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EDITORIAL

Improving outcomes after critical illness: harder than we thought!

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Introduction

In this edition of *Intensive Care Medicine*, Nordisk et al. report the results of the RAPIT study [1], a pragmatic, multicenter, randomized controlled trial of a nurse-led individualized intensive care unit (ICU) recovery program compared to standard care. The intervention group received consultations that included a guided illness narrative supported with photographs taken by ICU nurses during ICU care. This trial randomized 386 adults and found no difference in the primary outcome of health-related quality of life (QoL). It adds to the growing number of trials that have failed to improve patient-centered outcomes after critical illness (Table 1), and we reflect on factors that may contribute to this state of affairs.

The wrong patients?

The goal of any intervention is to target a modifiable process. When a heterogeneous group of patients is recruited to a study, including patients with co-morbid conditions, we need to carefully consider their impact on the outcomes at question [2, 3]. Pre-existing mental health problems are an important risk factor for poor QoL and for psychiatric diagnoses after critical illness and may interact with physical outcomes in ways we do not yet understand [4]. Similarly, severe chronic physical co-morbidity can interact with acute physical conditions in ways that may prevent or impair the effectiveness of physical rehabilitation strategies [3, 5]. A recent publication on the heterogeneity of treatment effects encourages us to carefully consider how we perform patient selection, stratification and analyses for known risk factors [6]. For example, a study of the use of patient diaries suggested that patients at higher risk of psychological morbidity may be the only ones to benefit from a diary intervention [7].

The wrong interventions?

As always in studies where the primary outcome shows no effect, the most plausible and reasonable conclusion of the study is that the intervention was indeed ineffective. Another hypothesis is that the intervention may have been effective if delivered with a different dose or at a different time point in the patient's trajectory [8]. This latter possibility has been highlighted with the fact that some [9]—but certainly not all—studies of early physical interventions that start in the ICU have shown benefit compared to studies in which interventions commence later when the pathophysiological changes in the patient may be more difficult to reverse [10]. At present, the time point at which to intervene to improve mental health and QoL outcomes is unclear, but a recent systematic review of longitudinal studies reported that there was very little change in depressive symptoms in the 12 months after ICU discharge [4].

The wrong clinical team?

Previous research has shown that post-intensive care syndrome is complex and so perhaps review by expert physicians should be considered a key part of our multidisciplinary approach [2]. Specifically, the healthcare specialists with the most expertise at improving mental health outcomes are surely mental health specialists. Likewise, the professionals with the greatest expertise for the management of older patients with complex comorbidities following acute conditions are geriatric and rehabilitation specialists. To date, partly due to an inability to engage such specialties, and out of our own genuine

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desire to help "our" patients, we have tried to design and deliver these interventions in isolation as an intensive care team. It is likely that this should change in the future.

The wrong trial designs?

Outcome measures Quality of life is the most common outcome in such trials and, based on its primacy in the World Health Organization classification of function and disability [11], this seems to be appropriate. However, it remains unclear whether generic QoL tools are appropriately responsive and have adequate construct validity to describe key domains of patient's experience after critical illness. In a recent study evaluating measures of health-related QoL, substantial gaps in the coverage of important aspects of survivorship were reported, including finances, place of residence, appearance and personality [12]. The 36-Item Short Form Health Survey (SF-36) demonstrated a moderate to strong correlation with anxiety and depression symptoms from specific psychological screening tools, but with a low specificity for mental health disorders [13]. The authors noted that because negative predictive values were high, the best use of the SF-36 in studies is to help rule out patients with mental health disorders.

Power One of the most important aspects of trial design is the sample size required to detect a difference between groups. Ideally, sample size calculations are determined from studies in a similar group of patients with the same intervention or from similar previous studies that used the outcome measure planned in the proposed trial. This is particularly important when the aim of the study is to detect a small difference between the groups. A systematic review of QoL after critical illness found that the mental health domain differed the least from norms and, consequently, may be a signal that is difficult to detect [14].

Control group The purpose of a control group is to provide a comparator where the independent variable being tested cannot influence the results. One of the difficulties of pragmatic clinical trials is where a control group receives "standard care" where co-interventions may indeed influence the independent variable. In this and

Table 1 Patient and trial characteristics in larger (n >100) intensive care unit follow-up trials

Trial	N	Patient group	Nature of intervention	Timing of Intervention	Team delivering intervention	Control group	Primary Outcome	Primary outcome timing (max follow up)	Effect	Power based on previous data from similar population	Loss to follow up at maximal follow up time point
Studies showing benefit											
Schweickert *et al* 2009[9]	104	**ICU admissions (ventilated for >72 hours)**	Physical and occupational therapy	**During ICU stay**	Physiotherapists within ICU team	Usual care **(no physiotherapy)**	Functional status (ADL)	**Hospital discharge (Hospital discharge)**	Benefit for intervention	Yes (observational data)	**0%, non-differential**
Jones *et al* 2010[7]	352	**ICU admissions (ventilated for >72 hours)**	**ICU diaries**	One month after ICU discharge	Nurse led within ICU team	Usual care	**Not stated** but study powered on new diagnosis of PTSD	3 months (3 month)	Benefit for intervention	Yes (previous cohort study)	**3%, non-differential**
Studies showing no effect											
Cuthbertson *et al* 2009[2]	286	Ventilated ICU admissions	**Complex intervention (with physical and psychological interventions)**	Hospital (after ICU stay) - 9 months after discharge	Nurse led within ICU team	Usual care (no rehabilitation)	**Quality of life (SF-36)**	**12 months (12 months)**	No effect	Anchored using standard deviations	17%, differential towards treatment group
Elliot *et al* 2011[16]	195	ICU admissions (ventilated for >24 hours)	Physical therapy	**After hospital discharge – 8 weeks**	Physiotherapists, nurse or exercise physiologist	Usual care (no rehabilitation)	Physical function (SF-36)	6 months (6 months)	No effect	**No**	4%, non-differential
Denehy *et al* 2013[5]	150	ICU admissions	Physical therapy	**ICU stay – after hospital discharge care**	Physiotherapist led within ICU team	Usual care **(physiotherapist guided)**	Functional outcome (6 minute walk test)	6 months (12 months)	No effect	Anchored using standard deviations	**24%,** non-differential
Walsh *et al* 2015[17]	240	ICU admissions (ventilated for >48 hours)	**Complex intervention (including dedicated rehabilitation practitioner)**	**ICU stay - 3 months**	ICU team	Usual care **(including ICU rehabilitation manual)**	Physical function score (Rivermead Mobility Index)	3 months (12 months)	No effect	Pilot data	**24%, possibly differential towards control group**
Morris *et al* 2016[10]	300	Ventilated ICU admissions	Physical therapy	**ICU stay - hospital discharge**	Physiotherapist led within ICU team	Usual care **(including physiotherapy)**	**Hospital length of stay (days)**	Hospital discharge (6 months)	No effect	**No**	**21%**
Moss *et al* 2016[15]	120	Ventilated ICU admissions	Physical therapy	**ICU stay for 28 days**	ICU team	**Usual care (including physiotherapy)**	Physical function (PFP score)	**1 month** (6 months)	No effect	Yes	**34% observed**, non-differential
Jensen *et al* 2016[1]	386	ICU admissions (ventilated for >48 hours)	**Complex intervention (including diaries)**	1 – 10 months after ICU admission	Nurse led within ICU team	**Usual care (including rehabilitation care)**	Mental health quality of life (SF-36)	**12 months (12 months)**	No effect	**No**	**Unclear but >20%, possibly differential**

The specific study characteristics which may have contributed to the results are highlighted in bold

ICU Intensive care unit, *ADL* Activities of Daily Living Inventory, *PTSD* posttraumatic stress disorder, *SF-36* 36-Item Short Form Health Survey, *PFP* physical function performance

other cases, it may be ethically difficult for investigators to remove any treatment that is considered "standard care" in the trial centers, even though the evidence base may not support the practice [1, 5]. In the RAPIT study [1], the authors discuss the potential limitations of the control group who received a significant amount of physical rehabilitation, a factor that may have an impact on mental health outcomes in the control group, thus reducing the magnitude of any effect. In this field, as is so often the case, the specification of the control group may be more even important than specifying the intervention.

Retention An important consideration of interventional studies that measure long-term outcomes following critical illness is the fidelity of the intervention and loss to follow-up [15]. In the RAPIT study the intervention was not delivered to 28 % of recruited patients [1]. Loss to follow-up can introduce a bias if it is differential and particularly if attributable to the outcome being measured—for example if mental health issues are responsible for patient loss. Research in long-term outcomes following critical illness needs to consider improved methodologies and registry linkages to accurately determine long term outcomes.

Despite our best efforts, effective interventions after ICU care to improve patient-centered outcomes remain elusive, and many of our interventions have been proven to be ineffective (Table 1). In order to achieve progress in the field and, most importantly, to improve outcomes for our patients, we need to recruit the right patients, at the right time in their disease trajectories, using interventions designed and delivered by a care team with the appropriate skills and expertise. Currently, we may not have sufficient knowledge to identify some or even many of these factors.

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Compliance with ethical standards

Conflicts of interest
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