs in early sepsis resulting in loss of cholesterol's protective effects.* We have demonstrated in sepsis that: 1) cholesterol levels drop precipitously, and drop-severity predicts death(Guirgis, Dodani, et al., 2017); 2) low baseline LDL-C levels are associated with increased long-term community-acquired sepsis risk(Guirgis, Donnelly, et al., 2016), and 3) inflammation leads to pro-inflammatory, dysfunctional cholesterol, which predicts organ failure and adverse outcomes.(Guirgis, Dodani, et al., 2017; Guirgis, Leeuwenburgh, et al., 2017) Our research and others strongly suggest that the drastic cholesterol reduction and pro-inflammatory lipid alterations seen in early sepsis are linked to early organ failure and poor outcomes.(J.-Y. Chien, Jerng, Yu, & Yang, 2005a; Y.-F. Chien, Chen, Hsu, Chen, & Yu, 2015; Guirgis, Dodani, et al., 2017) However, it is unknown whether attempting to elevate cholesterol levels in septic patients will improve clinical outcomes.

We propose to address this gap in evidence via an *interdisciplinary, multi-institution partnership* (UF Health Jacksonville (UF-JAX), UF Sepsis and Critical Illness Research Center (SCIRC), & UCLA) and a pilot randomized clinical trial **LIPIDS-P** (LIPid Intensive Drug therapy for Sepsis - Pilot). A novel lipid injectable emulsion (LIE) containing 15% fish oil is FDA-approved for nutritional purposes among septic and critically ill patients and may have the ability to raise cholesterol levels and will be tested in septic patients. Furthermore, lipid therapies were recently highlighted as a top ten area for clinical testing in septic shock by thought leaders in sepsis.(Perner et al., 2017)

The rationale for this randomized clinical trial (RCT) is two-fold: (i) LIE may provide substrate for cholesterol synthesis and essential free fatty acids as metabolic fuel during septic stress, and (ii) fish oil LIE contains potent anti-inflammatory ω-3 fatty acids that have been associated with improved organ function and reduced mortality in sepsis.(Hall et al., 2015) Supporting rationale (i), a multi-center RCT of a phospholipid emulsion for gram-negative severe sepsis(Dellinger et al., 2009) initially demonstrated no effect on mortality, but when limited to patients with albumin ≥ 1.5 g/dL, and cholesterol ≥ 40 mg/dL *or* HDL-C ≥ 20 mg/dL, demonstrated sepsis mortality reductions of 6.6% ($p < 0.025$) and 10.8% ($p< 0.005$), respectively.("Parker TS," n.d.) That study establishes that adequate liver function and a minimum quantity of cholesterol are needed for effective lipid-mediated defense against sepsis. Supporting rationale (ii), a RCT of IV 10% fish oil in 60 ICU sepsis patients showed significant improvements in organ failure (all sepsis) and improved mortality (sub-population) compared to placebo.(Hall et al., 2015) **Therefore, the central hypothesis is that fish oil LIE will improve quantitative and qualitative lipid measures, provide substrate for bacterial toxin clearance and steroid synthesis, and lead to improvements in early organ function and mortality in sepsis patients.** *Our group has demonstrated access to the patient population needed for this study. In an ongoing collaborative study between UF JAX and the UF SCIRC, 120 of 223 (54%) sepsis patients met proposed enrollment criteria including total cholesterol ≤ 100 mg/dL.* This pilot study will gather data for a multicenter clinical trial (R01) and has the following specific aims:

**Aim 1: Test if early fish oil LIE in sepsis patients will lead to achievement of 48-hour total cholesterol goals compared to controls**. Recruit 48 moderate organ-failure sepsis patients with adequate liver function (albumin > 1.5 mg/dL, total bilirubin < 2 mg/dL) within 24h of sepsis recognition and obtain demographics, interventions, and quantitative and qualitative cholesterol measures. Because we will use the hospital's Sepsis Alert system, there may be up to 1084 subjects screened for inclusion in the study. For the Phase II trial, 48 patients will be randomized to LIE (24 patients) or active control (24 patients - no drug). Quantitative lipid measures (total cholesterol, LDL-C, HDL-C, triglycerides) will be measured (upon enrollment, 48h, 72h, and 7d after drug) to assess the ability of LIE to achieve delta total cholesterol (48-hr – enrollment) of 0 to +5 mg/dL based on preliminary data.

**Aim 2: Test if sepsis patients will have a reduction in lipid oxidation measures, and improvements in HDL function, cumulative organ failure, and 28-day mortality after fish oil LIE versus controls.** In 48 patients (Aim 1), the following will be collected at enrollment, 48h and 7d after enrollment: (i) lipid oxidation (cell free assay), (ii) HDL function (cholesterol efflux assay), (iii) SOFA score, and (iv) 28-day mortality.

## 2.0 BACKGROUND AND SIGNIFICANCE

**2.1 Sepsis is common, costly, and deadly.** Recent published US estimates report up to 850,000 ED sepsis visits per year(Wang, Jones, & Donnelly, 2017) costing nearly 17 billion dollars. Sepsis is also lethal, resulting in death in approximately one of every four cases and nearly 215,000 deaths per year in the US.(Angus et al., 2001)

**2.2 Sepsis causes organ dysfunction which leads to chronic critical illness and death.** In a prospective study of 115 sepsis patients from the UF Health Jacksonville (UF JAX) ED, 63% had organ dysfunction on admission, which was still present in 27% of survivors at 28-90 days. *Notably, in-hospital mortality was 20%, but long-term mortality was 47% at 3 years*.(Guirgis, Brakenridge, et al., 2016) The UF Sepsis and Critical Illness Research Center (P50 GM111152-02) has described chronic critical illness (CCI) in intensive care unit (ICU) patients with sepsis, characterized by ICU stays ≥ 14 days, progressive cachexia, manageable organ dysfunction, and frequent indolent death.(Gentile et al., 2012; Mira et al., 2016) Clinical trajectories were early death (12%), rapid recovery (RAP) (29%), and CCI (59%).

**2.3 Preventing and limiting early organ dysfunction may prevent CCI and death.** Early organ failure is strongly predictive of both progression to CCI and death.(Levy et al., 2005; Shapiro et al., 2006) SOFA score is a validated measure of organ dysfunction that directly relates to mortality(Angus et al., 2001; Shapiro et al., 2006) and is used as an endpoint in clinical trials.(Marshall et al., 2005; Vincent, 2004) Furthermore, our group has demonstrated that early SOFA elevation is predictive of persistent organ dysfunction, and that early and post-resuscitation organ failure is also highly predictive of progression to CCI.(Guirgis et al., 2014; Stortz et al., 2017)

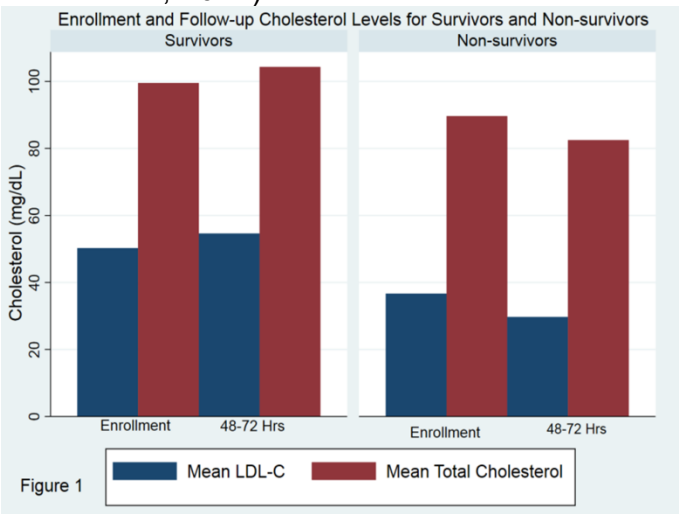


Figure 1

**2.4 Cholesterol protects against sepsis-associated organ dysfunction.** Both LDL and HDL are protective against sepsis. Specifically LDL-C facilitates bacterial toxin clearance in sepsis via hepatic LDL receptors or via HDL (reverse cholesterol transport).(Boyd et al., 2016; Feingold & Grunfeld, 1997; Weerapan Khovidhunkit et al., 2004; Walley et al., 2014) High density lipoprotein cholesterol (HDL-C) is protective against sepsis by several mechanisms: i) bacterial toxin binding,(Catapano, Pirillo, Bonacina, & Norata, 2014; W Khovidhunkit et al., 2004) ii) suppression of inflammatory cell migration, iii) prevention of inflammatory cytokine release,(Murphy et al., 2008, 2011) and inhibition of vascular and intercellular adhesion molecules expression,(Heitzer, Schlinzig, Krohn, Meinertz, & Münzel, 2001; Rosenson et al., 2015) and iv) stimulation of endogenous corticosteroid release.(Guo et al., 2013, 2014)

**2.5 Sepsis non-survivors have lower enrollment total cholesterol and LDL-C levels, which drop rapidly in the first 3 days (Figure 1).** Conversely, survivors have higher baseline levels, which increase early after admission (223 UF sepsis patients). In addition, low LDL-C, total cholesterol, and HDL-C levels are associated with increased sepsis risk and poor outcomes after sepsis.(J.-Y. Chien, Jerng, Yu, & Yang, 2005b; Y.-F. Chien et al., 2015; Guirgis, Donnelly, et al., 2016; Lagrost et al., 2014; van Leeuwen et al., 2003) Decreased cholesterol levels also predict organ dysfunction and death from sepsis.(Weerapan Khovidhunkit et al., 2004)

## 3.0 INNOVATION AND POTENTIAL IMPACT OF RESEARCH

***3.1 Enhanced reverse cholesterol transport to improve sepsis outcomes.*** This study will describe for the first time a potential therapy which enhances reverse cholesterol transport to clear bacterial toxins. Reverse cholesterol transport is the process by which HDL actively uptakes lower density lipids (including bound bacterial toxins) from peripheral macrophages (foam cells) and transports them to the liver for elimination. This study will test the hypothesis that lipid emulsion administration will provide a substrate for bacterial toxin

binding during sepsis and steroid synthesis leading to improved reverse cholesterol transport through the liver as well as transport of cholesterol to the adrenal glands in sepsis. **(Figure 2)**

***3.2 Fish oil lipid injectable emulsion for sepsis.*** *Lipid-based therapies were recently highlighted as one of the top ten areas for future clinical testing in septic shock by thought leaders in sepsis.*(Perner et al., 2017) *Fish oil lipid emulsions contain anti-inflammatory long-chain ω-3 fatty acids, which may be protective in sepsis.*(Li et al., 2015; Shih et al., 2016) There are four main mechanisms for these effects: i) metabolism into anti-inflammatory eicosanoid inflammatory mediators, ii) alteration of membrane lipid rafts, iii) inhibition of nuclear receptor activation (nuclear factor [NF]–κB) to modulate production of inflammatory mediators, and, iv) metabolism into novel pro-resolving/anti-inflammatory mediators (resolvins and protectins). Exogenous administration of ω -3 may be necessary to overcome the massive inflammatory response that occurs during sepsis. *A recent randomized controlled trial of 60 ICU sepsis patients demonstrated a significant improvement in organ failure after IV administration of 10% fish oil.*(Hall et al., 2015)

***3.3 Fish-oil lipid emulsions may safely elevate cholesterol and improve outcomes in sepsis***.(D'Ascenzo et al., 2014) This may be beneficial in sepsis as increased cholesterol and phospholipids have the potential to bind and clear bacterial toxins. In addition, low cholesterol levels are associated both with poor outcomes and increased sepsis risk.(J.-Y. Chien et al., 2005a; Y.-F. Chien et al., 2015; Guirgis, Dodani, et al., 2017; Guirgis, Donnelly, et al., 2016; Guirgis, Leeuwenburgh, et al., 2017) *It is not known, however, whether transiently elevating cholesterol will improve outcomes in sepsis.* The proposed LIE contains medium chain triglycerides, ω-6, and ω-3 fatty acids and is FDA approved for IV nutrition in critically ill adults and has the potential to elevate cholesterol. A secondary analysis of a multi-center, double-blinded phase II RCT of a phospholipid emulsion for gram-negative severe sepsis(Dellinger et al., 2009) demonstrated (patient subset with serum albumin ≥ 1.5 g/dL, and either a cholesterol ≥ 40 mg/dL or HDL-C ≥ 20 mg/dL), a reduction in *overall sepsis mortality by 6.6% ($p < 0.025$) and 10.8% ($p < 0.005$)*, respectively.[10]

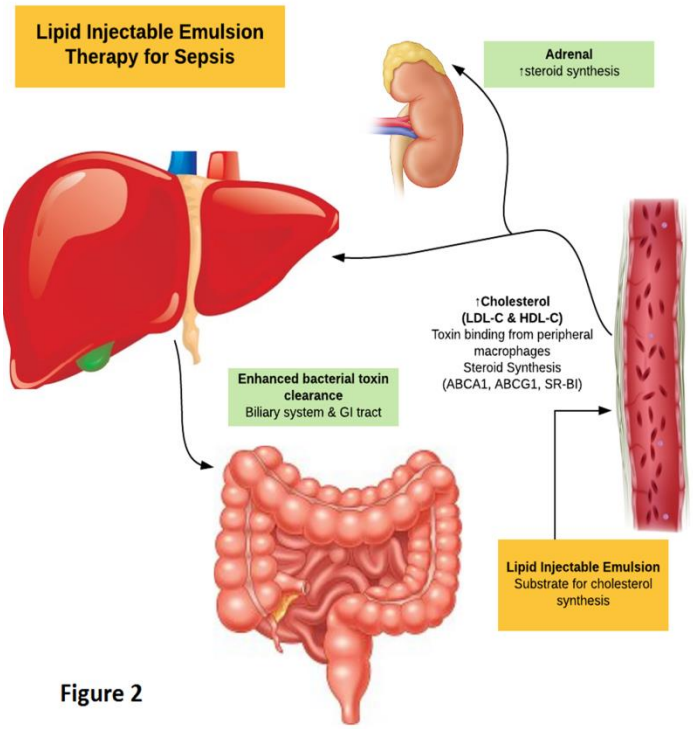


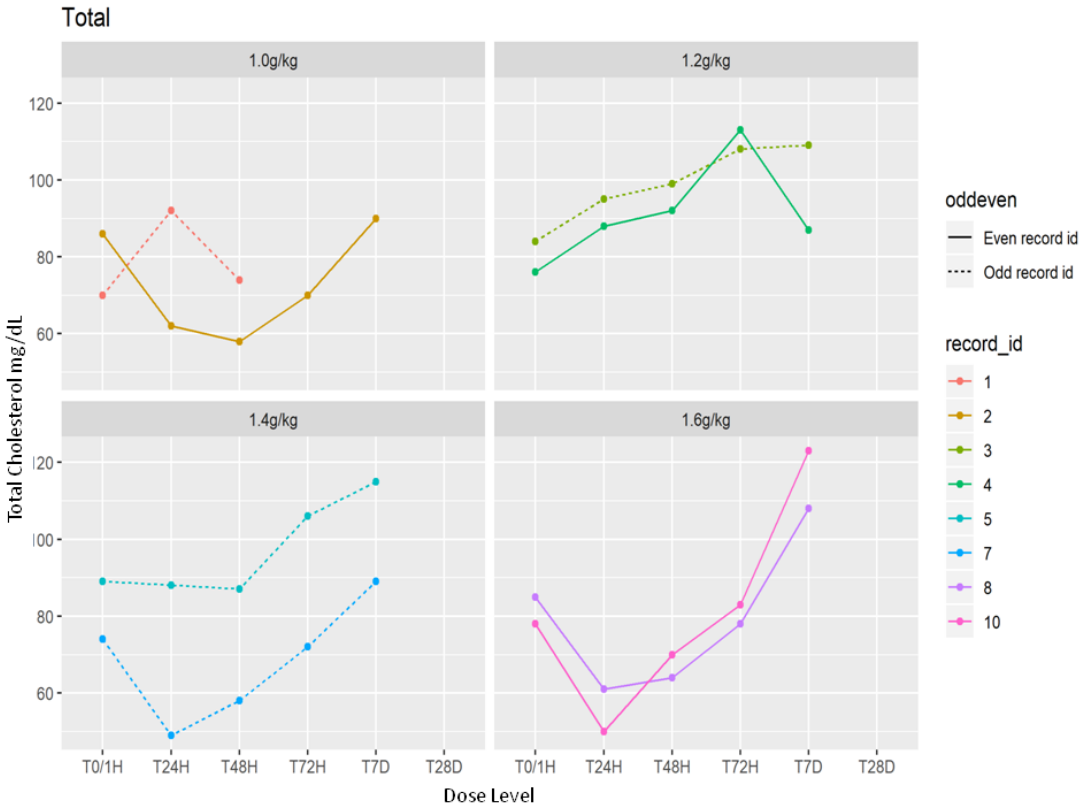
Figure 2

***3.4 Novel total cholesterol enrollment criteria and goals for a pilot sepsis clinical trial.*** To select for potential responders to LIE, baseline total cholesterol must be low upon enrollment. Based on preliminary data from 223 UF JAX ED and UF Surgical ICU sepsis patients, initial mean total cholesterol levels differed between survivors (89 mg/dL) and non-survivors (100 mg/dL); and mean delta total cholesterol for survivors was + 5 mg/dL (95%CI 1-9) vs. -9 mg/dL (95%CI -22, +3, p = 0.012) for non-survivors over 48 hours. These data form the basis for the inclusion criteria of total cholesterol < 100 mg/dL, and goal delta total cholesterol of 0 to +5 mg/dL. *This is the first clinical trial to use serum cholesterol levels to screen for sepsis patients who may respond to lipid-based therapy, and attempt to modulate cholesterol levels to improve outcomes. Furthermore, 54% of previous study patients (120/223) met proposed enrollment criteria.*

**3.5 Phase I Study Findings.** Our recently completed Phase I dose escalation study with a Bayesian Optimal Interval Design safely allocated 10 patients to increasing doses of Smoflipid (LIE) starting at 1.0 g/kg and escalating by 0.2 g/kg increments to 1.6 g/kg. Eight of the ten patients successfully completed the Phase I study, stopping short of the preplanned maximal dose of 1.8 g/kg at the recommendation of the DSMB. Of the two patients who did not complete the study protocol, one patient withdrew from the study and did not complete the first two doses of study drug and left the hospital against medical advice. The second patient was found to have a displaced gastrostomy tube in her abdomen and was taken emergently to the operating room. Her triglycerides were elevated at 451, which did not meet the prespecified criteria for a dose limiting toxicity of triglycerides > 1000 mg/dL. However, the safety monitor and PI agreed that it would not be prudent to administer a second dose of the study drug under the circumstances and also assessed that the hypertriglyceridemia was more likely due to peritonitis and potential pancreatitis than due to study drug

administration. Of the eight patients who completed two doses of the study drug at each of the four dose levels, results for the primary end point of 48-hour mean total cholesterol level were 66 mg/dL (SD 11.3) for 1.0 g/kg, 95.5 (SD 4.9) for 1.2 g/kg, 72.5 (SD 20.5) for 1.4 g/kg, and 67 (SD 4.2) for 1.6 g/kg. Tests for significance were not performed, however graphical presentations of total cholesterol levels over time for each dose level are presented below.

With regards to adverse events (AEs), there was one patient who died within 7 days of study enrollment and two patients who died within 28 days. Other serious adverse events (SAEs) included endotracheal intubation, a below the knee amputation, chest tube placement for a pleural effusion, and emergency surgery for a misplaced gastrostomy tube. *None of the SAEs were deemed to be related to study interventions.* Adverse events included hyperglycemia, anemia, elevated AST, elevated triglycerides, elevated bilirubin, intravenous catheter infiltration, and elevated PT/INR values. The most common possibly related AEs included elevated liver function tests*. No patients met the prespecified criteria for a dose limiting toxicity. Please see full DSM report.* At the recommendation of the DSM, the Phase I study was concluded at a maximal dose of 1.6g/kg and did not proceed to 1.8 g/kg given the low likelihood of added benefit of dose escalation to 1.8g/kg body weight and feasibility issues with line infiltration given prolonged drug infusions with increasing doses. *The DSM unanimously recommended proceeding to the Phase II study with the design outlined below.*




**4.0 APPROACH AND RESEARCH DESIGN**

**4.1 Design and Objectives**. This is a prospective, pilot RCT of early infusion of LIE in early sepsis patients with moderate organ dysfunction (SOFA ≥ 4 with at least 2 points being new or sepsis with vasopressor dependence). The LIPIDS-P clinical trial will assess the following: 1) safety and tolerability of lipid injectable emulsion and adverse effects, 2) the drug's ability to optimally, transiently elevate cholesterol, and 3) preliminary measures of biological activity and clinical outcomes.

**4.2 Study Settings**, Screening and Enrollment.

A. Adult ED at UF JAX is a high volume, high acuity ED which treats approximately 80,000 patients per year. From October 2013 through November 2015 the UF JAX ED treated 2665 cases of sepsis who were admitted. The UF JAX ED is the current site of enrollment for 3 prospective sepsis research studies (one RCT) and , 3 full-time research coordinators, and 3 part-time research assistants experienced in sepsis studies, as well as a biomedical laboratory.

B. UF North ED in Jacksonville. The UF North ED is a high-volume community ED with approximately 55,000 patient volume per year. The Research Division in the Department of Emergency Medicine is capable of enrolling patients from the UF North ED.

C. Screening and Enrollment. The "Possible Sepsis" notification system as well as the Sepsis Alert systems will be used to identify patients for prospective enrollment into sepsis research studies. The "possible sepsis" notifications send hourly pages and generate a daily list of potentially septic patients throughout the hospital and is currently used by the Hospital Sepsis Taskforce. The Sepsis Alert system is activated when a patient is highly suspected of sepsis and is being managed with the hospital sepsis care bundle." For patients who meet all other inclusion and exclusion criteria a lipid panel will be obtained and added on to current lab tests to evaluate cholesterol criteria for enrollment.

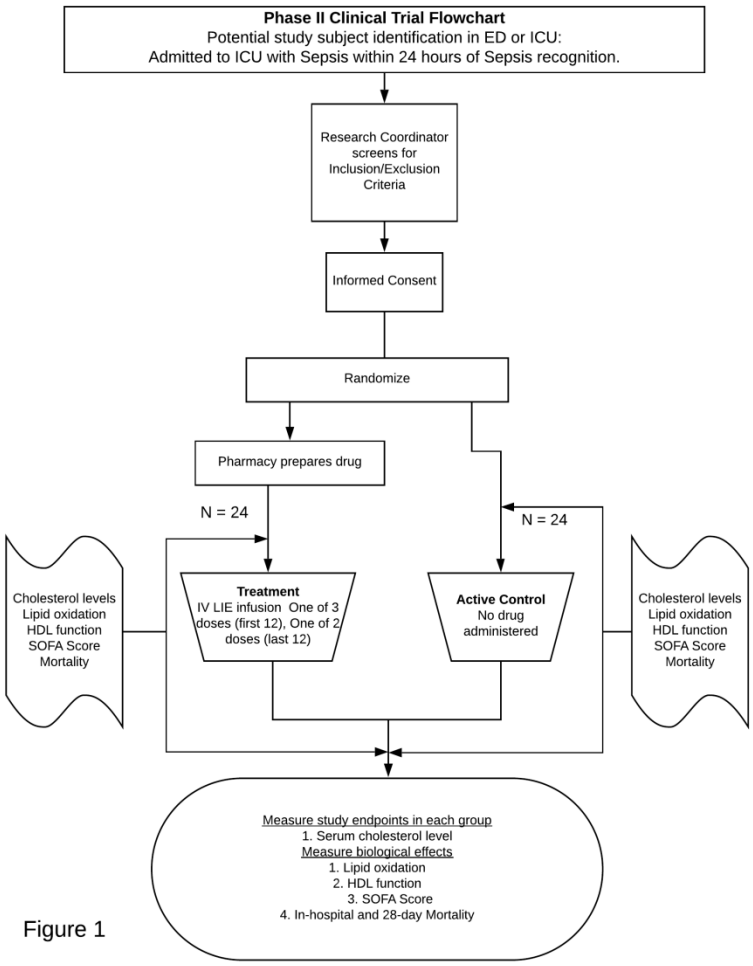


Figure 1

D. UF Jacksonville sepsis recruitment. UF JAX Emergency Dept. patients meeting criteria will be identified by the PI and Co-I (Dr. Black) and the research team who will be notified via pager. Prior to approaching the patient or the LAR for consent in the study, the clinical staff will approach the patient or LAR and ask them about their interest in hearing about the study. If the patient or LAR express interest, the research team will review eligibility criteria, and will seek consent.Time block sampling will be used to enroll patients between the hours of 7am and 12am, 7 days/week.[45] The team has enrolled a mean of 5 patients per month in previous studies, including Dr. Guirgis' K23 study.

**4.3. Enrollment Criteria.**

**A. Inclusion Criteria**: 1) age ≥ 18, 2) primary diagnosis of sepsis and within 24 hours of sepsis recognition and treated with institutional sepsis algorithm, 3) SOFA score ≥ 4 with at least 2 points being new or sepsis with vasopressor dependence, 4) screening total cholesterol ≤ 100 mg/dL or HDL-C + LDL-C ≤ 70 mg/dL, Screening lipids will be billed to the study.

**B. Exclusion Criteria:** 1) total bilirubin > 2 mg/dL, 2) serum albumin < 1.5 mg/dL, 3) hypersensitivity to fish, egg, soybean, or peanut protein, or to any of the active ingredients or excipients, 4) severe hyperlipidemia or severe disorders of lipid metabolism with serum triglycerides > 400 mg/dL, 5) alternative/confounding diagnosis causing shock or critical illness (e.g., myocardial infarction or pulmonary embolus, massive hemorrhage, trauma), 6) significant traumatic brain injury (evidence of neurologic injury on CT scan and a GCS <8), 7) refractory shock (likely death within 12 hours), 8) advanced directives restricting aggressive care or treating physician deems aggressive care unsuitable, 9) anticipated requirement for surgery that would interfere with drug infusion, 10) severe primary blood coagulation disorder, 11) acute pancreatitis accompanied by hyperlipidemia, 12) acute thromboembolic disease, 13) uncontrollable source of sepsis (e.g., irreversible disease state such as unresectable dead bowel), 14) severe immunocompromised state (e.g. subject has neutropenia receiving cytotoxic chemotherapy with absolute neutrophil count < 500/ul or expected to decline to < 500/uL within the next 3 days), 15) pregnancy or lactation, 16) already receiving intravenous lipid formulations (e.g., TPN, propofol, clevidipine) will be excluded from the study as lipid infusion will interfere with interpretation of the study results, 17) Child Pugh Class B/C liver disease patients or liver transplant recipient ,

18) actively on extracorporeal membrane oxygenation (ECMO) or anticipated need for ECMO within 48 hours of enrollment.

**4.4 Protocol.** The flow diagram (**Figure 3**) represents the primary research methodology. The research team will review eligibility criteria, and will seek the appropriate consent when criteria are met. Many sepsis patients may have altered mental status or pharmacologic sedation, but would be regarded as prospective research subjects. We ask for delayed consent only for the collection of a lipid panel for these potential subjects due to the severity of the illness, the vulnerable nature of the patient at this early time point, and the challenge in reaching the patient's legal representatives. The lipid panel can frequently be added on to the patient's blood chemistry panel that nearly all septic patients already have as part of usual care. This means that it will usually not require an additional blood draw. In the unusual case that the patient does need an additional blood draw for the lipid panel, the blood will be drawn from existing venous access. For patients on whom a lipid panel is drawn prior to obtainment of written consent from the patient or LAR, we will seek written consent within 48 hours. Three attempts will be made to locate the patient or family, and each attempt will be documented in the Data Collection Forms, as well as the time, method of contact, and date. If we are unable to obtain written consent within that time period, all data will be destroyed. Only the reason for the screen failure will be recorded. Due to potential conflict of interest (patent), the PI will refrain from recruiting, and consenting patients. For fully enrolled patients, the study drug will be infused as early as practical after study enrollment and within the first 24 hours of sepsis recognition. Hours for study enrollment are based on previously completed sepsis trials. Written informed consent and written authorization will be obtained from all patients or their legal representatives prior to drug infusion in compliance with the Declaration of Helsinki and the HIPAA privacy rule. Eligible patients must be enrolled within 24 hours of sepsis recognition.

*Standard of Care Treatment*: All patients will be treated in the ED or in a monitored inpatient setting at UF JAX. All patients will undergo standard emergent interventions and treatment with institutional sepsis protocols, an institutional standard of care and comprised of early, evidence-based treatment of sepsis that is utilized hospital-wide. It has been shown to result in improved outcomes.(Croft et al., 2014; Guirgis, Jones, et al., 2017)

**4.5 Investigational Treatment.** Within 24 hours of sepsis recognition, eligible patients (or their legal representatives in the case of inability to consent) will be approached for study enrollment. If a LAR is utilized and the subject gains the capacity to consent, the subject will be re-consented. After informed consent the following study procedures will be followed:

**A. Treatment.** The LIE is Smoflipid (20% lipid emulsion for injection; Fresenius Kabi), which contains soybean oil, MCTs, olive oil, and fish oil in a 30:30:25:15 ratio. Smoflipid also contains 0.163 to 0.225 mg/mL of all-rac-α-tocopherol. Initial infusion rate of LIE will occur at a rate of 0.5 mL/min for the first 30 minutes. If tolerated, the infusion will proceed at the maximum FDA approved rate of 0.11g/kg/hr, and not to exceed 0.5 mL/kg/hr. The proposed dose of LIE is based on current manufacturer recommended dosing for nutritional purposes for this specific drug. The approved dose range is 1 to 2 g/kg/day, and not to exceed 2.5 g/kg/day. Since this is a pilot study, and because the lipid emulsion appears white and will be visible to the treatment team, the study will not be blinded. All infusion bags and hospital equipment that will be used for administration of LIE are standard use in the hospital and approved by the FDA, and non-PVC tubing and a 1.2 micron in-line filter will be used. All study treatments will be administered either via an existing central venous catheter or via a single lumen peripheral intravenous catheter. This approved method of administration has been shown to be safe.

**B. Weight-based dosing**. Dosing will be based on actual body weight in kilograms, except in cases of morbid obesity defined as actual weight (AW) > 200% ideal body weight (IBW). For morbidly obese patients, adjusted body weight (AdjBW) will be used for Smoflipid dosing according to the following formula:

AdjBW = IBW + 0.4( ABW - IBW).

Ideal body weight in (kg) will be calculated as follows.

Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.

Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.

**C. Adverse reactions**: nausea, vomiting, hyperglycemia, flatulence, pyrexia, abdominal pain, increased blood triglycerides, hypertension, sepsis, dyspepsia, urinary tract infection, anemia and device related infection, headache, sweating, dizziness, flushing, rash, urticaria, erythema, fish-like taste in mouth, coagulation defects.

**4.6 Investigational Measurements.**

**Blood Sampling.** Blood will be drawn for cholesterol levels, lipid oxidation, HDL function, inflammatory biomarkers, and SOFA score (**Appendix Table 1**). For Jacksonville subjects only, if the subject is re-admitted to the hospital for sepsis within 6 months from the index visit, we may draw an additional amount, up to 10 mL, of blood when at the time of re-admission. The additional blood draw is to assess lipid biomarkers in the subset of patients who are readmitted for sepsis and compare them to their admission baseline. These additional samples will be processed by Research Assistants in the UF Health Jacksonville Biomedical Research Laboratory and stored in the Emergency Medicine Research Data and Tissue Bank. These additional tests will be of no additional cost to the subject.

**A. Cholesterol Levels.** Blood will be drawn for serial lipid panels upon enrollment, then at 48 and 72h, and then at day 7. For patients discharged from the hospital prior to day 7, a phlebotomy service will be sent to the patient's place of residence (home, nursing facility, etc.) to draw their blood.

**B. Lipid Oxidation.** Tests of lipid oxidation including HDL inflammatory index will be performed as in current studies at UCLA using the cell free assay as in previous studies(Navab et al., 2001) after preparation at UF. This will be drawn at enrollment, at 48h, as well as 7d later to assess change over time. To prevent oxidative degradation of the samples, an antioxidant buffer will be added to samples prior to storage. (Myzak & Carr, 2002)

**C. HDL Function.** The cholesterol efflux assay measures the ability of HDL to move lower density lipids from peripheral macrophages to the liver for clearance. HDL-mediated cellular cholesterol efflux assays will be performed to assess potential improvements in HDL function with LIE vs. control as in previous.(Guirgis, Leeuwenburgh, et al., 2017)

**D. SOFA Score.** Assessment will occur at enrollment and 48h later as well as 7 days later to determine change in SOFA score over time as well as serum lactate. Necessary labs will be paid for by the study unless already ordered by the treating team.

**E. Future Testing.** In addition, the patient or LAR will be presented with a consent for a biobank study for future testing should they choose to participate. The biobank, Emergency Medicine Research Data and Tissue Bank, has previously been approved by the UF Jacksonville IRB and has been assigned study number IRB201601987.

**Stool Sampling.** A stool sample will be collected for determining lipid absorption within 24 hours of each time point when available (enrollment, 48h, 7 days) utilizing standard of care procedures by nursing and medical technicians.

**4.7 Comparison Group.** Phase II of this study will randomize patients to receive one of three doses of LIE or no investigational drug. The control group will receive all standard treatments mandated by the institutional Sepsis Alert protocol. For purposes of statistical outcomes analysis, the control group will be the comparison group.

**4.8 Efficacy Endpoints**

**A. Primary Endpoints**

- Delta (48h - enrollment) serum total cholesterol of 0 to 5 mg/dL

**B. Secondary Endpoints**

- Lipid oxidation (HDL inflammatory index)
- HDL function (cholesterol efflux capacity)
- Change in SOFA score over the first 48h and 7 days
- In-hospital mortality
- Change in cholesterol level from enrollment to 7 days

**4.9 Study Procedures.**

**A. Randomization**

**Phase II of this study/trial will use an adaptive design**. As the study progresses, the dose of the study drug that proves least efficacious for stabilizing cholesterol levels will be dropped. For the first 24 patients, patients will be randomized to receive one of three doses of the study drug, or no drug (active control). The first 24 patients will be randomized using the following allocations: 4:4:4:12. From the first 24 patients, we will select the two doses that have the best performance in the primary endpoint, Delta (48h - enrollment) serum total cholesterol of 0 to 5 mg/dL, among the ones that are acceptable in safety. We will also evaluate Delta SOFA score at 48 hours (organ failure score, from 48h-enrollment) as well as Delta 7 days for serum total cholesterol (7 day – enrollment) to select the two most efficacious doses. For the last 24 patients in the study, patients will be randomized to receive one of the two most efficacious doses of study drug based on results from the first 24 patients in the following manner: 6:6:12, or no drug (active control). The overall study groups will include 24

patients in the experimental arm and 24 patients in the control arm as originally designed. The study will employ a permuted blocked randomization technique. Permuted blocked randomization has several advantages in that it supports group balance at the end of the trial and it supports continuous balance during trial progression by assuring that sequential patients are distributed equally between groups. The study statistician will generate the randomization sequence that will be stored in REDCap and accessed by the study coordinators at the time of patient enrollment.

**B. Blinding.** Because this is a pilot study, and because the lipid emulsion appears white and will be visible to the treatment team, the study will not be blinded. Data abstractors will, however, be blinded to the treatment effect. As the treatment effects are objective measurements (lipid levels, SOFA score, etc.) the likelihood of bias is low.

**C. Drug Accountability.** The drug for this study will be supplied by the hospital pharmacy and paid for by the study. A SOP will be used to track lot numbers of LIE administered.

**D. Sample Size.** Our preliminary data suggests that with proposed enrollment criteria, patients experienced an average decrease of 17 mg/dL (SD = 23) in cholesterol at 48 hours. If the treatment group can stop the decline or increase by 2 mg/dL in cholesterol, which correspond to between group difference with Cohen's effect size of 0.74 or 0.83. Then, at a significance level of 0.05, 24 patients in each arm (N = 48) will be able to detect the difference at 71% or 80% power, respectively. Recruitment feasibility: Based upon extensive prior work by the senior PI at the research hospital, we expect to enroll approximately 2 patients/month and all study patients within 4 years.

**E. Safety Monitoring.** This study will employ a Data Safety Monitoring Plan (see full plan at end of study protocol) that includes a primary physician safety monitor (not a co-investigator) who will have expertise in critical care and the study drug. The DSM plan also includes a second safety monitor (not a co-investigator) who is a clinical trialist who also has experience in critical care. The third member of the DSM plan is a biostatistician with experience in clinical trials and critical care studies and with prior DSMB experience. All DSM meetings to evaluate for safety will be coordinated by the study monitor. Since the Phase I study has been completed (10 patients) and the DSM has approved the start of Phase II, subsequent meetings will occur after the thirtieth, and forty fifth patients are enrolled and after study completion. The DSM will have the authority to make one of three written recommendations to the study PI after each meeting: suspend the study, continue the study without restriction, or continue the study with contingency on review of additional data regarding adverse events, adjustments to the protocol, or individual patient's clinical history.

AE and SAE Monitoring

Any reaction deemed to be severe (as listed below) and related to the drug infusion while it is being infused, will result in discontinuation of the study drug after discussion with the PI. Potential expected AEs include the following:

1. Hypersensitivity reactions resulting in facial, head or neck swelling, airway compromise, shortness of breath or hypoxia will result in cessation of drug infusion on a study patient. No patients experience allergic drug reactions will continue to receive or receive additional doses of study drug.
   *Dose Escalation and Dose-Limiting Toxicities include:*
2. Respiratory distress or hypoxia occurring very soon after initiation of study drug.
3. Fat Overload or Hypertriglyceridemia (> 1000 mg/dL)
4. Parenteral nutrition associated liver disease or hepatitis characterized by a marked elevation of liver function tests or total bilirubin.

For AEs that do not meet criteria of SAEs or deemed to be "not related" or "possibly related" the PI and Co-Investigators will make decisions regarding management based on the clinical scenario (See DSMP Adverse Events Monitoring Section I).

"Hypersensitivity reactions resulting in facial, head or neck swelling, airway compromise" as detailed in the AE and SAE monitoring section. Though considered SAEs, these will not be considered dose limiting toxicities as allergic reactions are not dose-related. Therefore dose escalation in the Phase I study can continue even if a patient experiences a hypersensitivity reaction. Hypersensitivity reactions, when severe as defined above, will however result in stopping of the study drug.

**F. Patient Bedside Monitoring.**

- Only patients admitted to a monitored inpatient setting or ICU an ICU setting will be enrolled in the study to ensure adequate monitoring during and after drug infusion.
- Laboratory monitoring will occur under the supervision of the study pharmacist or nutritionist with experience using the proposed LIE. The following laboratory measures will be monitored for the first 48

hours: serum triglycerides, fluid and electrolyte status, blood glucose, liver and kidney function, blood count including platelets, and coagulation parameters.

- Bedside nurse monitoring will occur for the first hour of drug infusion on day 1 of the study. Nurse monitoring will include monitoring for all of the following: tachypnea, dyspnea, hypoxia, bronchospasm, tachycardia, hypotension, cyanosis, vomiting, nausea, headache, sweating, dizziness, altered mentation, flushing, rash, urticaria, erythema, pyrexia, or chills. Vascular access will also be monitored for thrombophlebitis, erythema, pain.

**G. Statistical Analysis.** The primary method of analysis will be using an unpaired t-test of change in mean lipid levels between the groups (48 hours – enrollment) and Wilcoxon ranksum test between groups for change in SOFA score (48 hours – enrollment). Normally distributed numerical data will be compared using unpaired t-test while non-normally distributed data will be compared using Wilcoxon's ranksum. Finally categorical data will be compared using Chi squared test. For all statistical tests $P<0.05$ will be considered significant.

**H. Trial Organization.** This study will be conducted at UF JAX and overseen by Faheem W. Guirgis, MD.

## I. Data Safety Monitoring Plan

### OVERSIGHT RESPONSIBILITIES

Trial Oversight is provided by the Principal Investigator (PI), Dr. Faheem W. Guirgis, MD, and Frederick A. Moore, MD, and Dr. Lauren Black, MD ("co-investigators" throughout).
The Safety Monitors are Dr. Sophia Sheikh, MD (primary) and Dr. Dominick Angiolillo, MD (secondary).
The Study Statisticians are Dr. Shiva Gautam, PhD at UF JAX and Dr. Sam Wu, PhD at UF Health (Gainesville).
The Study Monitor is Ms. Morgan Henson, MPH, CCRP.

### MONITORING PROCEDURES

Dr. Guirgis assures that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. Study data will be accessible at all times for the PI and co-investigators to review. The PI and co-investigators will review study conduct including participant accrual, drop-outs, and protocol deviations on a weekly, basis. The primary safety monitor (Dr. Sheikh) will review AEs individually in real-time. Both safety monitors (Sheikh and Angiolillo) will review AEs in aggregate on a monthly basis. The safety monitors will also review serious adverse events (SAEs) including dose-limiting toxicities and drug-related effects. Co-investigators, safety monitors, as well as the study pharmacist or nutritionist will monitor for laboratory abnormalities including serum triglycerides, fluid and electrolyte status, blood glucose, liver and kidney function, blood count including platelets, and coagulation parameters throughout treatment (first 48 hours). The PI ensures all protocol deviations, AEs, and SAEs are reported to the IRB according to the applicable regulatory requirements.

### COLLECTION, SPECIFICATION, AND REPORTING OF SAEs AND AEs

#### Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to LIE, all events of death, and any study specific issue of concern.

#### Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of LIE in this study. The study-specific definition of "temporally related" includes up to twelve hours after discontinuation of LIE infusion.

**This includes the following:**

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period.
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Laboratory values that are abnormal to a degree such that the value falls into the range specified as abnormal by local standards, and the abnormality leads to specific medical corrective action.

**Serious Adverse Events**
An AE should be classified as an SAE if:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

**Methods and Timing for Assessing AND Recording Safety variables**
The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s) in accordance with CFR 312.32 (IND Safety Reports).

**Adverse Event Reporting Period**
The reporting period for all study-defined adverse events will begin at the time of LIE infusion and for 12 hours after the second infusion on day 2 of the study. Patients will then be followed until the longer of 7 days or discharge. AEs will be captured by the research nurse or study team during and after the two study drug infusions and by review of the hospital chart.

**Assessment of Adverse Events**
All AEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported up until 12 hours after LIE. Abnormal laboratory values will be considered an AE if the value falls into an abnormal range based upon the hospital's laboratory standards, and the abnormality was not preexisting prior to enrollment, and the abnormality leads to a new treatment within the AE time frame.

Each reported SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to LIE and actions taken. To ensure consistency of SAE causality assessments, investigators will apply the following general guideline:

<u>AEs are graded according to the following severity scale:</u>

Mild: An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:

Not related: the AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

More likely than not related: an event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

Related: The AE is clearly related to the study procedures.

**Sepsis Related Exempted Events**
The following signs, symptoms, observations and events are frequently observed in association with sepsis and are exempted from regulatory reporting unless known to be caused by the study drug: dyspnea, chest pain, fever, hypoxemia, rapid pulse, rapid respiratory rate, dizziness, syncope, altered mental status, seizure, confusion, anxiety, generalized weakness, anorexia, nausea, abdominal pain, back pain, constipation, vomiting, pneumonia, skin infection, cancer, surgery not related to treatment of sepsis, electrocardiography abnormalities (atrial arrhythmias, right bundle branch block, and ST and T wave changes), elevated troponin level, elevated BNP or NT ProBNP level, high white blood cell count, pulmonary infiltrate, pleural effusion, cardiomegaly, need for oxygen therapy, need for vasopressor, need for blood product transfusion, need for inotropic therapy, need for mechanical ventilation, need for physical or occupational therapy.

**Expected AEs associated with the study drug (Smoflipid) include**: nausea, vomiting, hyperglycemia, flatulence, pyrexia, abdominal pain, increased blood triglycerides, hypertension, sepsis, dyspepsia, urinary tract infection, anemia and device related infection, headache, sweating, dizziness, flushing, rash, urticaria, erythema, in real-time which will be recorded by the research nurse and research team.

**AE Management**
Any AE classified as an SAE (as per above definitions) and deemed to be related to the drug infusion will result in discontinuation of the study drug after discussion with the PI. Potential expected AEs include the following:

1. Hypersensitivity reactions resulting in rash, nausea, vomiting, shortness of breath or hypoxia
2. Respiratory distress or hypoxia occurring very soon after initiation of study drug
3. Dose Escalation and Dose-Limiting Toxicities including Fat Overload, Hypertriglyceridemia, and Refeeding Complications
4. Parenteral nutrition associated liver disease or hepatitis characterized by an elevation of liver function tests or total bilirubin

For AEs that do not meet criteria of SAEs or deemed to be “not related” or “possibly related” the PI and Co-Investigators will make decisions regarding management based on the clinical scenario.

**Procedures for eliciting, recording, and reporting adverse events**
Specific Instructions for Recording Adverse Events
Investigators will use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis will be reported rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it will be reported based upon the information that is currently available. If a diagnosis is subsequently established, it will be reported as follow-up information.

b. Deaths

All deaths that are "more likely than not" related to the study and that occur during the protocol-specified AE reporting period will be reported to the appropriate parties.

When recording a death, the event or condition that caused or contributed to the fatal outcome will be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions will be reported as medical and surgical history.

A preexisting medical condition will be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in prolonged hospitalization will be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, will be reported as the SAE.

Hospitalizations for the following reasons do not require reporting: Prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions, or hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

Pregnant patients will be excluded from study. In women of child-bearing age who have a uterus, pregnancy can be excluded by either urine pregnancy testing or appropriate history of abstinence, contraception with reliable menstrual history.

f. Post-Study Adverse Events

The investigator will expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior LIE.

If the investigator becomes aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this will be reported as an SAE.

**Data Quality Assurance and monitoring plan**

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures. The CRF will be populated in hand by an appropriately qualified study coordinator. To qualify, the coordinator must be trained in Good Clinical Practice (GCP), and listed on the IRB-approved protocol, and must have a bachelor's degree from college and a clinical degree (e.g., coordinator, MD, or PA). Currently, our Division of Research employs 4 GCP-trained study coordinators. Study coordinators will receive a training course via teleconference. This course will present the methods for accurate completion of CRFs and expected gray-zone issues with data entry, and the coordinators will receive a guidance document for completing the CRF. Data for CRFs will derive from one of two source documents, either the study collection template, which will contain data obtained by interview by a study coordinator, or the medical record. Sites will keep certified copies of medical records relevant to the reporting period. Sites will maintain CRFs to allow a study monitor to inspect.

**Safety Monitoring**
The Data Safety Monitoring Plan that includes a primary physician safety monitor (not a co-investigator) who will have expertise in critical care and the study drug. The DSM plan also includes a second safety monitor (not a co-investigator) who is a clinical trialist who also has experience in critical care. The third member of the DSM plan is a biostatistician with experience in clinical trials and critical care studies and with prior DSMB experience. All DSM meetings to evaluate for safety will be coordinated by the study monitor. The primary safety monitor will review the study data and procedures after the first patient is enrolled to evaluate the case history and any adverse events. The DSM will then meet after the fourth and eighth patient are enrolled, and at completion of the Phase I study for which results will be submitted to the IRB as a miscellaneous reportable event. Once the DSM makes the decision to move the study to Phase II, that recommendation will be submitted to the IRB, and IRB approval will be required for Phase II initiation. Subsequent meetings will occur after the thirtieth, and forty fifth patients are enrolled and after study completion. The DSM will have the authority to make one of three written recommendations to the study PI after each meeting: suspend the study, continue the study without restriction, or continue the study with contingency on review of additional data regarding adverse events, adjustments to the protocol, or individual patient's clinical history. The DSM can make additional recommendations regarding safety or study conduct as indicated for the safe and successful completion of the trial.

Data Safety Monitoring Board reports for Phase I will be submitted to the IRB for review prior to the start of the Phase II portion of the project.

**Statistical Analysis**
The primary method of analysis will be using an unpaired t-test of change in mean lipid levels between the groups (48 hours – enrollment) and Wilcoxon ranksum test between groups for change in SOFA score (48 hours – enrollment). Normally distributed numerical data will be compared using unpaired t-test while non-normally distributed data will be compared using Wilcoxon's ranksum. Finally, categorical data will be compared using Chi squared test. For all statistical tests $P<0.05$ will be considered significant.

## Review Board
This study will be reviewed by the UF Health Jacksonville IRB.

**Table 1. Schedule of Events**

| **Assay** | Serum (SST) | Plasma | Screen | T0 | | T48 | T72 | 7 Days | 28 days |
|---|---|---|---|---|---|---|---|---|---|
| *Hospital Processed Labs* | | | | | | | | | |
| Total cholesterol | | | ■ | | | | | | |
| Hepatic function: total bilirubin and albumin | | | ■ | | | | | | |
| Lipid Panels | | | | ■ | | ■ | ■ | ■ | |
| SOFA – platelet, creatinine, total bilirubin (if SOC labs not available for SOFA calculation) | | | | ■ | | ■ | | ■ | |
| | | | | | | | | | |
| *Research Processed Labs and Procedures* | | | | | | | | | |
| Lipid absorption (from stool samples) | | | | ■ | | ■ | | ■ | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Lipid oxidation and HDL function | ■ | | | ■ | | ■ | | ■ | |
| Phone follow up | | | | | | | | | ■ |

**Table 2.** Sequential Organ Failure Assessment Score.

| **SOFA Score** | **0** | **1** | **2** | **3** | **4** |
|---|---|---|---|---|---|
| **Respiratory**<br>$PaO_2/FiO_2$<br>$SpO_2/FiO_2$ | >400<br><br>*>302* | <400<br>*<302* | <300<br>*<221* | <200<br>*<142* | <100<br>*<67* |
| **Cardiovascular** | MAP ≥ 70 mm Hg | MAP ≤ 70 mm Hg | Dopamine ≤5 or ANY Dobutamine | Dopamine >5 or Norepinephrine ≤0.1 Phenylephrine ≤0.8 | Dopamine >15 or Norepinephrine >0.1 Phenylephrine >0.8 ANY Vasopressin |
| **Liver Function** Bilirubin, mg/dL | < 1.2 | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | > 12 |
| **Renal** Creatinine, mg/dL | < 1.2 | 1.2-1.9 | 2.0-3.4 | 3.5-4.9 | >5.0 |
| **Coagulation** Platelets x $10_{3/mm}3$ | ≥ 150 | <150 | < 100 | <50 | <20 |
| **Neurologic** GCS | 15 | 13-14 | 10-12 | 6-9 | <6 |

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