**Appendix A: Agenda for the May 21st, 2019, international consensus conference on prediction and identification of long-term impairments after critical illness.**

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| **Topic** | **Speaker** | **Time Allocation** |
| Breakfast |  | **7:00am – 7:30am** |
| Introduction: Outline agenda; goals for the day and timeline | Co-Chairs: Mark Mikkelsen and Mary Still | **7:30am – 7:40am** |
| Ground rules and fundamental group commitments | Jack Iwashyna | **7:40am – 7:50am** |
| Patients’ insights | Hali Felt & Alison Clay | **7:50am – 8:10am** |
| General goal, through the first 2 questions, is to be able to address the question: “Who should be screened for new, long-term impairments in cognition, mental health, or physical health (hereafter, PICS) after hospital discharge?” In question 3, we tackle the question “what should be used to screen for PICS (and when should we assess)?” |
| **Question 1: 8:15am – 9:45am** |
| Can we predict new, long-term cognitive, mental health, or physical impairment (i.e., PICS) in adult survivors of critical illness? Lessons learned from an original systematic review.Co-Leads: Kimberley Haines and Jo McPeakeStatistical Advisor: Michael Harhay |
| Goals  | Speaker | Time Allocation |
| Framing for our review - Methodological discussion and how our approach evolved | Michael Harhay  | **8:15am – 8:30am** |
| What we did – PICO question, methodology employed What we found – Screening results and results from random sample of 30 studies (study characteristics, outcome measurement, predictors) | Kimberley Haines | **8:35am – 8:50am** |
| Next steps, preliminary conclusions, and 3-5 suggestions to advance the field in the future  | Joanne McPeake  | **8:55am – 9:10am** |
| **9:15am – 9:45am** |
| Moderated discussion, led by Jack Iwashyna, focused on the preliminary conclusions and future directions to be able to “predict long-term impairment in survivors of critical illness,” including agreement on 3-5 future research agenda items related to PICS prediction (c. 30 minutes). Goals at the conclusion: * Establish agreement on 3-5 future research agenda items related to this question.
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| **9:45am – 10:00am – break** |
| **Question 2:** **10:00am – 12:00pm** |
| Can we identify survivors most likely to develop new impairments in cognition, mental health, or physical health after critical illness? Lessons learned from prior systematic reviews and recent original research Co-Leads: Lauren Ferrante and Nate Brummel |
| Risk factors associated with long-term cognitive impairment after critical illness | Mona Hopkins and Brian Anderson | **10:00am - 10:15am** |
| Risk factors associated with long-term mental health impairment after critical illness | Jim Jackson and Joe Bienvenu | **10:20am – 10:35am** |
| Risk factors associated with long-term physical impairment after critical illness | Lauren Ferrante and Nate Brummel | **10:40am – 10:55am** |
| Original research: Development and validation of a risk prediction tool for post-ICU functional decline (physical function domain) | Lauren Ferrante | **11:00am – 11:15am** |
| Risk factors associated with PICS | Nate Brummel | **11:20am – 11:35am** |
| A Complementary Look: Risk Factors Identified Through Question 1 Systematic Review of Original Research | Kimberley Haines, Joanne McPeake, and Michael Harhay | **11:40am – 11:55am** |
| **12:00pm – 1:00pm Working Lunch** |
| Moderated discussion, led by Jack Iwashyna, related to question 2 (30-45 minutes). Goals at the conclusion: * Can we recommend risk factors that would trigger interventions and screening assessments for cognitive/mental health/physical impairment?
* Do these align with current practice (e.g., ICU diaries, post-ICU clinics)?
* Establish agreement on 3-5 future research agenda items related to this question.
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| **Question 3:** **1:00pm – 3:00pm** |
| How and when should we screen for long-term cognitive, mental health, and physical impairments in survivors of critical illness? * Co-Leads: Carla Sevin and Ashley Montgomery-Yates
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| Review of core outcomes set for research among survivors of acute respiratory failure (focus on instruments selected to assess cognitive, mental health, and physical function) | Dale Needham | **1:00pm – 1:30pm** |
| Original research: PICS screening tool  | Babar Khan  | **1:35pm – 1:50pm** |
| Screening tests employed in clinical practice, a report from the Thrive Post-ICU Clinic Collaborative  | Carla Sevin and Ashley Montgomery-Yates | **1:55pm – 2:10pm** |
| When to screen? | Carla Sevin and Ashley Montgomery-Yates | **2:15pm – 2:30pm** |
| **2:30pm – 3:00pm** |
| Moderated discussion, led by Jack Iwashyna, related to question 3 Goals at the conclusion: * Can we recommend screening tests to identify potential PICS patients (1 tool per domain? Multiple?)
* Establish agreement on 3-5 future research agenda items related to this question.
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| Wrap-up and next steps | Mark Mikkelsen and Mary Still | **3:00pm – 3:30pm**  |

**Appendix B: Background on “Can We Predict PICS?”**

 For the original systematic review, we designed a search strategy, in consultation with an experienced information specialist, using a 10-year publication window (i.e., 2009-2019) to identify contemporary publications in the peer-reviewed literature that would reflect the current state of PICS prediction. For additional detail of the methodology used for the systematic review, please refer to the accompanying manuscript by Haines *et al* (17).

The search strategy identified more than 130 full-text articles that were potentially eligible for inclusion based on our criteria (PROSPERO CRD42018117255). Through full-text assessment, the majority of these studies were not classified as “prediction” studies, but rather as “predictor finding studies.” These types of studies, also known as risk factor or prognostic factor studies, differ from “prediction” studies as they aim to identify individual predictors, such as age, disease stage, or biomarkers, that contribute to the prediction of a diagnostic or prognostic outcome (18). The goal of these types of studies can be thought of as causal or etiologic in nature.

Comparatively, “prediction model studies” aim to develop, validate, or update a multivariable prediction model. The goal of a prediction model is not to “explain” or “identify” factors associated with a future health state after critical illness. In contrast, the goal of a prediction model is to use multiple predictors in combination, to most accurately estimate the overall patient-specific probabilities of the likelihood of a future health state after critical illness (18).

At the May 2019 meeting, preliminary results, separated into “predictor finding studies” and “prediction model studies,” were presented. Due to the large volume of full-text eligible for inclusion, we reviewed a random sample of thirty full-texts studies, including both “predictor finding” and “prediction model” studies, as a representative example of the state of the literature.

Recommendations for future research were discussed and include standardized timing of outcome measurement(s), use of recommended measurement instruments to support across study comparisons and synthesis, and improving methodological rigor and reporting for prediction studies—potentially aligning with recent work on Core Outcome Measures (16), even though such core outcome measure development processes were not, per se, designed for this exact purpose.

Following the May meeting, the systematic review was completed, focused on prediction model studies. As summarized in the accompanying paper by Haines et al (17), prediction models of long-term outcomes after critical illness are extremely limited, with only three studies that developed a score or formula to predict a PICS domain, none of which included external validation.

**Appendix C: Can we identify survivors at high-risk?**

Using the pre-existing systematic reviews, risk factors associated with long-term cognitive, mental health, and physical impairment were summarized. In addition, relevant original research, identified pre-conference, was presented, including studies that examined risk factors associated with new, long-term impairments (4) and the development and validation of a risk prediction tool for post-ICU functional decline (19). In the former, more years of education was protective of developing new long-term impairments at three and 12-months, and frailty was a risk (4).

To identify pre-existing systematic reviews, an experienced medical information specialist developed and tested the search strategy. The search strategies (available upon request to the corresponding author) were reviewed by another senior information specialist using the PRESS Checklist (20) and with the review team. The searches were performed in the PubMed and Cochrane Library databases in April, 2019.

We applied a systematic review filter and limited our search to systematic reviews published within the last 20 years. We did not apply language restrictions. Experts subsequently reviewed their own files for studies that met the criteria but were not included in the search. Two reviewers independently reviewed each study abstract to determine if the study met criteria for full text review.

Inclusion criteria were systematic reviews that included studies of adult ICU patients in which post-ICU cognitive function, mental health, or physical function was assessed and risk factors were assessed. Studies that were solely descriptive, were prevalence studies only, included pediatric patients, family of ICU patients, or primarily included unique ICU populations (e.g. cardiac surgery, traumatic brain injury, transplant) were excluded.

**Cognitive Impairment**

A total of 97 studies were identified through database searches; 9 studies were duplicates resulting in a total of 88 unique studies identified through the database search. Experts identified 4 additional studies from personal files and references. Of the 92 studies that were reviewed, 80 studies were excluded after abstract review and 12 studies underwent full text review. Of the 12 studies that underwent full text review, 8 were subsequently excluded (cognitive function not assessed in 4 studies, risk factors not assessed in 3, only included animal studies in 1) leaving 4 studies for data extraction (21-24). Due to heterogeneity, none of the 4 systematic reviews were able to perform meta-analyses of suspected risk factors.

The first systematic review focused on the association of delirium and post-ICU cognitive function. Therein, the presence of delirium and the duration of delirium were identified as risk factors for worse global cognitive function at 3 and 12 months (21).

The second systematic review evaluated benzodiazepine treatment during an ICU stay and its association with short and long-term cognitive impairment and psychiatric outcomes (23). Overall, there was weak evidence for an association of benzodiazepine treatment during an ICU stay with worse executive function (23).

The third systematic review evaluated a broad array of potential risk factors for post-ICU cognitive impairment (24). Similar to the systematic review by Salluh and colleagues (21), delirium was found to be a risk factor for post-ICU cognitive impairment (24). The results for other risk factors found positive associations between cognitive impairment and mechanical ventilation (2 of 14 studies), ICU length of stay (2 of 11 studies), hypoxia (2 of 4 studies), and glucose dysregulation (2 of 2 studies) (24).

The fourth systematic review specifically evaluated risk factors for post-ICU cognitive impairment in sepsis survivors and identified sepsis as an important risk factor for post-ICU cognitive impairment (22). Pre-morbid depression was also found to be a potential risk factor, but was only significant in a single study (22).

**Mental Health**

 Of the 98 studies that underwent title and abstract screening, 9 were eligible for data extraction (25-33). An additional eligible systematic review was identified in the cognitive function search (34).

Five main results are noteworthy. First, having a history of psychiatric illness (e.g., prior anxiety or depressive illness) was a consistent risk factor for post-traumatic stress disorder (PTSD), anxiety, and depressive symptoms after the stress of a critical illness (26, 29, 31-32). Second, early post-ICU memories of frightening in-ICU experiences (e.g., visual hallucinations, persecutory delusions, nightmare-like experiences, pain, and breathing difficulties) were consistently associated with long-term PTSD, anxiety, and depressive symptoms (26-28, 31-32). Third, the dose of in-ICU sedative (especially benzodiazepine) administration was associated with long-term PTSD and anxiety symptoms (26, 29, 32-33), but not depressive symptoms (27, 31). Notably, light sedation protocols were associated, if anything, with less long-term psychiatric morbidity than heavy sedation protocols (30, 34). Fourth, early psychiatric morbidity was associated with later psychiatric morbidity (27, 31-32), and PTSD, anxiety, and depressive symptoms tended to co-occur (27, 29, 31-32). Fifth, age, sex, critical illness severity, and length of stay were consistently not associated with post-ICU psychiatric morbidity (26-27, 29, 31-32).

**Physical Function**

 Of the 76 studies that underwent title and abstract screening, 10 studies underwent full-text review. Of these, 7 studies were ineligible (wrong outcomes or wrong study design), leaving 3 studies eligible for data extraction.

The first study, a systematic review of post-ICU dependency in instrumental activities of daily living (IADLs) (35), identified pre-ICU IADL dependency, cognitive impairment, and mechanical ventilation as being positively associated with post-ICU IADL dependency. There were inconsistent results regarding ICU delirium as a risk factor. Importantly, older age and severity of illness were not consistently associated with post-ICU IADL dependency. The second study, a systematic review of frailty and post-ICU outcomes (36), included critical care studies that used the three most common frailty indices: the Fried frailty phenotype (37), the "accumulation of deficits" index (38), or the Clinical Frailty Scale (39). This review found that frailty was associated with increased disability (measured with the Katz Index of Independence in Activities of Daily Living) (40) or death at 6 months and 1 year as well as IADL disability at 12 months. The third systematic review was mostly descriptive, without identifying any specific risk factors for physical function impairment, but did note that patients who returned to work were younger (39 vs. 51 years) and in better preadmission health (41).

Experts identified 10 additional articles from their own files that were not included in systematic reviews (42-51). These 10 articles reported 5 factors associated with worse disability and 5 factors associated with worse physical function. Factors associated with worse disability (e.g., activities of daily living and mobility) included hospitalization for sepsis (42), mechanical ventilation (43), sensory impairment (i.e., hearing impairment or vision impairment) (44), worse functional trajectory (i.e., greater disability) in the months prior to critical illness (45), older age (46-47), and ICU length of stay (46). Factors association with worse physical function (e.g., worse muscle strength, slower walking speed) included older age (48-51), coexisting medical conditions (50-51), more days of bed rest (48), more days of continuous sedation (49), greater severity of illness (51), and longer length of stay in the ICU (49-50).

**Appendix D: How and When to Screen?**

The Healthy Aging Brain Care Monitor Self Report (HABC-M SR) is a 27-item self-administered survey; 3 subscales assess physical, psychological, and cognitive symptoms. Wang et al sought to validate the HABC-M SR as a clinical tool for detecting post-intensive care syndrome in 142 patients attending a post-ICU clinic within 3 months of hospital discharge (58). Mean age was 52.3 years; 48% were female, 46% were African American. Mean length of ICU stay was 12.1 days. Almost all had acute respiratory failure; 46% had delirium. The total scale and all subscales had good to excellent internal consistency (Cronbach α, 0.83-0.92). Scores on the psychological subscale strongly correlated with standardized measures of psychological symptoms (Spearman correlation coefficient, 0.68-0.74). Results on the cognitive subscale correlated with the delayed memory measure (-0.51). Scores on the physical subscale correlated with the Physical Self-Maintenance Scale (-0.26). Patients with post-intensive care syndrome had significantly worse scores on subscales and total scores on the Healthy Aging Brain Care Monitor than did primary care patients.

The Thrive Post-ICU Clinic Collaborative is comprised of clinician teams at 21 centers; 19 of these were actively seeing patients in a dedicated, outpatient clinic at the time of the May 2019 meeting and 18 of these 19 reported data presented at the conference. The selection of tools used to screen for PICS-associated problems is an iterative process, subject to constant refinement by individual centers, and in many cases informed by the Collaborative as a group. The evolving focus of these centers has been on clinically actionable data, although many of the tools used in this population were developed for research purposes. The clinical application of these tools in pragmatic ICU survivor populations is to be described in more detail in a separate report from the SCCM Thrive Post-ICU Collaboratives.