Simplified Severe Sepsis Protocol-2 (SSSP-2): A Randomized Controlled Trial of a Bundled Intervention for Severe Sepsis in Zambia

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EXECUTIVE SUMMARY

Background: Despite expanding ART coverage in sub-Saharan Africa, early mortality after starting treatment remains high. At the University Teaching Hospital in Lusaka, sepsis—the systemic inflammatory response to infection—is the leading cause of death among adult medical patients, disproportionately affecting those who are HIV positive. In recent years, evidence-based protocols of bundled therapies have improved survival of severe sepsis in developed countries. However, management of sepsis in sub-Saharan Africa remains variable. Simple therapies such as IV fluids and early antibiotics are frequently under-utilized. The original SSSP pilot study evaluated a simplified management protocol for treating severe sepsis, but it included a heterogeneous population of septic patients with variable pathophysiological bases underlying the observed organ dysfunctions. No studies in sub-Saharan Africa have evaluated interventions to improve outcomes in patients with septic shock or severe sepsis and hypotension.

General Objective: The overall objective of this study is to ascertain the effectiveness and costs of the simplified severe sepsis protocol in patients with severe sepsis or septic shock and to assess methods for diagnosing tuberculosis in HIV positive patients with severe sepsis.

Specific Aims:
1. To assess the impact on survival of a simple evidence-based protocol for severe sepsis or septic shock
2. To evaluate the cost of implementation for a simplified severe sepsis protocol
3. To develop a clinical diagnostic score for identifying tuberculosis in HIV positive patients with severe sepsis
4. To assess the performance of the Xpert TB/RIF rapid PCR system and urine lipoarabinomannan assay for diagnosing tuberculosis in HIV positive patients with severe sepsis

Hypothesis: The Simplified Severe Sepsis Protocol will significantly decrease in-hospital mortality in patients with severe sepsis with hypotension.

Methodology
Study Design: This study will be a randomized controlled trial. The design is based on the original SSSP study with minor modifications to the inclusion criteria and sample size.
Patients: Adult patients presenting to the UTH Adult filter clinic with severe sepsis. Severe sepsis is defined as all 3 of the following
   1) infection suspected by the treating physician
   2) 2 or more of the following SIRS criteria:
     – Heart rate >90/min   --Respiratory rate >20/min
     – Temperature ≥ 38° C or < 36° C   --White blood count > 12,000 or < 4,000/µL
   3) 1 of the following:
     – Systolic BP ≤ 90 mm Hg
     – Mean arterial blood pressure (MAP) ≤ 65 mm Hg OR

We will exclude patients with volume overload, assessed by looking at the patients' neck veins. We will also exclude patients with hypoxemic respiratory failure.

Intervention: The intervention will be a bundled treatment protocol. All components of the protocol are currently used in the hospital in an unbundled and non-standardized fashion. The protocol will guide more standardized usage:

1. All patients randomized to intervention will receive rapid infusion of 2 Liters of IV fluids.
2. If patients are not volume overloaded they will then receive 2 additional Liters in 4 hours.
3. Patients with low blood pressures after the first 2 Liters of fluid will receive a continuous infusion of dopamine to raise the BP.
4. Blood cultures will be drawn from each patient and antibiotics started after blood cultures, preferably within one hour of assessment.
5. Patients with severe anaemia, defined as haemoglobin < 7 or severe pallor, will receive blood transfusion as soon as blood is available, if patient consents.

Control: The control arm will receive care as directed by emergency room physicians' orders. Study nurses will ensure treatments are carried out as ordered in both arms.

Primary outcome measure: In-hospital all-cause mortality

Secondary outcome measures:
1. 28-day all-cause mortality
2. In-hospital and 28-day mortalities adjusted for illness severity
3. Time to death
4. Culture proven tuberculosis infection
5. Process measures, including IV fluid and dopamine quantities administered, and change in antibiotics based on culture results

Analysis: Primary and secondary analysis will use Mantel-Haenszel tests of comparison. Adjusted mortality will use multivariable logistic regression. TB diagnostic score will also be derived using logistic regression of pooled data from SSSP and SSSP-2 studies. Performance of diagnostic score, Xpert, and urine lipoarabinomannan assay will be assessed by sensitivity, specificity, and positive and negative predictive values.

BACKGROUND

Two-thirds of the world's 33 million HIV-infected persons live in sub-Saharan Africa. As a result of collaborative international efforts, approximately 44% of the 7 million patients with advanced HIV disease in the region are now receiving anti-retroviral therapy (ART)[1]. Although ART has improved survival, early mortality remains high immediately after initiation of therapy[2-4]. In Africa, tuberculosis, cryptococcal meningitis, and acute bacterial sepsis are the leading causes of death among early- or pre-ART HIV positive patients[2,5-6]. Most critically ill patients with tuberculosis and cryptococcal meningitis also present with sepsis, a syndrome consisting of systemic inflammatory response to severe infection. Sepsis was present in 96% of critically ill Brazilian patients with TB and 84% of Taiwanese patients with culture positive cryptococcal disease[7, 8]. Hence, it is likely that the majority of patients who die from HIV-related causes are septic at the time of presentation to the hospital.

In recent years, the management of sepsis in developed countries has followed a bundled protocol-based approach as outlined by the Surviving Sepsis Campaign[9, 10]. These evidence-based guidelines highlight the importance of early fluid resuscitation, infection management and hemodynamic support for improving sepsis outcomes. The limited sepsis data from sub-Saharan Africa, however, show deficiencies in even the simplest evidence-based interventions, such as early fluid resuscitation and antibiotic administration[11, 12]. Additionally, although tuberculosis is the leading cause of sepsis in sub-Saharan Africa, early diagnosis is difficult and late initiation of treatment contributes to poor outcomes[13].

The overall objective of this study is to ascertain the effectiveness and costs of a simplified severe sepsis protocol in severe sepsis patients and to assess methods for diagnosing tuberculosis in HIV positive patients with severe sepsis. The study is greatly strengthened by lessons learned during the original SSSP pilot study and by existing partnershipsbetween Vanderbilt University, the University of Zambia, School of Medicine, and the University Teaching Hospital. The far-reaching goal of this research is to improve sepsis care and outcomes at UTH and throughout the region.

LITERATURE REVIEW AND PRELIMINARY DATA

Overview

Despite expanding ART coverage in sub-Saharan Africa, early mortality after starting treatment remains high. Studies of HIV positive patients initiating ART in Senegal and Uganda found sepsis to be the leading cause of death[11,12]. Quality improvement audit data of 332 deaths in the Department of Internal Medicine at UTH in Zambia (unpublished, Table 1) show that sepsis, tuberculosis, and meningitis are the leading causes of in-hospital death and disproportionately affect those who are HIV positive.

A high case fatality rate contributes to the high disease burden of severe sepsis worldwide. In-hospital mortality rates have ranged from 17 to 45% in randomized controlled trials[14-16]. In one Ugandan study, inpatient mortality was 23.7%, with a total 30-day mortality of 43%[11]. In Zambia, Dr. Sophie Chimese's unpublished M.Med dissertation, entitled *Aetiology and Outcome of Patients Presenting with Septicaemia at UTH*, found 46 (50.5%) of 91 severe sepsis patients died in the hospital.

Yet, although sepsis is a prominent cause of morbidity and mortality in the region, few studies have described it in detail. High HIV prevalence and other social and epidemiologic factors raise questions about generalizability of many treatments proven effective in the West[17,18]. Even when confidence exists regarding optimum treatment, treatment protocols are

Table 1. Causes of death in Internal Medicine Department at UTH

HIV Positive (n=207)		HIV Negative (n=37)		Unknown HIV Status (n=92)	
Sepsis	36 (17)	CHF	8 (22)	CVA	14 (15)
TB	36 (17)	CVA	5 (14)	Sepsis	14 (15)
Meningitis	27 (13)	Sepsis	5 (14)	CHF	12 (13)
Pneumonia	23 (11)	Pneumonia	4 (11)	Meningitis	8 (9)
Crypto Mening	16 (8)	Renal Failure	4 (11)	Pneumonia	8 (9)
Renal Failure	10 (5)	Anemia	2 (5)	Renal Failure	5 (5)
Hepatic failure	9 (4)	Meningitis	2 (5)	TB	4 (4)
Anemia	7 (3)	TB	2 (5)	Aspiration pna	3 (3)
CHF	6 (3)	Lung CA	1 (3)	Crypto Mening	2 (2)
GE	5 (2)	GI bleeding	1 (3)	GE	2 (2)
KS	4 (2)	Hepatic failure	1 (3)	Malaria	2 (2)
		Hypoglycemia	1 (3)		
		Spontaneous PTX	1 (3)		

notably absent, and best practices aren't always adhered to. In the United States and Europe, early antibiotics[19], recombinant activated protein C[15], corticosteroids[20], low tidal volume mechanical ventilation[21], and a protocol of early intravenous fluids with vasopressors, blood transfusion, and inotropes[14] have improved survival in patients with severe sepsis (all except corticosteroids) or refractory septic shock (corticosteroids). In Africa, however, even the simplest of these interventions are at times underutilized. The Simplified Severe Sepsis Protocol will focus on 4 evidence-based interventions: early aggressive fluid resuscitation, dopamine for patients in septic shock, early blood cultures and antibiotics, and blood transfusion in anaemic patients.

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Early aggressive fluid resuscitation: In 2001, Rivers et al. demonstrated that a protocol of intensive hemodynamic monitoring linked with aggressive fluids, vasopressors, dobutamine and blood transfusion, led to a 15% absolute reduction in mortality in septic patients with elevated lactate levels or septic shock[14]. Although increased fluid administration was not a specified part of the intervention, one observed difference between the two groups that may have contributed to the improved outcomes was the amount of fluid administered in the first six hours (mean of 5.0 liters in intervention group vs. 3.5 liters in controls). The ongoing PROCESS study is seeking to find if less expensive, less complicated protocols could provide similar benefits in an American setting[22]. The limited data on severe sepsis in sub-Saharan Africa show that insufficient amounts of IV fluids are administered to septic patients. In a national referral hospital in Uganda, Jacob et al. found that only 35% of patients with sepsis and hypotension received one or more liters of fluid in the first six hours[11]. Only 32% of patients received antibiotics within one hour. In Livingstone, Zambia, Theodosis et al. observed that only 7% of patients with sepsis and hypotension had appropriate and timely orders written for fluids and antibiotics[12]. These findings are consistent with observations at UTH, where 84.2% of patients received ≤ 1 Litre of fluid in the first 6 hours of admission (Chimese, unpublished). A follow-up study by Jacob, et al., in Uganda has shown a considerable improvement in outcomes just by increasing the intravenous fluid administration, but that study had some design flaws, including confounders inherent to before-after studies[23].

Peripherally infused dopamine for patients in septic shock: Standard of care for septic shock in developed countries involves the use of vasopressors infused through central venous catheters[9]. In Zambia, dopamine is the only available vasopressor, and its availability is mainly restricted to UTH, the central referral hospital. Because of the dearth of central venous catheters in Zambia, dopamine, when used, is typically infused through a peripheral IV catheter. This method is known to lead to occasional infiltration of the subcutaneous tissue and, rarely, limb ischemia[24], although these complications have not been reported in this setting.

Blood cultures and antibiotics: Jacob et al. found that only 32% of septic patients in Uganda received antibiotics within the first hour of hospitalization[11]. The numbers at UTH are almost identical (28.6%) (Chimese, unpublished) This contrasts with recommendations from a Canadian study that showed that each hour of delay in appropriate antibiotic treatment raises the mortality by an additional 7.6% in patients with septic shock[19]. Although culture yields at UTH have anecdotally been low, Dr. Chimese, found that, after excluding probable contaminants, 36 (22.3%) of 161 septic patients had positive aerobic blood cultures.

Blood transfusion: In developed countries, target hemoglobin level in septic patients varies based on the stage of treatment. Early goal-directed therapy protocols recommend transfusing to a hematocrit ≥ 30 g/dL if central venous oxygen saturation is < 70% in the first 6 hours of treatment[14]. Outside of the initial resuscitation, however, a transfusion threshold hemoglobin of ≥ 7 g/dL is as safe as a hemoglobin of ≥10 g/dL[25]. In sub-Saharan Africa, severe anemia is common among patients with severe sepsis[11]. In HIV positive patients, anemia of chronic inflammation, frequently associated with tuberculosis, is the primary culprit[26].

Jugular venous examination: The SSSP protocol will require the assessment of patients' jugular venous pressure to guide fluid administration. Evidence suggests that it is possible to accurately identify raised JVP of greater than 3 cm above the sternal angle[27]. This level (approximately 8 cm above the right atrium) equates to a CVP of 10-11 mm Hg, which approximates the target CVP for Rivers' early goal-directed therapy protocol[14].

Tuberculosis-associated severe sepsis: More than 40% of the world's 34 million people living with HIV are also co-infected with tuberculosis (TB)[28]. 380,000 die from HIV-associated TB each year, the majority in sub-Saharan Africa[29]. Thus, it comes as no surprise that the leading cause of severe sepsis in the region is tuberculosis[11]. Among severe sepsis patients with an identified etiology, 32% have tuberculosis mycobacteremia[11], yet the subject of TB sepsis has been mostly ignored since the days when it was described as *sepsis tuberculosis gravissima*[30]. As previously mentioned, evidence-based guidelines place an emphasis on obtaining blood cultures and initiating broad-spectrum antibiotics within one hour of diagnosis. However, mycobacterial blood cultures are generally not helpful in acute care, taking an average of 5 weeks to turn positive[31]. Furthermore, many patients with severe sepsis are too sick to produce an adequate sputum sample for smear and culture, and selecting patients for empiric anti-tuberculous therapy is still a matter of controversy[32,33]. This is a serious problem when one considers that a delay in initiation of therapy for hospitalized patients with tuberculosis more than triples the odds of inpatient death[13]. New diagnostic methods, most notably the Cepheid Xpert MTB/RIF device, might provide the answer to this problem, but their effectiveness and affordability remain untested in many clinical settings[34,35].

Diagnostic scores for tuberculosis: Several clinical scoring systems exist for identifying hospitalized patients with high likelihood of tuberculosis[36]. However, most of those systems have been developed in high-income countries among patients with moderate severity of illness and with the expressed intent of isolating contagious patients from other hospital inpatients. Many existing models use variables that are irrelevant to the African setting, e.g. foreign place of birth or tuberculin skin test result.[36,37] At least one score included as a variable a positive acid-fast sputum smear[38], which is already the standard for clinical diagnosis of tuberculosis in most of Africa.

On physical exam, lymphadenopathy has been the predictive variable most often assessed[39]. Wasting and pallor due to anaemia are frequently encountered in tuberculosis patients in sub-Saharan Africa, but these have not been incorporated into any of the previous diagnostic scores. More commonly, models are heavily reliant on chest x-ray findings[36,40]. Most common findings associated with tuberculosis have been cavitary lesions, upper lobe infiltrates, miliary pattern, and pleural effusions [36,40,41]. X-ray-based models can also be of use in sub-Saharan Africa, but it is often difficult to transport severe sepsis patients for x-rays, so a non-radiographic scoring system would be most useful.

Xpert MTB/RIF system: The WHO recently endorsed a fully automated DNA test, the Cepheid Xpert MTB/RIF ("Xpert"), for rapid diagnosis of pulmonary TB, including multi-drug resistant TB, from sputum samples[42]. Preliminary results from testing extrapulmonary specimens (excluding blood) with the Xpert further support the idea that it could play a significant role in early diagnosis of hospitalized patients with severe sepsis[43]. However, the most appropriate testing strategy needs to be determined.

Urine Lipoarabinomannan (LAM): Lipoarabinomannan is a glycolipid portion of the mycobacterial cell wall of *Mycobacterium tuberculosis*. LAM is frequently secreted in the urine in patients with tuberculosis infection and poor cellular immunity but rarely in patients with intact immune systems[44,45]. Thus, it is an attractive diagnostic test for HIV positive patients with suspected tuberculous meningititis or other disseminated tuberculosis[46]. The high rate of positive TB blood cultures in the original SSSP study and the long incubation times suggest that a rapid surrogate for TB blood cultures, such as urine LAM, might be clinically useful for diagnosing disseminated TB in septic patients.

Blood lactate and sepsis: Circulating lactic acid levels are an indicator of tissue hypoperfusion in severe sepsis. A hand-held portable whole blood lactate device has been validated with results correlating well with standard laboratory serum lactate measurements[47,48]. In a Ugandan study of septic patients, increasing portable whole blood lactate levels correlated with an increased risk of in-hospital mortality[49]. International guidelines utilize a lactate level above 4 mmol/L as an indication for initiating protocolized fluid resuscitation[9]. Other studies have incorporated lactate levels to guide protocolized decision points[50]. In the absence of lactate measurement, the SSSP pilot study and other studies in the region[51] have had difficulties in identifying normotensive septic patients with tissue hypoperfusion who would be most likely to benefit from aggressive volume resuscitation.

SSSP study: In the first SSSP study, we have enrolled 89 participants with severe sepsis and randomized them in a 1:1 fashion to either the sepsis protocol or usual care. Baseline characteristics are shown in Table 2. Primary outcome data is available for 74 participants. Patients in the intervention group have received a mean of 2.7 litres of IV fluid during the 6 hour active management period as compared with 1.8 liters of fluid in the usual care group (p<0.001). There has been no difference between the intervention and control groups for the primary outcome of in-hospital mortality (68.6% vs. 64.1%). Of note, in-hospital mortality has been 92% (11 of 12) among participants with respiratory rate (RR) greater than 40 and a measured oxygen saturation (SpO2) less than 90%.

Table 2. Baseline characteristics in SSSP participants

	Total n=76	SSSP n=36	Control n=44
Age, mean (SD)	35.1 (10.0)	35.2 (10.6)	35.1 (9.6)
HIV positive	57 (75)	26 (72)	31 (78)
Organ dysfunction			
Confusion	49 (65)	22 (61)	27 (68)
Respiratory Rate > 40	29 (38)	15 (42)	14 (35)
SBP < 90 or MAP < 65	26 (34)	13 (36)	13 (33)
Metabolic acidosis*	29 (38)	16 (44)	13 (33)
Acidotic or hypotensive	40 (53)	23 (64)	17 (42)

* Metabolic acidosis defined as bicarbonate level less than 20 mmol/L
SBP = Systolic blood pressure; MAP = Mean arterial pressure

The study investigators, in consultation with experts in the field of sepsis, have decided to close the original SSSP study in order to open the new SSSP-2 study with inclusion criteria limited to those with evidence of tissue hypoperfusion who are the most likely to benefit from the SSSP intervention. Because of their extremely high risk of death with or without

fluid administration, the new study will exclude participants with hypoxemic respiratory failure (RR > 40 and SpO2 <90%).

JUSTIFICATION OF THE STUDY

Management of sepsis in sub-Saharan Africa has been highly variable and often sub-optimal. Bundled treatment protocols improve outcomes in severe sepsis and have become standard of care throughout the developed world. However, most of these protocols are too expensive or cumbersome for use in sub-Saharan Africa. This study will assess the performance and costs of a simple treatment protocol that was developed in Zambia by the investigators. The Simplified Severe Sepsis Protocol (SSSP) implemented the highest-yield components of American protocols, devoid of their most costly aspects, such as invasive central venous pressure and oxygen monitoring in a heterogeneous population of patients with severe sepsis, with organ dysfunction most likely owing to a variety of pathophysiological mechanisms. SSSP-2 will evaluate the effectiveness of the SSSP treatment protocol in a group of patients who are most likely to benefit from this intervention, namely those with hypotension.

Additionally, although tuberculosis has been recognized as a leading cause of severe sepsis in HIV positive patients in Africa, TB-associated severe sepsis has not been described as a distinct entity in the era of HIV. TB-associated severe sepsis is also difficult to diagnose in a timely manner. Rapid clinical and laboratory-based diagnostic algorithms are needed in order to facilitate timely diagnosis and treatment. Combined data from SSSP-2 and the original SSSP will be used in developing a clinical diagnostic score to identify TB-associated severe sepsis in severely ill patients, the patient population most in need of early appropriate therapy. The results of the combined SSSP-1 and SSSP-2 studies will provide new evidence that could be incorporated into a novel diagnostic algorithm for identifying severe sepsis patients with a high probability of TB and to select the appropriate confirmatory diagnostics.

OBJECTIVES

General objective

The overall objective of this study is to ascertain the effectiveness and costs of a simplified severe sepsis protocol in patients with severe sepsis and evidence of tissue hypoperfusion, and to assess methods for diagnosing tuberculosis in HIV positive patients with severe sepsis.

Specific Aims

1. To assess the impact on survival of a simplified evidence-based protocol for severe sepsis with evidence of tissue hypoperfusion
2. To evaluate the cost of implementation for a simplified severe sepsis protocol
3. To develop a clinical diagnostic score for identifying tuberculosis in HIV positive patients with severe sepsis
4. To assess the performance of the Xpert TB/RIF rapid PCR system for diagnosing tuberculosis in HIV positive patients with severe sepsis

HYPOTHESIS

The Simplified Severe Sepsis Protocol will significantly decrease in-hospital mortality in patients with severe sepsis.

METHODOLOGY

Specific Aim 1: SSSP Effectiveness

Study design: Randomized control trial.

Setting: The University Teaching Hospital in Lusaka, Zambia is a 1400-bed tertiary care hospital that serves as the national referral hospital. It is also a major primary care hospital for the city of Lusaka. Medical patients are initially brought to a 50-bed intake unit called the Adult Filter Clinic (AFC) that includes a three bed Emergency Room (ER) (Figure 1). Patients spend up to 24 hours in AFC for stabilization and triage.

Patients:

Patients who are 18 years old and above will be eligible for enrolment if they meet the criteria for severe sepsis upon presentation to the ER.
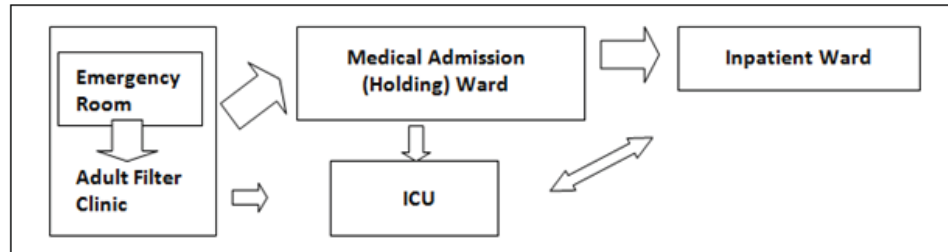

Figure 1 Internal Medicine hospital flow diagram

Additionally, patients who manifest severe sepsis after arrival will be eligible if they have been in AFC for less than 24 hours and are within 4 hours of first meeting SIRS criteria (item 2 below).

In this study, **severe sepsis** will be defined as the presence of all 3 of the following:
1) infection suspected by the treating physician
2) 2 or more of the following SIRS criteria:
   – Heart rate >90/min   --Respiratory rate >20/min
   – Temperature ≥ 38° C or < 36° C   --White blood count > 12,000 or < 4,000/μL
3) 1 of the following:
   – Systolic blood pressure (SBP) ≤ 90 mm Hg
   – Mean arterial blood pressure (MAP) ≤ 65 mm Hg

Patients will be excluded if they have a gastrointestinal bleed in the absence of fever; or require immediate surgery. Due to limited ICU capacity and high mortality rate, we will also exclude septic patients with hypoxemic respiratory failure defined as a respiratory rate greater than 40/min with oxygen saturation less than 90%. Patients will be excluded if they have suspected congestive heart failure exacerbation, end-stage renal disease, or raised jugular venous pressure (JVP) at baseline. Prisoners who are currently incarcerated will also be excluded.

Patient recruitment and consent

Patients will only be approached for study enrolment after they have been seen by an ER doctor in AFC and usual care has been initiated (see Figure 2). This will ensure that the consent procedure does not delay initiation of care for the patient. Patients with sepsis who agree to be screened by the study nurse will have vital signs recorded and a finger-stick to check the whole blood lactate level.

Those patients who meet eligibility criteria and agree to consent will be enrolled. If a patient lacks decision-making capacity, then the patient's next of kin will be asked to consent, as per Zambian law. Baseline labs will be drawn on all patients, and then patients will be randomized to either usual care or SSSP. Patient randomization will be performed by administrative staff using sealed opaque envelopes.

Patients will be blinded with regards to group assignment. Treatment for control patients will be as ordered by the ER doctors prior to enrolment. These patients will receive non-protocolized care but may still benefit from more frequent assessments provided by the study nurses.

Simplified Severe Sepsis Protocol

Table 3 describes the components of the SSSP. Prior to initiation of

Figure 2. Enrolment flow diagram

the study, the research nurse and student research assistant(s), will be trained regarding the identification of severe sepsis, the clinical assessment of jugular venous pressure, calculating MAP, calculating dopamine infusion rates, and the SSSP protocol itself. ER doctors and nurses not involved in the study will be blinded to the contents of the protocol.

All patients in the SSSP group will receive an initial 2 litre bolus of normal saline or lactated Ringer's within 1 hour of assessment. After the initial bolus, an investigator or study nurse will evaluate the patient's JVP, using a level and a ruler. Patients who do not have raised JVP will receive an additional 2 litres of fluid over 4 hours, for a total of 4 litres in the first 5-6 hours in the hospital. Patients may receive fluids at a faster rate at the discretion of the primary admitting physicians. Within one hour of the recognition of severe sepsis, all patients will have aerobic and mycobacterial blood cultures and malaria blood smears sent to the lab, and empiric broad-spectrum antibiotics initiated. Additional antimicrobials, such as anti-tuberculous therapy, empiric anti-malarials, or high-dose sulfamethoxazole/ trimethoprim, may be used at the discretion of the treating physicians. If a patient's MAP remains below 65mm Hg after the initial 2 liter bolus of fluids, then a dopamine infusion will be initiated at a starting rate of 10 mcg/kg/min. Those receiving dopamine will be monitored for dopamine-related complications. Whenever hourly blood pressures are checked and dopamine infusions are titrated, the IV site will be examined for signs of extravasation. Dopamine infusion will be titrated to the lowest possible rate to maintain a MAP ≥65 mmHg.
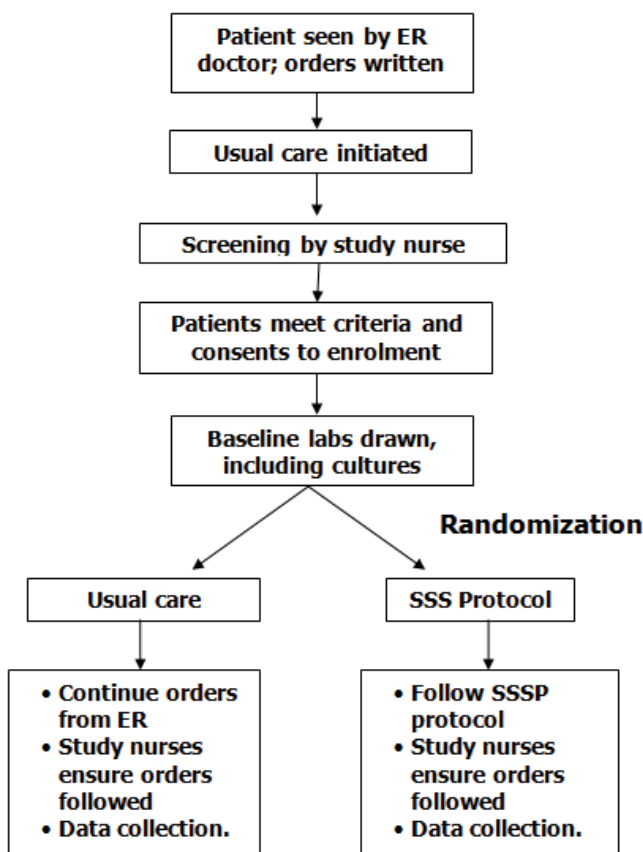
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Table 3. Simplified Severe Sepsis Protocol

Intervention	Simplified Severe Sepsis Protocol
IV fluids	2 liters in first hour* 2 additional liters in next 4 hours*
Blood cultures	Drawn within 1 hour of arrival
Malaria blood smear	Drawn within 1 hour of arrival
Antibiotics	Antibiotic selection by ER physician; 1st dose after culture, within 1 hour of arrival/sepsis diagnosis
Dopamine	If MAP < 65 after 2 liter bolus, then add dopamine and titrate to MAP ≥65
Blood transfusion	Will recommend blood transfusion, when available for Hb < 7 g/dL or severe pallor

* Jugular venous pressure (JVP) examined after 1st 2 liters;
   if JVP is raised, then fluid is held.
MAP – mean arterial pressure, Hb – hemoglobin, Hct – hematocrit

Evaluation of Patients: Baseline characteristics including demographic information and information on pre-existing conditions, organ function, markers of disease severity, infection, and hematologic and other laboratory tests will be assessed within 24 hours of enrolment. The following laboratory tests will be collected as part of routine care (standard of care):

      Biochemistry: Urea, Na, K ("U and E's"), Creatinine, Bilirubin, AST, ALT, Albumin ("LFT's"),
      Hematology: Full blood count with differential
      Rapid test: HIV ELISA (opt out)
      Virology: CD4 (if HIV positive)
      Aerobic blood culture
      Malaria parasite smear, in selected patients

The study staff will record the results of these routine labs as they are collected and analyzed in the course of patient care. The study will also provide resources to ensure that these investigations are completed in the event of shortages.

The study staff will also obtain blood for the following laboratory tests that are not part of routine clinical care:

      Serum bicarbonate level (4 mL)
      One tube of blood (4 mL) will be drawn at baseline and an additional tube (4mL) will be drawn 48 hours later. This blood will be stored for further immunologic testing.
      Mycobacterial blood cultures (5 mL) will be drawn in HIV positive patients.
      Additional tuberculosis laboratory testing is described under Aims 3 and 4 below.

A total of 12 mL of blood in HIV negative patients and 17 mL of blood in HIV positive patients will be drawn in addition to the standard clinical investigations. Specific patient consent will be requested to refrigerate and store any specimens for future studies. Banked blood will be stored with de-identified coded labels, and UNZA REC approval will be required for any subsequent usage. Specimens will be stored for a maximum of 5 years.

Information about medical management throughout hospitalization—such as antibiotics selection, fluid administration, ICU admission, hemodialysis, and mechanical ventilation—and final clinical diagnosis will be recorded. UTH admits approximately 4-5 patients with severe sepsis every day. We will try to enrol all eligible patients for consent using the combined workforce of the study nurses, student research assistant(s), and investigators. The estimated time necessary to identify the patient as eligible, obtain informed consent, and collect the clinically available data (including hospital treatments and outcome) as well as the study data is approximately 4 hours per patient. Patient's address and a telephone number of the patient and at least one relative will be obtained from patients. Patients will be telephoned to ascertain vital status. Study personnel will visit the homes of patients who are unreachable by telephone.

Outcomes

Primary outcome: Primary outcome will be in-hospital all-cause mortality.

Secondary outcomes:

  Mortality: The following mortality outcomes will also be assessed:
  - 28-day all-cause mortality
  - In-hospital all-cause mortality adjusted for disease severity score (SAPS3)
  - 28-day all-cause mortality adjusted for disease severity score (SAPS3)

  Time to death

  Process measures: The following process measures will be used to assess adherence to protocol, impact of various protocol components and resource utilization:
  - Volume of IVF's administered within 6, 24, and 72 hours
  - Proportion of patients receiving antibiotics within 1 hour; cultures within 1 hour; and blood transfusion
  - Proportion of patients whose antibiotics were changed based on culture results
  - Total amount of dopamine used

  Adverse events: Study personnel will monitor patients for dopamine extravasation, dopamine-associated tissue ischemia or necrosis, iatrogenic pulmonary oedema, and transfusion-related adverse events.

Sample size: The SSSP study has found a 65% in-hospital mortality rate among patients with severe sepsis. We use this figure as the expected mortality in the control group. Assuming a two-sided type I error rate of 5 percent, and a power of 80 percent, a sample size of 212 patients will permit the detection of a 20 percent absolute reduction in in-hospital mortality. The patients will be randomized on a 1:1 basis.

We will enrol consecutive patients who meet the inclusion criteria and consent. However, budget limitations may limit enrolment to daytime hours Monday through Friday. If this limitation occurs, REC and IRB will be notified. We expect to complete enrolment in 6-8 months.

Analysis: Continuous variables will be presented as mean and standard deviation and will be analyzed using t-test and analysis of variance. Categorical variables will be presented as proportions and will be analyzed using chi-squared, Fisher exact, or Mantel-Haenszel tests. Secondary analyses will include adjusted hazard ratios, adjusting for disease severity using quartiles of the Simplified Acute Physiology Score -3 (SAPS3)[52]. Time to event analysis will include Kaplan Meier plot, log rank test, and Cox proportional hazards modelling. P value of less than 0.05 will be considered statistic-ally significant.

Secondary analyses will also assess the primary outcome in relevant subgroups (Table 4) to see if particular groups benefit most from intervention. Due to the small sample sizes in this study, these subgroup analyses will be used primarily for hypothesis generation.

Table 4. Aim 1 Subgroups for hypothesis generation

Subgroup	Rationale
HIV+ vs. HIV-	HIV+ pts more likely to have undiagnosed, untreated mycobacterial or fungal infections that may attenuate benefits of SSSP
GCS 13-15 vs. 9-12 vs. <9	GCS is a strong predictor of mortality in sepsis patients in Zambia. To assess whether SSSP effect varies based on GCS stratification
Hb ≥7 vs. <7	To assess benefit of protocol among patients with severe anaemia
Above vs. below median SAPS	To assess whether the effect varies according to disease severity
Lactate <4.0 vs. ≥4.0	To assess whether the benefit varies according to lactate stratification

Mantel-Haenszel will be used, and p values for subgroup analyses will be considered significant if they are less than 0.01 (=0.05/5 subgroups). Because the management in the standard care arm may "drift" towards SSSP interventions over time, we will perform an "as-treated" analysis comparing patients who received ≥ 3 litres of fluid in the first 6 hours of enrolment versus those who received < 3 litres, adjusting for SAPS3 score and site of infection using multivariable logistic regression. Furthermore, we will assess the utility of blood cultures based on how frequently antibiotics regimens were changed when culture results became available.

Specific Aim 2: Budget Impact Analysis of SSSP

To assess the costs of the SSSP, we will conduct a budget impact analysis to be used for real-world implementation decisions. A budget impact analysis is an important tool "to estimate the financial consequences of adoption and diffusion of a new health-care intervention within a specific health-care setting or system context given inevitable resource constraints"[53]. Budget impact analyses are less complex and less generalizable than full scale cost effectiveness analyses, but they are extremely useful for estimating the potential implementation costs for the site where the study was performed. Our study will follow the guidelines for conducting budget impact analyses as proposed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [53]. Dr. Ted Speroff, health economics expert from Vanderbilt University will provide technical assistance for this portion of the study.

Model description: The budget impact model will be an Excel-based spreadsheet with primary inputs from the direct measurements of the above interventional study supplemented with micro cost analysis of detailed costs measured for a randomly selected subset of patients.

Perspective: Zambian Ministry of Health (government payer that supports UTH)

Scenarios to be compared: Current usual care (including low-level utilization of IVF's, dopamine, blood cultures, antibiotics, and blood transfusion) versus SSSP-guided care

Population: Patients presenting to the University Teaching Hospital with severe sepsis; this will be calculated by counting the number of patients enrolled and estimating the percentage of eligible patients who were not enrolled due to timing of presentation and/or refusing consent. The total number of patients meeting severe sepsis criteria upon presentation to UTH will then be calculated and divided by the number of months to obtain monthly average.

Time horizon: One month, disaggregated into in-hospital and post-discharge periods

Costing: *Methods for deriving budget impact estimates*

Only direct costs will be measured. Costs will be divided into startup costs, consisting of time and materials utilized in training personnel regarding the identification and protocolized treatment of severe sepsis, plus the difference in steady-state costs between current practice and SSSP-driven practice. Startup costs are only applicable for the SSSP scenario.

> Total cost = Startup cost + Inpatient (SSSP steady-state costs - Current steady state costs) + Cost due to adverse events (i.e. treatment side effects) + Post-discharge costs

The difference in steady state costs will be calculated as the incremental increase of the sum of component steady state costs:

> Steady state costs = Cost(clinical personnel's time) + Cost(lab) + Cost(culture) + Cost(ICU)*
> + Cost(Hospital bed) + Cost(supplies) + Cost(hemodialysis) +
> Cost(fluids) + Cost(medications) + Cost(Blood transfusion)
> * ICU costs include costs associated with mechanical ventilator use

> Post-discharge costs = Cost (clinical personnel's time + clinic overhead + medications)

Costs of steady-state components will be further subdivided. Lab costs are shown as an example:

> Cost(lab) = Cost(blood draw + transport + lab fixed cost + lab variable cost + documentation cost)

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Data sources

Unit costs and overhead costs will all be obtained directly from the hospital administration. Table 5 illustrates the source of information regarding resource utilization and unit costs.

Table 5. Sources for utilization estimates and unit costs

Measured resource	Utilization	Unit cost
Start-up training costs	Direct measure	Hospital employment data or survey employees directly
SSSP treatment costs		
Personnel time	Microcost observation	
Medications	Microcost observation	Hospital financial data
Intravenous fluids	Direct measure & microcost observation*	Hospital financial data
Blood transfusion	Direct measure	Calculated from Hospital financial and personnel data and interviews with blood bank staff
Medications	Microcost observation	Hospital financial data
Recurrent training costs	Measured or estimated	Hospital employment data or survey employees directly
Laboratory costs		
General labs	Microcost observation	Calculated from Hospital financial and personnel data and interviews with laboratory staff
Cultures	Direct measure	
Lodging costs		
ICU days	Direct measure	Hospital financial data
Non-ICU hospital days	Direct measure	Hospital financial data
Other inpatient costs		
Supplies	Microcost observation	Hospital financial data
Hemodialysis days	Direct measure	Hospital financial data
Cost due to adverse events	Direct measure and extrapolation	Hospital financial data
Post-discharge costs	Microcost observation	Hospital financial data

* IV fluids will be measured directly for the first 72 hours. Fluid utilization will be measured for the entire length of stay in patients selected for microcost observation.

Hours of training and number and rank of those in attendance at training sessions will be recorded for determining startup costs. Blood cultures and transfusions will be measured directly, as will days in the hospital, in the ICU, and on hemodialysis. Detailed inpatient data will be collected for 10 randomly selected patients in the pre-implementation group and 10 patients in the post-implementation group, using a micro cost accounting method. The average values will be used as the representative cost/utilization, and the range will be used for sensitivity analysis. Micro cost accounting will also assess blood bank and laboratory utilization of personnel time, screening tests, preservatives, supplies, and reagents with respect to each unit of blood or each individual laboratory test. If a treatment-related adverse event occurs, it will trigger a detailed listing of related costs incurred.

In 10 patients from each group who survive to discharge, medical records will be reviewed 4-6 weeks after discharge. These patients will be evenly divided into those with disability at discharge and those without. We will assess the number of patients' follow-up visits at the UTH outpatient clinic and the medications prescribed at those visits, plus any re-hospitalizations. Hospital financial data will be used to assess the per-visit and

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subsidized outpatient prescription costs to the hospital. Patients discharged from UTH are generally followed up in the UTH-based clinic, so this method is expected to reflect accurate post-discharge healthcare utilization. Microcosting data from the original SSSP study may also be utilized in the costing model.

Sensitivity Analysis: Multivariable sensitivity analysis will be performed varying the quantity of resources used within directly-measured ranges for variables measured by microcost observation, and within the 95% confidence intervals for variables measured in all patients. Results will be presented in a Tornado diagram.

Discounting: ISPOR does not recommend discounting because budget impact analyses represent financial streams over time, and budget holders are "concerned with the cost budgets will realize each year rather than the value, in present-day terms, of any costs brought about through the reimbursement of a new therapy."[54]

Limitations: The time horizon for this analysis is limited to one month due to financial constraints. Costs incurred beyond that time frame, resulting from increased survival and disability, will not be accounted for.

Specific Aims 3 and 4: Tuberculosis-associated severe sepsis

Specific Aims 3 and 4 will evaluate the HIV positive cohort of patients enrolled in the combined SSSP and SSSP-2 studies. We will implement intensive tuberculosis case-finding measures to identify tuberculosis in severe sepsis patients and to assess the performance of diagnostic approaches. In addition to the evaluation and investigations described in Aim 1, the following TB-specific investigations will be performed:

TB-specific Laboratory Investigations

For all HIV positive patients, mycobacterial blood cultures (5 mL, as noted under Specific Aim 1) will be collected in BACTEC Myco/F Lytic culture bottles (Becton Dickinson, Sparks, Maryland, USA) on the day of admission and will be incubated in a BACTEC machine. Positive cultures will have confirmatory PCR line probe testing to differentiate TB vs non-tuberculous mycobacteria. All patients will also have urine collected and sent for culture, lipoarabinomannan, and Xpert testing. For each patient who is capable of producing sputum, 3 samples will be collected over a 2-day period (2 spot and 1 morning), consistent with the standard of care. 3 samples will undergo standard Ziehl-Neelsen staining. One sample will be cultured and also tested using the Xpert system.

We will collect specimens from the following procedures, if performed as a part of routine care by the treating physician: lumbar puncture (cerebrospinal fluid, CSF), bronchoscopy (lavage washings), thoracentesis (pleural fluid), and paracentesis (ascites fluid). Collected specimens will be sent for culture and for Xpert testing. All specimens other than blood will be cultured on a Bactec MGIT (Mycobaterial Growth Indicator Tube) 960 System. Positive cultures will undergo confirmatory TB PCR testing. All TB-specific investigations will be performed at one of the following sites:
- UTH microbiology lab
- UTH tuberculosis lab
- CIDRZ research lab in Kalingalinga, Lusaka, Zambia

All specimens under Specific Aims 3 and 4 may be subject to freezing and storage for up to 5 years in order to allow for testing of newer tuberculosis diagnostics. REC and IRB approval will be sought prior to any testing not specified above.

Outcomes

Primary outcome for Aims 3 and 4: culture-confirmed tuberculosis sepsis based on a positive TB culture from any site.

Secondary outcomes for Aim 4:
- Xpert positive test from any site
- Tuberculosis blood culture positivity
- Time to positive culture from any site.

Analysis

Sample Size
The parent SSSP study will enrol 342 HIV positive and negative patients. With an HIV prevalence of 68% among admitted sepsis patients, we expect to enroll 233 for this TBASS sub-study. For a TB prevalence of 20% in our cohort, we will be powered to detect sensitivity of Xpert within the range 70% +/- 13% and specificity of 95% +/- 3%.

Clinical diagnostic score
The following variables will be recorded on admission to be included as candidate variables for the clinical diagnostic score:
From the patient's history:

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- Cough of any duration – A recent study suggested that chronic cough was insensitive for TB and any cough should be worked up further for TB[55].
- Duration of symptoms greater than 2 weeks – This will include cough, fever, night sweats, or weight loss.
- Prior history of TB treatment – History of treatment will include patients treated for smear positive as well as smear negative TB.

From the physical exam:

- Signs of wasting – These will be the clinician's subjective assessment based on temporal wasting, sunken eyes, and limb and trunk muscle wasting. We will also compare the clinician's assessment with an administered Subjective General Assessment, a well validated method for identifying malnutrition in critically ill patients[56].
- Pallor – Pallor will be used as a surrogate of anemia in the initial assessment.
- Lymphadenopathy

The primary model will not include laboratory investigations because laboratory results are not usually available immediately. However, 2 laboratory investigations will be incorporated into a secondary model:

- Hemoglobin
- CD4 count

Candidate variables will be incorporated into a multivariable logistic regression model with the primary outcome variable of culture confirmed tuberculosis. The model will be repeated in a step-wise fashion after the variable with the highest p value >0.05 is removed each iteration until only those with p<0.05 are included. A simple numbering system will then be devised based on the magnitude and direction of the model coefficients. The sensitivity and specificity of various cut-offs will then be assessed and an ROC curve created. Area under the curve (AUC) will be calculated using Open Epi (open source, developed by CDC). If more than 4 variables remain in the final model, then every possible 4-variable combination will be assessed and sensitivities, specificities, and AUC's will be compared. This process will be repeated for the second model inclusive of the haemoglobin and CD4 count variables, both variables will be categorized *a priori*.

Post hoc analyses of SSSP and SSSP-2 data may investigate the associations of any of the following variables with the outcomes of suspected or confirmed tuberculosis: urea, Na, K, creatinine, bilirubin, AST, ALT, albumin, full blood count components, CD4 count, any of the collected physical exam variables, prior history of tuberculosis, and/or chest x-ray results.

Xpert assessment
Sensitivity, specificity, AUC, and kappa value will be calculated for the Xpert. For the primary analysis, positive Xpert test from any site will be considered a test positive, and positive culture from any site will be a true positive. We will repeat the same analysis using Xpert results from individual sites against positive culture from any site in order to assess performance of individual Xpert tests for TB-associated severe sepsis. Finally, we will compare Xpert tests from individual sites against cultures from those same sites to determine performance of Xpert for a particular body fluid.

ETHICAL CONSIDERATIONS

Confidentiality: Confidentiality of the patients' medical records will be maintained by using password-protected secure databases to store patient information. Medical charts will be kept in a locked office with access limited to only the study investigators and study staff involved in data collection and data entry.

Ethics approval and consent: Approval for the study protocol will initially be sought from the Biomedical Research Ethics Committee of University of Zambia. After approval is granted, the investigators will apply for exemption from Vanderbilt University's Institutional Review Board. The research project will take place only after the above review boards have met and approved the study.

When study candidates are identified, details will be carefully discussed with them, and they will be asked to read and sign the consent form. If a patient does not have the capacity to consent, then the next of kin as defined by Zambian law will be asked to consent. If the participant or next of kin are unable to read, the process for consenting illiterate participants, as defined by UNZA REC, will be followed. The consent form may be administered in English or either of two local languages, Nyanja or Bemba.

Patients' participation in this study is voluntary, and patients may withdraw from the study at any time without giving reason for withdrawal. Patients who withdraw will receive usual care for their medical condition, and they will still receive the results of any study investigations that have already been tested.

Risks to the subjects: The individual components of the Simplified Severe Sepsis Protocol are all currently used at UTH in a non-protocolized manner. This includes the use of dopamine via peripheral infusion, the standard method of administration in Zambia. Therefore, we do not expect this study to pose an increased risk to patients. However, the investigators recognize that even with the current standard of care, peripheral dopamine infusion carries some risk, include IV infiltration and subsequent tissue hypoperfusion. Also, increased IV fluid resuscitation carries with it a mild risk of iatrogenic pulmonary edema.

Protection against risks*:* The study protocol includes close monitoring for adverse events by a trained research nurse. Details of monitoring procedures are described in the RESEARCH STRATEGY. Because this close level of monitoring will likely lead to earlier identification of events than in standard care, the investigators believe that enrollment in this study will provide a net reduction, rather than increase, in risk.

Potential benefits to the subjects and others: Availability of laboratory tests in Zambia is frequently limited to those who can afford the lab fees. The investigators have budgeted to pay the standard lab fees for subjects who enroll in this study who cannot afford standard tests. Any relevant tests that are not part of standard care will also be funded by the study, and these results will be made available to the treating physicians to facilitate improved patient care. In both the control and intervention arms, a study nurse will ensure that doctor's orders are carried out in a timely fashion. The increased attention of the study nurse in the first day of admission may also be considered a benefit to the patients.

Importance of the knowledge to be gained: If the Simplified Severe Sepsis Protocol (SSSP) is proven effective, then its implementation at UTH and other hospitals in sub-

Saharan Africa could result in significantly decreased hospital mortality due to sepsis. Improvements in tuberculosis diagnosis, either via a diagnostic scoring system or Xpert MTB/RIF, could further improve survival. Our findings could have a significant impact on clinical care and healthcare funding decisions throughout the region.

Data and Safety Monitoring Plan: A Data and Safety Monitoring Board (DSMB) will be appointed to monitor progress of the evaluation with respect to enrollment, follow-up, drop-outs, adverse events, and interim analyses. The DSMB will consist of Dr. Phil Seidenberg from Boston University and the Zambian Center for Applied Health Research and Development (ZCAHRD); Dr. Selestine Nzala, Assistant Dean - Postgraduate of the University of Zambia School of Medicine (UNZA SOM); Dr. Cosmas Zyaambo, Lecturer in the Department of Public Health at UNZA SOM; and Prof. Sten Vermund, Director of the Vanderbilt Institute for Global Health (VIGH). Biostatistical aspects of the interim analysis will be coordinated by Dr. Zyaambo. The DSMB will review safety and mortality data at the midpoint of patient enrolment and will notify the PI and the co-investigators about any safety concerns that need to be addressed. If the DSMB feels that these concerns are not addressed sufficiently, then DMSB will have the authority to report findings directly to the Vanderbilt IRB and UNZA REC. At the time of midpoint interim analysis, the study may be stopped if one arm is significantly superior to the other, with a p value of <0.001, or at the discretion of the DSMB.

SSSP and SSSP-2: The SSSP study is currently ongoing with a target enrolment of 342 participants. However, the SSSP study will close enrolment prior to the initiation of SSSP-2. Because of the smaller sample size for SSSP-2, the combined enrolment of SSSP and SSSP-2 will not exceed the original SSSP sample size projection of 342 participants. **The informed consent form for SSSP-2 is the same as the informed consent currently used for SSSP, with minor modifications.**

STUDY BUDGET

	US Dollars	Kwacha
Personnel		
Study nurse, full time x 10 months	$8,000	40,000,000
Study nurses, part time x 10 months	2,000	10,000,000
Supplies		
Dopamine	$ 300	1,500,000
Additional IV fluids	500	2,500,000
Laboratory investigations (excluding TB)	8,000	40,000,000
Tuberculosis-related labs	20,000	100,000,000
Portable lactate meter and strips	5,000	25,000,000
Printing and stationary	500	2,500,000
Other		
Ethical approval fees	500	2,500,000
Telephone air time	600	3,000,000
Transportation	400	2,000,000
Total	$45,800	229,000,000

TIMELINE

	2012								2013						
	May	June	July	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	July
Ethical review and revisions	●—●														
Participant enrolment			●—————————●												
Data collection			●———————————●												
Interim safety analysis						●—●									
Data cleaning											●—●				
Data analysis											●—●				
Manuscript preparation												●————————●			

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DECLARATION OF CONFLICT OF INTEREST

None of the investigators has any conflict of interest to report.

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