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Effectiveness of a sepsis programme implemented in a resource-limited setting: a natural experiment

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3 **1 Effectiveness of a sepsis programme implemented in a resource-limited setting: a natural**
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3 **33 Abstract**
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5 **34 Objective:** To evaluate the effectiveness of a Sepsis Fast Track programme (SFT) implemented
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8 **35** at a referral hospital
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10 **36 Design:** A natural experiment using the data of an observational study on sepsis patients (Ubon-
11
12 **37** sepsis) from March 2013 to January 2017
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14 **38 Setting:** General medical wards and medical intensive care units (ICUs) of a referral hospital
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16 **39 Participants:** 3,716 patients with community-acquired sepsis observed under the Ubon-sepsis
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19 **40** cohort. Sepsis was defined as modified Sequential Organ Failure Assessment (SOFA) score ≥ 2 .
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21 **41 Interventions:** The SFT was a protocol to identify and initiate sepsis care on hospital admission
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23
24 **42** and to admit patients directly to the ICUs when available. The SFT implemented at the study
25
26 **43** hospital in January 2015.
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28 **44 Main outcome measures:** The primary outcome was 28-day mortality. The secondary outcomes
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31 **45** were measured sepsis management.
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33 **46 Results:** Of 3,716 patients with community-acquired sepsis, 899 were detected and enrolled in the
34
35 **47** SFT of the study hospital (SFT group) and 2,817 received standard of care (control group). Patients
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38 **48** in the SFT group had more organ dysfunction, were more likely to receive measured sepsis
39
40 **49** management and to be admitted directly to the ICUs. 28-day mortality was 23% (205/899) in the
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42 **50** SFT group and 20% (560/2,817) in the control group. In the primary analysis, patients in the SFT
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44 **51** group were more likely to survive (adjusted hazard ratio for death 0.70; 95%CI 0.57-0.86,
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46
47 **52** $p < 0.001$) adjusted for admission year, gender, age, comorbidities, organ dysfunctions and direct
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49 **53** admission to the ICUs. An interaction test showed that the effect of the SFT programme was not
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51 **54** influenced by direct admission to the ICUs ($p = 0.71$).
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3 55 **Conclusions:** An implementation of SFT programme can improve sepsis care and reduce mortality
4
5 56 of sepsis patients in rural Thailand, where some critical care resources are limited. The survival
6
7 57 benefit is present even when patients could not be admitted directly into the ICUs.
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10 58 **Study registration number:** NCT02217592
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16 60 **Strengths and limitations of this study**

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18 61 • The study estimated the interventional effect of an implementation of sepsis protocol in a
19
20 62 tropical resource-limited setting by utilizing a natural experiment study design and data
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22 63 from a large prospective observational study.
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25 64 • This study had the control group from both pre and post-intervention periods, and
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27 65 estimated the interventional effect by adjusting for important confounding factors which
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29 66 were systematically measured throughout the study period.
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32 67 • The study hospital was a referral tertiary-care hospital in Thailand, and our findings may
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34 68 have limited generalizability to the more restricted resources settings in other LMICs.
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69 INTRODUCTION

70 Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to
71 infection,¹ and is the primary cause of death from infection, especially if not recognized and treated
72 promptly.²⁻⁴ Sepsis is a major cause of health loss worldwide and is associated with approximately
73 eleven million deaths each year, most of which occur in low and middle-income countries
74 (LMICs).⁵ The United Nations World Health Assembly has recognized sepsis as a global health
75 priority and adopted a resolution on improving its worldwide prevention, diagnosis and
76 management.⁶ Comprehensive guidelines such as those developed by the Surviving Sepsis
77 Campaign have been associated with reduced mortality in high-income countries,²⁻⁴ but
78 effectiveness of these guidelines in LMICs needs more evaluation.⁷⁻¹⁰

79
80 Following the Surviving Sepsis Campaign (SSC) 2012,¹¹ the Ministry of Public Health Thailand
81 and the Thai Society of Critical Care Medicine developed local recommendations on sepsis based
82 on resource availability and local context.¹² The recommendations suggest that secondary-care and
83 tertiary-care hospitals in the country should develop a Sepsis Fast Track (SFT) so that, on
84 presentation, sepsis patients can be identified, treated and directly admitted to the ICUs when
85 available. One small retrospective study showed lower mortality among sepsis patients enrolled
86 than those not enrolled in the SFT (21% vs. 43%) at the study hospital,¹³ while the other study did
87 not find an association between SFT and mortality outcome.¹⁴ Those studies are subject to
88 selection biases due to their retrospective nature.^{13 14} Interventional studies to randomize patients
89 to receive or not receive the SFT, however, would be unethical and impractical after the national
90 recommendations.

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5 92 It is increasingly recommended to evaluate the impact of healthcare interventions using routine
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7 93 data, particularly when a wide range of routinely collected data is available.¹⁵ A few methods can
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10 94 be used to perform an impact evaluation; including natural experiments (for natural or unplanned
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12 95 interventions), or quasi experiments (for planned or intentional interventions). Natural experiment
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14 96 studies have certain advantages when it is impossible to manipulate exposure to the intervention.¹⁶
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17 97 Nonetheless, a natural experiment study requires a good understanding of the process determining
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19 98 exposure to the intervention, a careful choice and combination of analytical methods, and
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21 99 transparent reporting.¹⁶
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26 101 Here, we developed a natural experiment study by using data from our prospective observational
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28 102 study of community-acquired sepsis patients presenting to a referral hospital in Thailand over four
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30 103 years (from March 2013 to January 2017)^{17 18} to evaluate the effectiveness of a SFT programme
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33 104 which was implemented at the study hospital in January 2015. The study is defined as a natural
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35 105 experiment because the detection and enrollment of patients in to the SFT programme and
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37 106 admission to the ICUs were neither manipulated nor influenced by the research team of the
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39 107 observational study.^{17 18} The design, analysis and reporting of this study follow the guideline on
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42 108 natural experiments recently published.¹⁶
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110 MATERIAL AND METHODS

111 Trial design

112 In this natural experiment, we evaluated the effectiveness of the SFT programme by using the data
113 of a prospective observational study (Ubon-sepsis).^{17 18} The SFT programme was implemented at
114 the study hospital in January 2015. The SFT programme at the study hospital included (1)
115 diagnostic criteria for attending physicians and medical teams to systematically identify sepsis
116 patients on hospital admission (Supplementary Table 1), (2) a recommended sepsis care protocol
117 and (3) direct admission to the ICUs when available. The SFT programme at the study hospital
118 was generated by the SFT committee of the study hospital (S.B., S.S., C.B., P.P., B.S., O.W., P.C.
119 and P.T.) based on SSC 2012,¹¹ resource availability and local context.¹²

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121 Details of the Ubon-sepsis cohort have been published elsewhere.^{17 18} In short, the Ubon-sepsis
122 research team, who were not attending physicians or medical teams at the study hospital,
123 conducted a prospective observational study of community-acquired infections and sepsis from
124 March 2013 to January 2017.^{17 18} The research team prospectively enrolled adult patients ≥ 18
125 years old who were admitted to the general medical wards and medical intensive care units (ICUs)
126 with a primary diagnosis of infection made by the attending physician, were within 24 hours of
127 admission to the study hospital, and had three of 20 systemic manifestations of infection
128 documented in the medical records (Supplementary Table 2). The 20 systemic manifestations of
129 the infections were consolidated from the 22 variables proposed as diagnostic criteria for sepsis
130 for SSC 2012.¹¹ The study team sequentially screened all medical patients by reviewing admission
131 logs in the emergency department (ED), medical wards, and medical ICUs twice daily (morning

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3 132 and afternoon) on each working day. The Ubon-sepsis cohort was initiated in 2012 prior to the
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5 133 implementation of SFT at the study hospital. The research team were not involved in any clinical
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8 134 interventions; enrollment in the SFT programme and all medical treatment was performed by
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10 135 attending physicians and medical teams. The research team did not adjust the study protocol,
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12 136 inclusion criteria and exclusion criteria of the Ubon-sepsis cohort during the entire study period,
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14
15 137 and the research team recorded whether participants in the Ubon-sepsis cohort were enrolled in
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17 138 the SFT programme.
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21 140 This study was defined as a natural experiment study using the definitions that (1) the intervention
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23 141 (enrollment in the SFT programme) was not undertaken for the purposes of research (Ubon-sepsis
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25 142 cohort), and (2) the variation in exposure (decision to enroll in the SFT programme) and outcomes
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27 143 were analysed using methods that attempt to make causal inferences.¹⁶
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33 145 The reporting of this study follows the CONSORT guidelines and the guideline on natural
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35 146 experiments recently published.¹⁶ Written, informed permission was obtained from participants
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37 147 prior to enrollment in the Ubon-sepsis cohort.
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42 149 **Participants**
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44 150 For this study, we evaluated patients who were included into the Ubon-sepsis cohort and had
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46 151 community-acquired sepsis. Sepsis was defined as an infection with organ dysfunction in
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48 152 accordance with the 2016 international Consensus (Sepsis-3) guidelines for sepsis.¹ Organ
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50 153 dysfunction was determined by a modified sequential (sepsis-based) organ failure assessment
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3 154 (SOFA) score ≥ 2 as previously described.^{17 18} The Ubon-sepsis cohort excluded patients who were
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5 155 suspected of having hospital-acquired infections (determined by the attending physician),
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7 156 hospitalized within 30 days prior to the current admission, or hospitalized in other hospital longer
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10 157 than 72 hours prior to study hospital admission.
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159 **Study group assignment and blinding**

160 All patients included in the Ubon-sepsis cohort from March 2013 to December 2014 were
161 designated as the control group. Patients included in the Ubon-sepsis cohort from January 2015 to
162 January 2017 who received standard of care or were assigned to the SFT programme by attending
163 medical teams using their criteria on admission (Supplementary Table 1) were designated as
164 additional controls or as the SFT group, respectively. The Ubon-sepsis research team were not
165 involved in decision-making regarding enrollment to the SFT programme. Due to the nature of the
166 intervention, there was no blinding. All attending physicians and medical teams in the ED, OPD
167 and admission awards were informed whether patients were enrolled in SFT programme.

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169 **Interventions**

170 Patients in the control group received standard care according to local guidelines. Patients in the
171 SFT group received the standard of care along with a recommended sepsis care protocol of the
172 SFT programme. First, preprinted recommended doctor orders for the SFT programme were used
173 as of January 2015 (Supplementary Figure 1). The recommended orders included oxygen
174 administration, intravenous fluid loading and fluid administration to achieve the recommended
175 target of 30 mL/kg crystalloid, blood culture, recommended stat (immediate) doses and choices of

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3 176 parenteral antibiotics including ceftriaxone, ceftazidime, cloxacillin, metronidazole and
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5 177 gentamycin, contact ICU for ICU admission (if available), oxygen supplementation, close
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7 178 monitoring of vital signs and urine output, and a set of diagnostic tests including chest radiography,
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10 179 electrocardiogram, rapid blood glucose test, serum lactate, complete blood count, blood urea
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12 180 nitrogen, creatinine, electrolytes, liver function tests, albumin level, prothrombin time and partial
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14 181 thromboplastin time. Second, as of March 2016, the resuscitation workflow to normalize and
15
16 182 maintain a mean arterial pressure (MAP) ≥ 65 mmHg, systolic blood pressure (SBP) ≥ 90 mmHg
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18 183 and urine output ≥ 0.5 mL/kg/hr within the first six hours was formally implemented and
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20 184 recommended (Supplementary Figure 2). The resuscitation workflow included fluid resuscitation,
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22 185 measurement of central venous pressure (CVP) and central venous oxygen saturation (SCVO₂),
23
24 186 administration of adrenergic agents, blood transfusion for haematocrit $< 30\%$ and hydrocortisone
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26 187 if adequate fluid resuscitation and vasopressor therapy could not restore hemodynamic stability.
27
28 188 The resuscitation workflow was pre-printed and included in the clinical chart of every SFT patient
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30 189 (together with pre-printed doctor's order), and was recommended even if patients could not be
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32 190 admitted directly to the ICU. A separate set of documents, recommended management and
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34 191 recommended frequency of vital signs monitoring for nurses (i.e. nurse notes for SFT patients)
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36 192 were also used for every SFT patient. Preparation and regular meetings to implement and monitor
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38 193 SFT programme were organized by the SFT committee of Sunpasithiprasong Hospital.
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47 **Outcome measures**

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49 196 The primary outcome measure was 28-day mortality as recorded in the Ubon-sepsis cohort.¹⁷ 28-
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51 197 day mortality data were collected via telephone contact if subjects were no longer hospitalized and
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3 198 had been discharged alive.¹⁷ The secondary outcome measures were sepsis management
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5 199 interventions; including antibiotics administration, blood cultures, mechanical ventilation,
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7 200 adrenergic agents, acute haemodialysis and placement of a urinary catheter within the first day of
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9
10 201 hospitalization.^{17 18}
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14 203 **Sample size**

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17 204 The sample size of the study was determined by the sample size of Ubon-sepsis cohort. In this
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19 205 natural experiment study, we estimated that about 50% of 3,716 sepsis patients in the Ubon-sepsis
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21 206 cohort were enrolled after the implementation of SFT programme, of which 50% were enrolled in
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23 207 the SFT programme (i.e. 794 and 2,382 patients were estimated to be the intervention and control
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25 208 group, respectively). We assumed that the mortality of the control group was 21% as previously
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27 209 published.^{17 18} With a risk of type I error of 5% and a type II error of 20%, we calculated that our
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29 210 data set (n=3,716) would provide adequate power to detect the mortality difference if the mortality
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31 211 ratio in the SFT group compared with the control group was 0.78.
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34 213 **Statistical analysis**

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36 214 All sepsis patients were included in the analysis regardless of whether they were enrolled before
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38 215 or after the implementation of the SFT programme. We used the Chi-square test and Mann-
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40 216 Whitney test to compare the proportions of binary variables and median of continuous variables
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42 217 between groups, respectively. The interquartile range is presented as 25th and 75th percentiles.
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3 219 In the primary analysis, we used multivariable Cox proportional hazard models to evaluate the
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5 220 effectiveness of SFT programme on 28-day mortality. The multivariable Cox proportional hazard
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7 221 model was used to adjust the difference between those receiving the intervention and the others
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10 222 for the natural experiment.¹⁶ To reduce bias in the model development, we used the previous
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12 223 multivariable Cox proportional hazard model as the base model,¹⁷ added the intervention variable
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14 224 and direct admission to the ICU, and modified by adding a time variable to represent possible
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16 225 changes over time and by using continuous modified SOFA score on admission rather than as a
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18 226 binary variable (modified SOFA score ≥ 2). Due to a very small number of patients enrolled in
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20 227 early 2017 (n=28), we considered them as enrolled in 2016. The continuous modified SOFA score
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22 228 was used to improve regression adjustment for disease severity of the model. The other variables
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24 229 included in the model were gender, age group, transfer from other hospital, comorbidities (diabetes
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26 230 mellitus, chronic kidney disease, liver disease and malignancy) and blood culture positive for
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28 231 pathogenic organisms. We tested potential predefined interactions between intervention and direct
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30 232 admission to the ICUs. The goodness of fit for the multivariable Cox proportional hazard model
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32 233 was tested with a Hosmer and Lemeshow test. Number needed to treat (NNT) was defined as the
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34 234 number of sepsis patients needed to be included in the SFT to avert one 28-day mortality. The
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36 235 NNT was estimated by using estimated hazard ratio from Cox proportional hazard model as
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38 236 described previously.¹⁹
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46 238 For the secondary endpoints, we used multivariable logistic regression models with similar
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48 239 independent variables as the model for 28-mortality outcome and used each sepsis management
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50 240 process as an outcome. The multivariable logistic regression models were used to adjust for
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3 241 difference in characteristics and disease severity of the patients in each group. We preformed
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5 242 sensitivity analyses by excluding patients enrolled prior to the implementation of the SFT
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8 243 programme. We also performed another sensitivity analysis by replacing direct admission to the
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10 244 ICUs with admission to the ICUs within the first hospital day. All analyses were performed with
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12 245 STATA 15.1 (StataCorp, College Station, TX, USA).
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16 17 247 **Patient and public involvement**

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19 248 No patients were involved in setting the research question or the outcome measures, nor were they
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21 249 involved in developing plans for recruitment, design, or implementation of the study. No patients
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24 250 were asked to advice on interpretation or writing the results. The trial results will be disseminated
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26 251 to the public through online social media.
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30 31 253 **RESULTS**

32 33 254 **Baseline characteristics**

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35 255 The observational cohort study (Ubon-sepsis) included 5,001 patients presenting with community-
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37 256 acquired infections from March 2013 to January 2017. 3,716 (74%) met criteria for sepsis within
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40 257 the first 24 hours of admission with a modified SOFA score ≥ 2 , and were included for this natural
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42 258 experiment study. Figure 1 shows the flow of participants through the study. Among 3,716 sepsis
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45 259 patients, 899 were enrolled in the SFT programme and defined as the SFT group, and 2,817 were
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47 260 not enrolled in the SFT programme, received standard of care, and defined as the control group.
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49 261 Of 2,817 sepsis patients in the control group, 1,599 were included in the observational cohort study
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262 prior to the implementation of SFT programme and 1,218 were after the implementation of the
263 programme.

264
265 Table 1 shows the characteristic of the study patients. Patients in the SFT group were older and
266 more likely to have underlying diseases of diabetes mellitus, cerebrovascular diseases and
267 dyslipidemia. Patients included in the SFT group had higher severity of organ dysfunction
268 determined by the modified SOFA score compared with the control group (median 6 [IQR 4-8]
269 vs. 4 [IQR 3-6], $p < 0.001$). A higher proportion of patients in the SFT group were admitted directly
270 to the ICU compared with the control group (19% vs 5%, $p < 0.001$).

271
272 **Table 1| Baseline characteristics of sepsis patients enrolled in the Sepsis Fast Track**
273 **programme¹ (SFT group) or standard of care (control group). Values are number**
274 **(percentages) unless stated otherwise**

Characteristics	SFT group ² (n=899)	Control group ³ (n=2817)	P value
Male gender	523 (58%)	1616 (57%)	0.70
Age (years) (median [IQR])	63 (49-74)	56 (39-70)	<0.001
Age group (years)			
18-40	98 (11%)	628 (22%)	<0.001
>40-60	277 (31%)	858 (30%)	
>60-70	214 (24%)	501 (18%)	
>70	310 (34%)	830 (29%)	
Comorbidities			
Hypertension	239 (27%)	696 (25%)	0.26
Diabetes mellitus	213 (24%)	575 (20%)	0.04
Chronic kidney disease	129 (14%)	386 (14%)	0.63
Dyslipidemia	66 (7%)	145 (5%)	0.01
Heart disease	47 (5%)	177 (6%)	0.25

Characteristics	SFT group ² (n=899)	Control group ³ (n=2817)	P value
Lung disease	65 (7%)	227 (8%)	0.42
Liver disease	33 (4%)	91 (3%)	0.52
Cerebrovascular disease	29 (3%)	54 (2%)	0.02
Malignancy	13 (1%)	44 (2%)	0.81
Human immunodeficiency virus (HIV)	6 (1%)	31 (1%)	0.26
Organ dysfunction			
Modified SOFA score (median [IQR])	6 (4-8)	4 (3-6)	<0.001
Renal dysfunction ⁴	705 (78%)	1814 (64%)	<0.001
Cardiovascular dysfunction ⁴	800 (89%)	1374 (49%)	<0.001
Coagulation dysfunction ⁴	391 (43%)	1467 (52%)	<0.001
Liver dysfunction ⁴	311 (35%)	818 (29%)	0.002
Respiratory dysfunction ⁴	287 (32%)	600 (21%)	<0.001
Central nervous system dysfunction ⁴	166 (18%)	523 (19%)	0.96
Transferred from other hospitals	874 (97%)	2372 (84%)	<0.001
Duration of symptoms (median [IQR])	2 (1-3)	3 (1-5)	<0.001
≤ 2 days	503 (56%)	1157 (41%)	
3-7 days	361 (40%)	1445 (51%)	
> 7 days	35 (4%)	215 (8%)	
Presenting clinical syndromes⁵			
Septic shock	686 (76%)	730 (26%)	<0.001
Acute febrile illness	205 (23%)	918 (33%)	<0.001
Lower respiratory infection	221 (25%)	839 (30%)	0.003
Sepsis	223 (25%)	265 (9%)	<0.001
Others	13 (1%)	446 (16%)	<0.001
Diarrheal illness	150 (17%)	261 (9%)	<0.001
Admitted directly to an ICU upon admission	169 (19%)	128 (5%)	<0.001
Admitted to an ICU within 24 hours of admission	267 (30%)	360 (13%)	<0.001
Blood culture positive for pathogenic organisms	176 (20%)	435 (15%)	0.002
Year			
2013	N/A	790 (28%)	<0.001
2014	N/A	809 (29%)	
2015	355 (39%)	634 (23%)	
2016	532 (59%)	568 (20%)	
2017	12 (1%)	16 (1%)	

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3 276 ¹ SFT programme was implemented at the study hospital in January 2015. This natural experiment evaluated patients
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5 277 in the Ubon-sepsis cohort from March 2013 to January 2017.

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7 278 ² 899 patients of the Ubon-sepsis cohort were enrolled in SFT programme after the implementation of the SFT
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9 279 programme (Figure 1)

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11 280 ³ Included 1,599 and 1,218 patients in the Ubon-sepsis cohort before and after the implementation of the SFT
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13 281 programme, respectively.

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15 282 ⁴ Organ dysfunction defined as modified SOFA score was ≥ 1 for each organ system.¹⁷

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17 283 ⁵ Patients may have more than one presenting clinical syndrome.

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20 21 285 **Primary outcomes**

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24 286 The primary outcome, mortality within 28 days, occurred in 205 of 899 (23%) in the SFT group
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26 287 and 560 of 2,871 (20%) in the control group. In an unadjusted comparison, there was a borderline
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28 288 evidence showing that 28-day mortality of the SFT group was higher than control group (23% vs
29
30 289 20%, $p=0.06$). In the primary analysis, the risk of mortality was 30% lower in the SFT group
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32 290 compared to the control group (adjusted hazard ratio [aHR] 0.70, 95% CI 0.57-0.86, $p<0.001$;
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34 291 Table 2) adjusted for baseline characteristics, severity of sepsis and direct admission the ICUs.
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36 292 Older age, high modified SOFA score, underlying disease of malignancy, blood culture positive
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38 293 for pathogenic organisms and direct admission to the ICUs were associated with mortality
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40 294 outcome.
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296 **Table 2| Factors associated with 28-day mortality using multivariable Cox proportional**
 297 **hazards model**

Variables	Died (n=765)	Survived (n=2951)	Adjusted hazard ratio (95%CI)	P value
SFT group¹	205 (27%)	694 (24%)	0.70 (0.57- 0.86)	<0.001
Male gender	473 (58%)	2186 (52%)	0.91 (0.78- 1.06)	0.21
Age group (years) (n [%])				
• 18-40	68 (8%)	1072 (26%)	1.0	<0.001
• >40-60	235 (29%)	1308 (31%)	1.72 (1.28- 2.30)	
• >60-70	164 (20%)	745 (18%)	2.12 (1.56- 2.88)	
• >70	352 (43%)	1045 (25%)	3.30 (2.48- 4.39)	
Transferred from other hospital	749 (91%)	3067 (74%)	1.23 (1.20- 1.25)	0.07
Modified SOFA score (median, IQR)	7 (4-9)	4 (3-6)	1.23 (1.20- 1.25)	<0.001
Comorbidities				
• Diabetes mellitus	213 (26%)	793 (19%)	1.08 (0.91- 1.28)	0.37
• Chronic kidney disease	142 (17%)	403 (10%)	1.22 (1.01- 1.48)	0.04
• Liver disease	39 (5%)	94 (2%)	1.31 (0.94- 1.82)	0.11
• Malignancy	25 (3%)	57 (1%)	2.72 (1.78- 4.16)	<0.001
Blood culture positive for pathogenic organisms	221 (29%)	390 (13%)	1.90 (1.62- 2.22)	<0.001
Year				
• 2013	165 (22%)	625 (21%)	1	0.35
• 2014	177 (23%)	632 (21%)	1.00 (0.81- 1.24)	
• 2015	203 (27%)	786 (27%)	1.03 (0.82- 1.29)	
• 2016 ²	220 (29%)	908 (31%)	0.87 (0.69- 1.09)	
Direct admission to the ICU	128 (17%)	169 (6%)	1.70 (1.38- 2.09)	<0.001

298 ¹ Enrolled in the Sepsis Fast Track (SFT) programme

299 ² Included 28 patients in 2017

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3 301 In a pre-specified interaction test, we found consistency of the intervention when stratifying by
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5 302 direct admission to the ICUs (interaction test $p=0.71$). In the multivariable model including an
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7 303 interaction variable, the intervention effect was comparable among those admitted directly to the
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9 304 ICUs (aHR 0.74, 95% CI 0.51 to 1.08) and those admitted directly to the general medical wards
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11 305 (aHR 0.69, 95% CI 0.57 to 0.86).
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17 307 We estimated NNT by assuming that the adjusted HR 0.70 (95% CI 0.57 to 0.66) was the size of
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19 308 effect caused by the SFT programme. The NNT to prevent one case of death involving community-
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21 309 acquired sepsis was 8.1 (95% CI 5.0 to 19.8).
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25 26 311 **Secondary outcomes**

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28 312 Using multivariable logistic regression models, we found that patients in the SFT group were more
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30 313 likely to receive most sepsis management interventions than patients in the control group adjusting
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32 314 for baseline characteristics and severity of sepsis (Table 3). Those included antibiotics, blood
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34 315 cultures, adrenergic agents, and placement of a urinary catheter within the first day of
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36 316 hospitalization. However, sepsis patients in the SFT group were less likely to receive mechanical
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38 317 ventilation compared with those in the control group (adjusted odds ratio [aOR] 0.32; 95% CI 0.25
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40 318 to 0.40) adjusted for baseline characteristics, severity of sepsis and direct admission to the ICUs.
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42 319 We found that direct admission to the ICUs (aOR 6.93, 95% CI 5.01 to 9.58) and transfer from
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44 320 other hospitals (aOR 4.49, 95% CI 3.08 to 6.55) were strongly associated with receiving
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46 321 mechanical ventilation.
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323 **Table 3| Clinical management within the first day of hospital**

Clinical management	SFT group (n=899)	Control group (n=2817)	Adjusted odds ratio (95% CI)	P value
Antibiotic	870 (97%)	2356 (84%)	14.12 (6.11 to 32.68)	<0.001
Blood culture	826 (92%)	2310 (82%)	1.79 (1.32 to 2.42)	<0.001
Urinary catheterization	858 (95%)	1599 (57%)	10.79 (7.51 to 15.50)	<0.001
Acute dialysis	10 (1%)	23 (0.8%)	1.90 (0.63 to 5.75)	0.26
Adrenergic agent	706 (79%)	900 (32%)	10.70 (8.42 to 13.60)	<0.001
Mechanical ventilation	305 (34%)	845 (30%)	0.32 (0.25 to 0.40)	<0.001

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325 **Sensitivity Analyses**

326 We performed a sensitivity analysis by excluding the 1,599 patients enrolled in the observational
 327 study prior to the implementation of SFT programme. Similar differences in baseline
 328 characteristics were observed when comparing 899 patients in the SFT group to the 1,218 patients
 329 in the control group enrolled after the implementation of the SFT programme (Supplementary
 330 Table 3). A lower risk of mortality in the SFT group compared to the control group was also
 331 observed (aHR 0.65, 95% CI 0.53 to 0.81, $p < 0.001$; Supplementary Table 4). There was no
 332 interaction between the intervention and direct admission to the ICUs ($p = 0.71$).

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334 We also performed another sensitivity analysis by replacing direct admission to the ICUs with
 335 admission to the ICUs within the first hospital day. Of 3,716 patients, 627 (17%) were admitted to
 336 the ICUs within the first day of admission. A lower risk of mortality in the SFT group compared
 337 to the control group was also observed (aHR 0.67, 95% CI 0.53 to 0.86, $p < 0.001$). There was also
 338 no interaction between the intervention and admission to the ICUs within the first day of admission
 339 ($p = 0.56$).

340

341 **DISCUSSION**

342 In this natural experiment evaluating 3,716 patients with community acquired sepsis, enrollment
343 into a programme to identify and initiate sepsis care implemented at the study hospital (SFT
344 programme) was associated with 30% lower risk of mortality (aHR 0.70, 95% CI 0.57 to 0.86). In
345 recent years, there has been an increasing need to understand benefit and cost effectiveness of
346 implementation of sepsis care interventions in LMICs because of concerns that international sepsis
347 guidelines¹¹ may not be extrapolated to patients with tropical infectious diseases⁷⁻⁹ and to resource-
348 limited settings with poor ICU capacity.¹⁰ In this trial we show effectiveness of implementation of
349 sepsis protocol modified based on resource availability in a tropical country, where causes of
350 community-acquired sepsis include malaria and tropical viral diseases.^{17 20 21} Access to the ICU
351 increased after the implementation of the SFT programme, but the majority of sepsis patients were
352 still managed on the general wards, including those with respiratory failure or shock. Nonetheless,
353 our study shows that enhancing sepsis care in the emergency department and general medical
354 wards, as well as improving access to ICUs can reduce sepsis mortality in a LMIC.

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356 The negative association between the intervention and received mechanical ventilation could be a
357 sign of improved sepsis care. Patients in the SFT group are monitored closely either in or outside
358 the ICUs, and the attending physicians aim to obviate the need for airway intubation when
359 possible.⁷ Attending physicians may tend to provide mechanical ventilation to patients in the
360 control group based on broad indications such as (1) airway protection, (2) hypercapnic respiratory
361 failure, (3) hypoxemic respiratory failure or (4) circulatory failure^{22 23} because they may not be

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3 362 able to monitor patients' breathing and oxygen saturation as often as those enrolled in the SFT
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5 363 programme.
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10 365 Patients in the SFT group had more organ dysfunction than those in the control group because the
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12 366 SFT programme enrolled patients on admission and, therefore, could not use laboratory test results
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14 367 from blood samples drawn on admission. However, the control group were defined as having
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16 368 sepsis based on clinical findings and all laboratory test results within 24 hours of admission (per
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18 369 protocol of Ubon-sepsis cohort study^{17 18}). Therefore, the control group could use laboratory test
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20 370 results (i.e. liver function tests, creatinine level, international normalised ratio and activated partial
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22 371 thromplastin time) from blood specimens drawn on admission. Therefore, the SFT programme
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24 372 were more likely to enroll patients with obvious signs of sepsis and septic shock; such as acute
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26 373 respiratory failure and hypotension, while Ubon-sepsis cohort could include sepsis patients with
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28 374 relatively lower modified SOFA score.
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35 376 **Comparison with other studies**

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37 377 Our study is not the first to evaluate effectiveness of sepsis intervention in LMICs. Early
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39 378 recognition and protocol directed intervention improves outcomes of sepsis in adults²⁴ and severe
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41 379 infection in children²⁵ in LMICs. The optimal method of fluid resuscitation in sepsis in tropical
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43 380 LMICs has not been determined.^{8 24 26 27} Our resuscitation protocol is a simple guideline, and the
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45 381 SFT recommend doctors to be careful and adjust fluid resuscitation based on preliminary
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47 382 diagnoses, underlying diseases and rapid diagnostic test results (i.e. if sepsis is caused by malaria
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49 383 or dengue infection). The implementation of the SFT programme in our study hospital and in
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3 384 Thailand is consistent with the recommendation of “SCAN-TEACH-TREAT” programme
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5 385 developed by Sepsis in Resource-Limited Settings Workgroup of the Surviving Sepsis Campaign.⁷
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8 386 The SFT programme evaluated resources in the setting (SCAN component), focused on
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10 387 educational interventions on early recognition and management of sepsis among medical personnel
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12 388 including physicians, nurses and students (TEACH component) and implemented pragmatic and
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14 389 simple bundles into practice (TREAT component). In addition, the SFT programme has the strong
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17 390 support and endorsement of local health and governmental leaders.¹²
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392 **Strength and limitations of the study**

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24 393 This study features three strengths. First, it took advantage of a robust prospective observational
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26 394 study design that strengthened causal inference by providing pre-intervention information, having
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28 395 an appropriate control group from both pre and post-intervention periods, and controlling
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30 396 important confounding factors (i.e. the modified SOFA score) which were measured
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32 397 systematically throughout the study period. Second, this study incorporated several predictors of
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34 398 interest (measured sepsis management interventions and admission to the ICUs). This allows us to
35
36 399 identify that most measured sepsis interventions increased and that admission to the ICUs were
37
38 400 not associated with the interventional effect. Third, the focus on sepsis at a public tertiary-care
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40 401 hospital in Thailand helped us to estimate the interventional effect of an implementation of sepsis
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42 402 protocol in a tropical resource-limited setting.
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49 404 Our study had several limitations. First, our findings may not be able to generalize to all hospitals
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51 405 and all sepsis protocols in LMICs. It is recommended that each resource-limited setting should set
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3 406 up their own SCAN-TEACH-TREAT programme, and closely monitor and evaluate the
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5 407 effectiveness of an intervention implemented.⁷ Second, a modified SOFA score was used because
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7 408 the dosage of dobutamine, dopamine, epinephrine and norepinephrine were not recorded and
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9 409 arterial blood gases were rarely performed. The modified SOFA score (maximum 23) may be
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11 410 lower than the SOFA score (maximum 24). Nonetheless, the modified SOFA score is strongly
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13 411 associated with mortality in sepsis.^{17 18} Third, the cost of implementing the SFT programme was
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15 412 not formally estimated.
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21 414 **Conclusions and future implications**

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24 415 Our study successfully measured effectiveness of a sepsis programme implemented in a LMIC.
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26 416 Measuring effectiveness of a sepsis programme is a complex issue, and we utilized a natural
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28 417 experiment and carefully controlled for severity of sepsis and temporal trends in our analyses. Care
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30 418 in sepsis patients improved after the implementation of the programme. While the natural
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32 419 experiment adds to our knowledge of effectiveness of a sepsis programme, additional research is
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34 420 needed to better understand cost of the intervention, long-term benefits and impact of the
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36 421 programme on a national scale. National policies aimed at saving lives from sepsis in LMICs
37
38 422 should not hesitate to analyze their resources and situations, and then develop, implement and
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40 423 monitor their programmes.
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20

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22
23 434 conception development and study design. SB, VH, PT, TEW and DL contributed to study
24
25 435 conduct, data collection, and study administration. VH and DL performed the statistical analysis
26
27 436 and interpreted the data and had full access to all of the data in the study. Both authors can take
28
29 437 responsibility for the integrity of the data and the accuracy of the data analysis. DL is a guarantor.
30
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32
33 439 interpretation, and critically revised and approved the final submitted manuscript. The
34
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36
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2
3 447 conduct of the study, all study procedures, data collection, data analyses, data interpretation,
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5 448 writing of the report, and the decision to submit the article for publication.
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10 450 **Competing interests:**

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12 451 The authors declare that they have no completing interests.
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17 453 **Ethics approvals:**

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19 454 The study was conducted the study in full compliance with the principles of good clinical practice
20
21 455 (GCP), and the ethical principles of the Declaration of Helsinki. The study protocol and related
22
23 456 documents were approved by Sunpasitthiprasong Hospital Ethics Committee (039/2556), the
24
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26
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28
29 459 Research Ethics Committee at the University of Oxford (OXTREC172-12). Signed or
30
31 460 fingerprinted informed consent was obtained from the participants or their representatives before
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33 461 enrollment.
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40 463 **Data sharing:**

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42 464 The final database with the data dictionary are publicly available online
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44 465 <https://doi.org/10.6084/m9.figshare.12102627>.
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47 466 The lead authors (SB, VH and DL) affirm that the manuscript is an honest, accurate, and
48
49 467 transparent account of the study being reported; that no important aspects of the study have been
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51 468 omitted; and that any discrepancies from the study as planned have been explained. This is an
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12 473

13 14 474 **Patient and Public Involvement**

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16
17 475 No patients were involved in setting the research question or the outcome measures, and
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19 476 interpretation or writing up of results. The results of this study will be disseminated to physicians
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21 477 at the study hospital, health care providers, policy makers, and academic communities through
22
23 478 various mediums, including printed report, internal hospital meetings, academic conferences, and
24
25 479 institutional networks. The results from this study will be used to inform the current Sepsis Fast
26
27 480 Track programme at Sunpasitthiprasong hospital and the community hospitals which are located
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29 481 in jurisdiction of the study hospital catchment areas in the Northeast Thailand. The study results
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31 482 will not be disseminated to patients or general population, because study results are in medical
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33 483 context.
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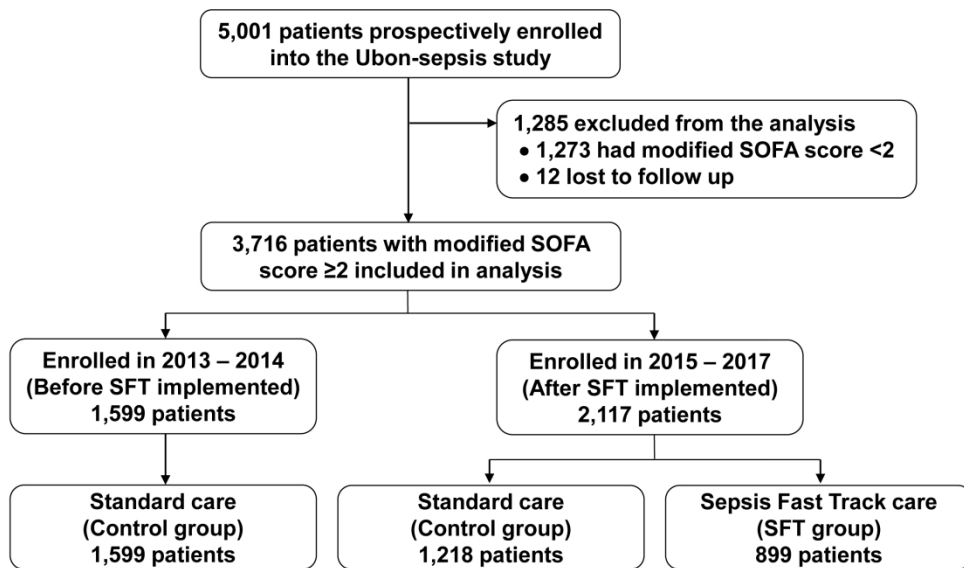
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6 **572 Figure legends**

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9 **573 Figure 1| Flow of participants through study**

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11 **574 Footnote of figure 1:** This natural experiment used the data of an observational study on sepsis
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13 patients (Ubon-sepsis) from March 2013 to January 2017 to evaluate the effectiveness of a Sepsis
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16 **576** Fast Track (SFT) programme implemented at the study hospital in January 2015
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3 **1 Effectiveness of a sepsis programme implemented in a resource-limited setting: a natural**
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5 **2 experiment**
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11 4 Suchart Booraphun MD¹, Viriya Hantrakun PhD², Suwatthiya Siriboon MD¹, Chaiyaporn Boonsri
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13 5 MD¹, Pulyamon Poomthong MD¹, Bung-Orn Singkaew BNS¹, Oratai Wasombat BNS¹, Parinya
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15 6 Chamna MD, PhD¹, Ratapum Champunot MD³, Kristina Rudd MD, MPH^{4, 5}, Nicholas P.J. Day^{2,6}
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24 10 Short Title: Sepsis Fast Track Thailand
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24 **Supplementary Table 1 | Criteria used to systematically enroll patents into Sepsis Fast Track**
25 **(SFT) upon admission**

26 **1. Present with 2 or more of below Signs of systemic inflammatory response syndrome**
27 **(SIRS)**

- 28 • Body temperature $> 38.3\text{ }^{\circ}\text{C}$ or $< 36.0\text{ }^{\circ}\text{C}$
- 29 • Heart rate > 90 bpm
- 30 • Respiratory rate > 20 pm or $\text{PaCO}_2 < 32$ mmHg
- 31 • WBC $> 12,000/\mu\text{L}$ or $< 4,000/\mu\text{L}$ or Band forms $> 10\%$

32 **2. Suspected sources of infection**

- 33 • Pneumonia
- 34 • Urinary track infection
- 35 • Intra-abdominal infection
- 36 • Skin and soft tissue infection
- 37 • CNS infection
- 38 • Others infections or unspecified source of infection

39 **3. Diagnostic criteria for severe sepsis:** patient met criteria in no 1 and 2 and has at least
40 one of the following criteria

- 41 • Mottled skin
- 42 • Capillary refilling time ≥ 3 seconds
- 43 • Urine output < 0.5 ml/kg/hour
- 44 • Abrupt change in mental status
- 45 • Acute respiratory failure
- 46 • Platelet count $< 100,000/\mu\text{L}$
- 47 • Disseminated intravascular coagulation
- 48 • Lactate > 2 mmol/L
- 49 • SBP < 90 mmHg or MAP < 65 mmHg

50 **4. Diagnostic criteria for septic shock:** patient who are severe sepsis and has at least 1 of
51 the following criteria

- 52 • SBP < 90 mmHg or MAP < 65 mmHg after crystalliod administration ≥ 40 -60
53 ml/kg of body weight OR after colloid administration ≥ 20 -30 ml/kg of body weight
- 54 • Require administration of dopamine $> 5\mu\text{g}/\text{kg}$ of BW/min or norepinephrine /
55 epinephrine $> 0.02\ \mu\text{g}/\text{kg}$ of BW/min to maintain MAP to be > 65 mmHg

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3 **57 Supplementary Table 2 | Systemic manifestation of infection criteria used for enrollment in**
4
5 **58 Ubon-Sepsis Cohort**

6
7 **59 General parameters**

- 8 60 1. Fever or hypothermia (Core body temperature defined as > 38.3 °C or < 36.0 °C)
9
10 61 2. Tachycardia (heart rate > 90 beats per minute)
11
12 62 3. Tachypnea (respiratory rate > 20 per minute)
13
14 63 4. Altered mental status with Glasgow Coma Score (GCS) < 15 or < 10 if intubated
15
16 64 5. Hyperglycemia (plasma glucose > 140 mg/dL) in the absence of diabetes

17 **65 Inflammatory parameters**

- 18 66 6. Leukocytosis (white blood cell count $> 12,000/\mu\text{L}$), leukopenia (white blood cell count $<$
19 $4000/\mu\text{L}$) or immature forms $> 10\%$
20
21 67 7. Plasma C-reactive protein > 2 SD above the normal value
22
23 68 8. Plasma procalcitonin > 2 SD above the normal value
24

25 **70 Hemodynamic parameters**

- 26 71 9. Arterial hypotension (systolic blood pressure (SBP) < 90 mmHg, mean arterial pressure
27 (MAP) < 70 mmHg, or SBP decrease > 40 mmHg)
28
29

30 **73 Organ dysfunction parameters**

- 31 74 10. Low oxygen saturation determined by pulse oximetry ($\text{SpO}_2 < 95\%$) determined by pulse
32 oximetry
33
34 75 11. Arterial hypoxemia ($\text{PaO}_2 / \text{FIO}_2 < 300$)
35
36 76 12. Acute oliguria (urine output < 0.5 mL/kg/hr or 45 mmol/L for 2 hours)
37
38 77 13. Creatinine increase > 0.5 mg/dL
39
40 78 14. Coagulation abnormalities (international normalised ratio > 1.5 or activated partial
41 thromboplastin time > 60 seconds)
42
43 79 15. Thrombocytopenia (Platelet count $< 100,000$ cells/ μL)
44
45 80 16. Ileus (absent bowel sounds)
46
47 81 17. Hyperbilirubinaemia (plasma total bilirubin > 4 mg/dL)
48

49 **84 Tissue perfusion parameters**

- 50 85 18. Hyperlactatemia (> 1 mmol/L)
51
52 86 19. Decreased capillary refill or mottling
53
54 87 20. Significant edema or positive fluid balance
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89 **Supplementary Table 3 | Baseline characteristics of sepsis patients included in the Sepsis Fast**
 90 **Track (SFT) programme or standard of care (control) after the implementation of SFT**
 91 **programme. Values are number (percentages) unless stated otherwise**

Characteristics	SFT group ² (n=899)	Control group ³ (n=1218)	P value
Male gender	523 (58%)	702 (58%)	0.82
Age (years) (median [IQR])	63 (49-74)	59 (41-73)	<0.001
Age group (years) (n [%])			
18-40	98 (11%)	282 (23%)	<0.001
>40-60	277 (31%)	342 (28%)	
>60-70	214 (24%)	221 (18%)	
>70	310 (34%)	373 (31%)	
Comorbidities	484 (54%)	639 (52%)	0.53
Hypertension	239 (27%)	332 (27%)	0.73
Diabetes mellitus	213 (24%)	274 (23%)	0.52
Chronic kidney disease	129 (14%)	195 (16%)	0.29
Dyslipidemia	66 (7%)	76 (6%)	0.32
Heart disease	47 (5%)	96 (8%)	0.02
Lung disease	65 (7%)	116 (10%)	0.06
Liver disease	33 (4%)	46 (4%)	0.90
Cerebrovascular disease	29 (3%)	25 (2%)	0.09
Malignancy	13 (1%)	32 (3%)	0.06
Human immunodeficiency virus (HIV)	6 (1%)	9 (1%)	0.85
Organ dysfunction⁴			
Total modified SOFA score (median [IQR])	6 (4-8)	4 (3-6)	<0.001
Renal dysfunction ⁴	705 (78%)	728 (60%)	<0.001
Cardiovascular dysfunction ⁴	800 (89%)	437 (36%)	<0.001
Coagulation dysfunction ⁴	391 (43%)	612 (50%)	0.002
Liver dysfunction ⁴	311 (35%)	314 (26%)	<0.001
Respiratory dysfunction ⁴	287 (32%)	339 (28%)	0.04
Central nervous system dysfunction ⁴	166 (18%)	214 (18%)	0.61
Transferred from other hospitals	874 (97%)	1009 (83%)	<0.001
Duration of symptoms (median [IQR])	2 (1-3)	3 (1-5)	<0.001
≤ 2 days	503 (56%)	519 (43%)	<0.001
3-7 days	361 (40%)	624 (51%)	
> 7 days	35 (4%)	75 (6%)	

Characteristics	SFT group² (n=899)	Control group³ (n=1218)	P value
Presenting clinical syndromes⁵ (n [%])			
Septic shock	686 (76%)	179 (15%)	<0.001
Acute febrile illness	205 (23%)	469 (39%)	<0.001
Lower respiratory infection	221 (25%)	431 (35%)	<0.001
Sepsis	223 (25%)	131 (11%)	<0.001
Others	13 (1%)	163 (13%)	<0.001
Diarrheal illness	150 (17%)	102 (8%)	<0.001
Admitted directly to an ICU upon admission	169 (19%)	39 (3%)	<0.001
Blood culture positive for pathogenic organisms	176 (20%)	164 (13%)	<0.001
Year			
2015	355 (39%)	634 (52%)	<0.001
2016	532 (59%)	568 (47%)	
2017	12 (1%)	16 (1%)	

92

93 ¹Organ dysfunction is defined by modified SOFA ≥ 2 94 ²Sepsis patients who were identified and treated in Sepsis-FT system in 2015 – January 2018.95 ³Sepsis patients whom were not in Sepsis-FT system; 1599/2871 patients were enrolled into the
96 study during 2013-2014 before Sepsis-FT implemented in the hospital.97 ⁴Organ dysfunction defined as modified SOFA score was ≥ 1 for each organ system [13].98 ⁵Patients may have more than one presenting clinical syndrome.

99

100 **Supplementary Table 4 | Factors associated with 28-day mortality using multivariable Cox**
 101 **proportional hazards model in 2,117 patients enrolled into the study after the**
 102 **implementation of the Sepsis Fast Track (SFT) programme**

Variables	Died (n=423)	Survived (n=1694)	Adjusted hazard ratio (95%CI)	P value
SFT group	205(48%)	694(41%)	0.65 (0.53- 0.81)	<0.001
Male gender	251(59%)	974(57%)	0.91 (0.75- 1.12)	0.38
Age group (years) (n [%])				
• 18-40	30(7%)	350(21%)	1	<0.001
• >40-60	125(30%)	494(29%)	2.05 (1.37- 3.06)	
• >60-70	83(20%)	352(21%)	1.93 (1.26- 2.97)	
• >70	185(44%)	498(29%)	3.19 (2.14- 4.74)	
Transferred from other hospital	403(95%)	1480(87%)	1.82 (1.15- 2.90)	0.01
Modified SOFA score (median, IQR)	7 (5-10)	4 (3-6)	1.25 (1.21- 1.28)	<0.001
Comorbidities				
• Diabetes mellitus	120(28%)	367(22%)	1.06 (0.85- 1.33)	0.59
• Chronic kidney disease	83(20%)	241(14%)	1.21 (0.94- 1.56)	0.14
• Liver disease	22(5%)	57(3%)	1.06 (0.68- 1.64)	0.81
• Malignancy	19(4%)	26(2%)	3.10 (1.94- 4.96)	<0.001
Blood culture positive for pathogenic organisms	115(27%)	225(13%)	1.80 (1.44- 2.24)	<0.001
Year				
• 2015	203(48%)	786(46%)	1	0.10
• 2016	220(52%)	908(54%)	0.85 (0.70- 1.03)	
Direct admission to the ICU	85(20%)	123(7%)	1.71 (1.31- 2.23)	<0.001

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105 **Supplementary Figure 1 | Preprinted recommended doctor orders for sepsis fast track**
 106 **programme used at the Emergency Department at Sunpasitthiprasong Hopsital from 1**
 107 **January 2015**

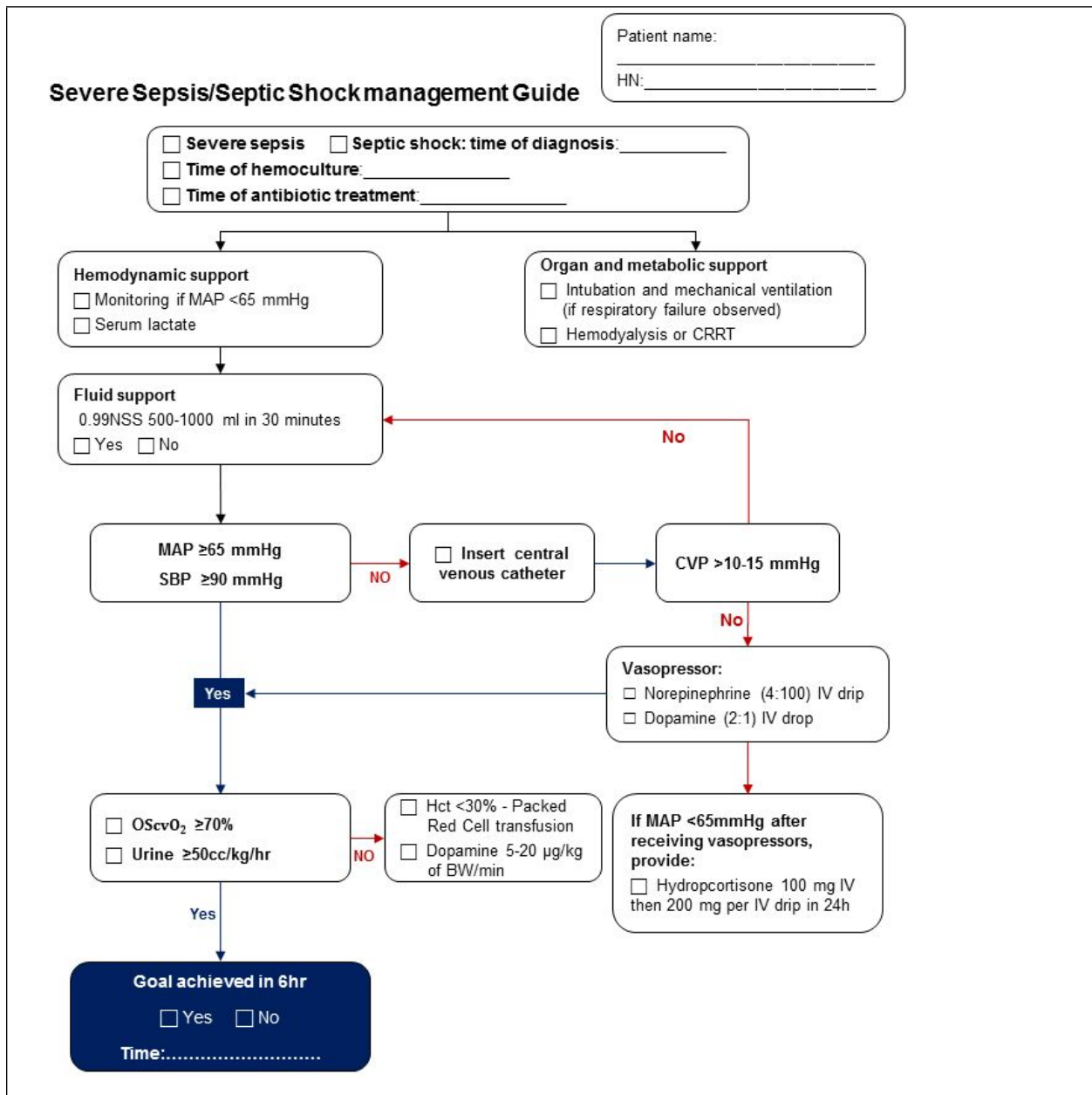
SAPPASITTIPRASONG HOSPITAL ๖๖.6/3

DOCTOR'S ORDER SHEET (Rev. 2: พ.ศ. 48)

FFM	PROGRESS NOTE	Date Time	ORDER FOR ONE DAY	Date Time	CONTINUOUS ORDER	Date of Sign
HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN..... HN.....	ER NON TRAUMA		Dx. <input type="checkbox"/> Sepsis <input type="checkbox"/> Severe Sepsis <input type="checkbox"/> Septic Shock - Consult ICU Admit..... - CxR - EKG..... - DTX. Stat..... - Serum lactate - CBC, PT, PTT, U/A - BUN, Cr., E'lyte - Liver Function Test,alb - HC x II stat at ER.....M. - HC x II at รพ.....M. - V/S q 1 hr. x II then as usual - on O2 canular 3 LPM if O2 sat < 95 % - Retained Foley's cath - NSS1,000 ml IV load.....in 10 min then IV drip ml/hr (30ml/kg)		- NPO - Record V/S, N/S, I/O Medication ชัก Hx เพื่อยา <input type="checkbox"/> ไม่มี <input type="checkbox"/> มี..... ตรวจสอบ Hx เพื่อยา ในHOMC <input type="checkbox"/> ไม่มี <input type="checkbox"/> มี.....	
	Time onset					
	Date					
	Time					
	Onset					
	Date					
	Time					
	E V M					
	BP /					
	HR T C					
	Source of infection					
	<input type="checkbox"/> Respiratory <input type="checkbox"/> GI					
	<input type="checkbox"/> Skin, soft tissue <input type="checkbox"/> CNS					
	<input type="checkbox"/> Cardiovascular					
	<input type="checkbox"/> Others.....					
	Systemic infection					
	<input type="checkbox"/> Leptospirosis <input type="checkbox"/> Malaria					
	<input type="checkbox"/> Rickettsia <input type="checkbox"/> Denque					
	พียง IV bolus.....ml					
	BP / HR					
IVF รพ.....ml						
IVF at ER.....ml						

108

109 **Supplementary Figure 2 | The Sepsis Fast Track sepsis resuscitation workflow used at the**
 110 **Emergency Department at Sunpasitthiprasong Hopsital from 1 March 2016**



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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5-6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	8-9
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	-
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	-

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11-13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13-14
	13b	For each group, losses and exclusions after randomisation, together with reasons	-
Recruitment	14a	Dates defining the periods of recruitment and follow-up	13
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	14-15
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	16-17
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	16-19
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	17-19
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	19
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	22-23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	23
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	20-22
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	24-25

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Effectiveness of a sepsis programme in a resource-limited setting

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Date Submitted by the Author:	19-Oct-2020
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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Infectious diseases, Epidemiology
Keywords:	Epidemiology < INFECTIOUS DISEASES, INFECTIOUS DISEASES, INTENSIVE & CRITICAL CARE

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3 **33 Abstract**
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5 **34 Objective:** To evaluate the effectiveness of a Sepsis Fast Track (SFT) programme initiated at a
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7 regional referral hospital in Thailand in January 2015
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10 **36 Design:** A retrospective analysis using the data of a prospective observational study (Ubon-sepsis)
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12 from March 2013 to January 2017
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14 **38 Setting:** General medical wards and medical intensive care units (ICUs) of a study hospital
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16 **39 Participants:** Patients with community-acquired sepsis observed under the Ubon-sepsis cohort.
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18 Sepsis was defined as modified Sequential Organ Failure Assessment (SOFA) score ≥ 2 .
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21 **41 Main exposure:** The SFT programme was a protocol to identify and initiate sepsis care on hospital
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23 admission, implemented at the study hospital in 2015. Patients in the SFT programme were
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25 admitted directly to the ICUs when available. The non-exposed group comprised of patients who
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27 received standard of care.
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30 **45 Main outcome:** The primary outcome was 28-day mortality. The secondary outcomes were
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32 measured sepsis management interventions.
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35 **47 Results:** Of 3,806 sepsis patients, 903 (24%) were detected and enrolled in the SFT programme
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37 of the study hospital (SFT group) and 2,903 received standard of care (non-exposed group).
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39 Patients in the SFT group had more organ dysfunction, were more likely to receive measured sepsis
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41 management and to be admitted directly to the ICU (19% vs. 4%). Patients in the SFT group were
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43 more likely to survive (adjusted hazard ratio 0.72; 95% CI 0.58 to 0.88, $p=0.001$) adjusted for
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45 admission year, gender, age, comorbidities, modified SOFA score and direct admission to the
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47 ICUs. The benefit of the SFT programme was not influenced by direct admission to the ICUs
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52 (p=0.44).
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3 55 **Conclusions:** The SFT programme is associated with improved sepsis care and lower risk of death
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5 56 in sepsis patients in rural Thailand, where some critical care resources are limited. The survival
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7 57 benefit is observed even when patients enrolled in the programme could not be admitted directly
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9 58 into the ICUs.

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12 59 **Study registration number:** NCT02217592
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18 61 **Strengths and limitations of this study**

- 20 62 • The study hospital utilized the published framework, SCAN-TEACH-TREAT programme
21 63 to develop a context specific quality of care improvement for sepsis in a tropical resource-
22 64 limited setting.
- 23 65 • The study took advantage of a robust prospective observational study design that
24 66 strengthened causal inference by providing pre-intervention information, having an
25 67 appropriate control group from both pre and post-intervention periods, and controlling
26 68 important confounding factors (i.e. the modified SOFA score).
- 27 69 • We found that most measured sepsis interventions increased and that admission to the ICUs
28 70 were not associated with the survival benefit of the sepsis programme.
- 29 71 • The study did not record dosage of dobutamine, dopamine, epinephrine and
30 72 norepinephrine, arterial blood gases were rarely performed, and the modified SOFA score
31 73 (maximum 23) may be lower than the SOFA score (maximum 24).
- 32 74 • The observational study may have residual confounding factors such as improvement of
33 75 care and profile of organ failure recognition overtimes.

76 INTRODUCTION

77 Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to
78 infection,¹ and is the primary cause of death from infection, especially if not recognized and treated
79 promptly.²⁻⁴ Sepsis is a major cause of health loss worldwide and is associated with approximately
80 eleven million deaths each year, most of which occur in low and middle-income countries
81 (LMICs).⁵ The United Nations World Health Assembly has recognized sepsis as a global health
82 priority and adopted a resolution on improving its worldwide prevention, diagnosis and
83 management.⁶ Comprehensive guidelines such as those developed by the Surviving Sepsis
84 Campaign have been associated with reduced mortality in high-income countries,²⁻⁴ but
85 effectiveness of these guidelines in LMICs needs more evaluation.⁷⁻¹⁰

86
87 Following the Surviving Sepsis Campaign (SSC) 2012,¹¹ the Ministry of Public Health Thailand
88 and the Thai Society of Critical Care Medicine developed local recommendations on sepsis based
89 on resource availability and local context.¹² The recommendations suggest that secondary-care and
90 tertiary-care hospitals in the country should develop a Sepsis Fast Track (SFT) so that, on
91 presentation, sepsis patients can be identified, treated and directly admitted to the ICUs when
92 available. One small retrospective study showed lower mortality among sepsis patients enrolled
93 than those not enrolled in the SFT (21% vs. 43%) at the study hospital,¹³ while another study did
94 not find an association between SFT and mortality outcome.¹⁴ These studies were subject to
95 selection biases due to their retrospective nature.¹³⁻¹⁴ Interventional studies to randomize patients
96 to receive or not receive the SFT, however, would be unethical and impractical after the national
97 recommendations have been implemented. It is increasingly recommended to evaluate the impact

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3 98 of healthcare interventions using routine data, particularly when a wide range of routinely collected
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5 99 data is available.¹⁵
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10 101 Here, we analysed data from our prospective observational study of community-acquired sepsis
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12 102 patients presenting to a referral hospital in Thailand over four years (from March 2013 to January
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14 103 2017)¹⁶⁻¹⁷ to retrospectively evaluate the effectiveness of a SFT programme which was
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16 104 implemented at the study hospital in January 2015.
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21 22 106 **MATERIAL AND METHODS**

23 24 107 **Study design**

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27 108 We conducted a retrospective study to evaluate the effectiveness of the SFT programme by using
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29 109 the data of a prospective observational study (Ubon-sepsis).¹⁶⁻¹⁷ The SFT programme was
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31 110 implemented at the study hospital in January 2015. The SFT programme at the study hospital
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33 111 included (1) diagnostic criteria for attending physicians and medical teams to systematically
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35 112 identify sepsis patients on hospital admission (Supplementary Table 1), (2) a recommended sepsis
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37 113 care protocol and (3) direct admission to the ICUs when available. The SFT programme at the
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39 114 study hospital was generated by the SFT committee of the study hospital (S.B., S.S., C.B., P.P.,
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41 115 B.S., O.W., P.C. and P.T.) based on SSC 2012,¹¹ resource availability and local context.¹²
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48 117 Details of the Ubon-sepsis cohort have been published elsewhere.¹⁶⁻¹⁷ In short, the Ubon-sepsis
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50 118 research team, who were not attending physicians or medical teams at the study hospital,
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52 119 conducted a prospective observational study of community-acquired infections and sepsis from
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3 120 March 2013 to January 2017.¹⁶⁻¹⁷ The research team prospectively enrolled adult patients ≥ 18
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5 121 years old who were admitted to the general medical wards and medical intensive care units (ICUs)
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7 122 with a primary diagnosis of infection made by the attending physician, were within 24 hours of
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9 123 admission to the study hospital, and had three of 20 systemic manifestations of infection
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11 124 documented in the medical records (Supplementary Table 2). The 20 systemic manifestations of
12
13 125 the infections were consolidated from the 22 variables proposed as diagnostic criteria for sepsis
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15 126 for SSC 2012.¹¹ The study team sequentially screened all medical patients by reviewing admission
16
17 127 logs in the emergency department (ED), medical wards, and medical ICUs twice daily (morning
18
19 128 and afternoon) on each working day. The Ubon-sepsis cohort was initiated in 2012 prior to the
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21 129 implementation of SFT at the study hospital. The research team was not involved in any clinical
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23 130 interventions; enrollment in the SFT programme and all medical treatment was performed by
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25 131 attending physicians and medical teams. The research team did not adjust the study protocol,
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27 132 inclusion criteria and exclusion criteria of the Ubon-sepsis cohort during the entire study period,
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29 133 and the research team recorded whether participants in the Ubon-sepsis cohort were enrolled in
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31 134 the SFT programme.
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40 136 The reporting of this study follows the STROBE guidelines. Written, informed permission was
41
42 137 obtained from participants prior to enrollment in the Ubon-sepsis cohort.
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47 139 **Participants**

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49 140 For this study, we evaluated patients who were included into the Ubon-sepsis cohort and had
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51 141 community-acquired sepsis. Sepsis was defined as an infection with organ dysfunction in
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3 142 accordance with the 2016 international Consensus (Sepsis-3) guidelines for sepsis.¹ Organ
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5 143 dysfunction was determined by a modified sequential (sepsis-based) organ failure assessment
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7 144 (SOFA) score ≥ 2 as previously described.¹⁶⁻¹⁷ The study was conducted in 2013 prior to the Sepsis-
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9 145 3 definition, and inotropic and vasopressor agent doses were not recorded into the CRF.^{1, 18} For
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11 146 the cardiovascular component of the SOFA score, the scoring was modified such that subjects
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13 147 were scored a maximum of 2 (on a 4-point scale) if they received only dobutamine or dopamine,
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15 148 and scored a maximum of 3 if they received epinephrine or norepinephrine. For the respiratory
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17 149 component of the SOFA score, as PaO₂/FiO₂ indices were not available for the majority of
18
19 150 subjects due to infrequency of arterial blood gas tests, the score was modified as follows: Subjects
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21 151 were scored a maximum of 2 (4-point scale) if they received advanced respiratory support
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23 152 (endotracheal tube, gas powered or electrical powered mechanical ventilation) and arterial blood
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25 153 gas test was not performed.¹⁶⁻¹⁷ The Ubon-sepsis cohort excluded patients who were suspected of
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27 154 having hospital-acquired infections (determined by the attending physician), hospitalized within
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29 155 30 days prior to the current admission, or hospitalized at any facility for a total duration longer
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31 156 than 72 hours prior to enrollment.
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40 158 **Main exposure**

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42 159 Main exposure of the study was the SFT programme. All patients included in the Ubon-sepsis
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44 160 cohort from March 2013 to December 2014 who received standard care were considered as the
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46 161 non-exposed group. Patients included in the Ubon-sepsis cohort from January 2015 to January
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48 162 2017 who received standard care or were received care in the SFT programme by attending
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50 163 medical teams using their criteria on admission (Supplementary Table 1) were considered as the
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3 164 additional non-exposed group or as the SFT group, respectively. The Ubon-sepsis research team
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5 165 were not involved in decision-making regarding enrollment to the SFT programme.
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10 167 Patients in the non-exposed group received standard care according to local guidelines. Patients in

11
12 168 the SFT group received the standard of care along with a recommended sepsis care protocol of the

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14 169 SFT programme. First, preprinted recommended doctor orders for the SFT programme were used

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17 170 as of January 2015 (Supplementary Figure 1). The recommended orders included oxygen

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19 171 administration, intravenous fluid loading and fluid administration to achieve the recommended

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21 172 target of 30 mL/kg crystalloid, blood culture, recommended stat (immediate) doses and choices of

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23 173 parenteral antibiotics including ceftriaxone, ceftazidime, cloxacillin, metronidazole and

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25 174 gentamycin, contact ICU for ICU admission (if available), oxygen supplementation, close

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27 175 monitoring of vital signs and urine output, and a set of diagnostic tests including chest radiography,

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29 176 electrocardiogram, rapid blood glucose test, serum lactate, complete blood count, blood urea

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31 177 nitrogen, creatinine, electrolytes, liver function tests, albumin level, prothrombin time and partial

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33 178 thromboplastin time. Second, as of March 2016, the resuscitation workflow to normalize and

34
35 179 maintain a mean arterial pressure (MAP) ≥ 65 mmHg, systolic blood pressure (SBP) ≥ 90 mmHg

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37 180 and urine output ≥ 0.5 mL/kg/hr within the first six hours was formally implemented and

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39 181 recommended (Supplementary Figure 2). The resuscitation workflow included fluid resuscitation,

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41 182 measurement of central venous pressure (CVP) and central venous oxygen saturation (SCVO₂),

42
43 183 administration of adrenergic agents, blood transfusion for haematocrit $< 30\%$ and hydrocortisone

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45 184 if adequate fluid resuscitation and vasopressor therapy could not restore hemodynamic stability.

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47 185 The resuscitation workflow was pre-printed and included in the clinical chart of every SFT patient

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3 186 (together with pre-printed doctor's orders), and was recommended even if patients could not be
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5 187 admitted directly to the ICU. A separate set of documents, recommended management and
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7 188 recommended frequency of vital signs monitoring for nurses (i.e. nurse notes for SFT patients)
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10 189 were also used for every SFT patient. Preparation and regular meetings to implement and monitor
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12 190 the SFT programme were organized by the SFT committee of Sunpasitthiprasong Hospital.
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16 17 192 **Outcome measures**

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19 193 The primary outcome measure was 28-day mortality as recorded in the Ubon-sepsis cohort.¹⁶ 28-
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21 194 day mortality data were collected via telephone contact if subjects were no longer hospitalized and
22
23 195 had been discharged alive.¹⁶ The secondary outcome measures were sepsis management
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25 196 interventions; including antibiotics administration, blood cultures, mechanical ventilation,
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27 197 adrenergic agents, acute haemodialysis and placement of a urinary catheter within the first day of
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29 198 hospitalization.¹⁶⁻¹⁷
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33 199 34 35 200 **Sample size**

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37 201 The sample size of the study was determined by the sample size of Ubon-sepsis cohort. We
38
39 202 assumed that about 50% of 3,806 sepsis patients in the Ubon-sepsis cohort were enrolled after the
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41 203 implementation of the SFT programme, of which 50% were enrolled in the SFT programme (i.e.
42
43 204 952 and 2,854 patients were estimated to be the SFT and non-exposed group, respectively). We
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45 205 assumed that the mortality of the non-exposed group was 21% based on published data.¹⁶⁻¹⁷ Our
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47 206 current sample size of 3,806 would provide a power of 80% at an alpha error of 5% to detect a
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49 207 4% difference in the mortality outcome.
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209 Statistical analysis

210 All sepsis patients were included in the analysis regardless of whether they were enrolled before
211 or after the implementation of the SFT programme. We used the Chi-square test and Mann-
212 Whitney test to compare the proportions of binary variables and median of continuous variables
213 between groups, respectively. The interquartile range is presented as 25th and 75th percentiles.

214
215 In the primary analysis, we used multivariable Cox proportional hazard models to evaluate the
216 effectiveness of SFT programme on 28-day mortality. The multivariable Cox proportional hazard
217 model was used to adjust the difference between those receiving the SFT programme and the
218 others.¹⁹ To reduce bias in the model development, we used the previous multivariable Cox
219 proportional hazard model as the base model,¹⁶ added the SFT group variable and direct admission
220 to the ICU, and modified by adding a time variable to represent possible changes over time and by
221 using continuous modified SOFA score on admission rather than as a binary variable (modified
222 SOFA score ≥ 2). Twenty eight patients enrolled in early 2017 were considered as enrolled in
223 2016. The continuous modified SOFA score was used to improve regression adjustment for disease
224 severity of the model. The other variables included in the model were gender, age group, transfer
225 from other hospital, comorbidities (diabetes mellitus, chronic kidney disease, liver disease and
226 malignancy) and blood culture positive for pathogenic organisms. We tested potential predefined
227 interactions between the SFT programme and direct admission to the ICUs. Using a conceptual
228 framework, we also consider that admission directly to the ICU could also be caused by the SFT;
229 therefore, we developed another multivariable model not including the variable for direct

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3 230 admission to the ICU. The goodness of fit for the multivariable Cox proportional hazard model
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5 231 was tested with a Hosmer and Lemeshow test. For the Cox proportional hazard model, we assessed
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8 232 whether the hazard ratio was constant over time using Schoenfeld residuals.
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12 234 For the secondary endpoints, we used multivariable logistic regression models with similar
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14 235 independent variables as the model for 28-mortality outcome and used each sepsis management
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16 236 process as an outcome. We estimated the total effect of the SFT on each sepsis management by
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18 237 using the multivariable logistic regression models adjusted for difference in characteristics and
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20 238 disease severity of the patients. This was because each sepsis management could be caused by
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22 239 characteristics of the patients, disease severity and the SFT.²⁰
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28 241 We also performed sensitivity analyses by excluding patients enrolled prior to the implementation
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30 242 of the SFT programme and by replacing direct admission to the ICUs with admission to the ICUs
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32 243 within the first hospital day. All analyses were performed with STATA 15.1 (StataCorp, College
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34 244 Station, TX, USA).
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40 246 **Patient and public involvement**
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42 247 No patients were involved in setting the research question or the outcome measures, nor were they
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44 248 involved in developing plans for recruitment, design, or implementation of the study. No patients
45
46 249 were asked to advice on interpretation or writing the results. The results will be disseminated to
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48 250 the public through online social media.
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252 RESULTS

253 Baseline characteristics

254 The observational cohort study (Ubon-sepsis) included 5,001 patients presenting with community-
255 acquired infections from March 2013 to January 2017, and 12 patients were excluded due to
256 unknown 28-day mortality outcome. 3,806 (76%) met criteria for sepsis within the first 24 hours
257 of admission with a modified SOFA score ≥ 2 , and were included for the analysis. Figure 1 shows
258 the flow of participants through the study. Among 3,806 sepsis patients, 903 were enrolled in the
259 SFT programme and considered as the SFT group, and 2,903 were not enrolled in the SFT
260 programme, received standard of care, and considered as the non-exposed group. Of 2,903 sepsis
261 patients in the non-exposed group, 1,636 were included in the observational cohort study prior to
262 the implementation of SFT programme and 1,267 were after the implementation of the programme.

263
264 Table 1 shows the characteristics of the study patients. Patients in the SFT group were older and
265 more likely to have underlying diseases of diabetes mellitus, cerebrovascular diseases and
266 dyslipidemia. Patients included in the SFT group had higher severity of organ dysfunction
267 determined by the modified SOFA score compared with the non-exposed group (median 6 [IQR
268 4-9] vs. 4 [IQR 3-6], $p < 0.001$). A higher proportion of patients in the SFT group were admitted
269 directly to the ICU compared with the non-exposed group (19% vs 5%, $p < 0.001$).

270

271 **Table 1| Baseline characteristics of sepsis patients enrolled in the Sepsis Fast Track**
 272 **programme¹ (SFT group) or standard of care (non-exposed group). Values are number**
 273 **(percentages) unless stated otherwise**

Characteristics	SFT group ² (n=903)	Non-exposed group ³ (n=2903)	P value
Male gender	526 (58%)	1653 (57%)	0.49
Age (years) (median [IQR])	63 (49-74)	56 (39-70)	<0.001
Age group (years)			
18-40	100 (11%)	647 (22%)	<0.001
>40-60	277 (31%)	875 (30%)	
>60-70	214 (24%)	513 (18%)	
>70	312 (35%)	868 (30%)	
Comorbidities			
Hypertension	239 (26%)	726 (25%)	0.38
Diabetes mellitus	213 (24%)	594 (20%)	0.05
Chronic kidney disease	129 (14%)	391 (13%)	0.53
Dyslipidemia	66 (7%)	152 (5%)	0.02
Heart disease	48 (5%)	183 (6%)	0.28
Lung disease	67 (7%)	239 (8%)	0.43
Liver disease	33 (4%)	91 (3%)	0.44
Cerebrovascular disease	29 (3%)	55 (2%)	0.02
Malignancy	13 (1%)	47 (2%)	0.71
Human immunodeficiency virus (HIV)	6 (1%)	33 (1%)	0.22
Organ dysfunction			
Modified SOFA score (median [IQR])	6 (4-9)	4 (3-6)	<0.001
Renal dysfunction ⁴	706 (78%)	1846 (64%)	<0.001
Cardiovascular dysfunction ⁴	811 (90%)	1532 (53%)	<0.001
Coagulation dysfunction ⁴	419 (46%)	1562 (54%)	<0.001
Liver dysfunction ⁴	311 (34%)	822 (28%)	0.001
Respiratory dysfunction ⁴	337 (37%)	853 (29%)	<0.001
Central nervous system dysfunction ⁴	166 (18%)	530 (18%)	0.92
Transferred from other hospitals	874 (97%)	2372 (84%)	<0.001
Duration of symptoms (median [IQR])	2 (1-3)	3 (1-5)	<0.001
≤ 2 days	505 (56%)	1191 (41%)	
3-7 days	362 (40%)	1488 (51%)	
> 7 days	36 (4%)	224 (8%)	

Characteristics	SFT group ² (n=903)	Non-exposed group ³ (n=2903)	P value
Presenting clinical syndromes⁵			
Septic shock	687 (76%)	733 (25%)	<0.001
Acute febrile illness	206 (23%)	940 (32%)	<0.001
Lower respiratory infection	223 (25%)	890 (31%)	0.001
Sepsis	225 (25%)	273 (9%)	<0.001
Others	13 (1%)	456 (16%)	<0.001
Diarrheal illness	150 (17%)	264 (9%)	<0.001
Admitted directly to an ICU upon admission	170 (19%)	128 (4%)	<0.001
Admitted to an ICU within 24 hours of admission	270 (29%)	370 (13%)	<0.001
Blood culture positive for pathogenic organisms	175 (19%)	347 (12%)	<0.001
Year			
2013	N/A	1047 (26%)	<0.001
2014	N/A	1156 (29%)	
2015	369 (39%)	956 (24%)	
2016	556 (59%)	869 (21%)	
2017	14 (1%)	22 (1%)	

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275 ¹ SFT programme was implemented at the study hospital in January 2015.

276 ² 903 patients of the Ubon-sepsis cohort were enrolled in SFT programme after the implementation of the SFT
277 programme (Figure 1)

278 ³ Included 1,636 and 1,267 patients in the Ubon-sepsis cohort before and after the implementation of the SFT
279 programme, respectively.

280 ⁴ Organ dysfunction defined as modified SOFA score was ≥ 1 for each organ system.¹⁶

281 ⁵ Patients may have more than one presenting clinical syndrome.

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283 Primary outcomes

284 The primary outcome, mortality within 28 days, occurred in 205 of 903 (23%) in the SFT group
285 and 574 of 2,903 (20%) in the non-exposed group. In the primary analysis, patients in the SFT
286 group were more likely to survive adjusted for baseline characteristics, severity of sepsis and direct

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3 287 admission the ICUs (adjusted hazard ratio [aHR] 0.72, 95% CI 0.58-0.88, p=0.001; Table 2). Older
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5 288 age, higher modified SOFA score, underlying disease of malignancy and chronic kidney disease,
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7 289 blood culture positive for pathogenic organisms and direct admission to the ICUs were associated
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10 290 with risk of mortality.
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For peer review only

292 **Table 2| Factors associated with 28-day mortality using multivariable Cox proportional**
 293 **hazards model**

Variables	Died (n=779)	Survived (n=3027)	Adjusted hazard ratio ² (95%CI)	P value
SFT group¹	205 (26%)	698 (23%)	0.72 (0.58- 0.88)	0.001
Male gender	445 (57%)	698 (23%)	0.87 (0.75- 1.01)	0.06
Age group (years) (n [%])				
• 18-40	59 (8%)	688 (23%)	1	<0.001
• >40-60	222 (29%)	930 (31%)	1.72 (1.28- 2.30)	
• >60-70	159 (20%)	568 (19%)	2.10 (1.54- 2.86)	
• >70	339 (44%)	841 (28%)	3.41 (2.57- 4.53)	
Transferred from other hospital	715 (92%)	2595 (86%)	1.14 (0.88- 1.49)	0.33
Modified SOFA score (median, IQR)	6 (4-9)	4 (3-6)	1.23 (1.21- 1.26)	<0.001
Comorbidities				
• Diabetes mellitus	205 (26%)	602 (20%)	1.06 (0.90- 1.26)	0.47
• Chronic kidney disease	141 (18%)	379 (13%)	1.22 (1.01- 1.48)	0.04
• Liver disease	39 (5%)	85 (3%)	1.27 (0.91- 1.76)	0.16
• Malignancy	24 (3%)	36 (1%)	2.64 (1.75- 3.99)	<0.001
Blood culture positive for pathogenic organisms	190 (24%)	332 (11%)	1.83 (1.55- 2.17)	<0.001
Year				
• 2013	165 (21%)	637 (21%)	1	0.30
• 2014	183 (23%)	651 (22%)	1.03 (0.83- 1.27)	
• 2015	207 (27%)	808 (27%)	1.05 (0.84- 1.31)	
• 2016 ²	224 (29%)	931 (31%)	0.88 (0.70- 1.11)	
Direct admission to the ICU	128 (16%)	170 (6%)	1.68 (1.36- 2.06)	<0.001

294 ¹ Enrolled in the Sepsis Fast Track (SFT) programme.

295 ² The hazard ratio of SFT was adjusted for gender, age group, transferred from other hospital, modified SOFA score,
 296 comorbidities, blood culture positive for pathogenic organisms, year and direct admission to the ICU. The hazard
 297 ratios of other variable could be considered as the controlled direct effect of those variables.²⁰

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3 298 ²Included 28 patients in 2017
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7 300 In a pre-specified interaction test, we found consistency of the association between the SFT and
8
9 301 lower risk of mortality when stratifying by direct admission to the ICUs (interaction test p=0.44).
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11 302 In the multivariable model including an interaction variable, the effect of SFT was comparable
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13 303 among those admitted directly to the ICUs (aHR 0.81, 95% CI 0.56 to 1.18) and those admitted
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15 304 directly to the general medical wards (aHR 0.69, 95% CI 0.56 to 0.86). Using a conceptual
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17 305 framework, we considered that admission directly to the ICU could also be caused by the SFT;
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19 306 therefore, we developed another multivariable model that did not adjust for direct admission to the
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21 307 ICU. We observed that the effect of the SFT was comparable (aHR 0.77, 95% CI 0.63 to 0.94;
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23 308 Supplementary Table 3).
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30 310 **Secondary outcomes**

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32 311 Using multivariable logistic regression models, we found that patients in the SFT group were more
33
34 312 likely to receive most sepsis management interventions than patients in the non-exposed group
35
36 313 adjusting for baseline characteristics and severity of sepsis (Supplementary Table 4). Those
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38 314 included antibiotics, blood cultures, adrenergic agents, and placement of a urinary catheter within
39
40 315 the first day of hospitalization. However, sepsis patients in the SFT group were less likely to
41
42 316 receive mechanical ventilation compared with those in the non-exposed group adjusting for
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44 317 baseline characteristics, severity of sepsis and direct admission to the ICUs group (adjusted odds
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46 318 ratio [aOR] 0.30; 95% CI 0.24 to 0.38). We found that direct admission to the ICUs (aOR 5.77,
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3 319 95% CI 4.20 to 7.92) and transfer from other hospitals (aOR 3.45, 95% CI 2.42 to 4.91) were
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5 320 strongly associated with the requirement of mechanical ventilation.
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10 322 **Sensitivity Analyses**

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12 323 We performed a sensitivity analysis by excluding the 1,636 patients enrolled in the observational
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14 324 study prior to the implementation of SFT programme. Similar differences in baseline
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16 325 characteristics were observed when comparing 903 patients in the SFT group to the 1,267 patients
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18 326 in the non-exposed group enrolled after the implementation of the SFT programme
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20 327 (Supplementary Table 5). A higher chance of survival in the SFT group compared to the non-
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22 328 exposed group was also observed (aHR 0.68, 95% CI 0.55 to 0.84, $p < 0.001$; Supplementary Table
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24 329 6). There was no interaction between the management intervention and direct admission to the
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26 330 ICUs ($p = 0.92$).
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33 332 We also performed another sensitivity analysis by replacing direct admission to the ICUs with
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35 333 admission to the ICUs within the first hospital day. Of 3,806 patients, 640 (17%) were admitted to
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37 334 the ICUs within the first day of admission. A higher chance of survival in the SFT group compared
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39 335 to the non-exposed group was also observed (aHR 0.72, 95% CI 0.59 to 0.88, $p = 0.002$). There was
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41 336 also no interaction between the management intervention and admission to the ICUs within the
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43 337 first day of admission ($p = 0.29$).
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3 **339 DISCUSSION**
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5 340 In this study evaluating patients with community-acquired sepsis, enrollment into a programme to
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7 341 identify and initiate sepsis care implemented at the study hospital (SFT programme) was associated
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10 342 with 28% lower risk of mortality. In recent years, there has been an increasing need to understand
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12 343 benefit and cost effectiveness of implementation of sepsis care interventions in LMICs because of
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14 344 concerns that international sepsis guidelines¹¹ may not be extrapolated to patients with tropical
15
16 345 infectious diseases⁷⁻⁹ and to resource-limited settings with poor ICU capacity.¹⁰ In this study we
17
18 346 show the effectiveness of sepsis protocol modified based on resource availability in a tropical
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20 347 country, where causes of community-acquired sepsis include malaria and tropical viral diseases.¹⁶
21
22 348 ²¹⁻²² Access to the ICU increased after the implementation of the SFT programme, but the majority
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24 349 of sepsis patients were still managed on the general wards, including those with respiratory failure
25
26 350 or shock. Nonetheless, our study shows that enhancing sepsis care in the emergency department
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28 351 and general medical wards, as well as improving access to ICUs can reduce sepsis mortality in a
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30 352 LMIC.
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37 354 The lower odds of receiving mechanical ventilation in the SFT group could be a sign of improved
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39 355 sepsis care. Patients in the SFT group are monitored closely either in or outside the ICUs, and the
40
41 356 attending physicians aim to obviate the need for airway intubation when possible.⁷ Attending
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43 357 physicians may tend to provide mechanical ventilation to patients in the non-exposed group based
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45 358 on broad indications such as (1) airway protection, (2) hypercapnic respiratory failure, (3)
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47 359 hypoxemic respiratory failure or (4) circulatory failure²³⁻²⁴ because they may not be able to monitor
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49 360 patients' breathing and oxygen saturation as often as those enrolled in the SFT programme.
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5 362 It is not surprising that patients in the SFT group had more organ dysfunction than those in the
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7 363 non-exposed group. This is because the severity of organ dysfunction among patients with septic
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9 364 shock, respiratory failure and alteration of conscious can be assessed clinically on admission, and
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11 365 those patients could be enrolled in the SFT programme when the laboratory test results were not
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13 366 yet available. However, the non-exposed group were defined as having sepsis based on clinical
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15 367 findings and all laboratory test results within 24 hours of admission (per protocol of Ubon-sepsis
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17 368 cohort study¹⁶⁻¹⁷). Therefore, the non-exposed group could use laboratory test results (i.e. liver
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19 369 function tests, creatinine level, international normalised ratio and activated partial thromplatin
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21 370 time) from blood specimens drawn on admission. Therefore, the SFT programme were more likely
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23 371 to enroll patients with obvious signs of sepsis and septic shock; such as acute respiratory failure
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25 372 and hypotension, while Ubon-sepsis cohort could include sepsis patients with relatively lower
26
27 373 modified SOFA scores.
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35 375 **Comparison with other studies**

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37 376 Our study is not the first to evaluate effectiveness of sepsis intervention in LMICs. Early
38
39 377 recognition and protocol directed intervention improves outcomes of sepsis in adults²⁵⁻²⁷ and
40
41 378 severe infection in children²⁸ in LMICs. The optimal method of fluid resuscitation in sepsis in
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43 379 tropical LMICs has not been determined.^{8, 25, 29-30} Our resuscitation protocol is a simple guideline,
44
45 380 and the SFT recommend doctors to be careful and adjust fluid resuscitation based on preliminary
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47 381 diagnoses, underlying diseases and rapid diagnostic test results (i.e. if sepsis is caused by malaria
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49 382 or dengue infection). The implementation of the SFT programme in our study hospital and in
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3 383 Thailand is consistent with the recommendation of “SCAN-TEACH-TREAT” programme
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5 384 developed by Sepsis in Resource-Limited Settings Workgroup of the Surviving Sepsis Campaign.⁷
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8 385 The SFT programme evaluated resources in the setting (SCAN component), focused on
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10 386 educational interventions on early recognition and management of sepsis among medical personnel
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12 387 including physicians, nurses and students (TEACH component) and implemented pragmatic and
13
14 388 simple bundles into practice (TREAT component). In addition, the SFT programme has the strong
15
16 389 support and endorsement of local health and governmental leaders.¹²
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19 390

391 **Strength and limitations of the study**

392 This study features four strengths. First, the study hospital utilized the published framework,
393 SCAN-TEACH-TREAT programme to develop a context specific quality of care improvement for
394 sepsis,⁷ and we closely monitor and evaluate the effectiveness of an intervention. Second, the study
395 took advantage of a robust prospective observational study design that strengthened causal
396 inference by providing pre-intervention information, having an appropriate non-exposed group
397 from both pre and post-intervention periods, and controlling important confounding factors (i.e.
398 the modified SOFA score) which were measured systematically throughout the study period.
399 Third, this study incorporated several predictors of interest (measured sepsis management
400 interventions and admission to the ICUs). This allows us to identify that most measured sepsis
401 interventions increased and that admission to the ICUs were not associated with the survival
402 benefit of the SFT programme. Fourth, the focus on sepsis at a public tertiary-care hospital in
403 Thailand helped us to estimate the effect of sepsis protocol in a tropical resource-limited setting
404 with large sample size.

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5 406 Our study had several limitations. First, a modified SOFA score was used because the dosage of
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7 407 dobutamine, dopamine, epinephrine and norepinephrine were not recorded and arterial blood gases
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9 408 were rarely performed. The modified SOFA score (maximum 23) may be lower than the SOFA
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11 409 score (maximum 24). Nonetheless, the modified SOFA score is strongly associated with mortality
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13 410 in sepsis.¹⁶⁻¹⁷ Second, the proportional hazards assumption was met for all variables, including
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15 411 the main variable (the SFT), except one controlled variable (the modified SOFA score). The
16
17 412 adjusted effect estimates could be under or overestimated due to residual confounding factors such
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19 413 as improvement of care and profile of organ failure recognition overtimes.
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25 26 415 **Conclusions and future implications**

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28 416 Our study successfully demonstrated effectiveness of a sepsis programme implemented in a LMIC.
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30 417 Measuring effectiveness of a sepsis programme is a complex issue, and we utilized a data of a
31
32 418 prospective observational study and carefully controlled for severity of sepsis and temporal trends
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34 419 in our analyses. Care in sepsis patients improved after the implementation of the programme.
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36 420 Additional research is needed to better understand cost of the intervention, long-term benefits and
37
38 421 impact of the programme on a national scale. National strategies aimed at saving lives from sepsis
39
40 422 in LMICs should be encouraged. Such strategies should include analysis of resources and local
41
42 423 circumstances, followed by development, implementation and assessment of customized
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44 424 programmes.
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19 433 **Contributors:**
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22
23 435 conception development and study design. SB, VH, PT, TEW and DL contributed to study
24
25 436 conduct, data collection, and study administration. VH and DL performed the statistical analysis
26
27 437 and interpreted the data and had full access to all of the data in the study. Both authors can take
28
29 438 responsibility for the integrity of the data and the accuracy of the data analysis. DL is a guarantor.
30
31 439 SB, VH, PT, TEW, and DL wrote the first draft of a manuscript, with input from SS, CB, PC, KR,
32
33 440 and AD. PP, BS, OW, and RC provided scientific or administrative support. All authors
34
35 441 contributed to results interpretation, critically revised, and approved the final submitted
36
37 442 manuscript. The corresponding author attests that all listed authors meet authorship criteria and
38
39 443 that no others meeting the criteria have been omitted.
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4
5 449 conduct of the study, all study procedures, data collection, data analyses, data interpretation,
6
7
8 450 writing of the report, and the decision to submit the article for publication.
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11
12 452 **Competing interests:**

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15 453 The authors declare that they have no completing interests.
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19 455 **Ethics approvals:**

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21 456 The study was conducted the study in full compliance with the principles of good clinical practice
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23 457 (GCP), and the ethical principles of the Declaration of Helsinki. The study protocol and related
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26 458 documents were approved by Sunpasitthiprasong Hospital Ethics Committee (039/2556), the
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28 459 Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (MUTM2012-024-
29
30 460 01), the University of Washington Institutional Review Board (42988) and the Oxford Tropical
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32 461 Research Ethics Committee at the University of Oxford (OXTREC172-12). Signed or
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34 462 fingerprinted informed consent was obtained from the participants or their representatives before
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37 463 enrollment.
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42 465 **Data sharing:**

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44 466 The final database with the data dictionary are publicly available online

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47 467 <https://doi.org/10.6084/m9.figshare.12102627>.

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49 468 The lead authors (SB, VH and DL) affirm that the manuscript is an honest, accurate, and
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51 469 transparent account of the study being reported; that no important aspects of the study have been
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3 470 omitted; and that any discrepancies from the study as planned have been explained. This is an
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5 471 Open Access article distributed in accordance with the terms of the Creative Commons Attribution
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10 473 medium, provided the original work is properly cited. See:
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17 476 **Dissemination to participants and related patient and public communities:**
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19 477 The results of this study will be disseminated to physicians at the study hospital, health care
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21 478 providers, policy makers, and academic communities through various mediums, including printed
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23 479 report, internal hospital meetings, academic conferences, and institutional networks. The results
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25 480 from this study will be used to inform the current Sepsis Fast Track programme at
26
27 481 Sunpasitthiprasong hospital and the community hospitals which are located in jurisdiction of the
28
29 482 study hospital catchment areas in the Northeast Thailand. The study results will not be
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31 483 disseminated to patients or general population, because study results are in medical context.
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6 582 **Figure legends**

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9 583 **Figure 1| Flow of participants through study**

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11 584 **Footnote of figure 1:** This study used the data of an observational study on sepsis patients (Ubon-
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13 585 sepsis) from March 2013 to January 2017 to evaluate the effectiveness of a Sepsis Fast Track
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15 586 (SFT) programme implemented at the study hospital in January 2015
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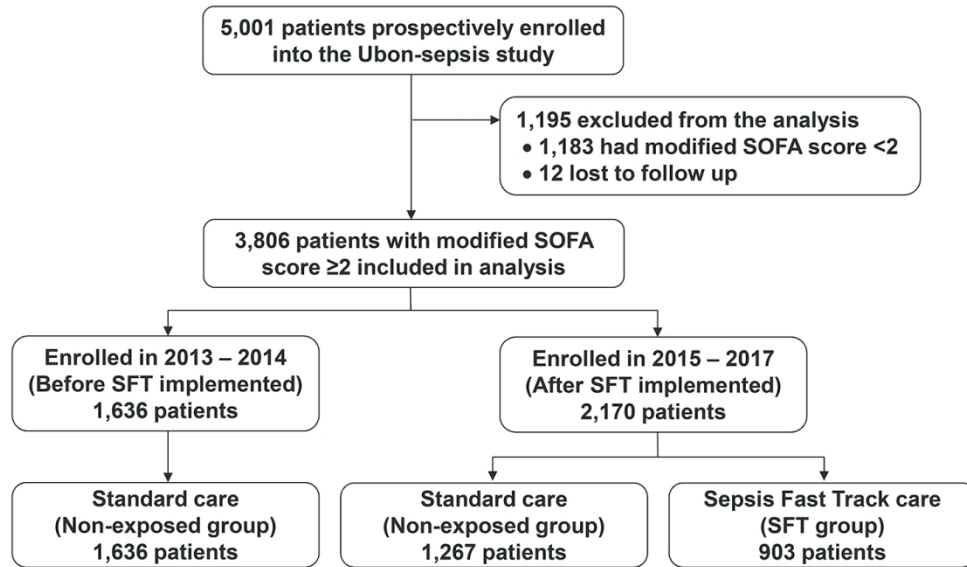


Figure 1 | Flow of participants through study

24 **Supplementary Table 1 | Criteria used to systematically enroll patents into Sepsis Fast Track**
25 **(SFT) upon admission**

26 **1. Present with 2 or more of below Signs of systemic inflammatory response syndrome**
27 **(SIRS)**

- 28 • Body temperature > 38.3 °C or < 36.0 °C
- 29 • Heart rate > 90 bpm
- 30 • Respiratory rate > 20 pm or PaCO₂ < 32 mmHg
- 31 • WBC > 12,000 /μL or < 4,000 /μL or Band forms > 10%

32 **2. Suspected sources of infection**

- 33 • Pneumonia
- 34 • Urinary track infection
- 35 • Intra-abdominal infection
- 36 • Skin and soft tissue infection
- 37 • CNS infection
- 38 • Others infections or unspecified source of infection

39 **3. Diagnostic criteria for severe sepsis:** patient met criteria in no 1 and 2 and has at least
40 one of the following criteria

- 41 • Mottled skin
- 42 • Capillary refilling time ≥ 3 seconds
- 43 • Urine output < 0.5 ml/kg/hour
- 44 • Abrupt change in mental status
- 45 • Acute respiratory failure
- 46 • Platelet count < 100,000 /μL
- 47 • Disseminated intravascular coagulation
- 48 • Lactate > 2 mmol/L
- 49 • SBP < 90 mmHg or MAP < 65 mmHg

50 **4. Diagnostic criteria for septic shock:** patient who are severe sepsis and has at least 1 of
51 the following criteria

- 52 • SBP < 90 mmHg or MAP < 65 mmHg after crystalliod administration ≥ 40-60
53 ml/kg of body weight OR after colloid administration ≥ 20-30 ml/kg of body weight
- 54 • Require administration of dopamine > 5μg/kg of BW/min or norepinephrine /
55 epinephrine > 0.02 μg/kg of BW/min to maintain MAP to be > 65 mmHg

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3 57 **Supplementary Table 2 | Systemic manifestation of infection criteria used for enrollment in**

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5 58 **Ubon-Sepsis Cohort**

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8 59 **General parameters**

- 9 60 1. Fever or hypothermia (Core body temperature defined as > 38.3 °C or < 36.0 °C)
- 10 61 2. Tachycardia (heart rate > 90 beats per minute)
- 11 62 3. Tachypnea (respiratory rate > 20 per minute)
- 12 63 4. Altered mental status with Glasgow Coma Score (GCS) < 15 or < 10 if intubated
- 13 64 5. Hyperglycemia (plasma glucose > 140 mg/dL) in the absence of diabetes

14 65 **Inflammatory parameters**

- 15 66 6. Leukocytosis (white blood cell count $> 12,000/\mu\text{L}$), leukopenia (white blood cell count $< 4000/\mu\text{L}$) or immature forms $> 10\%$
- 16 67
- 17 68 7. Plasma C-reactive protein > 2 SD above the normal value
- 18 69 8. Plasma procalcitonin > 2 SD above the normal value

19 70 **Hemodynamic parameters**

- 20 71 9. Arterial hypotension (systolic blood pressure (SBP) < 90 mmHg, mean arterial pressure (MAP) < 70 mmHg, or SBP decrease > 40 mmHg)

21 72 **Organ dysfunction parameters**

- 22 73 10. Low oxygen saturation determined by pulse oximetry ($\text{SpO}_2 < 95\%$) determined by pulse oximetry
- 23 74
- 24 75 11. Arterial hypoxemia ($\text{PaO}_2 / \text{FIO}_2 < 300$)
- 25 76
- 26 77 12. Acute oliguria (urine output < 0.5 mL/kg/hr or 45 mmol/L for 2 hours)
- 27 78
- 28 79 13. Creatinine increase > 0.5 mg/dL
- 29 80
- 30 81 14. Coagulation abnormalities (international normalised ratio > 1.5 or activated partial thromboplastin time > 60 seconds)
- 31 82
- 32 83 15. Thrombocytopenia (Platelet count $< 100,000$ cells/ μL)
- 33 84
- 34 85 16. Ileus (absent bowel sounds)
- 35 86
- 36 87 17. Hyperbilirubinaemia (plasma total bilirubin > 4 mg/dL)

37 88 **Tissue perfusion parameters**

- 38 89 18. Hyperlactatemia (> 1 mmol/L)
- 39 90
- 40 91 19. Decreased capillary refill or mottling
- 41 92
- 42 93 20. Significant edema or positive fluid balance
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89 **Supplementary Table 3| Factors associated with 28-day mortality using multivariable Cox**
 90 **proportional hazards model without a variable of the direct admission to the ICU**

Variables	Died (n=779)	Survived (n=3027)	Adjusted hazard ratio (95%CI)	P value
SFT group¹	205 (26%)	698 (23%)	0.77 (0.63- 0.94)	0.01
Male gender	445 (57%)	698 (23%)	0.86 (0.74- 1.00)	0.05
Age group (years) (n [%])				
• 18-40	59 (8%)	688 (23%)	1	<0.001
• >40-60	222 (29%)	930 (31%)	1.69 (1.26- 2.26)	
• >60-70	159 (20%)	568 (19%)	2.07 (1.52- 2.81)	
• >70	339 (44%)	841 (28%)	3.32 (2.50- 4.41)	
Transferred from other hospital	715 (92%)	2595 (86%)	1.16 (0.89- 1.52)	0.26
Modified SOFA score (median, IQR)	6 (4-9)	4 (3-6)	1.25 (1.22- 1.27)	<0.001
Comorbidities				
• Diabetes mellitus	205 (26%)	602 (20%)	1.08 (0.91- 1.27)	0.39
• Chronic kidney disease	141 (18%)	379 (13%)	1.20 (0.99- 1.45)	0.07
• Liver disease	39 (5%)	85 (3%)	1.24 (0.89- 1.72)	0.20
• Malignancy	24 (3%)	36 (1%)	2.52 (1.67- 3.81)	<0.001
Blood culture positive for pathogenic organisms	190 (24%)	332 (11%)	1.83 (1.54- 2.16)	<0.001
Year				
• 2013	165 (21%)	637 (21%)	1	0.34
• 2014	183 (23%)	651 (22%)	0.98 (0.79- 1.21)	
• 2015	207 (27%)	808 (27%)	1.01 (0.81- 1.26)	
• 2016 ²	224 (29%)	931 (31%)	0.85 (0.68- 1.07)	

91 ¹ Enrolled in the Sepsis Fast Track (SFT) programme

92 ² Included 28 patients in 2017

93 **Supplementary Table 4 | Clinical management within the first day of hospital**

Clinical management ¹	SFT group (n=903)	Control group (n=2903)	Adjusted odds ratio (95% CI)	P value
Antibiotic	897 (99%)	2497 (86%)	14.10 (6.10-32.60)	<0.001
Blood culture	829 (92%)	2387 (82%)	1.77 (1.31-2.38)	<0.001
Urinary catheterization	862 (95%)	1642 (57%)	11.04 (7.71-15.80)	<0.001
Acute dialysis	10 (1.1%)	23 (0.8%)	2.08 (0.69-6.25)	0.19
Adrenergic agent	706 (78%)	902 (31%)	11.25 (8.86-14.28)	<0.001
Mechanical ventilation	290 (32%)	840 (29%)	0.30 (0.24-0.38)	<0.001

94 ¹The effect of SFT on each clinical management were estimated by using the multivariable logistic regression
 95 models adjusted for admission year, gender, age, comorbidities, modified SOFA score, transfer from other hospital,
 96 blood culture positive for pathogenic organisms, and direct admission to the ICU.

97 **Supplementary Table 5 | Baseline characteristics of sepsis patients included in the Sepsis Fast**
 98 **Track (SFT) programme or standard of care (control) after the implementation of SFT**
 99 **programme. Values are number (percentages) unless stated otherwise**

Characteristics	SFT group ² (n=903)	Non-exposed group ³ (n=1267)	P value
Male gender	526 (58%)	720 (57%)	0.54
Age (years) (median [IQR])	63 (49-74)	59 (41-73)	<0.001
Age group (years) (n [%])			
18-40	100 (11%)	293 (23%)	<0.001
>40-60	277 (31%)	350 (28%)	
>60-70	214 (24%)	230 (18%)	
>70	312 (35%)	394 (31%)	
Comorbidities	486 (54%)	666 (53%)	0.56
Hypertension	239 (26%)	349 (28%)	0.58
Diabetes mellitus	213 (24%)	286 (23%)	0.58
Chronic kidney disease	129 (14%)	197 (16%)	0.42
Dyslipidemia	66 (7%)	80 (6%)	0.36
Heart disease	48 (5%)	98 (8%)	0.03
Lung disease	67 (7%)	126 (10%)	0.04
Liver disease	33 (4%)	46 (4%)	0.98
Cerebrovascular disease	29 (3%)	25 (2%)	0.07
Malignancy	13 (1%)	33 (3%)	0.06
Human immunodeficiency virus (HIV)	6 (1%)	9 (1%)	0.90
Organ dysfunction⁴			
Total modified SOFA score (median [IQR])	6 (4-9)	4 (3-6)	<0.001
Renal dysfunction ⁴	706 (78%)	743 (59%)	<0.001
Cardiovascular dysfunction ⁴	811 (90%)	546 (43%)	<0.001
Coagulation dysfunction ⁴	419 (46%)	650 (51%)	0.03
Liver dysfunction ⁴	311 (34%)	318 (25%)	<0.001
Respiratory dysfunction ⁴	337 (37%)	400 (32%)	0.01
Central nervous system dysfunction ⁴	166 (18%)	217 (17%)	0.61
Transferred from other hospitals	878 (97%)	1041 (82%)	<0.001
Duration of symptoms (median [IQR])	2 (1-3)	3 (1-5)	<0.001
≤ 2 days	505 (56%)	537 (42%)	<0.001
3-7 days	362 (40%)	650 (51%)	
> 7 days	36 (4%)	80 (6%)	
Presenting clinical syndromes⁵ (n [%])			
Septic shock	687 (76%)	179 (14%)	<0.001

Characteristics	SFT group ² (n=903)	Non-exposed group ³ (n=1267)	P value
Acute febrile illness	206 (23%)	485 (38%)	<0.001
Lower respiratory infection	223 (25%)	457 (36%)	<0.001
Sepsis	225 (25%)	137 (11%)	<0.001
Others	13 (1%)	168 (13%)	<0.001
Diarrheal illness	150 (17%)	105 (8%)	<0.001
Admitted directly to an ICU upon admission	170 (19%)	39 (3%)	<0.001
Blood culture positive for pathogenic organisms	175 (19%)	160 (13%)	<0.001
Year			
2015	356 (39%)	659 (52%)	<0.001
2016	535 (59%)	592 (47%)	
2017	12 (1%)	16 (1%)	

¹Organ dysfunction is defined by modified SOFA ≥ 2

²Sepsis patients who were identified and treated in Sepsis-FT system in 2015 – January 2017.

³Sepsis patients whom were not in Sepsis-FT system.

⁴Organ dysfunction defined as modified SOFA score was ≥ 1 for each organ system.

⁵Patients may have more than one presenting clinical syndrome.

105 **Supplementary Table 6 | Factors associated with 28-day mortality using multivariable Cox**
 106 **proportional hazards model in 2,170 patients enrolled into the study after the**
 107 **implementation of the Sepsis Fast Track (SFT) programme**

Variables	Died (n=431)	Survived (n=1739)	Adjusted hazard ratio (95%CI)	P value
SFT group	205(48%)	698(40%)	0.68 (0.55- 0.84)	<0.001
Male gender	254(59%)	992(57%)	0.89 (0.73- 1.09)	0.26
Age group (years) (n [%])				
• 18-40	30(7%)	363(21%)	1	<0.001
• >40-60	125(29%)	502(29%)	1.97 (1.31- 2.95)	
• >60-70	85(20%)	359(21%)	1.97 (1.28- 3.03)	
• >70	191(44%)	515(30%)	3.33 (2.24- 4.95)	
Transferred from other hospital	406(94%)	1513(87%)	1.49 (0.99- 2.26)	0.06
Modified SOFA score (median, IQR)	7 (5-10)	4 (3-6)	1.24 (1.21- 1.28)	<0.001
Comorbidities				
• Diabetes mellitus	122(28%)	377(22%)	1.08 (0.87- 1.35)	0.49
• Chronic kidney disease	84(19%)	242(14%)	1.23 (0.96- 1.58)	0.11
• Liver disease	22(5%)	57(3%)	1.10 (0.71- 1.70)	0.68
• Malignancy	19(4%)	27(2%)	2.90 (1.81- 4.63)	<0.001
Blood culture positive for pathogenic organisms	110(26%)	225(13%)	1.64 (1.31- 2.05)	<0.001
Year				
• 2015	207(48%)	808(46%)	1	0.08
• 2016	224(52%)	931(54%)	0.84 (0.69- 1.02)	
Direct admission to the ICU	85(20%)	124(7%)	1.78 (1.37- 2.32)	<0.001

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110 **Supplementary Figure 1 | Preprinted recommended doctor orders for sepsis fast track**
 111 **programme used at the Emergency Department at Sunpasitthiprasong Hopsital from 1**
 112 **January 2015**

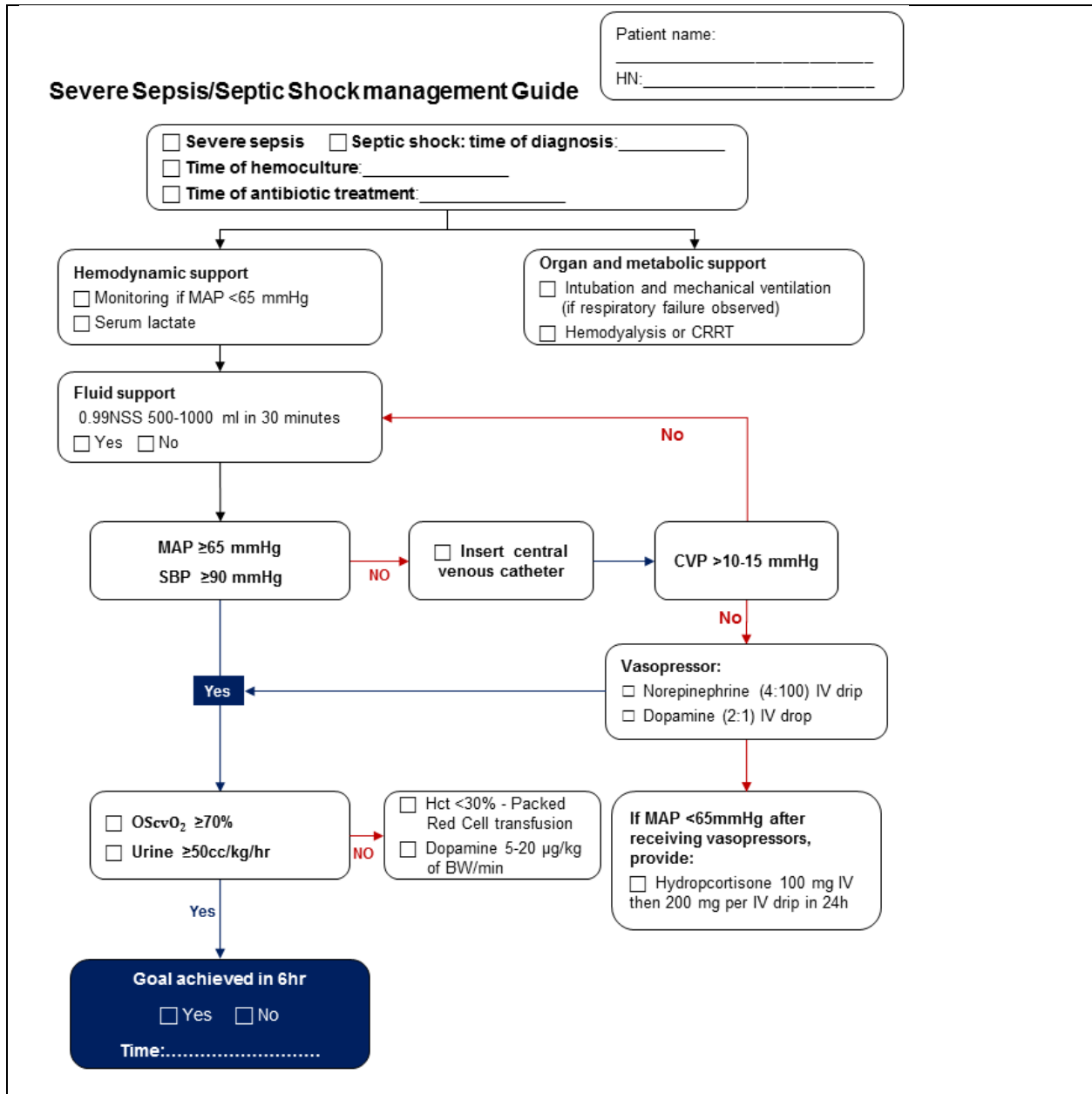
SAPPASITTIPRASONG HOSPITAL ๖๗.6/3

DOCTOR'S ORDER SHEET (Rev. 2: พ.ศ. 48)

FFM	PROGRESS NOTE	Date Time	ORDER FOR ONE DAY	Date Time	CONTINUOUS ORDER	Date of Sign
HN..... ชื่อ-สกุล..... หมู่บ้าน.....	ER NON TRAUMA Time onset Date Time Onset Date Time E V M BP / HR T C		Dx. <input type="checkbox"/> Sepsis <input type="checkbox"/> Severe Sepsis <input type="checkbox"/> Septic Shock - Consult ICU Admit..... - CxR - EKG..... - DTX. Stat..... - Serum lactate - CBC, PT, PTT, U/A - BUN, Cr., E'lyte - Liver Function Test,alb - HC x II stat at ER.....M. - HC x II at รพพ.....M. - V/S q 1 hr. x II then as usual - on O2 canular 3 LPM if O2 sat < 95 % - Retained Foley's cath - NSS1,000 ml IV load.....in 10 min then IV drip ml/hr (30ml/kg)		- NPO - Record V/S, N/S, I/O Medication ชัก Hx เพื่อยา <input type="checkbox"/> ไม่มี <input type="checkbox"/> มี..... ตรวจสอบ Hx เพื่อยา ในHOMC <input type="checkbox"/> ไม่มี <input type="checkbox"/> มี.....	
	Source of infection <input type="checkbox"/> Respiratory <input type="checkbox"/> GI <input type="checkbox"/> Skin, soft tissue <input type="checkbox"/> CNS <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Others..... Systemic infection <input type="checkbox"/> Leptospirosis <input type="checkbox"/> Malaria <input type="checkbox"/> Rickettsia <input type="checkbox"/> Denque พ้อง IV bolus.....ml BP / HR IVF รพพ.....ml IVF at ER.....ml		- Levophed..... IV drip ml/hr - Dopamine..... IV drip ml/hr <input type="checkbox"/> Ceftriaxone 2 gm IV statM. <input type="checkbox"/> Cefazidime 2 gm IV statM. <input type="checkbox"/> Cloxacilin 2 gm IV statM. <input type="checkbox"/> Metronidazole 500 mg IV statM. <input type="checkbox"/> Gentamicin 240 mg IV statM. - Notify แพทย์เวร นพ. ชัยพร			

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114 **Supplementary Figure 2 | The Sepsis Fast Track sepsis resuscitation workflow used at the**
 115 **Emergency Department at Sunpasitthiprasong Hopsital from 1 March 2016**



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STROBE Statement

Checklist of items that should be included in reports of observational studies

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Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	8-9
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Data sources/measurement	8*	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Bias	9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Study size	10	Describe any efforts to address potential sources of bias	11-12
Quantitative variables	11	Explain how the study size was arrived at	10
Statistical methods	12	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-12
		(a) Describe all statistical methods, including those used to control for confounding	11-12
		(b) Describe any methods used to examine subgroups and interactions	11-12
		(c) Explain how missing data were addressed	8
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	6
<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed			
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	12
		(e) Describe any sensitivity analyses	12

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-14
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	15-16
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-16
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17-19
Discussion			
Key results	18	Summarise key results with reference to study objectives	19-21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Effectiveness of a sepsis programme in a resource-limited setting: a retrospective analysis of data of a prospective observational study (Ubon-sepsis)

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Infectious diseases, Epidemiology
Keywords:	Epidemiology < INFECTIOUS DISEASES, INFECTIOUS DISEASES, INTENSIVE & CRITICAL CARE

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3 **1 Effectiveness of a sepsis programme in a resource-limited setting: a retrospective analysis of**
4 **2 data of a prospective observational study (Ubon-sepsis)**
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23

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3 34 **Abstract**
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5 35 **Objective:** To evaluate the effectiveness of a Sepsis Fast Track (SFT) programme initiated at a
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7 regional referral hospital in Thailand in January 2015
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10 37 **Design:** A retrospective analysis using the data of a prospective observational study (Ubon-sepsis)
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12 38 from March 2013 to January 2017
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14 39 **Setting:** General medical wards and medical intensive care units (ICUs) of a study hospital
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16 40 **Participants:** Patients with community-acquired sepsis observed under the Ubon-sepsis cohort.
17
18 Sepsis was defined as modified Sequential Organ Failure Assessment (SOFA) score ≥ 2 .
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20

21 42 **Main exposure:** The SFT programme was a protocol to identify and initiate sepsis care on hospital
22
23 admission, implemented at the study hospital in 2015. Patients in the SFT programme were
24
25 admitted directly to the ICUs when available. The non-exposed group comprised of patients who
26
27 received standard of care.
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30 46 **Main outcome:** The primary outcome was 28-day mortality. The secondary outcomes were
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32 measured sepsis management interventions.
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35 48 **Results:** Of 3,806 sepsis patients, 903 (24%) were detected and enrolled in the SFT programme
36
37 of the study hospital (SFT group) and 2,903 received standard of care (non-exposed group).
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39 Patients in the SFT group had more organ dysfunction, were more likely to receive measured sepsis
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41 management and to be admitted directly to the ICU (19% vs. 4%). Patients in the SFT group were
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43 more likely to survive (adjusted hazard ratio 0.72; 95% CI 0.58 to 0.88, $p=0.001$) adjusted for
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45 admission year, gender, age, comorbidities, modified SOFA score and direct admission to the
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49 54 ICUs.
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3 55 **Conclusions:** The SFT programme is associated with improved sepsis care and lower risk of death
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5 56 in sepsis patients in rural Thailand, where some critical care resources are limited. The survival
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7 57 benefit is observed even when all patients enrolled in the programme could not be admitted directly
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9 58 into the ICUs.

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12 59 **Study registration number:** NCT02217592
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18 61 **Strengths and limitations of this study**

- 20 62 • The study hospital utilized the published framework, SCAN-TEACH-TREAT programme
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22 63 to develop a context specific quality of care improvement for sepsis in a tropical resource-
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24 64 limited setting.
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27 65 • The study took advantage of a robust prospective observational study design that
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29 66 strengthened causal inference by providing pre-intervention information, having an
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31 67 appropriate control group from both pre and post-intervention periods, and controlling
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33 68 important confounding factors (i.e. the modified SOFA score).
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36 69 • We found that most measured sepsis interventions increased.
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39 70 • The study did not record dosage of dobutamine, dopamine, epinephrine and
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41 71 norepinephrine, arterial blood gases were rarely performed, and the modified SOFA score
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43 72 (maximum 23) may be lower than the SOFA score (maximum 24).
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46 73 • The observational study may have residual confounding factors such as improvement of
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48 74 care and profile of organ failure recognition overtimes.
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75 INTRODUCTION

76 Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to
77 infection,¹ and is the primary cause of death from infection, especially if not recognized and treated
78 promptly.²⁻⁴ Sepsis is a major cause of health loss worldwide and is associated with approximately
79 eleven million deaths each year, most of which occur in low and middle-income countries
80 (LMICs).⁵ The United Nations World Health Assembly has recognized sepsis as a global health
81 priority and adopted a resolution on improving its worldwide prevention, diagnosis and
82 management.⁶ Comprehensive guidelines such as those developed by the Surviving Sepsis
83 Campaign have been associated with reduced mortality in high-income countries,²⁻⁴ but
84 effectiveness of these guidelines in LMICs needs more evaluation.⁷⁻¹⁰

86 Following the Surviving Sepsis Campaign (SSC) 2012,¹¹ the Ministry of Public Health Thailand
87 and the Thai Society of Critical Care Medicine developed local recommendations on sepsis based
88 on resource availability and local context.¹² The recommendations suggest that secondary-care and
89 tertiary-care hospitals in the country should develop a Sepsis Fast Track (SFT) so that, on
90 presentation, sepsis patients can be identified, treated and directly admitted to the ICUs when
91 available. One small retrospective study showed lower mortality among sepsis patients enrolled
92 than those not enrolled in the SFT (21% vs. 43%) at the study hospital,¹³ while another study did
93 not find an association between SFT and mortality outcome.¹⁴ These studies were subject to
94 selection biases due to their retrospective nature.¹³⁻¹⁴ Interventional studies to randomize patients
95 to receive or not receive the SFT, however, would be unethical and impractical after the national
96 recommendations have been implemented. It is increasingly recommended to evaluate the impact

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3 97 of healthcare interventions using routine data, particularly when a wide range of routinely collected
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5 98 data is available.¹⁵
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10 100 Here, we analysed data from our prospective observational study of community-acquired sepsis
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12 101 patients presenting to a referral hospital in Thailand over four years (from March 2013 to January
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14 102 2017)¹⁶⁻¹⁷ to retrospectively evaluate the effectiveness of a SFT programme which was
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17 103 implemented at the study hospital in January 2015.
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21 22 105 **MATERIAL AND METHODS**

23 24 106 **Study design**

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27 107 We conducted a retrospective study to evaluate the effectiveness of the SFT programme by using
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29 108 the data of a prospective observational study (Ubon-sepsis).¹⁶⁻¹⁷ The SFT programme was
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31 109 implemented at the study hospital in January 2015 until now as per national recommendations.¹²
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33 110 The SFT programme at the study hospital included (1) diagnostic criteria for attending physicians
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35 111 and medical teams to systematically identify sepsis patients on hospital admission (Supplementary
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37 112 Table 1), (2) a recommended sepsis care protocol and (3) direct admission to the ICUs when
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39 113 available. The SFT programme at the study hospital was generated by the SFT committee of the
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41 114 study hospital (S.B., S.S., C.B., P.P., B.S., O.W., P.C. and P.T.) based on SSC 2012,¹¹ resource
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43 115 availability and local context.¹² The study hospital is a referral hospital to smaller district hospitals
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45 116 and provincial hospitals in three adjacent provinces. The referring hospitals were not involved in
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47 117 the SFT programme of the study hospital during the study period.
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3 119 Details of the Ubon-sepsis cohort have been published elsewhere.¹⁶⁻¹⁷ In short, the Ubon-sepsis
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5 120 research team, who were not attending physicians or medical teams at the study hospital,
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8 121 conducted a prospective observational study of community-acquired infections and sepsis from
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10 122 March 2013 to January 2017.¹⁶⁻¹⁷ The research team prospectively enrolled adult patients ≥ 18
11
12 123 years old who were admitted to the general medical wards and medical intensive care units (ICUs)
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14 124 with a primary diagnosis of infection made by the attending physician, were within 24 hours of
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16 125 admission to the study hospital, and had three of 20 systemic manifestations of infection
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18 126 documented in the medical records (Supplementary Table 2). The 20 systemic manifestations of
19
20 127 the infections were consolidated from the 22 variables proposed as diagnostic criteria for sepsis
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22 128 for SSC 2012.¹¹ The study team sequentially screened all medical patients by reviewing admission
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24 129 logs in the emergency department (ED), medical wards, and medical ICUs twice daily (morning
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26 130 and afternoon) on each working day. The Ubon-sepsis cohort was initiated in 2012 prior to the
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28 131 implementation of SFT at the study hospital. The research team was not involved in any clinical
29
30 132 interventions; enrollment in the SFT programme and all medical treatment was performed by
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32 133 attending physicians and medical teams. The research team did not adjust the study protocol,
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34 134 inclusion criteria and exclusion criteria of the Ubon-sepsis cohort during the entire study period,
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36 135 and the research team recorded whether participants in the Ubon-sepsis cohort were enrolled in
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38 136 the SFT programme.
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47 138 The reporting of this study follows the STROBE guidelines. Written, informed permission was
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49 139 obtained from participants prior to enrollment in the Ubon-sepsis cohort.
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141 **Participants**

142 For this study, we evaluated patients who were included into the Ubon-sepsis cohort and had
143 community-acquired sepsis. Sepsis was defined as an infection with organ dysfunction in
144 accordance with the 2016 international Consensus (Sepsis-3) guidelines for sepsis.¹ Organ
145 dysfunction was determined by a modified sequential (sepsis-based) organ failure assessment
146 (SOFA) score ≥ 2 as previously described.¹⁶⁻¹⁷ The study was conducted in 2013 prior to the Sepsis-
147 3 definition, and inotropic and vasopressor agent doses were not recorded into the CRF.^{1, 18} For
148 the cardiovascular component of the SOFA score, the scoring was modified such that subjects
149 were scored a maximum of 2 (on a 4-point scale) if they received only dobutamine or dopamine,
150 and scored a maximum of 3 if they received epinephrine or norepinephrine. For the respiratory
151 component of the SOFA score, as PaO₂/FiO₂ indices were not available for the majority of
152 subjects due to infrequency of arterial blood gas tests, the score was modified as follows: Subjects
153 were scored a maximum of 2 (4-point scale) if they received advanced respiratory support
154 (endotracheal tube, gas powered or electrical powered mechanical ventilation) and arterial blood
155 gas test was not performed.¹⁶⁻¹⁷ The Ubon-sepsis cohort excluded patients who were suspected of
156 having hospital-acquired infections (determined by the attending physician), hospitalized within
157 30 days prior to the current admission, or hospitalized at any facility for a total duration longer
158 than 72 hours prior to enrollment.

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160 **Main exposure**

161 Main exposure of the study was the SFT programme. All patients included in the Ubon-sepsis
162 cohort from March 2013 to December 2014 who received standard care were considered as the

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3 163 non-exposed group. Patients included in the Ubon-sepsis cohort from January 2015 to January
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5 164 2017 who received standard care or received care in the SFT programme by attending medical
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8 165 teams using their criteria on admission (Supplementary Table 1) were considered as the additional
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10 166 non-exposed group or as the SFT group, respectively. The Ubon-sepsis research team were not
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12 167 involved in decision-making regarding enrollment to the SFT programme.
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17 169 Patients in the non-exposed group received standard care according to local guidelines. Patients in
18
19 170 the SFT group received the standard of care along with a recommended sepsis care protocol of the
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21 171 SFT programme. First, preprinted recommended doctor orders for the SFT programme were used
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23 172 as of January 2015 (Supplementary Figure 1). The recommended orders included oxygen
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25 173 administration, intravenous fluid loading and fluid administration to achieve the recommended
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27 174 target of 30 mL/kg crystalloid, blood culture, recommended stat (immediate) doses and choices of
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29 175 parenteral antibiotics including ceftriaxone, ceftazidime, cloxacillin, metronidazole and
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31 176 gentamycin, contact ICU for ICU admission (if available), oxygen supplementation, close
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33 177 monitoring of vital signs and urine output, and a set of diagnostic tests including chest radiography,
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35 178 electrocardiogram, rapid blood glucose test, serum lactate, complete blood count, blood urea
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37 179 nitrogen, creatinine, electrolytes, liver function tests, albumin level, prothrombin time and partial
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39 180 thromboplastin time. Second, as of March 2016, the resuscitation workflow to normalize and
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41 181 maintain a mean arterial pressure (MAP) ≥ 65 mmHg, systolic blood pressure (SBP) ≥ 90 mmHg
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43 182 and urine output ≥ 0.5 mL/kg/hr within the first six hours was formally implemented and
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45 183 recommended (Supplementary Figure 2). The resuscitation workflow included fluid resuscitation,
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47 184 measurement of central venous pressure (CVP) and central venous oxygen saturation (SCVO₂),
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3 185 administration of adrenergic agents, blood transfusion for haematocrit <30% and hydrocortisone
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5 186 if adequate fluid resuscitation and vasopressor therapy could not restore hemodynamic stability.
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8 187 The resuscitation workflow was pre-printed and included in the clinical chart of every SFT patient
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10 188 (together with pre-printed doctor's orders), and was recommended even if patients could not be
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12 189 admitted directly to the ICU. A separate set of documents, recommended management and
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14 190 recommended frequency of vital signs monitoring for nurses (i.e. nurse notes for SFT patients)
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16 191 were also used for every SFT patient. Preparation and regular meetings to implement and monitor
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19 192 the SFT programme were organized by the SFT committee of Sunpasitthiprasong Hospital.
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23 24 194 **Outcome measures**

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26 195 The primary outcome measure was 28-day mortality as recorded in the Ubon-sepsis cohort.¹⁶ 28-
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28 196 day mortality data were collected via telephone contact if subjects were no longer hospitalized and
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30 197 had been discharged alive.¹⁶ The secondary outcome measures were sepsis management
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33 198 interventions; including antibiotics administration, blood cultures, mechanical ventilation,
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35 199 adrenergic agents, acute haemodialysis and placement of a urinary catheter within the first day of
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37 200 hospitalization.¹⁶⁻¹⁷
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42 202 **Sample size**
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44 203 The sample size of the study was determined by the sample size of Ubon-sepsis cohort. We
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46 204 assumed that about 50% of 3,806 sepsis patients in the Ubon-sepsis cohort were enrolled after the
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48 205 implementation of the SFT programme, of which 50% were enrolled in the SFT programme (i.e.
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50 206 952 and 2,854 patients were estimated to be the SFT and non-exposed group, respectively). We
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3 207 assumed that the mortality of the non-exposed group was 21% based on published data.¹⁶⁻¹⁷ Our
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5 208 current sample size of 3,806 would provide a power of 80% at an alpha error of 5% to detect a 4%
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7 209 difference in the mortality outcome.
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11 211 **Statistical analysis**

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14 212 All sepsis patients were included in the analysis regardless of whether they were enrolled before
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17 213 or after the implementation of the SFT programme. We used the Chi-square test and Mann-
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19 214 Whitney test to compare the proportions of binary variables and median of continuous variables
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21 215 between groups, respectively. The interquartile range is presented as 25th and 75th percentiles.
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26 217 In the primary analysis, we used multivariable Cox proportional hazard models to evaluate the
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28 218 effectiveness of SFT programme on 28-day mortality. The multivariable Cox proportional hazard
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30 219 model was used to adjust the difference between those receiving the SFT programme and the
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33 220 others.¹⁹ To reduce bias in the model development, we used the previous multivariable Cox
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35 221 proportional hazard model as the base model,¹⁶ added the SFT group variable and direct admission
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37 222 to the ICU, and modified by adding a time variable to represent possible changes over time and by
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39 223 using continuous modified SOFA score on admission rather than as a binary variable (modified
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41 224 SOFA score ≥ 2). Twenty eight patients enrolled in early 2017 were considered as enrolled in
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44 225 2016. The continuous modified SOFA score was used to improve regression adjustment for disease
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46 226 severity of the model. The other variables included in the model were gender, age group, transfer
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48 227 from other hospital, comorbidities (diabetes mellitus, chronic kidney disease, liver disease and
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50 228 malignancy) and blood culture positive for pathogenic organisms. We calculated the unadjusted
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3 229 and adjusted probability of survival at each timepoint using the Kaplan-Meier method (using the
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5 230 sts graph and stcurve command in STATA, respectively)
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10 232 Using a conceptual framework, we also consider that admission directly to the ICU could also be
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12 233 a mediator between the SFT and the primary outcome; therefore, we developed another
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14 234 multivariable model not including the variable for direct admission to the ICU. The goodness of
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16 235 fit for the multivariable Cox proportional hazard model was tested with a Hosmer and Lemeshow
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18 236 test. For the Cox proportional hazard model, we assessed whether the hazard ratio was constant
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20 237 over time using Schoenfeld residuals.
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26 239 For the secondary endpoints, we used multivariable logistic regression models with similar
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28 240 independent variables as the model for 28-mortality outcome and used each sepsis management
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30 241 process as an outcome. We estimated the total effect of the SFT on each sepsis management by
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32 242 using the multivariable logistic regression models adjusted for difference in characteristics and
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34 243 disease severity of the patients. This was because each sepsis management could be caused by
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36 244 characteristics of the patients, disease severity and the SFT.²⁰
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42 246 We also performed sensitivity analyses by using multivariable logistic regression model, excluding
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44 247 patients enrolled prior to the implementation of the SFT programme, and by replacing direct
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46 248 admission to the ICUs with admission to the ICUs within the first hospital day. All analyses were
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48 249 performed with STATA 15.1 (StataCorp, College Station, TX, USA).
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251 **Patient and public involvement**

252 No patients were involved in setting the research question or the outcome measures, nor were they
253 involved in developing plans for recruitment, design, or implementation of the study. No patients
254 were asked to advice on interpretation or writing the results. The results will be disseminated to
255 the public through online social media.

256

257 **RESULTS**

258 **Baseline characteristics**

259 The observational cohort study (Ubon-sepsis) included 5,001 patients presenting with community-
260 acquired infections from March 2013 to January 2017, and 12 patients were excluded due to
261 unknown 28-day mortality outcome. 3,806 (76%) met criteria for sepsis within the first 24 hours
262 of admission with a modified SOFA score ≥ 2 , and were included for the analysis. Figure 1 shows
263 the flow of participants through the study. Among 3,806 sepsis patients, 903 were enrolled in the
264 SFT programme and considered as the SFT group, and 2,903 were not enrolled in the SFT
265 programme, received standard of care, and considered as the non-exposed group. Of 2,903 sepsis
266 patients in the non-exposed group, 1,636 were included in the observational cohort study prior to
267 the implementation of SFT programme and 1,267 were after the implementation of the programme.

268

269 Table 1 shows the characteristics of the study patients. Patients in the SFT group were older and
270 more likely to have underlying diseases of diabetes mellitus, cerebrovascular diseases and
271 dyslipidemia. Patients included in the SFT group had higher severity of organ dysfunction
272 determined by the modified SOFA score compared with the non-exposed group (median 6 [IQR

273 4-9] vs. 4 [IQR 3-6], $p<0.001$). A higher proportion of patients in the SFT group were admitted
 274 directly to the ICU compared with the non-exposed group (19% vs 5%, $p<0.001$).

275
 276 **Table 1 | Baseline characteristics of sepsis patients enrolled in the Sepsis Fast Track**
 277 **programme¹ (SFT group) or standard of care (non-exposed group). Values are number**
 278 **(percentages) unless stated otherwise**

Characteristics	SFT group ² (n=903)	Non-exposed group ³ (n=2903)
Male gender	526 (58%)	1653 (57%)
Age (years) (median [IQR])	63 (49-74)	56 (39-70)
Age group (years)		
18-40	100 (11%)	647 (22%)
>40-60	277 (31%)	875 (30%)
>60-70	214 (24%)	513 (18%)
>70	312 (35%)	868 (30%)
Comorbidities		
Hypertension	239 (26%)	726 (25%)
Diabetes mellitus	213 (24%)	594 (20%)
Chronic kidney disease	129 (14%)	391 (13%)
Dyslipidemia	66 (7%)	152 (5%)
Heart disease	48 (5%)	183 (6%)
Lung disease	67 (7%)	239 (8%)
Liver disease	33 (4%)	91 (3%)
Cerebrovascular disease	29 (3%)	55 (2%)
Malignancy	13 (1%)	47 (2%)
Human immunodeficiency virus (HIV)	6 (1%)	33 (1%)
Organ dysfunction		
Modified SOFA score (median [IQR])	6 (4-9)	4 (3-6)
Renal dysfunction ⁴	706 (78%)	1846 (64%)
Cardiovascular dysfunction ⁴	811 (90%)	1532 (53%)
Coagulation dysfunction ⁴	419 (46%)	1562 (54%)
Liver dysfunction ⁴	311 (34%)	822 (28%)
Respiratory dysfunction ⁴	337 (37%)	853 (29%)
Central nervous system dysfunction ⁴	166 (18%)	530 (18%)

Characteristics	SFT group ² (n=903)	Non-exposed group ³ (n=2903)
Transferred from other hospitals	874 (97%)	2372 (84%)
Duration of symptoms (median [IQR])	2 (1-3)	3 (1-5)
≤ 2 days	505 (56%)	1191 (41%)
3-7 days	362 (40%)	1488 (51%)
> 7 days	36 (4%)	224 (8%)
Presenting clinical syndromes⁵		
Septic shock	687 (76%)	733 (25%)
Acute febrile illness	206 (23%)	940 (32%)
Lower respiratory infection	223 (25%)	890 (31%)
Sepsis	225 (25%)	273 (9%)
Others	13 (1%)	456 (16%)
Diarrheal illness	150 (17%)	264 (9%)
Direct admission to the ICU	170 (19%)	128 (4%)
Admission to the ICU within 24 hours of admission	270 (29%)	370 (13%)
Blood culture positive for pathogenic organisms	175 (19%)	347 (12%)
Year		
2013	N/A	1047 (26%)
2014	N/A	1156 (29%)
2015	369 (39%)	956 (24%)
2016	556 (59%)	869 (21%)
2017	14 (1%)	22 (1%)

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280 ¹ SFT programme was implemented at the study hospital in January 2015.

281 ² 903 patients of the Ubon-sepsis cohort were enrolled in SFT programme after the implementation of the SFT
282 programme (Figure 1)

283 ³ Included 1,636 and 1,267 patients in the Ubon-sepsis cohort before and after the implementation of the SFT
284 programme, respectively.

285 ⁴ Organ dysfunction defined as modified SOFA score was ≥ 1 for each organ system.¹⁶

286 ⁵ Patients may have more than one presenting clinical syndrome.

287

288 **Primary outcomes**

289 The primary outcome, mortality within 28 days, occurred in 205 of 903 (23%) in the SFT group
290 and 574 of 2,903 (20%) in the non-exposed group (Figure 2A). In the primary analysis, patients in
291 the SFT group were more likely to survive adjusted for baseline characteristics, severity of sepsis
292 and direct admission to the ICUs (adjusted hazard ratio [aHR] 0.72, 95% CI 0.58-0.88, $p=0.001$,
293 Figure 2B and Supplementary Table 3). Older age, higher modified SOFA score, underlying
294 disease of malignancy and chronic kidney disease, blood culture positive for pathogenic organisms
295 and direct admission to the ICUs were associated with risk of mortality.

297 **Sensitivity Analyses**

298 As we considered that direct admission to the ICU could be a mediator between the SFT and the
299 outcome, a sensitivity analysis was performed by excluding the variable direct admission to the
300 ICU (Supplementary Table 4). The effect of SFT (aHR 0.77, 95% CI 0.63-0.94, $p<0.001$) was also
301 observed. We observed that constant proportional hazard assumption was not strongly hold in one
302 variable (the modified SOFA score); therefore, additional sensitivity analyses were performed by
303 using logistic multivariable models. The similar effect of SFT was observed (Supplementary Table
304 5 and 6).

306 We also performed a sensitivity analysis by excluding the 1,636 patients enrolled in the
307 observational study prior to the implementation of SFT programme. Similar differences in baseline
308 characteristics were observed when comparing 903 patients in the SFT group to the 1,267 patients
309 in the non-exposed group enrolled after the implementation of the SFT programme

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3 310 (Supplementary Table 7). A higher chance of survival in the SFT group compared to the non-
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5 311 exposed group was also observed (aHR 0.68, 95% CI 0.55 to 0.84, $p < 0.001$; Supplementary Table
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7 312 7). We also performed another sensitivity analysis by replacing direct admission to the ICUs with
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9 313 admission to the ICUs within the first hospital day. Of 3,806 patients, 640 (17%) were admitted to
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11 314 the ICUs within the first day of admission. A higher chance of survival in the SFT group compared
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13 315 to the non-exposed group was also observed (aHR 0.72, 95% CI 0.59 to 0.88, $p = 0.002$).
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19 317 **Secondary outcomes**

21 318 Using multivariable logistic regression models, we found that patients in the SFT group were more
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23 319 likely to receive most sepsis management interventions than patients in the non-exposed group
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25 320 adjusting for baseline characteristics, severity of sepsis and direct admission to the ICU (Table 2).
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27 321 Those included antibiotics, blood cultures, adrenergic agents, and placement of a urinary catheter
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29 322 within the first day of hospitalization. However, sepsis patients in the SFT group were less likely
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31 323 to receive mechanical ventilation compared with those in the non-exposed group adjusting for
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33 324 baseline characteristics, severity of sepsis and direct admission to the ICUs group (adjusted odds
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35 325 ratio [aOR] 0.30; 95% CI 0.24 to 0.38). We found that direct admission to the ICUs (aOR 5.77,
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37 326 95% CI 4.20 to 7.92) and transfer from other hospitals (aOR 3.45, 95% CI 2.42 to 4.91) were
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39 327 strongly associated with the requirement of mechanical ventilation.
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47 329 **Table 2 | Clinical management within the first day of hospital**

Clinical management ¹	SFT group (n=903)	Control group (n=2903)	Adjusted odds ratio (95% CI)	P value
Antibiotic	897 (99%)	2497 (86%)	14.69 (6.36-33.91)	<0.001
Blood culture	829 (92%)	2387 (82%)	1.82 (1.35-2.45)	<0.001
Urinary catheterization	862 (95%)	1642 (57%)	12.02 (8.41-17.20)	<0.001
Acute dialysis	10 (1.1%)	23 (0.8%)	1.96 (0.66-5.87)	0.23
Adrenergic agent	706 (78%)	902 (31%)	11.53 (9.10-14.61)	<0.001
Mechanical ventilation	290 (32%)	840 (29%)	0.39 (0.31-0.49)	<0.001
Direct admission to the ICU	170 (18.8%)	128 (4.4%)	4.34 (2.96-6.36)	<0.001

330 ¹The effect of SFT on each clinical management were estimated by using the multivariable logistic regression models
 331 adjusted for admission year, gender, age, comorbidities, modified SOFA score, transfer from other hospital, and blood
 332 culture positive for pathogenic organisms, and direct admission to the ICU.

335 DISCUSSION

336 In this study evaluating patients with community-acquired sepsis, enrollment into a programme to
 337 identify and initiate sepsis care implemented at the study hospital (SFT programme) was associated
 338 with 28% lower risk of mortality. In recent years, there has been an increasing need to understand
 339 benefit and cost effectiveness of implementation of sepsis care interventions in LMICs because of
 340 concerns that international sepsis guidelines¹¹ may not be extrapolated to patients with tropical
 341 infectious diseases⁷⁻⁹ and to resource-limited settings with poor ICU capacity.¹⁰ In this study we
 342 show the effectiveness of sepsis protocol modified based on resource availability in a tropical
 343 country, where causes of community-acquired sepsis include malaria and tropical viral diseases.^{16,}
 344 ²¹⁻²² Majority of sepsis patients in our study were managed on the general wards, including those
 345 with respiratory failure or shock. Nonetheless, our study shows that enhancing sepsis care in the

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3 346 emergency department and general medical wards, as well as improving access to ICUs can reduce
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5 347 sepsis mortality in a LMIC.
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10 349 The lower odds of receiving mechanical ventilation in the SFT group could be a sign of improved
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12 350 sepsis care. Patients in the SFT group are monitored closely either in or outside the ICUs, and the
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14 351 attending physicians aim to obviate the need for airway intubation when possible.⁷ Attending
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16 352 physicians may tend to provide mechanical ventilation to patients in the non-exposed group based
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19 353 on broad indications such as (1) airway protection, (2) hypercapnic respiratory failure, (3)
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21 354 hypoxemic respiratory failure or (4) circulatory failure²³⁻²⁴ because they may not be able to monitor
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24 355 patients' breathing and oxygen saturation as often as those enrolled in the SFT programme.
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28 357 It is not surprising that patients in the SFT group had more organ dysfunction than those in the
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31 358 non-exposed group. This is because the severity of organ dysfunction among patients with septic
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33 359 shock, respiratory failure and alteration of conscious can be assessed clinically on admission, and
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35 360 those patients could be enrolled in the SFT programme when the laboratory test results were not
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38 361 yet available. However, the non-exposed group were defined as having sepsis based on clinical
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40 362 findings and all laboratory test results within 24 hours of admission (per protocol of Ubon-sepsis
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42 363 cohort study¹⁶⁻¹⁷). Therefore, the non-exposed group could use laboratory test results (i.e. liver
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44 364 function tests, creatinine level, international normalised ratio and activated partial thromplastin
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47 365 time) from blood specimens drawn on admission. Therefore, the SFT programme were more likely
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49 366 to enroll patients with obvious signs of sepsis and septic shock; such as acute respiratory failure
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3 367 and hypotension, while Ubon-sepsis cohort could include sepsis patients with relatively lower
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5 368 modified SOFA scores.
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9 10 370 **Comparison with other studies**

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12 371 Our study is not the first to evaluate effectiveness of sepsis intervention in LMICs. Early
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14 372 recognition and protocol directed intervention improves outcomes of sepsis in adults²⁵⁻²⁷ and
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16 373 severe infection in children²⁸ in LMICs. The optimal method of fluid resuscitation in sepsis in
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18 374 tropical LMICs has not been determined.^{8, 25, 29-30} Our resuscitation protocol is a simple guideline,
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21 375 and the SFT recommend doctors to be careful and adjust fluid resuscitation based on preliminary
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23 376 diagnoses, underlying diseases and rapid diagnostic test results (i.e. if sepsis is caused by malaria
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25
26 377 or dengue infection). The implementation of the SFT programme in our study hospital and in
27
28 378 Thailand is consistent with the recommendation of “SCAN-TEACH-TREAT” programme
29
30 379 developed by Sepsis in Resource-Limited Settings Workgroup of the Surviving Sepsis Campaign.⁷
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32
33 380 The SFT programme evaluated resources in the setting (SCAN component), focused on
34
35 381 educational interventions on early recognition and management of sepsis among medical personnel
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37 382 including physicians, nurses and students (TEACH component) and implemented pragmatic and
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39 383 simple bundles into practice (TREAT component). In addition, the SFT programme has the strong
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42 384 support and endorsement of local health and governmental leaders.¹²
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46 47 386 **Strength and limitations of the study**

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49 387 This study features four strengths. First, the study hospital utilized the published framework,
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51 388 SCAN-TEACH-TREAT programme to develop a context specific quality of care improvement for
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3 389 sepsis,⁷ and we closely monitor and evaluate the effectiveness of an intervention. Second, the study
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5 390 took advantage of a robust prospective observational study design that strengthened causal
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8 391 inference by providing pre-intervention information, having an appropriate non-exposed group
9
10 392 from both pre and post-intervention periods, and controlling important confounding factors (i.e.
11
12 393 the modified SOFA score) which were measured systematically throughout the study period.
13
14 394 Third, this study incorporated several predictors of interest (measured sepsis management
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16 395 interventions and admission to the ICUs). This allows us to identify that the increase in most
17
18 396 measured sepsis interventions associated with the SFT programme and that led to the survival
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20 397 benefit among sepsis patients. Fourth, the focus on sepsis at a public tertiary-care hospital in
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22 398 Thailand helped us to estimate the effect of sepsis protocol in a tropical resource-limited setting
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24 399 with large sample size.
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31 401 Our study had several limitations. First, a modified SOFA score was used because the dosage of
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33 402 dobutamine, dopamine, epinephrine and norepinephrine were not recorded and arterial blood gases
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35 403 were rarely performed. The modified SOFA score (maximum 23) may be lower than the SOFA
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37 404 score (maximum 24). Nonetheless, the modified SOFA score is strongly associated with mortality
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39 405 in sepsis.¹⁶⁻¹⁷ Second, the proportional hazards assumption was met for all variables, including
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41 406 the main variable (the SFT), except one controlled variable (the modified SOFA score). The
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43 407 adjusted effect estimates could be under or overestimated due to residual confounding factors such
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45 408 as improvement of care and profile of organ failure recognition overtimes. Third, due to the use of
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47 409 observational data, the observed effects of the SFT on 28-day mortality in our study should be
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49 410 interpreted conservatively as an association rather than a causation.
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5 412 **Conclusions and future implications**
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8 413 Our study successfully demonstrated effectiveness of a sepsis programme implemented in a LMIC.
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10 414 Measuring effectiveness of a sepsis programme is a complex issue, and we utilized a data of a
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12 415 prospective observational study and carefully controlled for severity of sepsis and temporal trends
13
14 416 in our analyses. Care in sepsis patients improved after the implementation of the programme.
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16 417 Additional research is needed to better understand cost of the intervention, long-term benefits and
17
18 418 impact of the programme on a national scale. National strategies aimed at saving lives from sepsis
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20 419 in LMICs should be encouraged. Such strategies should include analysis of resources and local
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22 420 circumstances, followed by development, implementation and assessment of customized
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24 421 programmes.
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3 **430 Contributors:**
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5 431 NPJD, TEW, and DL obtained grant funding. SB, VH, PT, TEW, and DL contributed to study
6
7 432 conception development and study design. SB, VH, PT, TEW and DL contributed to study
8
9 433 conduct, data collection, and study administration. VH and DL performed the statistical analysis
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11 434 and interpreted the data and had full access to all of the data in the study. Both authors can take
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13 435 responsibility for the integrity of the data and the accuracy of the data analysis. DL is a guarantor.
14
15 436 SB, VH, PT, TEW, and DL wrote the first draft of a manuscript, with input from SS, CB, PC, KR,
16
17 437 and AD. PP, BS, OW, and RC provided scientific or administrative support. All authors
18
19 438 contributed to results interpretation, critically revised, and approved the final submitted
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21 439 manuscript. The corresponding author attests that all listed authors meet authorship criteria and
22
23 440 that no others meeting the criteria have been omitted.
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38
39 446 conduct of the study, all study procedures, data collection, data analyses, data interpretation,
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41 447 writing of the report, and the decision to submit the article for publication.
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47 **449 Competing interests:**
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49 450 The authors declare that they have no completing interests.
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3 452 **Ethics approvals:**
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5 453 The study was conducted the study in full compliance with the principles of good clinical practice
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7 454 (GCP), and the ethical principles of the Declaration of Helsinki. The study protocol and related
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9 455 documents were approved by Sunpasitthiprasong Hospital Ethics Committee (039/2556), the
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11 456 Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (MUTM2012-024-
12
13 457 01), the University of Washington Institutional Review Board (42988) and the Oxford Tropical
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15 458 Research Ethics Committee at the University of Oxford (OXTREC172-12). Signed or
16
17 459 fingerprinted informed consent was obtained from the participants or their representatives before
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19 460 enrollment.
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26 462 **Data sharing:**
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28 463 The final database with the data dictionary are publicly available online
29
30 464 <https://doi.org/10.6084/m9.figshare.12102627>.
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32

33 465 The lead authors (SB, VH and DL) affirm that the manuscript is an honest, accurate, and
34
35 466 transparent account of the study being reported; that no important aspects of the study have been
36
37 467 omitted; and that any discrepancies from the study as planned have been explained. This is an
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39 468 Open Access article distributed in accordance with the terms of the Creative Commons Attribution
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43 470 medium, provided the original work is properly cited. See:
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3 **473 Dissemination to participants and related patient and public communities:**
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5 474 The results of this study will be disseminated to physicians at the study hospital, health care
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7 475 providers, policy makers, and academic communities through various mediums, including printed
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9 476 report, internal hospital meetings, academic conferences, and institutional networks. The results
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11 477 from this study will be used to inform the current Sepsis Fast Track programme at
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13 478 Sunpasitthiprasong hospital and the community hospitals which are located in jurisdiction of the
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15 479 study hospital catchment areas in the Northeast Thailand. The study results will not be
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17 480 disseminated to patients or general population, because study results are in medical context.
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6 579 **Figure legends**

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9 580 **Figure 1| Flow of participants through study**

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11 581 **Footnote of figure 1:** This study used the data of an observational study on sepsis patients (Ubon-
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13 582 sepsis) from March 2013 to January 2017 to evaluate the effectiveness of a Sepsis Fast Track
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15 583 (SFT) programme implemented at the study hospital in January 2015
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20 585 **Figure 2| (A) Unadjusted probability of survival and (B) Adjusted probability of survival**
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22 586 **based on the multivariable Cox proportional hazard regression model**
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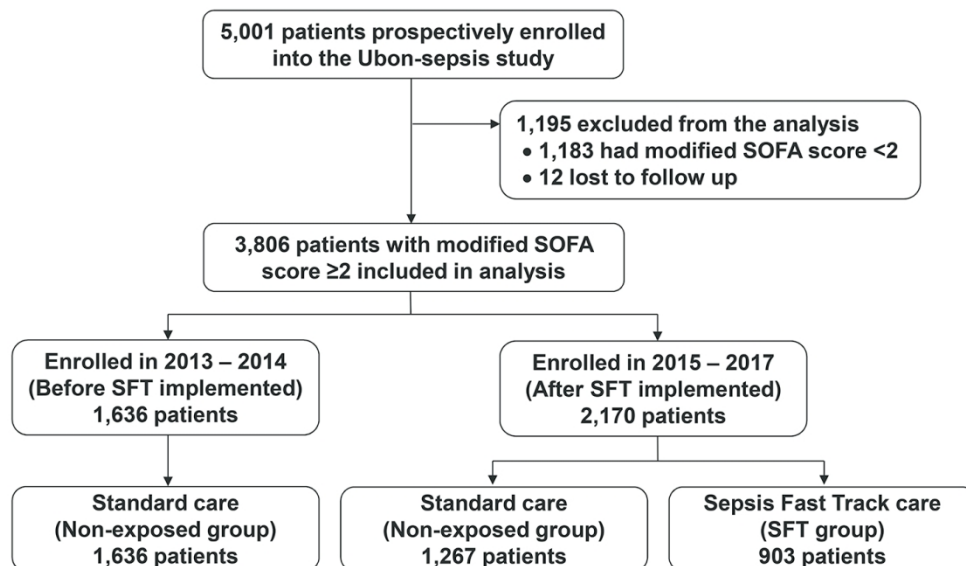


Figure 1 Flow of participants through study

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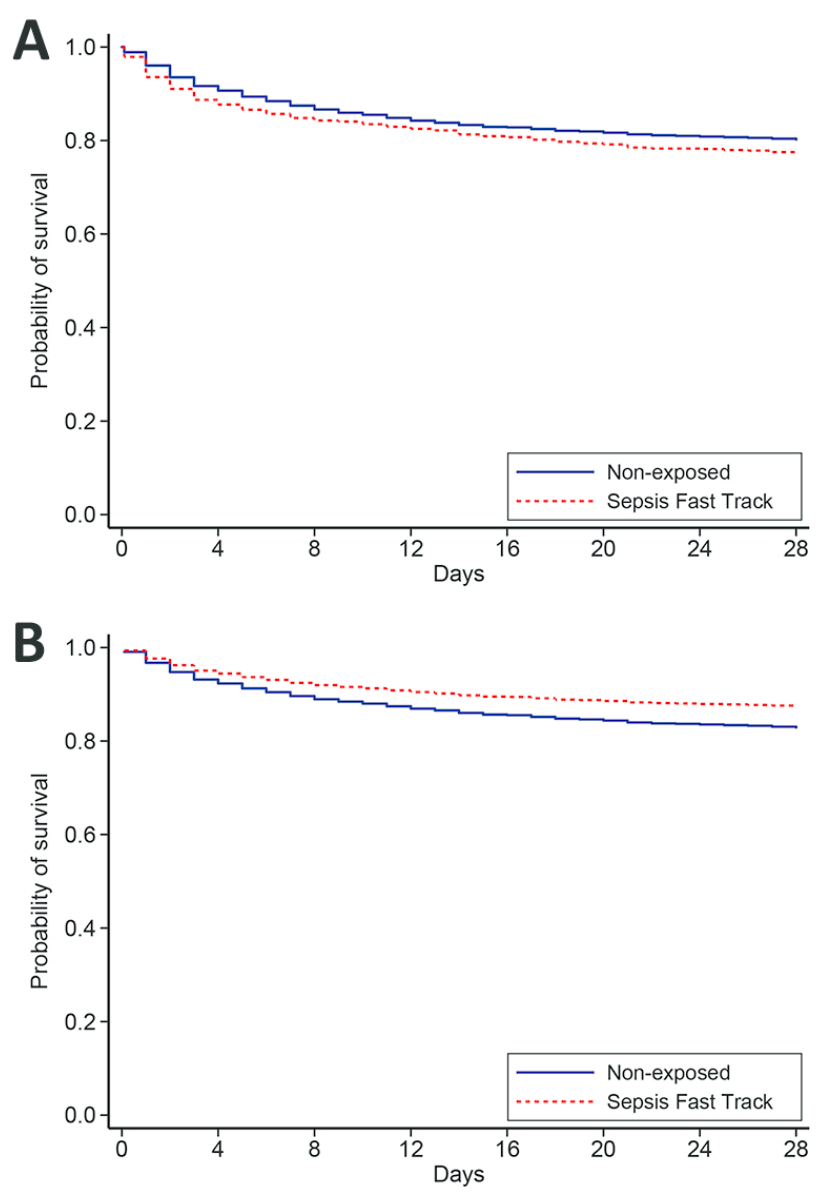


Figure 2 (A) Unadjusted probability of survival and (B) Adjusted probability of survival based on the multivariable Cox proportional hazard regression model

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1 **Effectiveness of a sepsis programme in a resource-limited setting: a retrospective analysis of**
2 **data of a prospective observational study (Ubon-sepsis)**

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Short Title: Sepsis Fast Track Thailand

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25 **Supplementary Table 1 | Criteria used to systematically enroll patents into Sepsis Fast Track**
26 **(SFT) upon admission**

27 **1. Present with 2 or more of below Signs of systemic inflammatory response syndrome**
28 **(SIRS)**

- 29 • Body temperature > 38.3 °C or < 36.0 °C
- 30 • Heart rate > 90 bpm
- 31 • Respiratory rate > 20 pm or PaCO₂ < 32 mmHg
- 32 • WBC > 12,000 /μL or < 4,000 /μL or Band forms > 10%

33 **2. Suspected sources of infection**

- 34 • Pneumonia
- 35 • Urinary track infection
- 36 • Intra-abdominal infection
- 37 • Skin and soft tissue infection
- 38 • CNS infection
- 39 • Others infections or unspecified source of infection

40 **3. Diagnostic criteria for severe sepsis:** patient met criteria in no 1 and 2 and has at least
41 one of the following criteria

- 42 • Mottled skin
- 43 • Capillary refilling time ≥ 3 seconds
- 44 • Urine output < 0.5 ml/kg/hour
- 45 • Abrupt change in mental status
- 46 • Acute respiratory failure
- 47 • Platelet count < 100,000 /μL
- 48 • Disseminated intravascular coagulation
- 49 • Lactate > 2 mmol/L
- 50 • SBP < 90 mmHg or MAP < 65 mmHg

51 **4. Diagnostic criteria for septic shock:** patient who are severe sepsis and has at least 1 of
52 the following criteria

- 53 • SBP < 90 mmHg or MAP < 65 mmHg after crystalliod administration ≥ 40-60
54 ml/kg of body weight OR after colloid administration ≥ 20-30 ml/kg of body weight
- 55 • Require administration of dopamine > 5μg/kg of BW/min or norepinephrine/
56 epinephrine > 0.02 μg/kg of BW/min to maintain MAP to be > 65 mmHg

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58 **Supplementary Table 2 | Systemic manifestation of infection criteria used for enrollment in**

59 **Ubon-Sepsis Cohort**

60 **General parameters**

- 61 1. Fever or hypothermia (Core body temperature defined as > 38.3 °C or < 36.0 °C)
- 62 2. Tachycardia (heart rate > 90 beats per minute)
- 63 3. Tachypnea (respiratory rate > 20 per minute)
- 64 4. Altered mental status with Glasgow Coma Score (GCS) < 15 or < 10 if intubated
- 65 5. Hyperglycemia (plasma glucose > 140 mg/dL) in the absence of diabetes

66 **Inflammatory parameters**

- 67 6. Leukocytosis (white blood cell count $> 12,000/\mu\text{L}$), leukopenia (white blood cell count $< 4000/\mu\text{L}$) or immature forms $> 10\%$
- 68 7. Plasma C-reactive protein > 2 SD above the normal value
- 69 8. Plasma procalcitonin > 2 SD above the normal value

70 **Hemodynamic parameters**

- 71 9. Arterial hypotension (systolic blood pressure (SBP) < 90 mmHg, mean arterial pressure (MAP) < 70 mmHg, or SBP decrease > 40 mmHg)

72 **Organ dysfunction parameters**

- 73 10. Low oxygen saturation determined by pulse oximetry ($\text{SpO}_2 < 95\%$) determined by pulse oximetry
- 74 11. Arterial hypoxemia ($\text{PaO}_2 / \text{FIO}_2 < 300$)
- 75 12. Acute oliguria (urine output < 0.5 mL/kg/hr or 45 mmol/L for 2 hours)
- 76 13. Creatinine increase > 0.5 mg/dL
- 77 14. Coagulation abnormalities (international normalised ratio > 1.5 or activated partial thromboplastin time > 60 seconds)
- 78 15. Thrombocytopenia (Platelet count $< 100,000$ cells/ μL)
- 79 16. Ileus (absent bowel sounds)
- 80 17. Hyperbilirubinaemia (plasma total bilirubin > 4 mg/dL)

81 **Tissue perfusion parameters**

- 82 18. Hyperlactatemia (> 1 mmol/L)
 - 83 19. Decreased capillary refill or mottling
 - 84 20. Significant edema or positive fluid balance
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90 **Supplementary Table 3 | Factors associated with 28-day mortality using multivariable Cox**
 91 **proportional hazards model**

Variables	Died (n=779)	Survived (n=3027)	Adjusted hazard ratio (95%CI)	P value
SFT group¹	205 (26%)	698 (23%)	0.72 (0.58-0.88)	0.001
Male gender	445 (57%)	698 (23%)	0.87 (0.75-1.01)	0.06
Age group (years) (n [%])				
• 18-40	59 (8%)	688 (23%)	1	<0.001
• >40-60	222 (29%)	930 (31%)	1.72 (1.28-2.30)	
• >60-70	159 (20%)	568 (19%)	2.10 (1.54-2.86)	
• >70	339 (44%)	841 (28%)	3.41 (2.57-4.53)	
Transferred from other hospital	715 (92%)	2595 (86%)	1.14 (0.88-1.49)	0.33
Modified SOFA score (median, IQR)	6 (4-9)	4 (3-6)	1.23 (1.21-1.26)	<0.001
Comorbidities				
• Diabetes mellitus	205 (26%)	602 (20%)	1.06 (0.90-1.26)	0.47
• Chronic kidney disease	141 (18%)	379 (13%)	1.22 (1.01-1.48)	0.04
• Liver disease	39 (5%)	85 (3%)	1.27 (0.91-1.76)	0.16
• Malignancy	24 (3%)	36 (1%)	2.64 (1.75-3.99)	<0.001
Blood culture positive for pathogenic organisms	190 (24%)	332 (11%)	1.83 (1.55-2.17)	<0.001
Year				
• 2013	165 (21%)	637 (21%)	1	0.30
• 2014	183 (23%)	651 (22%)	1.03 (0.83-1.27)	
• 2015	207 (27%)	808 (27%)	1.05 (0.84-1.31)	
• 2016 ²	224 (29%)	931 (31%)	0.88 (0.70-1.11)	
Direct admission to the ICU	128 (16%)	170 (6%)	1.68 (1.36-2.06)	<0.001

92 ¹ Enrolled in the Sepsis Fast Track (SFT) programme

93 ² Included 28 patients in 2017

94

95 **Supplementary Table 4 | Factors associated with 28-day mortality using multivariable Cox**
 96 **proportional hazards model without a variable of the direct admission to the ICU**

Variables	Died (n=779)	Survived (n=3027)	Adjusted hazard ratio (95%CI)	P value
SFT group¹	205 (26%)	698 (23%)	0.77 (0.63-0.94)	0.01
Male gender	445 (57%)	698 (23%)	0.86 (0.74-1.00)	0.05
Age group (years) (n [%])				
• 18-40	59 (8%)	688 (23%)	1	<0.001
• >40-60	222 (29%)	930 (31%)	1.69 (1.26-2.26)	
• >60-70	159 (20%)	568 (19%)	2.07 (1.52-2.81)	
• >70	339 (44%)	841 (28%)	3.32 (2.50-4.41)	
Transferred from other hospital	715 (92%)	2595 (86%)	1.16 (0.89-1.52)	0.26
Modified SOFA score (median, IQR)	6 (4-9)	4 (3-6)	1.25 (1.22-1.27)	<0.001
Comorbidities				
• Diabetes mellitus	205 (26%)	602 (20%)	1.08 (0.91-1.27)	0.39
• Chronic kidney disease	141 (18%)	379 (13%)	1.20 (0.99-1.45)	0.07
• Liver disease	39 (5%)	85 (3%)	1.24 (0.89-1.72)	0.20
• Malignancy	24 (3%)	36 (1%)	2.52 (1.67-3.81)	<0.001
Blood culture positive for pathogenic organisms	190 (24%)	332 (11%)	1.83 (1.54-2.16)	<0.001
Year				
• 2013	165 (21%)	637 (21%)	1	0.34
• 2014	183 (23%)	651 (22%)	0.98 (0.79-1.21)	
• 2015	207 (27%)	808 (27%)	1.01 (0.81-1.26)	
• 2016 ²	224 (29%)	931 (31%)	0.85 (0.68-1.07)	

97 ¹ Enrolled in the Sepsis Fast Track (SFT) programme

98 ² Included 28 patients in 2017

99 **Supplementary Table 5 | Factors associated with 28-day mortality using logistic**
 100 **multivariable model**

Variables	Died (n=779)	Survived (n=3027)	Adjusted odds ratio (95%CI)	P value
SFT group¹	205 (26%)	698 (23%)	0.61 (0.48-0.79)	<0.001
Male gender	445 (57%)	698 (23%)	0.88 (0.73-1.06)	0.18
Age group (years) (n [%])				
• 18-40	59 (8%)	688 (23%)	1	<0.001
• >40-60	222 (29%)	930 (31%)	1.91 (1.36-2.66)	
• >60-70	159 (20%)	568 (19%)	2.54 (1.78-3.63)	
• >70	339 (44%)	841 (28%)	4.76 (3.43-6.59)	
Transferred from other hospital	715 (92%)	2595 (86%)	1.21 (0.89-1.65)	0.23
Modified SOFA score (median, IQR)	6 (4-9)	4 (3-6)	1.30 (1.26-1.34)	<0.001
Comorbidities				
• Diabetes mellitus	205 (26%)	602 (20%)	1.12 (0.91-1.39)	0.29
• Chronic kidney disease	141 (18%)	379 (13%)	1.20 (0.94-1.53)	0.13
• Liver disease	39 (5%)	85 (3%)	1.34 (0.85-2.10)	0.21
• Malignancy	24 (3%)	36 (1%)	3.65 (2.05-6.51)	<0.001
Blood culture positive for pathogenic organisms	190 (24%)	332 (11%)	2.08 (1.66-2.61)	<0.001
Year				
• 2013	165 (21%)	637 (21%)	1	0.64
• 2014	183 (23%)	651 (22%)	1.05 (0.80-1.37)	
• 2015	207 (27%)	808 (27%)	1.05 (0.80-1.38)	
• 2016 ²	224 (29%)	931 (31%)	0.91 (0.69-1.21)	
Admitted directly to an ICU upon admission	128 (16%)	170 (6%)	1.95 (1.45-2.62)	<0.001

¹ Enrolled in the Sepsis Fast Track (SFT) programme

² Included 28 patients in 2017

104 **Supplementary Table 6 | Factors associated with 28-day mortality using logistic**
 105 **multivariable model without a variable of the direct admission to the ICU**

Variables	Died (n=779)	Survived (n=3027)	Adjusted odds ratio (95%CI)	P value
SFT group¹	205 (26%)	698 (23%)	0.67 (0.53-0.86)	0.002
Male gender	445 (57%)	698 (23%)	0.87 (0.73-1.05)	0.14
Age group (years) (n [%])				
• 18-40	59 (8%)	688 (23%)	1	<0.001
• >40-60	222 (29%)	930 (31%)	1.85 (1.33-2.58)	
• >60-70	159 (20%)	568 (19%)	2.44 (1.71-3.46)	
• >70	339 (44%)	841 (28%)	4.55 (3.29-6.28)	
Transferred from other hospital	715 (92%)	2595 (86%)	1.23 (0.90-1.68)	0.19
Modified SOFA score (median, IQR)	6 (4-9)	4 (3-6)	1.32 (1.28-1.36)	<0.001
Comorbidities				
• Diabetes mellitus	205 (26%)	602 (20%)	1.16 (0.94-1.43)	0.17
• Chronic kidney disease	141 (18%)	379 (13%)	1.17 (0.92-1.49)	0.20
• Liver disease	39 (5%)	85 (3%)	1.31 (0.84-2.06)	0.23
• Malignancy	24 (3%)	36 (1%)	3.49 (1.95-6.24)	<0.001
Blood culture positive for pathogenic organisms	190 (24%)	332 (11%)	2.08 (1.67-2.61)	<0.001
Year				
• 2013	165 (21%)	637 (21%)	1	0.70
• 2014	183 (23%)	651 (22%)	1.00 (0.77-1.31)	
• 2015	207 (27%)	808 (27%)	1.01 (0.77-1.33)	
• 2016 ²	224 (29%)	931 (31%)	0.89 (0.67-1.17)	

106 ¹ Enrolled in the Sepsis Fast Track (SFT) programme

107 ² Included 28 patients in 2017

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109 **Supplementary Table 7 | Factors associated with 28-day mortality using multivariable Cox**
 110 **proportional hazards model in 2,170 patients enrolled into the study after the**
 111 **implementation of the Sepsis Fast Track (SFT) programme**

Variables	Died (n=431)	Survived (n=1739)	Adjusted hazard ratio (95%CI)	P value
SFT group	205 (48%)	698 (40%)	0.68 (0.55-0.84)	<0.001
Male gender	254(59%)	992 (57%)	0.89 (0.73-1.09)	0.26
Age group (years) (n [%])				
• 18-40	30 (7%)	363(21%)	1	<0.001
• >40-60	125 (29%)	502 (29%)	1.97 (1.31-2.95)	
• >60-70	85 (20%)	359 (21%)	1.97 (1.28-3.03)	
• >70	191 (44%)	515 (30%)	3.33 (2.24-4.95)	
Transferred from other hospital	406 (94%)	1513 (87%)	1.49 (0.99-2.26)	0.06
Modified SOFA score (median, IQR)	7 (5-10)	4 (3-6)	1.24 (1.21-1.28)	<0.001
Comorbidities				
• Diabetes mellitus	122 (28%)	377(22%)	1.08 (0.87-1.35)	0.49
• Chronic kidney disease	84 (19%)	242 (14%)	1.23 (0.96-1.58)	0.11
• Liver disease	22 (5%)	57 (3%)	1.10 (0.71-1.70)	0.68
• Malignancy	19 (4%)	27 (2%)	2.90 (1.81-4.63)	<0.001
Blood culture positive for pathogenic organisms	110(26%)	225 (13%)	1.64 (1.31-2.05)	<0.001
Year				
• 2015	207 (48%)	808 (46%)	1	0.08
• 2016	224 (52%)	931 (54%)	0.84 (0.69-1.02)	
Direct admission to the ICU	85 (20%)	124 (7%)	1.78 (1.37-2.32)	<0.001

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3 114 **Supplementary Figure 1 | Preprinted recommended doctor orders for sepsis fast track**
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5 115 **programme used at the Emergency Department at Sunpasitthiprasong Hospital**
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7 116 **from 1 January 2015**
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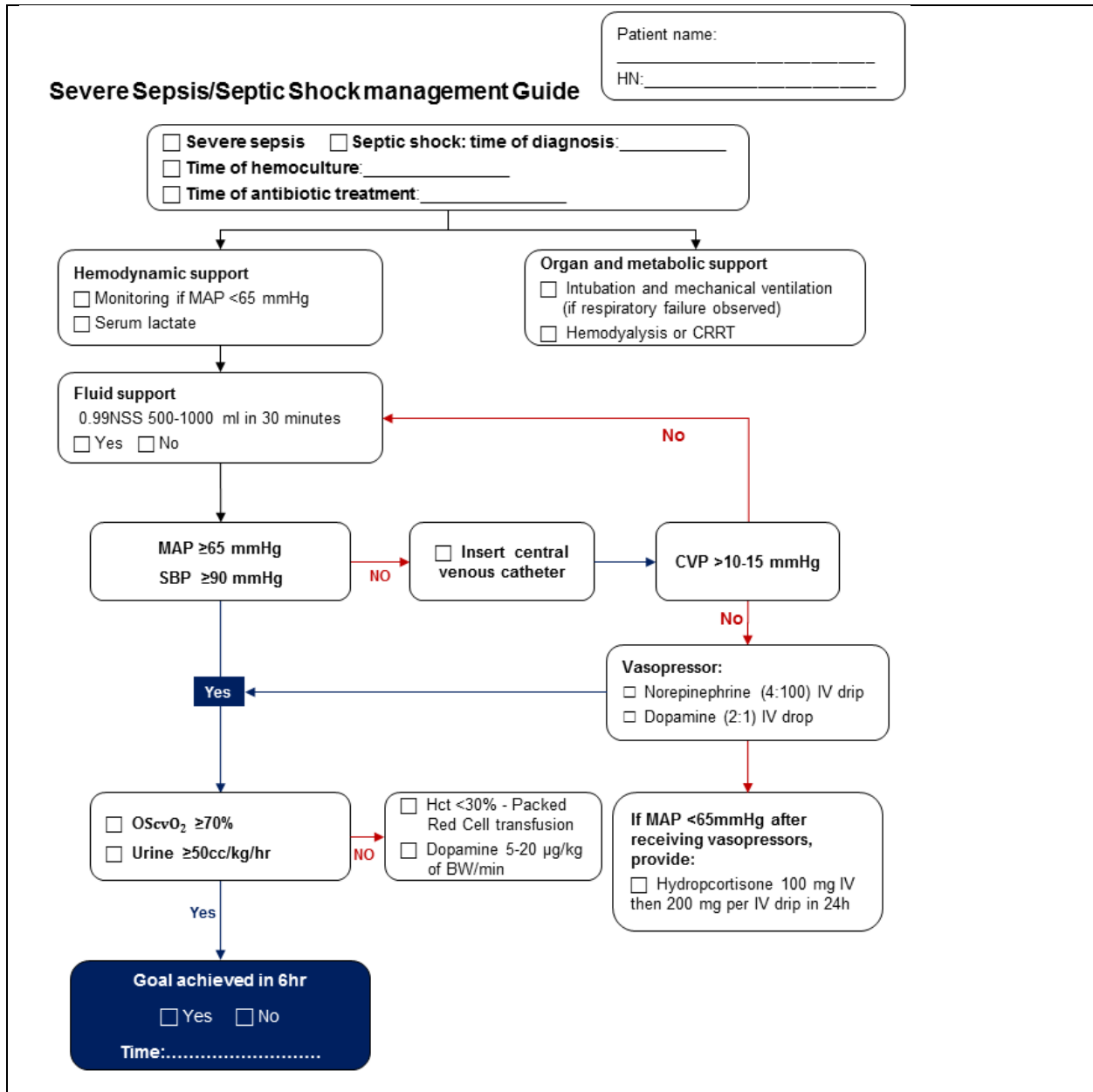
SAPPASITTIPRASONG HOSPITAL รพ.6/1

DOCTOR'S ORDER SHEET (Rev. 2: พ.ร. 48)

FFM	PROGRESS NOTE	Date Time	ORDER FOR ONE DAY	Date Time	CONTINUOUS ORDER	Date of Sign
HN..... ชื่อ-สกุล..... รหัสนิติบัตร.....	ER NON TRAUMA		Dx. <input type="checkbox"/> Sepsis <input type="checkbox"/> Severe Sepsis <input type="checkbox"/> Septic Shock - Consult ICU Admit..... - CxR - EKG..... - DTX. Stat..... - Serum lactate - CBC, PT, PTT, U/A - BUN, Cr., E'lyte - Liver Function Test,alb - HC x II stat at ER.....ม. - HC x II at รพ.....ม. - V/S q 1 hr. x II then as usual - on O2 canular 3 LPM if O2 sat < 95 % - Retained Foley's cath - NSS1,000 ml IV load.....in 10 min then IV drip ml/hr (30ml/kg)		- NPO - Record V/S, N/S, I/O Medication ชัก Hx เพื่อยา <input type="checkbox"/> ไม่มี <input type="checkbox"/> มี..... ตรวจสอบ Hx เพื่อยา ใน HOMC <input type="checkbox"/> ไม่มี <input type="checkbox"/> มี.....	
	Time onset					
	Date					
	Time					
	Onset					
	Date					
	Time					
	E V M					
	BP /					
	HR T C					
	Source of infection					
	<input type="checkbox"/> Respiratory <input type="checkbox"/> GI					
	<input type="checkbox"/> Skin, soft tissue <input type="checkbox"/> CNS					
	<input type="checkbox"/> Cardiovascular					
	<input type="checkbox"/> Others.....					
	Systemic infection					
	<input type="checkbox"/> Leptospirosis <input type="checkbox"/> Malaria					
	<input type="checkbox"/> Rickettsia <input type="checkbox"/> Denque					
	พียง IV bolus.....ml					
	BP / HR					
IVF รพ.....ml						
IVF at ER.....ml						

117

118 **Supplementary Figure 2 | The Sepsis Fast Track sepsis resuscitation workflow used at the**
 119 **Emergency Department at Sunpasitthiprasong Hospital from 1 March 2016**



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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 3-4
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-9
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	10-11
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Data sources/measurement	8*	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-11
Bias	9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-12
Study size	10	Describe any efforts to address potential sources of bias	11-12
Quantitative variables	11	Explain how the study size was arrived at	10-11
Statistical methods	12	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-12
		(a) Describe all statistical methods, including those used to control for confounding	11-12
		(b) Describe any methods used to examine subgroups and interactions	11-12
		(c) Explain how missing data were addressed	8
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	6
<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed			
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	12
		(e) Describe any sensitivity analyses	12

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-14
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	16-17
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-17
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	16-17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18-22
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20-21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21-22
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.