ONLINE SUPPLEMENT to Understanding and Enhancing Sepsis Survivorship: Priorities for Research and Practice

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Appendix 1: Colloquium Program and Participants

Stephen F. Lowry 2018 ISF Colloquium on Understanding and Enhancing Sepsis Survivorship
Chairs: Kathy Rowan, UK, Hallie Prescott, US, & Derek Angus, US

Day 1: Monday 5 February 2018, Scene setting
Welcome (**Simon Finfer**)
Introduction / Goals for Colloquium (**Kathy Rowan/Hallie Prescott**)
1. Patients' perspectives (**Cheryl Misak**)

Session 1: New symptoms and disability; Session Chairs: **Bronwen Connolly**, **Terri Hough**
2. Cognitive impairment (**Mona Hopkins**)
3. Physical dysfunction: ICU-acquired weakness, dysphagia (**Dale Needham**)
4. Psychological sequelae, Post-traumatic stress for patients and families (**James Jackson**)
5. Functional Outcomes in Critically ill Children (**Karen Choong**)
6. Is post-sepsis survival different from post-ICU syndrome? (**Simon Finfer**)
Group discussion (session chairs)
How does sepsis survivorship differ from other critical illnesses? Can we disentangle the later effects from sepsis from progression of pre-sepsis effects and general effects of hospitalization and critical care admission? When should sepsis survivorship be studied separately?

Session 2: Biological Mechanism; Session Chairs: **John Marshall, Flavia Machado**
7. Persistent inflammation (**Sachin Yende**)
8. Microbiome disruption (**Pinaki Panigrahi**)
9. Immune suppression (**Thierry Calandra**)
10. Mitochondrial Disruption (**Tim Girard**)
Group discussion (session chairs)
What ongoing pathophysiological derangements should be targeted to promote recovery? Can we use interventions from other disease processes with similar derangement(s)?

Session 3: In-hospital practices to improve longer-term outcomes; Session Chairs**: Simon Finfer, Kathy Rowan**, **Dale Needham**
11. Minimizing harm (the less is more movement e.g. fluids, ABx, vent, etc) (**John Marshall**)
12. Early mobility interventions (**Carol Hodgson**)
13. Early cognitive rehab (**Mona Hopkins**)
14. Reducing patient distress (**Linda Chlan**)
Group discussion (session chairs)
What is the right dose/timing for practices to improve longer-term outcomes? How do we tailor specific interventions to individual patients? How can we further reduce hazards of ICU and hospital care?

Session 4: Scaffolding patients and families after discharge; Session Chairs**: Hallie Prescott, Terri Hough**
15. Challenges of post-ICU/hospital discharge mgmt (will naturally recap Day 1) (**Hallie Prescott**)
16. ICU follow-up clinics, Telemedicine, visiting RNs (**James Jackson**)
17. Peer-to-peer support for patients and families (**Jack Iwashyna**)
18. Supporting survivors in lower resourced settings (**Flavia Machado**)
19. Monitoring and ensuring best outcomes (**Kathy Rowan**)
20. Spreading awareness of survivorship issues (**Konrad Reinhart**)

21. What are the biggest problems with post-discharge care (**Cheryl Misak**)
Group Discussion:
What is "successful" post-sepsis care (timing and content)? What are the right metrics to measure success of post-hospital care? Costs? Patient satisfaction? Patient outcomes?
What is the best practice model: ICU follow-up clinics, primary care education, telemedicine, case management? Should this differ around the world?
How should we prepare patients and families for what to expect after discharge?

Session 5: Improving research and research translation; Session Chairs: **Derek Angus, Simon Finfer, Bronagh Blackwood**
23. Lessons learned from rehabilitation interventions in other populations (**Alan Jette**)
24. Lessons learned from Geriatrics (**Luigi Ferrucci**)
25. Lessons learned from PM&R (**Ross Zafonte**)
26. Novel Study Designs, and FDA's support of these designs (**Derek Angus**)
Group discussion (Session Chairs)
What outcomes should be measured in RCTs evaluating interventions for acute sepsis?
How long should people be followed-up?
How should we handle discordant outcomes?

Wrap-up session: **major themes**
Session Chairs: **Hallie Prescott, Kathy Rowan**
Group discussion of important emerging themes/brain-storming for planned paper:
How is sepsis survivorship different from other critical illness?
When should it be studied separately?
What are the best outcomes for evaluation of in-hospital sepsis interventions?
What are the best outcomes for evaluation of post-discharge interventions?

Speaker instructions:
Provide a high-level overview of your topic as an expert.
Close with these three slides:

(1) Limitations: what are the limitations of the research you have reviewed/presented?
(2) Gaps: what are the gaps? (what hasn't been studied)
(3) Next steps: What are the key elements for the research agenda in this topic on a 3-5 year time horizon? (i.e. where should the field go based on the limitations and gaps of existing research?)

List of Participants

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Conflicts of Interest—None

Supplemental Table E1: Recent Systematic Reviews Pertinent to Sepsis Survivorship

Topic	Number of Reviews, Total (Sepsis-Specific)	Total Number of Included Studies
Outcomes		
Cognitive	3[1-3] (2[1,3])	168
Emotional	4[4-7] (0)	102
Functional	3[8-10] (0)	53
Mortality	2[11,12] (2[11,12])	69
Quality of Life	2[13,14] (1[13])	62
Other	2[15,16] (0)	44
Interventions		
Early Mobility	6[17-22] (1[21])	88
Rehabilitation	3[23-25] (0)	27
Other	4[26-29] (0)	31
Research Methods		
Performance of outcome measures	1[30] (0)	20
Total	**30 (6)**	592

Summaries of the 30 systematic reviews are presented in **Supplemental Table 2**.

Supplemental Table E2: Inclusions, Exclusions, and Main Findings of Recent Systematic Reviews Pertinent to Sepsis Survivorship

Review	Major Inclusions	Major Exclusions	Studies (Patients)*	Main Findings	Key gaps and limitations identified
Cognitive Outcomes					
Calsavara, *et al. Australian Critical Care*. 2018.[1]	Studies examining the association between sepsis and cognitive dysfunction using validated instruments, and/or examining at least one risk factor for sepsis-associated cognitive dysfunction.	Studies reporting subjective measures of cognitive function (*e.g.* clinician opinions regarding cognitive state).	16	Post-sepsis cognitive impairment was observed in 12.5% to 21% of sepsis survivors. Specific domains affected included attention, cognitive flexibility, processing speed, associative learning, visual perception, work memory, verbal memory, and semantic theory. Predictors of cognitive impairment included depressive symptoms, CNS infection, length of hospitalization, and temporal proximity with prior infection.	The studies used variable definitions, variable neuropsychological tests, and were generally of low overall quality. Timing of follow-up ranged from 28 days to 4 years.
Sakusic, *et al. Mayo Clin Proc.* 2018.[2]	Studies examining cognitive function at least 2 months after ICU discharge.	Studies focused on cardiac arrest, traumatic brain injury, or cardiac surgery patients.	28 (3,802)	Delirium and duration of delirium were associated with long-term cognitive impairment in 6 of 9 studies that assessed this risk factor. There were weaker, inconsistent associations reported for hypoglycemia, hyperglycemia, glucose variation, and in-hospital stress symptoms. Most studies found no association between long-term cognitive impairment and mechanical ventilation, medications, enteral feeding, vital signs, or length of ICU stay.	Definitions of cognitive impairment varied across studies, and a wide range of neuropsychological tools were used to evaluate cognitive function. Most studies were underpowered to assess for association between potential risk factors and cognitive function reliably. Overall, included studies had a moderate risk of bias. Findings were inconsistent across studies, which may relate to lack of power and/or variable definitions. Very few studies included baseline assessment of cognitive function.
Barichello, *et al. Mol Neurobiol,* 2019.[31]	Pre-clinical and clinical studies examining mechanisms by which sepsis induces long-term neurological sequelae and cognitive impairment.	In vitro studies, and studies including patients with previous disease as a risk factor for sepsis.	130	In pre-clinical sepsis models, cognitive impairment and neuropsychiatric-like behavior have been identified from early hours after sepsis until several months after recovery. The most common types of impairment were aversive memory, learning, locomotor and exploratory activities, short-term and long-term memories, depressive-like behavior, anxiety-like behavior, and fear memory. Pre-clinical studies have identified auto amplification of pro-inflammatory cytokines (e.g. TNF-α, IL-1β, and IL-6), increased blood-brain barrier permeability, elevated levels of matrix metalloproteinases, and increased levels of damage-associated molecular patterns as potential mediators of cognitive impairment. In human studies, sepsis has been associated with a 10.6% increase in the prevalence of	Many pre-clinical studies did not present data to identify the effect of adjuvant therapy on cognition. Included clinical studies had moderate amounts of bias.

				moderate-severe cognitive impairment in elderly sepsis survivors, as well as impaired school performance in children.	
Emotional Outcomes					
Parker, *et al. Crit Care Med.* 2015.[4]	Studies of adult general ICU survivors using a validated PTSD instrument to assess PTSD prevalence at ≥1 month post-ICU discharge.	Studies of specialty ICU patients or <10 patients.	36 (4,260)	The most common PTSD instrument was the Impact of Event Scare (IES). The pooled prevalence of PTSD across 6 studies using IES ≥ 20 was 44% (95%CI: 36%, 52%) at 1-6 months and 34% (95%CI: 22%, 50%) at 7-12 months. Prevalences using IES ≥ 35 were 25% (95%CI: 18%, 34%) and 17% (95%CI: 10%, 26%), respectively. The prevalence of PTSD did not differ by ICU admission diagnosis category in 7 of 7 studies that examined sub-groups by diagnosis. Risk factors for PTSD included comorbid psychopathology, treatment with benzodiazepines, and early memories of frightening ICU experiences.	There was heterogeneity of patient populations, PTSD symptoms instruments, and timing of outcome assessments, which made it difficult to pool study findings. Meta-analysis was limited to studies using the same scale.
Nikayin, *et al. Gen Hosp Psychiatry.* 2016.[5]	Studies assessing anxiety symptoms in adult ICU survivors using a validated instrument to measure anxiety.	Studies of <20 patients or focusing on a specific disease or specialty ICU.	27 (2,880)	The most common instrument was the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A) (81% of studies). The pooled prevalence of anxiety across 22 studies using HADS-A ≥8 was 32% (95%CI: 27%, 38%) at 2-3 months; 40% (95%CI: 33%, 46%) at 6 months; 34% (95%CI: 25%, 42%) at 12-14 months. Using HADS-A ≥ 11, prevalences were 17% (95%CI: 14%, 20%), 20% (95%CI: 16%, 25%), and 17% (95%CI: 12%, 22%), respectively. The prevalence of anxiety did not differ by ICU admission diagnosis category in 4 of 4 studies that examined sub-groups by diagnosis. In studies with longitudinal assessments, there was no change in anxiety score or prevalence over time.	Most studies in the review and all studies in the meta-analysis were conducted in Europe. There is a lack of data on pre-ICU anxiety symptoms, making it impossible to determine the extent to which post-ICU anxiety symptoms are a result of critical illness and its treatment.
Rabiee, *et al. Crit Care Med.* 2016.[6]	Studies evaluating depression in ICU survivors using a validated tool.	Studies with <20 patients from non-specialty ICUs.	38 (4,113)	The most common instrument was the Hospital Anxiety and Depression Scale-Depression subscale (HADS-D) (58% of studies). The pooled prevalence of depression across 22 studies using HADS-D ≥ 8 was 29% (95%CI: 22%, 36%) at 2-3 months; 34% (95%CI: 24%, 43%) at 6 months; 29% (95%CI: 23%, 34%) at 12-14 months. Using HADS-D ≥11, prevalences were 17% (95%CI: 12%, 21%), 17% (95%CI: 10%, 23%), and 13% (95%CI: 10%, 16%). The prevalence of depression did not differ by ICU admission diagnosis category in 5 of 6 studies that examined sub-groups by diagnosis. Risk factors for post-ICU depressive symptoms include pre-ICU psychopathology.	There was substantial statistical heterogeneity in the meta-analysis. Existing data to not clarify whether post-ICU depression symptoms are the result of critical illness and/or its treatment. Alternatively, depressive symptoms may reflect pre-morbid symptoms, or the effect of hospitalization more generally without any added contribution from the ICU. No post-ICU interventions had strong evidence for improvement in depressive symptoms.
Johnson, *et al. AnnalsATS*. 2019[7]	Studies examining depression, anxiety, or PTSD in family	Studies of specific patient populations (e.g. cardiac surgery,	40 (7,668)	Included studies were conducted in United States (N=15), Europe (N=12), Canada (N=2), South America (N=2), Australia (N=1), and India (N=1). 22 studies assessed psychological outcomes during the ICU, and 29 assessed outcomes after ICU	Variable instruments, definitions, and timing of follow-up limited direct comparisons across studies. Loss to follow-up ranged from 4% to 77%, but reasons for loss to

	caregivers of critically ill patients.	stroke, dementia, traumatic brain injury); studies of caregivers to patients who died in ICU; studies of caregivers to pediatric ICU populations.		discharge, with follow-up ranging from 1 to 53 months. Prevalences of psychological outcomes in family caregivers ranges from 4% to 94% for depression, 2% to 80% for anxiety, and 3% to 62% for PTSD. In 5 of 8 studies with longitudinal measurement, PTSD decreased over time. Common risk factors for psychological morbidity include young caregiver age, lower socioeconomic status, and female sex. There is some evidence for benefit of ICU diaries and communication facilitation for reducing caregiver PTSD and depression, respectively.	follow-up were rarely reported. Most studies were cohort studies, without a control or comparison group. Few studies assessed pre-morbid psychological factors. There were only 9 RCTs of caregiver interventions, and few that showed any positive effect.
Functional Outcomes					
Ong, *et al. Pediatr Crit Care Med*, 2016.[8]	Studies reporting functional outcomes of PICU survivors.	Studies of preterm infants.	25 (67,518)	Studies used 11 measures were used to assess functional status in PICU survivors: 3 global assessment tools and 8 multidimensional measures. Rates of acquired functional impairment ranged from 10%-36% at discharge, and 10%-13% at 2+ years. Risk factors for functional impairment included illness severity, length of ICU stay, and younger age.	Studies varies widely in measurement timing and tools used for assessment. Further studies using a combination of standardized measures at various timepoints are needed to establish comprehensive rates of physical impairment. Most studies used global functional measures which do not distinguish the type of functional disability.
Hopkins, *et al. AnnalsATS.* 2017.[9]	Studies evaluating instrumental activities of daily living (IADLs) in adult survivors of critical illness.	Studies of specific ICU populations, specialty ICUs, or with <10 patients.	16 (4,723)	Definitions of IADL impairment and pre-ICU IADL dependencies were highly variable across studies. 11 (69%) of studies found that survivors had new or worsening IADL dependencies. In 3 of 4 longitudinal studies, IADL dependencies decreased over time.	Most studies were single-center cohorts, with variable timing of follow-up. Only 2 studies reported individual IADL domain scores. There was significant variability in definitions of IADL limitation and rates of IADL limitation reported across studies. No risk factors were consistently associated with IADL dependency, potentially due to small samples sizes (low power) and variable definitions. Only 1 study assessed the relationship of cognitive impairment to IADL disability.
Ohtake, *et al. Physical Therapy.* 2018.[10]	Observational studies reporting physical outcomes in adult critical illness survivors during the first year following ICU discharge.	Studies including patients with cancer, neurological disorders (e.g. stroke, traumatic brain injury), cardiovascular surgery, or pregnancy.	15 (1,450)	Critical illness survivors experience impairments in body function and structure; activity limitation, and participation restrictions. These impairments include decreased pulmonary function, reduced strength of respiratory and limb muscles, reduced 6-minute walk distance, reduced ability to perform activities and instrumental activities of daily living (I/ADLs), and reduced ability to return to driving or paid employment.	Only 2 of 15 studies were from lower or middle-income countries. Robust measures of pre-ICU functional status are difficult to obtain, so it is challenging to determine the extent of impairment associated with critical illness.
Mortality Outcomes					

Fleishmann, *et al. AJRCCM*, 2016.[11]	Studies reporting population-level estimates of sepsis incidence and fatality in adult populations using consensus criteria.	Studies with insufficient details on inclusions, exclusions, or methods of data collection.	27	Among studies from high-income countries (Australia, Germany, Norway, Spain, Sweden, Taiwan, US) in the decade prior to publication, incidence rate for sepsis was 437 cases per 100,000 person-years, and hospital mortality for severe sepsis was 26%. Tentative extrapolation from high-income country data yielded global estimates of 19.4 million severe sepsis cases and 5.3 million sepsis deaths annually. There was substantial heterogeneity of incidence estimates across studies.	At the time of this review, there were no population-level sepsis incidence rates for lower-income countries, limiting the ability to estimate global incidence and deaths.
Shankar-Hari, *et al. Crit Care*. 2016.[12]	Studies in which one-year post-acute mortality in adult sepsis survivors was reported (or could be calculated from reported data).		43	Among 43 studies, one-year mortality among patients surviving a sepsis hospitalization was 16.1%, with substantial heterogeneity across individual studies. Among 16 studies with a non-sepsis control arm, sepsis was not consistently associated with a higher hazard ratio for post-acute mortality; hazard was greatest when sepsis survivors were compared to general population controls.	Additional epidemiologic studies with recent patient level data that address the pre-illness trajectory, confounding, and varying control groups are needed to estimate sepsis-attributable additional risk and modifiable risk factors to design interventional trials.
Quality of Life Outcomes					
Alam, *et al. Acute Med.* 2017.[13]	Studies assessing health-related quality of life among adult sepsis survivors who were treated in an ICU.		16 (5,333)	Studies were conducted in Europe (N=11), North America (N=2), South America (N=1), and Asia (N=1). The most common HRQOL assessment tools were the EuroQuol fie dimension questionnaire (EQ-5D, N=7) and the Short-Form (SF-36, N=6). Four studies comparing HRQOL of ICU sepsis survivors to other ICU survivors found no difference in HRQOL, whereas 12 studies comparing sepsis survivors to matched age- and/or sex-matched population controls found significant reductions in HRQOL, which persisted for months to years in longitudinal studies.	Studies used variable sepsis definitions, assessment tools, and timing of assessment, such that meta-analysis was not possible. Only 5 studies assessed baseline HRQOL prior to hospitalization.
Gerth *et al. Anesthesia.* 2019.[14]	Studies of adult patients discharged from a general ICU with quality of life assessments with a validated scale more than 3 months post-hospital discharge.	Studies limited to a specific disease (except sepsis), or uncontrolled intervention studies.	48	The most common HRQOL assessment tools were SF-36 (N=31) and EQ-5D (N=19). Follow-up ranged from 26%-100%. Outcome assessments occurred most commonly at 6 and 12 months post-hospitalization. 17 studies compared outcomes to a reference population, and 15 studies had retrospective assessment of quality of life before admission. Quality of life was consistently worse than age- and sex-matched population controls, including prior to admission. In 25 studies with longitudinal assessments, HRQOL improved to 1 year post-discharge. Physical function, physical role, vitality, and social function improved the most, but were also least likely to recover to population norms, as they were the most impaired after critical illness.	Only half of the included studies compared ICU survivors to a reference population, and none used a comparison cohort that had survived an acute illness. The variation in tool to measure HRQOL precluded quantitative pooling of study findings. Better methods are needed to establish HRQOL before critical illness and to adjust for pre-existing disease.
Other Outcomes					

Hashem, *et al*. *Critical Care*. 2016.[15]	Qualitative studies evaluating patient outcomes after hospital discharge for survivors of all-cause critical illness.	Studies of specific ICU populations or specialty ICUs.	22 (594)	Studies were conducted in 10 countries. They examined satisfaction with life (N=16), mental health (N =15), physical health (N=14), social health (N=7), and ability to participate in social roles and activities (N=6). While some survivors may experience positive emotions (acceptance, gratitude, positive outlook), many survivors experience a wide range of mental, physical, social, and functional sequelae occur after hospital discharge from critical illness. The study highlighted the importance of social health (social functioning and ability to participate in social roles), which is not well-captured in common quality of life instruments.	Few of the included studies reported a rationale for patient selection, data saturation, or inter-rater comparisons. Only a minority of included studies described a rationale for sample size, reported which patients were ineligible or declined to participate. None of the included studies reported on a theme on cognitive functioning.
Altman, *et al. AnnalsATS.* 2017.[16]	Studies of adult critical illness survivors with a primary outcome of sleep disturbance measured by standardized questionnaire or objective measurement tool.	Studies with a primary focus on postoperative, burn injury, or acute neurological injury (*e.g.* stroke or traumatic brain injury).	22 (3,480)	Assessment tools included questionnaires (N=17), polysomnography, and actigraphy. By questionnaire, prevalence of abnormal sleep was 50%-66.7% in 3 studies at 1 month; 34-64.3% in 5 studies at >1 to 3 months; 22%-57% in 8 studies at >3 to 6 months, and 10-61% in 5 studies at >6 months post-hospital discharge. In longitudinal measurement, 4 of 5 questionnaire studies and 5 of 5 polysomnography studies showed improvement over time. Sleep disturbance was commonly associated with psychological morbidity and impaired quality of life. In 2 of 3 three studies that included a reference population, sleep was significantly worse in ICU survivors versus population controls.	There was wide variability in assessment tools, study quality, and time to follow-up, which limits comparison across studies. Studies had conflicting findings on risk factors for poor sleep. More research is needed on risk factors for poor sleep and interventions to improve sleep in critical illness survivors.
Early Mobility Interventions					
Castro-Avila, *et al. PLoS One*, 2015.[17]	Randomized or controlled trials of active mobility exercises in adult ICU patients.	Studies including trauma patients and patients with neurological disease that may limit rehabilitation (*e.g.* stroke, traumatic brain injury, multiple sclerosis)	7 (774)	Early rehabilitation during ICU stay was not consistently associated with improvements in functional status at ICU discharge, muscle strength, quality of life or healthcare utilization, although may improve walking ability (walk distance and proportion walking without assistance) at hospital discharge compared to usual care.	Due to substantial variability in patients, interventions, and outcome timing/measures, it was not possible to poor results for the primary outcomes of functional status at ICU discharge. Description of interventions was limited. The impact of frequency, duration, intensity, and timing remain unknown.
Laurent, *et al. Anesthes Crit Care Med.* 2015.[18]	Studies examining early physical therapy in ICU, with a focus on “how to do”, “for which patients”, and “for what benefits”.	Studies of passive range of motion.	22 (1,757)	Studies of early exercise generally include patients who are stable hemodynamic and respiratory conditions, but require invasive mechanical ventilation. Studies use a variety of outcome measures, including development of polyneuropathy, respiratory muscle strength, respiratory muscle endurance, cross-sectional muscle diameters, walking distance, functional status, and quality of life. Very few studies examined longer-	There is a need for improved characterization of the effects of specific exercise types, as well as better description of interventions. The process to select patients must be improved to target those patients most likely to benefit from an early exercise program. More research is needs to

				term impacts to one-year. Study interventions include upper/lower limb exercises and respiratory muscle training; however, methods were generally insufficient to allow replication of study procedures.	clarify the optimal intensity, duration, and frequency of exercise interventions.
Nydahl, *et al. AnnalsATS*. 2017.[19]	Studies of mobilization-related intervention in the ICU.	Studies with <10 patients, majority of patients <18 years, or lack of data on safety events.	48 (7,546)	Among 22,351 mobilization/rehabilitation session, there were 583 (2.6%) potential safety events. Pooled incidence per 1,000 mobilization/rehabilitation sessions were: hemodynamic changes, 3.8 (1.3-11.4) and desaturation, 1.9 (0.9-4.3). In 24 studies of 3,404 patients, 0.6% of mobilization/rehabilitation sessions necessitates a change in management as a consequence of a potential safety events (*e.g.* increased vasopressor dose due to mobility-related hypotension).	There is wide heterogeneity in definitions of safety events in included studies, and significant heterogeneity in the rates of safety events reported across studies. Only 53% of included studies reported the consequences of potential safety events. Asymmetry in funnel plots for three types of potential safety events (low blood pressure, hemodynamic events, oxygen desaturation) raise concern for potential publication bias.
Tipping, *et al. Intensive Care Med.* 2017.[20]	Randomized or controlled clinical trials testing active mobilization and rehabilitation delivered in the ICU (including active exercises in bed; progression of mobility from sitting, to standing and ambulation; tilt table therapy or hoisting to a chair)	Studies investigating passive therapies only, cycle ergometry only, functional electrical muscle stimulation only, or studies in which rehabilitation started after ICU discharge.	14 (1,753)	Active mobilization and rehabilitation led to greater muscle strength (body function) at ICU discharge (MRC sum score mean difference 8.6 (95%CI: 1.4, 3.8), greater probability of walking without assistance (activity limitation) at hospital discharge (odds ratio 2.1 (95%CI: 1.2, 3.8)), and more days alive and out of hospital to day 180 (participation restriction) (mean difference 9.7 (95%CI: 1.7, 17.7)). There was no impact on short or long-term mortality. There were no consistent effects on function, quality of life, ICU or hospital length of stay, duration of mechanical ventilation or discharge destination.	There is insufficient evidence to determine the impact of active mobilization on longer term mortality. There was limited data on dosage of rehabilitation in many studies. More studies are needed to determine dosage and timing of therapy.
Taito, *et al. PLoS One*. 2018.[21]	RCTs assessing protocolized rehabilitation (including neuromuscular stimulation, passive range of motion, respiratory muscle training, active exercise designed to be more intensive or started earlier than usual care) during		2 (75)	Only two pilot RCTs with 75 total patients (44 intervention, 31 controls) were identified that met inclusion criteria. One study included electrical muscle stimulation, active and passive range of motion, sitting, transfers and ambulation; the second study involved electrical muscle stimulation. There was no difference in ICU or hospital mortality for either study. For one study, the intervention resulted in improved muscle strength at ICU discharge, SF-36 physical function, and SF-36 role physical scores.	There is very low certainty of evidence for the impact of in-hospital protocolized rehabilitation in patients with sepsis given the lack of studies on this topic.

	hospitalization in adult patients with sepsis.				
Cuello-Garcia, et al. J Pediatr. 2018.[22]	Studies assessing early mobilization-based interventions in critically ill children ≤18 years of age admitted to a PICU.	Studies focusing primarily on nonmobility or chest physiotherapy interventions, or interventions initiated after PICU discharge.	11 (1,178)	Study outcomes included mortality (N=11), PICU length of stay (N=7), and PICU-acquired morbidities (N=3). Across 9 observational studies examining mortality, only 4 deaths were reported in 494 children receiving mobilization (0.8%) vs 27 deaths in 720 control children (3.8%); across 2 RCTs, no deaths were reported. PICU length of stay findings were inconsistent across studies, with 3 studies favoring the mobility group, and 1 600-patient study favoring the control group.	Given the variability in study populations and interventions, and high risk of bias, meta-analysis was not possible. The efficacy of early mobilization in critically ill children remains undetermined.
Rehabilitation Interventions					
Mehlhorn, *et al. Crit Care Med*, 2014.[23]	Comparative studies of rehabilitation interventions in adult post-ICU patients measuring quality of life, functional outcome, mortality or hospital readmission.	Studies with interventions beginning in the ICU and studies of disease specific interventions (*e.g.* post-stroke, post-amputation)	18 (2,510)	Studies took place in inpatient (N=4), outpatient (N=9), and mixed settings. Four studies showed positive effects on post-traumatic stress disorder: 2 studies of ICU diaries, one study of an ICU follow-up clinic, and one study of a self-help manual. For no other outcomes did more than one study report positive impacts.	10 studies were rated as having poor methodological quality. All studies were conducted in high-income countries. 12 studies were single-center. 9 studies did not differentiate between primary and secondary outcomes. There was wide variation in outcome measures across studies.
Connolly, *et al. Cochrane Database Systematic Review*, 2015.[24]	Randomized or controlled clinical trials examining exercise interventions initiated after ICU discharge in adult ICU survivors who were mechanically ventilated for at least 24 hours compared to usual care or any other intervention.	Studies of participants who were receiving palliative care, and studies of participants with head injury, trauma, or post-cardiac surgery (since targeted rehabilitation pathways exist for these patients)	6 (483)	Exercise interventions were delivered on ward (N=2), in the community (N=3), or both ward and community (N=1). There was insufficient evidence to determine the impact of exercise-interventions initiated post-ISU on health-related quality of life or exercise capacity. Three studies reported positive results in favor of the intervention; one found a small, short-term benefit in anaerobic threshold, another found a benefit in exercise testing, and a third found improvement in self-reported physical function.	There was wide variability in the interventions, outcome measures, and data reporting. Overall quality of evidence was very low. Only two studies measured health-related quality of life. Meta-analysis was not possible due to the small number of studies and insufficient quality of evidence.
Fuke, *et al. BMJ Open.* 2018.[25]	RCTs examining early rehabilitation in adult ICU patients versus usual care. Early rehabilitation was defined as	Studies in which interventions were initiated prior to ICU admission, or in which early	6 (709)	Study outcomes included ICU-acquired weakness (N=2), muscle strength (N=2), delirium-free days (N=2), anxiety or depression (N=2), quality of life by EQ-5D (N=2), quality of life by SF-36 physical function score (N=2). Incidence of ICU-acquired weakness was reduced in the early rehabilitation group (Odds Ratio 0.42 (95%CI 0.22, 0.82), *p*=0.01. MRC scale score	There were few studies identified, and several were not powered to detect differences in physical or cognitive outcomes. Early mobility interventions varied across studies in terms of timing, intensity,

	starting earlier than usual care, within 7 days of ICU admission, and may include physiotherapy, occupational therapy, and palliative care-related support.	rehabilitation is compared to another intervention.		was improved in the early rehabilitation group, standardized mead difference 0.38 (95%CI 0.10, 0.66, *p*=0.009.	and initiation. Furthermore, interventions were not fully described in some studies
Other Interventions					
Weinreich, *et al. Occup Ther Health Care.* 2017.[26]	Studies evaluating occupational therapy in the ICU.		10 (1,138)	Studies were performed at one (N=7) or two (N=3) medical centers. Four of 10 studies were RCTs. Delirium was improved in 4 of 4 studies assessing it. Hospital and ICU length of stay was reduced in 3 of 3 studies.	Most studies were performed at single academic medical centers, limiting generalizability. Only one study gave specific details on the occupational therapy interventions performed. In all but one study, OT was combined with PT, so the specific contribution of occupational therapy cannot be measured.
Haines, *et al. Crit Care Med*. 2018.[27]	Studies examining peer support interventions in ICU survivors and families.		8 (92 patients; 192 family member)	There were one RCT, four comparative cohort studies, and three qualitative studies. The most common peer support model was group peer support during an ICU stay. Two studies of individual peer support reported reduced psychological morbidity, improved self-efficacy, and improved social support.	There was few studies examining peer support in ICU patients. All studies were conducted in high-income countries (US, Canada, Sweden). Overall methodological quality of included studies was low.
Schofield-Robinson, *et al. Cochrane Database Syst Rev*, 2018.[28]	Studies examining the impact of a structured follow-up programs in ICU survivors compared to no follow-up service or usual care.	Studies examining general post-ICU interventions (not specific to ICU survivors). Studies of specific populations with existing rehabilitation programs (*e.g.* stroke, spinal cord injury, traumatic brain injury)	5 (1,707)	Follow-up services were led by nurses in 4 studies, and a multi-disciplinary team in 1 study. There was no evidence to suggest improvement in quality of life or mortality at 1 year (RR 0.96, 95% CI 0.76 to 1.22). It is uncertain whether follow-up services reduce depression or anxiety, or improves physical function, cognition, or ability to return to work.	All studies were conducted in high-income countries. There is low certainty of evidence regarding follow-up services due to the small number of studies, differences between studies, and risk of bias due to study methodologies. Further evidence is required to establish whether follow-up services are effective in addressing physical and psychological effects of critical illness.

McIlroy, *et al. Crit Care Med.* 2019.[29]	The effect of ICU diaries on psychological outcomes and quality of life of survivors of critical illness and their relatives.		8 (1,208)	Outcome measures included anxiety and depression (N=3), PTSD (N=4) and quality of life (N=2). Length of follow-up ranges from 1 to 36 months. There was an improvement in patients' anxiety [risk ratio 0.3 (0.1, 0.9), *p*=0.02] and depression [risk ratio 0.4 (0.2, 0.9), *p*=0.02] with ICU diaries. There was no reduction in patients' PTSD symptoms [risk ratio 0.75 (0.3, 1.7), p=0.05] among studies that could be pooled, but two studies that could not be pooled reported reduction in PTSD.	Few studies met inclusion criteria. Many included studies were small, observational studies with substantial risk of bias. Differences in reporting methods and length of follow-up limited pooling of study findings; only a maximum of 3 studies were included in the meta-analysis for any of the outcomes.
Research Methods					
Robinson, *et al. J Clin Epi*. 2017.[30]	Studies evaluating the performance characteristics of instruments used to measure physical, cognitive, mental health, and health-related quality of life (HRQOL) in adult ICU survivors.	Studies with <20 patients, studies with only in-hospital outcome assessment.	20 (8,970)	The review identified 20 studies evaluating 21 instruments, of which 11 (52%) assessed quality of life, and few instruments assessed other domains.	There were very few studies for each outcome domain. Overall quality of eligible studies was poor to fair based on Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) initiative checklist. There was insufficient evidence to draw conclusions regarding measurement properties for instruments assessing physical, cognitive, mental health, or quality of life outcomes in adult survivors of intensive care.

*Number of patients is reported when this information is included in the review, or can be tallied from data presented in the review.

Abbreviations and Definitions: COSMIN, Consensus-based Standards for the selection of health Measurement Instruments; CNS, central nervous system; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale, range 0-21, higher scores represent greater anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale, range 0-21, higher scores represent greater depression; HRQOL, health-related quality of life; ICU, intensive care unit; IES, Impact of Event Scale, range 0-88, higher scores represent greater PTSD; IL, interleukin; MRC scale score, Medical Research Council scale score, range 0-5, higher scores indicated greater strength; TNF-α, tumor necrosis factor-alpha; PTSD, post-traumatic stress disorder; SF-36, short form 36, range 0-100, higher scores indicate better quality of life.

Supplemental Table E3: Limitations of Existing Research on Sepsis Survivorship

Topic	Session	Limitations of existing research
Patient Perspective	0 (Opening)	Narrative Evidence (Stories of post-ICU difficulties, but less knowledge of actual epi)
Cognitive Impairment	1 (New Symptoms & Disability)	Lack of data on pre-illness chronic health conditions
Cognitive Impairment	1 (New Symptoms & Disability)	Lack of data on pre-illness health trajectories
Cognitive Impairment	1 (New Symptoms & Disability)	Limited data on risk factor
Cognitive Impairment	1 (New Symptoms & Disability)	Few RCTs on cognitive outcomes
Cognitive Impairment	1 (New Symptoms & Disability)	Few interventional studies to improve recovery
Cognitive Impairment	1 (New Symptoms & Disability)	Lack of data on dose-response (severity of sepsis --> severity of cognitive impairment)
Cognitive Impairment	1 (New Symptoms & Disability)	Informant censoring due to death and loss to follow-up
Cognitive Impairment	1 (New Symptoms & Disability)	Lack of control groups; lack of knowledge of what constitutes an appropriate control group
Cognitive Impairment	1 (New Symptoms & Disability)	Need studies beyond 2 years
Cognitive Impairment	1 (New Symptoms & Disability)	Heterogeneity of Outcome Measures
Cognitive Impairment	1 (New Symptoms & Disability)	Concern (over estimation) of respondent burden
Physical Disability	1 (New Symptoms & Disability)	Lack of control groups
Physical Disability	1 (New Symptoms & Disability)	Lack of data on pre-illness chronic health conditions
Physical Disability	1 (New Symptoms & Disability)	Lack of data on pre-illness health trajectories
Physical Disability	1 (New Symptoms & Disability)	Volitional testing using in almost all studies (which is affected by neuro-psych testing)
Physical Disability	1 (New Symptoms & Disability)	Survivor bias and other missing data
Psychological	1 (New Symptoms & Disability)	Research on psychological outcomes is less sophisticated for ICU survivors compared to other populations (e.g. Veterans)
Psychological	1 (New Symptoms & Disability)	Research is not programmatic
Pediatric	1 (New Symptoms & Disability)	Paucity of pediatric-specific studies
Pediatric	1 (New Symptoms & Disability)	Not feasible to power for reduction all-cause PICU mortality
Pediatric	1 (New Symptoms & Disability)	Difficult & expensive to enroll patients
Is sepsis different?	1 (New Symptoms & Disability)	Lack of control groups
Is sepsis different?	1 (New Symptoms & Disability)	Lack of standard definitions
Is sepsis different?	1 (New Symptoms & Disability)	Lack of standard outcome groups
Microbiome	2 (Biological Mechanisms)	Microbiome is complex--affected by exposures, antibiotics, diet, hormones, immune status. Difficulty to identify

		precise driver(s).
Microbiome	2 (Biological Mechanisms)	Difficult to conduct longitudinal studies, where patient serves as its own control
Immune suppression	2 (Biological Mechanisms)	Sepsis definition: one syndrome, many diseases!
Immune suppression	2 (Biological Mechanisms)	Concept/model is an over-simplification
Immune suppression	2 (Biological Mechanisms)	compartment: bloodstream studies
Immune suppression	2 (Biological Mechanisms)	technology on an issue (single-cell, omics)
Immune suppression	2 (Biological Mechanisms)	analyses of big data, system biology
Mitochondrial Dysfunction	2 (Biological Mechanisms)	Measurements: tissue, function, DNA
Mitochondrial Dysfunction	2 (Biological Mechanisms)	Follow-up: death, duration
Mitochondrial Dysfunction	2 (Biological Mechanisms)	Sample size
Less Is More	3 (In-Hospital Practices)	Focus on mortality as outcome
Less Is More	3 (In-Hospital Practices)	Lack of measures of long-term consequences
Early Mobility	3 (In-Hospital Practices)	No phase III studies of early mobility in ICU / implementation without confirming benefit or harm
Early Mobility	3 (In-Hospital Practices)	Which intervention to use? (cycling, active v passive, functional rehab)
Early Mobility	3 (In-Hospital Practices)	Few studies in sepsis patients in particular
Early Mobility	3 (In-Hospital Practices)	Heterogeneity of Outcome Measures / unable to pool long-term functional data
Early Mobility	3 (In-Hospital Practices)	Loss to follow-up, up to 30% across rehab trials
Cognitive Rehab	3 (In-Hospital Practices)	Few studies of cognitive rehab in ICU populations
Cognitive Rehab	3 (In-Hospital Practices)	Limited rehabilitation methods evaluated
Cognitive Rehab	3 (In-Hospital Practices)	Small samples
Cognitive Rehab	3 (In-Hospital Practices)	Lack of longitudinal follow-up
Cognitive Rehab	3 (In-Hospital Practices)	Little differentiation of which cognitive deficit is being rehabilitated
Cognitive Rehab	3 (In-Hospital Practices)	Combined therapies; hard to assess what is causing effect
Cognitive Rehab	3 (In-Hospital Practices)	Compensatory strategies (ie adaptation) not tried
Cognitive Rehab	3 (In-Hospital Practices)	variable times and number of rehabilitation sessions
Cognitive Rehab	3 (In-Hospital Practices)	Lack of assessment of variables that may influence rehabilitation
Cognitive Rehab	3 (In-Hospital Practices)	Loss to follow-up
Reducing Patient Distress	3 (In-Hospital Practices)	Paucity of symptom-guided intervention studies to manage patient distress
Reducing Patient Distress	3 (In-Hospital Practices)	No comprehensive assessment of symptoms and factors that contribute to patient distress

Reducing Patient Distress	3 (In-Hospital Practices)	Limitations of pharmacological therapy only
Reducing Patient Distress	3 (In-Hospital Practices)	Symptoms are not adequately managed when medications are administered by clinicians based on patient motor movement only
Reducing Patient Distress	3 (In-Hospital Practices)	Illness severity and point of patient recovery
Reducing Patient Distress	3 (In-Hospital Practices)	Heterogeneity of responses and patient samples
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Residual confounding -- difficult to isolate impact of sepsis
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Variable cohort inclusions / exclusions
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Variable (or no) comparisons/controls
Post-ICU Clinic / telemed	4 (Scaffolding Post-D/C)	Little research in the "Post-ICU" space
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	Models have not been truly inter-disciplinary
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	Interventions have lacked robustness
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	Minimal family involvement
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	Patients often relatively healthy
Peer Support	4 (Scaffolding Post-D/C)	Peer Support is just another credible idea
Peer Support	4 (Scaffolding Post-D/C)	No proof that peer support works
Peer Support	4 (Scaffolding Post-D/C)	Peer support may be harmful in certain scenarios (e.g. pts with depression)
Peer Support	4 (Scaffolding Post-D/C)	Only beginning to formalize process of identifying "eligible" patients
Peer Support	4 (Scaffolding Post-D/C)	Supported by SCCM, UK Health Foundations, but not high-quality research organizations
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Data available is scarce
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Small studies
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Lack of appropriate controls
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Non-representative samples
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Post-discharge follow-up is incipient and not focused on sepsis
Awareness	4 (Scaffolding Post-D/C)	Awareness/advocacy limited to select countries
Physical Medicine & Rehabilitation	5 (Improve Research/Translation)	Issue of premorbid vulnerability
Physical Medicine & Rehabilitation	5 (Improve Research/Translation)	Risk factors
Physical Medicine & Rehabilitation	5 (Improve Research/Translation)	Extremophiles
Physical Medicine & Rehabilitation	5 (Improve Research/Translation)	Unequal access to rehab in US

Supplemental Table E4: Gaps of Existing Research on Sepsis Survivorship

Topic	Session	Gap (What hasn't been studied)
Patient Perspective	0 (Opening)	Lack of studies on persistent inflammation.
Cognitive Impairment	1 (New Symptoms & Disability)	Understand risk and protective factors
Cognitive Impairment	1 (New Symptoms & Disability)	Modifiable vs non-modifiable risk factors
Cognitive Impairment	1 (New Symptoms & Disability)	Genetic risk factors (e.g. Apoe 4)
Cognitive Impairment	1 (New Symptoms & Disability)	Interplay between environment and genes
Cognitive Impairment	1 (New Symptoms & Disability)	Little knowledge of recovery (one vs. multiple trajectories of physical, cognitive, mental health, etc. recovery)
Cognitive Impairment	1 (New Symptoms & Disability)	How does sepsis increase risk for dementia (?accelerate the ongoing health trajectories, new injury cascade to dementia, inflammatory cascade, damage to specific brain regions?)
Cognitive Impairment	1 (New Symptoms & Disability)	Is sepsis unique?
Cognitive Impairment	1 (New Symptoms & Disability)	Can cognitive impairment be prevented?
Cognitive Impairment	1 (New Symptoms & Disability)	Mechanism of injury in relation to morbidities
Cognitive Impairment	1 (New Symptoms & Disability)	Role of post-ICU events in cognitive impairment / dementia
Cognitive Impairment	1 (New Symptoms & Disability)	What interventions during critical illness can improve outcome
Cognitive Impairment	1 (New Symptoms & Disability)	The natural course of recovery?
Physical Disability	1 (New Symptoms & Disability)	Little combined investigation of mechanisms & strength & functional measures
Physical Disability	1 (New Symptoms & Disability)	Understanding unique contribution of critical illness vs. non-ICU hospitalization
Psychological	1 (New Symptoms & Disability)	Psychotherapeutic clinical trials are virtually non-existent
Psychological	1 (New Symptoms & Disability)	No development of distinctive treatment models
Psychological	1 (New Symptoms & Disability)	Little/no attention paid to the contributions of PTSD to cognitive impairment
Psychological	1 (New Symptoms & Disability)	Little focus on PTSD contribution to other conditions (e.g. substance abuse)
Psychological	1 (New Symptoms & Disability)	No studies of post-traumatic growth
Pediatric	1 (New Symptoms & Disability)	What is the most important outcomes for pediatric sepsis trials? Survival, physical function, quality of life? --> subject composite of death and residual morbidity
Pediatric	1 (New Symptoms & Disability)	How and when to measure patient outcomes (lots of different scales /measures in use)
Pediatric	1 (New Symptoms & Disability)	Are patient-importance outcomes amenable to PICU interventions? (Are there modifiable factors contributing to survivorship experience?)
Is sepsis different?	1 (New Symptoms & Disability)	What is specific to sepsis vs critical illness, treatments received?

Microbiome	2 (Biological Mechanisms)	Identification of normal vs abnormal signature patterns
Microbiome	2 (Biological Mechanisms)	Examination of host genetics
Microbiome	2 (Biological Mechanisms)	Attempt to link specific disease severity of changes in microbiome
Microbiome	2 (Biological Mechanisms)	Development of innate and acquired immunity as a result of exposure to specific microbes
Immune suppression	2 (Biological Mechanisms)	Longitudinal studies of immunity in sepsis
Immune suppression	2 (Biological Mechanisms)	Lack of an integrated functional measurement of net immunity
Immune suppression	2 (Biological Mechanisms)	Compartment: primary site
Immune suppression	2 (Biological Mechanisms)	Long-term implications
Immune suppression	2 (Biological Mechanisms)	Endpoints/outcomes (immunological, clinical)
Mitochondrial Dysfunction	2 (Biological Mechanisms)	Long-term effects of sepsis
Mitochondrial Dysfunction	2 (Biological Mechanisms)	Impact on Brain
Mitochondrial Dysfunction	2 (Biological Mechanisms)	Effect of sepsis vs. treatments
Less Is More	3 (In-Hospital Practices)	Understanding post-ICU trajectory
Less Is More	3 (In-Hospital Practices)	Impact on Family & Caregivers
Early Mobility	3 (In-Hospital Practices)	Which patients respond to early mobility?
Early Mobility	3 (In-Hospital Practices)	Are sepsis patients different?
Early Mobility	3 (In-Hospital Practices)	Baseline measures of function
Early Mobility	3 (In-Hospital Practices)	Timing of early mobility?
Early Mobility	3 (In-Hospital Practices)	Dose of early mobility?
Early Mobility	3 (In-Hospital Practices)	Type of intervention? Passive / active / combined with nutrition / pharmacological
Early Mobility	3 (In-Hospital Practices)	Long-term safety unclear
Early Mobility	3 (In-Hospital Practices)	Which functional outcome measure is best? When to measure?
Cognitive Rehab	3 (In-Hospital Practices)	Limited knowledge of cognitive rehabilitation
Cognitive Rehab	3 (In-Hospital Practices)	Limited knowledge of different types of cognitive rehabilitation
Cognitive Rehab	3 (In-Hospital Practices)	Limited knowledge of timing and number of sessions
Cognitive Rehab	3 (In-Hospital Practices)	Little knowledge of recovery
Cognitive Rehab	3 (In-Hospital Practices)	Link between cognitive impairment and dementia
Cognitive Rehab	3 (In-Hospital Practices)	Progressive vs stable impairments
Cognitive Rehab	3 (In-Hospital Practices)	Relationship between recovery and rehabilitation
Cognitive Rehab	3 (In-Hospital Practices)	Generalizability
Cognitive Rehab	3 (In-Hospital Practices)	Stability of cognitive effects over time
Cognitive Rehab	3 (In-Hospital Practices)	Pre-hab?
Cognitive Rehab	3 (In-Hospital Practices)	Cognitive impairments not amenable to damage (e.g. hippocampal damage/atrophy and memory)
Cognitive Rehab	3 (In-Hospital Practices)	Engaging participants in rehab

Cognitive Rehab	3 (In-Hospital Practices)	Lack of awareness of deficits
Cognitive Rehab	3 (In-Hospital Practices)	Lack of understanding of variables that may influence cognitive rehab
Reducing Patient Distress	3 (In-Hospital Practices)	Untangle complexity of patients' response to critical illness, sepsis, holistic perspective
Reducing Patient Distress	3 (In-Hospital Practices)	How to attempt symptoms assessments
Reducing Patient Distress	3 (In-Hospital Practices)	How to assess symptoms in unconscious/unresponsive patients? Biomarkers?
Reducing Patient Distress	3 (In-Hospital Practices)	Revisit clinical practice guidelines (e.g. PAD guideline); ethical to administer opioids?
Reducing Patient Distress	3 (In-Hospital Practices)	Patient respect and dignity
Reducing Patient Distress	3 (In-Hospital Practices)	Patient-centered outcomes over time besides mortality
Reducing Patient Distress	3 (In-Hospital Practices)	Adjunctive, multi-model symptoms management interventions for distress need to be tested
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Lack of data on certain later outcomes (e.g. cancer)
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Mechanisms of long-term morbidity (inflammation, immunopathy, microbiome disruption, etc.)
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Assessment of ongoing biological dysregulation in practice
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Treatment for ongoing derangements (e.g. inflammation, immunopathy)
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Lack of best clinical practices for managing patients post-sepsis
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Lack of data on comparative effectiveness of specialized post-ICU clinic, telemed, enhanced primary care, case mgmt, etc.
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	How to integrate inter-disciplinary teams
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	Exploration of dose-effect; how much treatment is needed to facilitate best outcomes
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	Limited information on what patients want from a post-ICU clinic
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	Limited knowledge of which outcomes to study
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	What represents the low-hanging fruit?
Peer Support	4 (Scaffolding Post-D/C)	Optimal matching of team, structure, patients, resources unknown; little effort to theorize matching
Peer Support	4 (Scaffolding Post-D/C)	How to include informal caregivers
Peer Support	4 (Scaffolding Post-D/C)	Unclear how to shape peer support conversation to maximize usefulness

Peer Support	4 (Scaffolding Post-D/C)	No clear funder who sees post-sepsis behavioral/social/environmental problems as a core problems
Peer Support	4 (Scaffolding Post-D/C)	No linkage on whether adaptations only cover for underlying physiology or can fix (like exercise -> cognition)
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Do not know burden of sepsis survivorship in LMIC
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	No national data from LMIC
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Don't know predictors for early death and hospital readmission
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Don't know predictors of long-term morbidity / mortality
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	What is the impact of post-discharge interventions?
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Lack of information for caregivers or survivors' alliances
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	No government initiatives
Awareness	4 (Scaffolding Post-D/C)	Lack of comprehensive & cohesive rehab concepts
Awareness	4 (Scaffolding Post-D/C)	Lack of sepsis-specific rehab services
Awareness	4 (Scaffolding Post-D/C)	Poor understanding of GPs, physiotherapist, rehab facilities on sepsis sequelae
Awareness	4 (Scaffolding Post-D/C)	Poor understanding of patients and families about long-term sepsis-related disabilities
Awareness	4 (Scaffolding Post-D/C)	Research deficits on sepsis sequelae
Physical Medicine & Rehabilitation	5 (Improve Research/Translation)	Predictive factors of long-term function
Physical Medicine & Rehabilitation	5 (Improve Research/Translation)	Lack of longer-term follow-up
Physical Medicine & Rehabilitation	5 (Improve Research/Translation)	Resilience factors
Physical Medicine & Rehabilitation	5 (Improve Research/Translation)	Longer-term genetic response
Physical Medicine & Rehabilitation	5 (Improve Research/Translation)	Activity dosage post-ICU

Supplemental Table E5: Aligning study control group to study question and interpretation

Control Population	Question	Interpretation*
 Age- and sex-matched population controls	How do outcomes differ between sepsis survivors and average people?	Differences in outcomes may be explained by sepsis, but may also be explained by the factors that put people at risk for sepsis (*e.g.* comorbid disease, frailty, *etc.*)
 Non-hospitalized controls, matched by age, sex, baseline health status, health trajectory.	What is the effect of sepsis, including the effect of being acutely ill and in the hospital?	Differences in outcomes may be explained by acute illness, hospitalization, or sepsis.
 Hospitalized controls with non-sepsis infection, matched by age, sex, baseline health status, health trajectory.	What is the incremental effect of sepsis, above and beyond the effect of being ill and in the hospital?	Difference in outcomes may be explained by acute organ injury and its treatment.
 Hospitalized controls matched by age, sex, baseline health status, health trajectory, and acute illness severity or acute physiologic derangement.	For a given degree of acute illness, does the outcome differ depending on whether the acute illness is due to sepsis versus due to other causes?	Differences in outcomes may be explained by differing impact of sepsis-related versus non-sepsis-related physiologic derangements, or by differences in treatment for sepsis-related versus non-sepsis-related physiologic derangements.

When designing and interpreting matched cohort studies, it is important to consider the control population. Here, we present common control groups used in sepsis studies, the questions answered by comparison to these control groups, and the interpretation of findings.
*For all observational studies, there is always the possibility that differences are explained by confounding–this is, by unmeasured characteristics, or any characteristic not including in the matching process (*e.g.* genetic predisposition to sepsis)

Supplemental Table E6: Next Steps Identified by Participants

Topic	Session	Next Steps
Cognitive Impairment	1 (New Symptoms & Disability)	How sepsis increases risk for dementia
Cognitive Impairment	1 (New Symptoms & Disability)	Why cognitive impairments develop in patients with no pre-illness impairments
Cognitive Impairment	1 (New Symptoms & Disability)	What factors determine trajectory of cognitive function after sepsis
Cognitive Impairment	1 (New Symptoms & Disability)	What mechanisms underpin cognitive impairments
Cognitive Impairment	1 (New Symptoms & Disability)	Studies of pre-illness brain imaging to track time course of recovery and link to cognitive function
Cognitive Impairment	1 (New Symptoms & Disability)	How do pathogens, inflammatory response, length of hospitalization, comorbidities, disability, and early rehabilitation contribute to outcomes?
Cognitive Impairment	1 (New Symptoms & Disability)	Studies of therapies and rehabilitation interventions to prevent / remediate cognitive impairments
Cognitive Impairment	1 (New Symptoms & Disability)	Can we predict in hospital who will develop long-term cognitive impairment (cognitive screening tests)
Physical Disability	1 (New Symptoms & Disability)	Advancing ultrasound as an assessment tool
Physical Disability	1 (New Symptoms & Disability)	Non-volitional assessment for ICUAW & instrumental tests (FEES & VFSS) for swallow
Physical Disability	1 (New Symptoms & Disability)	Integrative work (eg. combining respiratory, limb & swallowing muscles; simplified EPS, histology, imaging, strength & function; physical, cognitive & psych, including fatigue)
Physical Disability	1 (New Symptoms & Disability)	Understand value of frailty phenotype in ICU
Physical Disability	1 (New Symptoms & Disability)	Understanding other phenotypes and endotypes
Psychological	1 (New Symptoms & Disability)	Integrative neuro-imaging into investigations of PTSD
Psychological	1 (New Symptoms & Disability)	Develop & test distinctive models of treatment, eg for ICU-related PTSD
Psychological	1 (New Symptoms & Disability)	Cast a broader net on psychological outcomes beyond PTSD, anxiety, and depression
Psychological	1 (New Symptoms & Disability)	Determine which aspects of PSTD are most harmful to function, so that they can become intervention targets
Psychological	1 (New Symptoms & Disability)	Explore how to facilitate post-traumatic growth
Pediatric	1 (New Symptoms & Disability)	Screening criteria to identify at-risk patients & families, agreement on measurement metrics
Pediatric	1 (New Symptoms & Disability)	Core outcome sets
Pediatric	1 (New Symptoms & Disability)	Mechanistic studies
Pediatric	1 (New Symptoms & Disability)	Matching outcomes to interventions

Pediatric	1 (New Symptoms & Disability)	Alternative trial designs
Pediatric	1 (New Symptoms & Disability)	Qualitative evidence for post-PICU support
Is sepsis different?	1 (New Symptoms & Disability)	Longitudinal cohort studies with good baseline data, standardized sepsis diagnosis, agreed outcomes measures, detailed information during and after hospitalization
Microbiome	2 (Biological Mechanisms)	Stop empiric antibiotics in neonates
Microbiome	2 (Biological Mechanisms)	Combat antimicrobial resistance by stopping antibiotics and improving diversity of gut microbiota
Immune suppression	2 (Biological Mechanisms)	Well-defined homogenous clinical entities
Immune suppression	2 (Biological Mechanisms)	Phenotypes --> end types
Immune suppression	2 (Biological Mechanisms)	Registries and cohorts
Immune suppression	2 (Biological Mechanisms)	Long-term longitudinal studies
Immune suppression	2 (Biological Mechanisms)	De-compartmentalization of physician communities
Immune suppression	2 (Biological Mechanisms)	Patient-oriented research
Immune suppression	2 (Biological Mechanisms)	Defined end-points (morbidity)
Immune suppression	2 (Biological Mechanisms)	Proof of concept studies
Immune suppression	2 (Biological Mechanisms)	Data sharing
Mitochondrial Dysfunction	2 (Biological Mechanisms)	Truly long-term
Mitochondrial Dysfunction	2 (Biological Mechanisms)	Examine function
Mitochondrial Dysfunction	2 (Biological Mechanisms)	Large (mtDNA, plasma)
Mitochondrial Dysfunction	2 (Biological Mechanisms)	Multiple organs: animal models, clinical/translational
Less Is More	3 (In-Hospital Practices)	Taxonomy of care and consequences
Less Is More	3 (In-Hospital Practices)	Patient engagement and guidance
Less Is More	3 (In-Hospital Practices)	Anthology of stories
Less Is More	3 (In-Hospital Practices)	Follow-up Clinics
Early Mobility	3 (In-Hospital Practices)	Confirm long-term benefit or harm in large phase III trials
Early Mobility	3 (In-Hospital Practices)	Test EM intervention to determine optimal timing, dose, ability to deliver specified dose
Early Mobility	3 (In-Hospital Practices)	Reduce loss-to-follow-up
Early Mobility	3 (In-Hospital Practices)	Core outcome sets
Cognitive Rehab	3 (In-Hospital Practices)	Pre-illness brain imaging to track time course of recovery
Cognitive Rehab	3 (In-Hospital Practices)	Determine which therapies and rehabilitation interventions will prevent or remediate cognitive impairment
Cognitive Rehab	3 (In-Hospital Practices)	Comparison of cognitive interventions
Cognitive Rehab	3 (In-Hospital Practices)	Effect of computerized cognitive rehab therapy, e.g. game-playing
Cognitive Rehab	3 (In-Hospital Practices)	Brain imaging to assess effects of rehab (plasticity - increased cortical thickness)
Cognitive Rehab	3 (In-Hospital Practices)	How to evaluate partial completion of an intervention

Cognitive Rehab	3 (In-Hospital Practices)	Dose and time of intervention
Cognitive Rehab	3 (In-Hospital Practices)	Evaluation of interventions
Cognitive Rehab	3 (In-Hospital Practices)	Global vs focal interventions per cognitive domains
Reduce Pt Distress	3 (In-Hospital Practices)	Novel, multi-modal interventions
Reduce Pt Distress	3 (In-Hospital Practices)	Pragmatic, adaptive and mixed method designs (difficult to get funding, acceptance of risk)
Reduce Pt Distress	3 (In-Hospital Practices)	Large cohort studies over the trajectory of illness through long-term recovery
Reduce Pt Distress	3 (In-Hospital Practices)	leverage Big Data capabilities cooperatively
Reduce Pt Distress	3 (In-Hospital Practices)	Tailored precision medicine initiatives (patient center co- and self-management; omics, patient trajectory of PRO)
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Characterizing prevalence/variation/duration of ongoing biological derangements; and measuring association w/ outcomes
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Assessing ongoing dysregulation (e.g. immunopathy, microbiome derangement) in practice to enrich studies, facilitate epidemiologic evaluation, and clinical management
ICU / Hospital Discharge	4 (Scaffolding Post-D/C)	Exploring health-system solutions for addressing new morbidity; anticipating & mitigating risk for further set-backs
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	Need for focused, well-funded research programs
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	Need for education to facilitate "buy-in" from administrators to support such programs
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	Need to understand balance between "real" and "ideal"
Post-ICU Clinic / telemedicine	4 (Scaffolding Post-D/C)	Need to integrate telemed
Peer Support	4 (Scaffolding Post-D/C)	Continued exploration scaffolded by evaluation structure to allow key features to be extracted and standardized
Peer Support	4 (Scaffolding Post-D/C)	Develop culture of process/outcomes reporting to allow comparative evaluation
Peer Support	4 (Scaffolding Post-D/C)	Waiting list randomization to drive initial evaluations
Peer Support	4 (Scaffolding Post-D/C)	Partner with greater institutional support / evaluation
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Multinational studies to assess post-discharge morbidity and mortality
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Studies to assess predictors for post-discharge mortality and readmissions
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Post-discharge intervention studies and quality improvement
Lower/Middle Income Settings	4 (Scaffolding Post-D/C)	Awareness campaigns
Lower/Middle Income	4 (Scaffolding Post-D/C)	Advocacy

Settings		
Measuring Outcomes	4 (Scaffolding Post-D/C)	Realize on what we have -- build on these (large-scale data sharing / linkage)
Measuring Outcomes	4 (Scaffolding Post-D/C)	EPAD for sepsis?
Awareness	4 (Scaffolding Post-D/C)	Increased awareness of human and economic burden of sepsis-related disability
Awareness	4 (Scaffolding Post-D/C)	Increase number of countries with national sepsis plans in place
Awareness	4 (Scaffolding Post-D/C)	Creation of sepsis-specific rehab services
Awareness	4 (Scaffolding Post-D/C)	Update international sepsis guidelines to address diagnosis and therapy of sepsis sequelae
Awareness	4 (Scaffolding Post-D/C)	Education of patients, GPs, physiotherapist, and rehab facilities on sepsis sequelae
Awareness	4 (Scaffolding Post-D/C)	Certification of acute, long-term, and rehab facilities
Awareness	4 (Scaffolding Post-D/C)	Comprehensive sepsis centers
Rehabilitation	5 (Improve Research/Translation)	Clarify key short- and long-term outcomes in sepsis
Rehabilitation	5 (Improve Research/Translation)	Scan existing measures to see if conceptual needs can be met
Rehabilitation	5 (Improve Research/Translation)	Potential use and/or development of IRT outcome metrics
Rehabilitation	5 (Improve Research/Translation)	Importance of large-scale cohort studies looking across the entire episode
Trial Design	5 (Improve Research/Translation)	Replicate EPAD for sepsis (cast a big tent and invite all: patients, families, advocacy, industry, regulatory authorities, academia)
Trial Design	5 (Improve Research/Translation)	Create an international registry/cohort: promise help (short-term) and learning (for better long-term help)
Trial Design	5 (Improve Research/Translation)	Consider layering into the cohort an APT: multiple subgroups/subtypes; multiple putative interventions
Trial Design	5 (Improve Research/Translation)	Develop non-mortality outcome; Follow FDA "Critical Path" process for proxy outcome development

Supplemental Table E7: Prioritization of strategies to “do more with what we have”

Rank	Idea	Votes, N (%)
1	Merging ICU databases across countries/developing consensus harmonized data elements “share w/o sharing”	21 (15.2%)
1	Develop/disseminate educational materials for patients/families/outpatient documents for care transitions	21 (15.2%)
3	Deep connections with sepsis survivor groups to build research priorities	20 (14.5%)
4	Supporting learning networks of post-ICU clinics	16 (11.6%)
5	Linking ICU data to data sets of longer term outcomes	12 (8.7%)
6	Identify and collect data on key baseline factors modifying risk/treatment effect	10 (7.2%)
6	Phenotype/endotype patients	10 (7.2%)
8	Don’t wait to collect stool (at admission, discharge and later) for microbiome studies	8 (5.8%)
8	map what we have – systematic review of existing resources and knowledge	8 (5.8%)
10	Determine/define the patient important/core outcomes in Sepsis – adults and pediatrics	5 (3.6%)
11	Mixed Methods – Investigation of patient centered outcomes over trajectory of recovery	3 (2.2%)
11	Supporting global burden of disease study	3 (2.2%)
13	Robust funding for novel intervention studies that are adaptive to patient needs over trajectory of recover	1 (0.7%)

Supplemental Table E8: Prioritization of strategies to “develop and deliver more”

Rank	Idea	Votes, N (%)
1	Integrated global cohort study, linking mechanisms to long-term outcomes	24 (17.4%)
2	Global harmonized registry for sepsis patients	22 (15.9%)
3	Detailed long-term longitudinal follow up to characterize heterogeneity of recovery post-sepsis	20 (14.5%)
4	Automatic linage of Electronic Health Record data to cohorts/RCTs	18 (13.0%)
5	Consider impacts of sepsis on family	12 (8.7%)
6	Expansion and granular outcomes assessed in routine care	11 (8.0%)
7	Computerized adaptive testing (CAT) item-response theory (IRT) question bank for sepsis long-term outcomes	9 (6.5%)
8	Better animal models/mechanistic studies	7 (5.1%)
9	Linkages between cellular/behavioral systems	6 (4.3%)
10	Acceptance of post sepsis morbidity as a global health priority by government’s and major funders (Wellcome Trust, *etc.*)	5 (3.6%)
11	Sepsis Survivors Ribbon	4 (2.9%)

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