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Follow-up services for improving long-term outcomes in intensive care unit (ICU) survivors (Protocol)

Schofield-Robinson OJ, Lewis SR, Smith AF, McPeake J, Alderson P

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[Intervention Protocol]

Follow-up services for improving long-term outcomes in intensive care unit (ICU) survivors

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

Our main objective is to assess the effectiveness of follow-up services for ICU survivors that aim to identify and address unmet health needs related to the ICU period. We aim to assess the effectiveness in relation to health-related quality of life, mortality, depression and anxiety, post-traumatic stress disorder, physical function, cognitive function, ability to return to work or education and adverse events.

Our secondary objectives are, in general, to examine both the various ways that follow-up services are provided and any major influencing factors. Specifically, we aim to explore: the effectiveness of service organisation (physician versus nurse led, face to face versus remote, timing of follow-up service); possible differences in services related to country (developed versus developing country); and whether participants had delirium within the ICU setting.

BACKGROUND

In 2014 to 2015, approximately 150,000 patients were admitted to adult intensive care units (ICUs) in the UK - a large percentage of whom survived (ICNARC 2016). An ever-increasing number of people, in the UK and globally, are surviving the ICU, and short-term mortality for critical illnesses is decreasing in general (Needham 2012). Despite this progress, ICU stay has been linked with a number of physical and psychological sequelae which afflict these survivors - potentially for years after critical illness. ICU follow-up services are relatively recent developments in healthcare systems, the purposes of which are to help address this wide variety of impairments by identifying and addressing patients' health needs directly or by providing access to additional healthcare services.

Description of the condition

Critical illness, and the ICU stay itself, can be traumatic experiences which have been known to cause physical and psychological

distress that can extend far beyond the initial illness and any short-term treatment. The long-term problems arising from the ICU, known as 'post-intensive care syndrome' (PICS) (Needham 2012), include mortality, post-traumatic stress disorder (PTSD), anxiety, depression and physical impairments, and can also include sexual dysfunction, amnesia of the ICU period, and various related social problems (Griffiths 2007; Oeyen 2010). PICS not only affects ICU survivors, but also amplifies the burden for their families and dramatically increases costs for healthcare systems (Jones 1998; Needham 2011).

Mortality figures at one year after discharge range from 26% to 63%, and those for five years after discharge are reported to be between 40% and 58% (Williams 2005). Additionally, between 19% to 22% of ICU survivors are affected by PTSD up to ten years after critical illness, and for survivors of acute respiratory distress syndrome (ARDS) this figure could be as high as 44% (Davydow 2008a; Davydow 2008c).

Anxiety may affect 23% to 48% of ARDS survivors up to 28 months after illness. The incidence of depression in the same group ranges from 17% to 43%, and this incidence may affect 8% to 57% of the general ICU population at 14 months (Davydow 2008b; Davydow 2008c). The quality of life (QoL) scores of ICU survivors are lower than average (for an age- and gender-matched population), and while research shows that QoL and basic functionality does begin to slowly improve, this disparity compared with the general population tends to remain for at least five years after discharge (Cuthbertson 2005; Cuthbertson 2010; Eddleston 2000; Oeyen 2010), and may never fully return to preadmittance levels (van der Schaaf 2009). An individual's QoL can be further affected by sexual dysfunction, or by an inability to return to work (Griffiths 2006; Myhren 2010; Williams 2011). Even with this research, there exist significant gaps in our knowledge of post-ICU cognitive morbidities, and more attention may need to be paid in particular to the impact of delirium (Cuthbertson 2009; Needham 2012; NICE 2009; Pandharipande 2013).

Description of the intervention

For this review we define an ICU follow-up strategy as any service set up to address specifically the various health needs of ICU survivors, to prevent the development of physical, psychological and social problems over the long term. There is, however, no one accepted model for such services (Rattray 2007). The UK has been at the centre of research into critical care follow up (Lasiter 2016; Williams 2008), and there has been substantial investment in ICU follow-up services, leading to a doubling of their number between 2002 and 2006 (Cuthbertson 2003; Griffiths 2006).Though the first follow-up clinic in the UK was set up in 1985 (Griffiths 2006), and following official recommendations coming from the King's Fund Panel in 1989 (King's Fund 1989) and the 'Critical to Success' audit commission in 1999 (Audit Commission 1999), the development of ICU clinics has been an ad hoc, experimental process, not a systematic one (Angus 2003; Jensen 2015). Today, still, there is no standardisation of such services across National Health Service (NHS) trusts or other healthcare systems globally. Indeed, on a global level ICU follow-up programmes have seen mixed levels of attention and implementation. A recent 'push' by the Institute of Medicine in the USA has resulted in greater attention being paid to this important aspect of post-critical care (Lasiter 2016), with systems such as the Indiana University School of Medicine's Critical Care Recovery Center (CCRC) being set up (Khan 2015). In Scandinavian countries (Norway, Denmark and Sweden) there is evidence of local initiatives dating back to the early 1990s. While UK services have emphasised physical rehabilitation (NICE 2009) the programmes in the Scandinavian countries have tended to focus on patient-led initiatives, including diaries and dialogue (Egerod 2013; Jensen 2015). There appears to be a lack of available data from other countries, which is perhaps no surprise given the slow implementation even in more developed healthcare systems.

Types of services that may be offered to ICU survivors range from informal interviews to more organised sessions. They may be patient led and focus around the sharing of experiences, or led by healthcare personnel with the purpose of providing information to the patient; equally, they may be focused around physical rehabilitation, or around addressing cognitive dysfunction (NICE 2009). Guidelines published by the National Institude for Health and Care Excellence (NICE) recommended both that preventative measures should be started in the ICU setting and that multidisciplinary functional assessments should be conducted by appropriately trained personnel two to three months after ICU discharge (NICE 2009). Importantly however, these guidelines acknowledge the limitations of the current consensus surrounding ICU follow up (NICE 2009).

How the intervention might work

The general aims of a follow-up service in this review are to: provide a forum in which to identify and address any unmet health needs; and to identify possible PICS, and allow for their further management within or without the hospital setting. How such a service might achieve these aims can vary widely, however. Follow-up services may take the form of informal meetings that facilitate a patient-led sharing of experiences which can provide reassurance to the ICU survivor and potentially reduce depression or anxiety; or they may involve access to standard general practitioner services.

More organised sessions, which may either be nurse or physician led, might involve discussion of specific physical or psychological conditions and subsequent referral to appropriate health providers to manage these conditions. A follow-up service might be conducted face to face or by remote access. It might be assessed using locally-derived questionnaires, or through standardised questionnaires using validated scales. For complex interventions such as

this one, a preferred model may be one that is tailored to local circumstances rather than being completely standardised (Craig 2008). Equally, the inherent heterogeneity of the patient population within any single ICU might further complicate any standardisation of follow-up services. It has been suggested, for example, that patients who have had a longer ICU stay, or who have had incidents of delirium, may react to follow-up services differently. So while it might be beneficial for clinics to target their resources at those most likely to benefit (Aitken 2015; Cuthbertson 2009; Jensen 2015*),* the lack of a thorough epidemiological study base for these differences makes conclusions in this area speculative (Needham 2012).

Globally, ICUs treat people with a large range of diseases and general afflictions, and varying severities of conditions, patient backgrounds and socioeconomic factors. It is feasible that follow-up services may be more beneficial to particular patient groups. For example, the socioeconomic conditions of an individual can affect quality of life, cause or exacerbate anxiety and depression, and affect physical function, and, in less economically-developed countries, mortality. Another important consideration, and one which has been overlooked in much of the literature (Williams 2008), is that of ICU access. Access to hospital-based follow-up services, which may be relatively simple for UK-based patients, has the potential to be extremely difficult for those living in very large tertiary care catchment areas. This means that conclusions reached about these services may not be relevant for clinicians and patients in rural areas around the world.

Why it is important to do this review

Though there is a growing civil, scholarly, and governmental desire for information on the role that ICU follow-up services might play within an integrated recovery process which starts in the ICU and continues long afterwards, there has been, and still is, a lack of medical consensus (Angus 2003; NICE 2009). In the UK, the USA and around the world, ICU follow-up initiatives have not received as much dedicated funding or widespread implementation as those of oncology care, spinal injury care, or military veterans' care (Needham 2012). ICU follow-up services appear intuitively beneficial (Cuthbertson 2003; Rattray 2007), but it is still important that they are grounded in the principles of evidence-based medicine.

To date, there has been no Cochrane review of the efficacy of ICU follow-up services as a general system of care. We have identified a number of reviews dedicated to this subject (Jensen 2015; Niven 2014; Williams 2008). These reviews, among other differences, either require updating (Williams 2008), or have different emphases (Jensen 2015; Niven 2014). Niven 2014, for example, focuses on ICU transition services and the risk of readmission, whereas Jensen 2015 has subtle differences regarding inclusion criteria for studies. Jensen and colleagues only included randomised trials. Our emphasis in this review will be on both randomised and non-randomised trials and will be directed towards services that are both delivered by a healthcare professional and address unmet health needs related to the ICU period. This is an area of clinical importance which warrants a systematic approach.

OBJECTIVES

Our main objective is to assess the effectiveness of follow-up services for ICU survivors that aim to identify and address unmet health needs related to the ICU period. We aim to assess the effectiveness in relation to health-related quality of life, mortality, depression and anxiety, post-traumatic stress disorder, physical function, cognitive function, ability to return to work or education and adverse events.

Our secondary objectives are, in general, to examine both the various ways that follow-up services are provided and any major influencing factors. Specifically, we aim to explore: the effectiveness of service organisation (physician versus nurse led, face to face versus remote, timing of follow-up service); possible differences in services related to country (developed versus developing country); and whether participants had delirium within the ICU setting.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised trials and non-randomised trials. We will also include interrupted time series studies and controlled before-after studies. Controlled before-after studies can be defined as those in which observations are made before and after the implementation of an intervention, while interrupted time series studies use observations at multiple time points before and after an intervention (the interruption) in order to detect significant change over time (EPOC 2016). It has been acknowledged that while true experimental designs are preferred, they are not always practicable in trials with multi-faceted interventions (Craig 2008), and may not be the most appropriate study design for examining a system of care, rather than a single intervention (Cuthbertson 2003). We will include full-text studies, conference abstracts and unpublished data identified through initial database searches which contain sufficient information on study type, intervention data, and outcomes. We will not exclude studies based on outcomes or methods of analysis, but we will exclude interrupted time series designs for which a necessary reanalysis of data is not possible (see Measures of treatment effect). We will also exclude interrupted time series

studies if they do not have a clearly defined time point for the intervention and at least three data points before and after the intervention (EPOC 2016).

Types of participants

We will include adults who have been discharged from hospital following a stay in an ICU that required level three care. We will not exclude participants based on the reason they were admitted to the ICU, so long as they were subject to level three care. We define level three care, or the equivalent grade in other healthcare systems, as requiring advanced respiratory support, or care which requires the artificial support of at least two organs (Intensive Care Society 2009). We will include participants that have been admitted to any ICU, to include admission to high-dependency or critical care units or other hospital wards specifically designed to cater for patients who are critically ill.

We will exclude participants who are in any existing rehabilitation programme, for example those associated with traumatic brain injury, spinal cord injury, military trauma and cancer or cardiac care. We will not exclude otherwise eligible patients based on location, geographical dispersion, sex, or any other factor.

Types of interventions

We will include studies that assess a follow-up service (intervention), attended by ICU survivors on at least one occasion compared to either no follow-up service or standard care (control). We define a follow-up service as a consultation delivered by a healthcare professional or appropriately trained other person, which seeks to specifically identify or address unmet health needs directly related to the ICU period. We will include studies in which the service is conducted either face to face or remotely, for example through email or telephone contact, and which occurs at any time within six months of discharge from hospital. We will include studies in which the follow-up service seeks to address needs through immediate support or subsequent referrals. We will exclude studies that offer a follow-up service that only provides general (non-ICU related) information or educational materials to the patient, and we will exclude studies that are not delivered by a healthcare professional or appropriately trained other person. Standard care (control group) may include general practitioner visits and care related to ongoing known medical conditions that are not targeted at identifying and addressing unmet needs related to the period spent in ICU.

Types of outcome measures

We will assess the effectiveness of follow-up services by measuring differences in physical and psychological outcomes for study participants. Our main outcome is an overall assessment of health-related quality of life (HRQoL). We will collect data from studies that have used a validated tool to assess HRQoL and report an overall mean value for study participants from the validated tools, such as the SF-36 and Euroqol EQ-5D scales. The SF-36 scale assesses the following: physical functioning, social functioning, role limitations, pain, mental health, vitality, and general health perceptions; while the EQ-5D scale assesses mobility, self care, main activity, family/leisure activity, pain/discomfort, anxiety and depression (Brazier 1993; RAND). We will report physical function, for which data may have been collected from components of scales such as the SF-36 and EQ-5D, or results of tests such as the six-minute walk test. Cognitive function data will be collected according to any validated scale used by the study authors. We will report psychological outcomes in terms of anxiety or depression or both, and, again, may collect these data from components of the above scales or other validated tools such as HADS-A and HADS-D (Zigmond 1983). We will collect data on the number of deaths from any cause up to 12 months post-ICU. For post-traumatic stress disorder (PTSD) we will, again, measure data from validated scales such as PDS (Jones 2010; McCarthy 2008) or DSM-III, IV or V (American Psychiatric Association 2013; U.S. Department of Veterans Affairs). Data for the ability of participants to return to work may be collected in the percentage of patients who have returned to work at the follow-up time point.

We will collect data for adverse events as reported by study authors. Examples of adverse events may include increased or continued dependency on medical services rather than a transition into activities of daily living; potential exacerbation of PICS, for example because of formalised recollection of ICU experiences; or duplication or fragmentation of medical services as noted by study investigators, for example because the patient is offered access to an ICU physician-led follow-up service alongside other rehabilitation services. It is unlikely that these events will be reported using validated scales and we will report these events in the narrative of the review.

We will collect data for all outcomes at time points measured by study authors up to 12 months post-ICU discharge.

In summary, we will collect data for the following outcomes:

Primary outcomes

1. Health-related quality of life (HRQoL)
2. All cause mortality
3. Depression and anxiety

Secondary outcomes

1. Post-traumatic stress disorder (PTSD)
2. Physical function
3. Cognitive function
4. Ability to return to work or education
5. Adverse effects

Reporting of the outcomes listed here will not be an inclusion criterion for the review and we will include studies regardless of the assessed outcomes.

Search methods for identification of studies

Electronic searches

The Effective Practice and Organisation of Care (EPOC) Information Specialist (IS) will develop the search strategies in consultation with the review authors. We will search the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) for related systematic reviews.
We will search the following databases for primary studies, from inception to the date of search.

- Cochrane Central Register of Controlled Trials (CENTRAL) (current issue).
- MEDLINE (via Ovid) (from 1985 to the present).
- Embase (via Ovid) (from 1985 to the present).
- CINAHL (via EBSCO) (from 1985 to the present).

We will use two methodology search filters in the database searches to limit retrieval to appropriate study designs: a modified version of the Cochrane Highly Sensitive Search Strategy (sensitivity- and precision-maximizing version - 2008 revision; Lefebvre 2011) to identify randomised trials (Higgins 2011); and an EPOC methodology filter to identify non-randomised designs. See Appendix 1 for the MEDLINE search strategy, which we will adapt for other databases. We will not apply any limits on languages.

Searching other resources

Trial registries

We will search the following trial registers.

- WHO ICTRP (World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp).
- US National Institutes of Health Ongoing Trials Register, ClinicalTrials.gov (www.clinicaltrials.gov).

Grey literature

We will conduct a grey literature search to identify studies not indexed in the databases listed above. We will search the following sources.

- Healthcare Management Information Consortium (HMIC).
- National Technical Information Service (NTIS).
- National Institute for Health and Clinical Excellence (NICE).
- OpenGrey (www.opengrey.eu).
- Agency for Healthcare Research and Quality (AHRQ).

We will also review reference lists of all included studies and relevant systematic reviews for additional potentially-eligible primary studies. We will contact authors of included studies and relevant reviews to clarify reported published information and to seek unpublished data. We will contact researchers with expertise relevant to the review topic and to EPOC interventions. We will conduct cited reference searches for all included studies in ISI Web of Knowledge and screen individual journals and conference proceedings (e.g. handsearch). We will report all strategies used in appendices, including a list of sources screened and relevant reviews and primary studies reviewed.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database and remove duplicates. Sharon Lewis (SL) and Oliver Schofield-Robinson (OSR) will independently screen all titles and abstracts and will remove studies that are very unlikely to be eligible. We will identify potentially-eligible randomised trials and interrupted time series studies separately. If no abstract is available but the title is possibly relevant, we will obtain the full text of the article. We anticipate that we may need to get more full texts for controlled before-after and interrupted time series studies as abstracts may not contain sufficient detail to allow classification (Higgins 2011, Section 13.3.1.3). We will resolve any disagreement through informal discussion, and we will address any lack of consensus to a third author, Phil Alderson (PA), who will make a final decision.
When we have screened all titles and abstracts, SL and OSR will independently review the full text of potentially-relevant titles and record our decision on the study eligibility section of the data extraction form (EPOC 2013a). This has been modified to account for the interventions featured in this review. A draft version of this form is presented in Appendix 2. We will resolve any disagreement through discussion or, if required, we will consult a third review author (PA).
Studies that initially appeared to meet the inclusion criteria but were later excluded will be listed with reasons for exclusion in the table 'Characteristics of excluded studies'. We will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will also provide any information we can obtain about ongoing studies. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009).

Data extraction and management

For data extraction and management for all study designs, we will use Covidence software (Covidence). We will create a template using an adapted standard EPOC data collection form (EPOC 2013a) for study characteristics and outcome data (Appendix 2) which we will pilot on at least one study in the review. Two review

authors (SR and OSR) will independently extract the following study characteristics from the included studies.

1. Methods: study design, number of study centres and location (to include description of rural or urban centre), study setting, date of study, follow-up time point.
2. Participants: number, mean age, age range, ethnicity, gender, socioeconomic descriptions (e.g. economic status, education and employment status), APACHE II score, presence of ARDS, reason for ICU stay, episodes of delirium whilst in the ICU (CAM-ICU score; Ely 2001), withdrawals, diagnostic criteria, length of stay in the ICU, duration of sedation, inclusion criteria, exclusion criteria, other relevant characteristics.
3. Interventions: intervention components, comparison, direct or remote clinic, time point of intervention, time point of follow up, physician or nurse led, number of attended clinics.
4. Outcomes: main and other outcomes specified and collected, time points reported.
5. Notes: funding for trial, notable conflicts of interest of trial authors, ethical approval

We will note in the 'Characteristics of included studies' table if outcome data were reported in an unusable way, for example in graphs or figures with unclearly labelled axes. We will resolve disagreements by consensus or by involving a third review author (PA).

Assessment of risk of bias in included studies

Two review authors (SL and OSR) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and guidance from the EPOC group. Any disagreement will be resolved by discussion or by involving a third review author (PA). For randomised trials and controlled before-after studies we will assess the following criteria (EPOC 2009).

1. Was the allocation sequence adequately generated?
2. Was the allocation adequately concealed?
3. Were baseline outcome measurements similar?
4. Were baseline characteristics similar?
5. Were incomplete outcome data adequately addressed?
6. Was knowledge of the allocated interventions adequately prevented during the study?
7. Was the study adequately protected against contamination?
8. Was the study free from selective outcome reporting?
9. Was the study free from other risks of bias?

For interrupted time series studies, we will assess the following criteria (EPOC 2009).

1. Was the intervention independent of other changes?
2. Was the shape of the intervention effect prespecified?
3. Was the intervention unlikely to affect data collection?
4. Was knowledge of the allocated interventions adequately prevented during the study?
5. Were incomplete outcome data adequately addressed?
6. Was the study free from selective outcome reporting?
7. Was the study free from other risks of bias?

We will judge each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise 'Risk of bias' judgements across different studies for each of the domains listed. It is not feasible to blind personnel or participants to the study intervention in this review and therefore we will judge all randomised trials to have a high risk of performance bias for this review. There may be similar risks for detection bias because this review will contain patient-assessed outcomes, for example using validated questionnaires. We will assess blinding of outcome assessment for each reported outcome and consider whether lack of blinding for the each outcome would introduce a risk of bias to the results.

Where information on risk of bias relates to unpublished data or correspondence with a study author, we will note this in the 'Risk of bias' table. We will not exclude studies on the grounds of their risk of bias, but will clearly report the risk of bias when presenting the results of the studies. We will use EPOC 'Risk of bias' guidance information to help judgements (EPOC 2009). A draft of the modified 'Risk of bias' table is given in Appendix 3.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

For randomised trials and controlled before-after studies, we will collect continuous data from validated scales (HRQoL, depression and anxiety, PTSD, physical function, cognitive function), reported as mean scores at the end of follow-up time point (6 months or 12 months). If data are recorded as dichotomous in the included studies, we will contact the study authors for any available continuous data. We will collect dichotomous data for mortality, the number of participants who are able to return to work at the end of follow-up and the number of participants reporting an adverse event.

For interrupted time series designs, we will report a comparison of time trends before and after introduction of the intervention for each of our outcomes as reported by study authors. If necessary, we will reanalyse the data to ensure that study authors have not used inappropriate analyses (EPOC 2013b). In the event that data are presented graphically we will use software (Plot Digitizer) to read values from graphs and we will use guidance from EPOC to organise and reanalyse the data appropriately (EPOC 2013b; EPOC 2013c). As mentioned, if, after consultation, the data are still unsuitable for reanalysis, we will exclude the studies from our analyses.

Unit of analysis issues

If there is a unit of analysis error in the reported analysis for a study and there is insufficient information to reanalyse the results, we will contact the study authors to obtain the necessary data. If these data are not available, we will not report confidence intervals or P values for which there is a unit of analysis error. Because we are including within this review not only randomised trials but also non-randomised trials, interrupted time series, and controlled before-after studies, the unit of analysis might differ between our included studies.

Dealing with missing data

We will contact investigators in order to verify key study characteristics and obtain missing outcome data where possible (e.g. when a study is identified as abstract only). For data which are assumed to be missing at random we will use available case data as reported by study author. If data are assumed to be 'not missing at random', we will impute missing data with replacement values (e.g. using the last observation carried forward) (Higgins 2011). We will explore any decisions to manage missing data during the sensitivity analysis (see Sensitivity analysis).

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by consideration of study design, participants and how the follow-up clinics are conducted. Differences, for example in the socioeconomic background of the participants, may influence outcome data and substantial heterogeneity may warrant decisions not to pool data. We will assess statistical heterogeneity using the Chi^2 statistic (and related P value) or the I^2 statistic (with associated percentage values). We will use the following cut-offs as a guide to interpretation: I^2 at 0% to 40% is not considered important, 30% to 60% suggests moderate heterogeneity, 50% to 90% suggests substantial heterogeneity, and 75% to 100% is considerable heterogeneity (Higgins 2011). If we identify substantial clinical, methodological or statistical heterogeneity we will explore it by prespecified subgroup analysis.

We expect heterogeneity in randomised trials, controlled before-after, and interrupted time series studies to derive from:

1. type of follow-up clinic used (e.g. nurse led or physician led; face to face or remote);
2. time points of clinics;
3. time points of outcome assessment;
4. potential risk of developing PICS; and
5. socioeconomic conditions of participant.

Differences in the risk of acquiring PICS has the potential to contribute to clinical heterogeneity as it has been shown that certain factors may increase this likelihood. For example, ARDS patients who survive the ICU may potentially be at a higher risk of developing PICS elements such as depression, anxiety and PTSD (Davydow 2008c). Heterogeneity in this area may be assessed by collecting patients' baseline data in studies for presence of ARDS, length of ICU stay, length of sedation, and APACHE II and SAPS II scores, and making judgements based on the comparisons between these data.

Assessment of reporting biases

We will attempt to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, the impact of including such studies on the overall assessment of results will be explored by a sensitivity analysis. If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible publication biases, interpreting the results with caution (Sterne 2011).

Data synthesis

We will undertake meta-analysis only where this is meaningful, i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. We will pay attention to scales used to measure continuous outcomes and only combine data if these scales appear to be equivalent. However, while commonly-used scales such as SF-36 and EQ-5D are validated (Brazier 1993), we do not anticipate that the combined data for the two scales, or any equivalent scales, will be suitable for pooling. A common way that trialists indicate when they have skewed data is by reporting medians and interquartile ranges. When we encounter this, we will note that the data are skewed and consider the implication of this.

Given the differences in the HRQoL metrics, we will use the standardised mean difference for continuous data, together with the appropriate associated 95% confidence interval, and risk ratio for dichotomous data, together with the appropriate associated 95% confidence interval. We will ensure that an increase in scores for continuous outcomes can be interpreted in the same way for each outcome, explain the direction to the reader, and report where the directions were reversed if this was necessary. If we need to standardise different data sets, we will consult statistical support. The use of the standardised mean difference will account for anticipated differences in scales. We will calculate risk ratios for dichotomous outcomes using Mantel-Haenszel. If events are rare (1 per 1000) we will calculate Peto odds ratio (Higgins 2011) Our choice of a fixed-effect or random-effects model for both of these outcome measures will be based on heterogeneity (methodological or statistical or both). We will conduct any meta-analyses and calculate 95% confidence intervals using the RevMan calculator (RevMan), and we will use generic inverse variance in an attempt to address expected heterogeneity between the studies. We will consider whether there is any additional outcome information that was not able to be incorporated into meta-analyses, note this in the comments, and state if it supports or contradicts the information from the meta-analyses. We will report whether study authors

have presented adjusted or unadjusted data with factors that have been adjusted for. We will not combine adjusted and unadjusted data in the same analysis. If it is not possible to meta-analyse the data we will summarise the results in the text.

For interrupted time series designs we will conduct regression analysis or ARIMA analysis (EPOC 2013b). We will report the change in slope and the change in level. The change in slope shows the change in trend from pre- to post-intervention, reflecting the long-term effect of use of a follow-up service. The change in level will show a more immediate effect of the follow-up service.

Summary of findings

We will summarise the findings of the main intervention comparison for the most important outcomes (HRQoL, mortality, depression and anxiety, PTSD, physical and cognitive function, time (ability) to return to work or education, adverse effects) in a 'Summary of findings' table to draw conclusions about the certainty of the evidence within the text of the review. Two review authors will independently assess the certainty of the evidence (high, moderate, low, and very low) using the five GRADE considerations (study design, consistency of effect, imprecision and indirectness; Guyatt 2008). We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook* (Higgins 2011), and the EPOC worksheets (EPOC 2013d), and using GRADEpro software (GRADEpro GDT 2015). We will resolve disagreements on certainty ratings by discussion and provide justification for decisions to down- or up-grade the ratings using footnotes in the table. We will make comments to aid readers' understanding of the review where necessary. We will use plain language statements to report these findings in the review.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses, focusing on two distinct categories: particular patient groups, and style of service.

1. Physician-led clinic versus nurse-led clinic.
2. Face-to-face clinic versus remote clinic.
3. Participants from developing countries versus participants from developed countries (according to WDI).
4. Intervention conducted earlier than three months post-ICU versus three to six months.
5. Incidence of ICU delirium versus no delirium.

We will use subgroup analysis to assess whether certain follow-up services have disproportionate benefit for different groups. Organisation, style and timing of follow-up services between studies may introduce heterogeneity (Williams 2008) and some of these differences may be explained by socioeconomic factors according to the country of the study or inequity in access to healthcare services, or both. For example, current UK guidelines recommend face-to-face ICU follow-up at two to three months post-discharge (NICE 2009), which may be achievable in a developed health economy but not in a developing country. An important socioeconomic consideration is the influence specifically of a nation's status as a developing or developed economy, which can impinge upon its citizens' access to healthcare services. To this end, we will assess country of study according to the World Bank's World Development Index (WDI) (World Bank 2016). Delirium in the ICU and resultant cognitive dysfunction, which has been shown to be a prevalent affliction among the ICU survivor population and can affect quality of life (Gordon 2004), also have the potential to contribute to this clinical heterogeneity. Such a subgroup analysis might aid more precise targeting of resources in future studies.

We will use data collected during the Data extraction and management stage of the review to decide the group for each study. Subgroup analysis will be conducted if there are sufficient studies (i.e. 10 or more (Higgins 2011)). It is anticipated that information for these analyses will not be provided for each individual participant in included trials and therefore subgroup analyses will be conducted at the study level, not the participant level. We will only conduct subgroup analysis of our primary outcome, HRQoL. We will use Revman (RevMan) software to create subsets and test for subgroup interactions. It is possible that, through the interactions of multiple and competing variables between studies, the results of these analyses will give a misleading picture of the efficacy of ICU follow up for a particular group. We will interpret any subgroup findings with caution.

Sensitivity analysis

We will perform sensitivity analyses defined a priori to assess the robustness of our review methodology and explore its impact on effect sizes. This will involve the following.

1. Restricting the analysis to published studies.
2. Restricting the analysis to studies with a low risk of selection bias.
3. Using available case data or using imputed data (from last observation carried forward) where studies have missing data.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE <1946 to Present>

No.	Search terms
1	Aftercare/
2	exp Counseling/
4	Long-Term Care/
5	Disease Management/
6	(diary or diaries).mp.
7	Counsel?ing.mp.
8	email.mp.
9	telephone*.mp.
10	phone*.mp.
10	((follow up or discharge) adj2 (appointment* or consultation* or clinic* or program* or strateg* or service)).ti,ab
11	or/1-10
12	((after or post) adj (trauma or level 3 or level three)).ti,ab
13	(survivor* adj3 (trauma or level 3 or level three)).ti,ab.
14	Survivor/
15	exp intensive care unit/ or exp intensive care/ or exp Multiple Organ Failure/ or exp Multiple Trauma/ or exp Shock/ or exp sepsis/ or exp critical illness/ or exp Critical Care/ or (critical* adj (care or ill*)).ti,ab. or (intensive care unit* or ICU).ti,ab. or sepsis.ti,ab. or (serious$ adj injur$).ti,ab. or multiple organ$ failure$.ti,ab. or (major adj (trauma$ or shock)).ti,ab
16	14 and 15
17	12 or 13 or 15 or 16
18	randomized controlled trial.pt.
19	controlled clinical trial.pt.

(*Continued*)

20	multicenter study.pt.
21	pragmatic clinical trial.pt.
22	(random* or randomiz* or randomly).ti,ab.
23	groups.ab.
24	(trial or multicenter or multi center or multicentre or multi centre).ti
25	(intervention? or effect? or impact? or controlled or control group? or (before adj5 after) or (pre adj5 post) or ((pretest or pre test) and (posttest or post test)) or quasiexperiment* or quasi experiment* or pseudo experiment* or pseudoexperiment* or evaluat* or time series or time point? or repeated measur*).ti,ab
26	non-randomized controlled trials as topic/
27	Interrupted Time Series Analysis/
28	controlled before-after studies/
29	or/18-28
30	exp animals/
31	humans/
32	30 not (30 and 31)
33	review.pt.
34	meta analysis.pt.
35	news.pt.
36	comment.pt.
37	editorial.pt.
38	cochrane database of systematic reviews.jn.
39	comment on.cm.
40	(systematic review or literature review).ti.
41	or/32-40
42	29 not 41

(*Continued*)

43	11 and 17 and 42

Appendix 2. Data collection form

Intervention review - randomised trials and non-randomised trials

1. General information

1. Date form completed *(dd/mm/yyyy)*
2. Name/ID of person extracting data
3. Report title *(title of paper/ abstract/ report that data are extracted from)*
4. Report ID *(if there are multiple reports of this study)*
5. Reference details
6. Report author contact details
7. Publication type *(e.g. full report, abstract, letter)*
8. Study funding source *(including role of funder)*
Possible conflicts of interest *(for study authors)*
9. Notes:

2. Eligibility

Study characteristics	Review inclusion criteria	Yes/ No / Unclear	Location in text *(pg & ¶/fig/table)*
10. Type of study	Randomised trial		
	Controlled before-after study		
	Interrupted time series		
11. Participants			
12. Relevant comparison?			
13. Variables of comparison between groups			
14. How were groups formed?			
15. Post-hoc study design features			
16. Types of intervention			
17. Types of outcome measures			
18. Decision:			
19. Reason for exclusion			
20. Notes:			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Population and setting

	Description	Location in text *(pg & ¶/fig/table)*
21. Population description *(from which study participants are drawn)*		

(*Continued*)

22. Setting *(including location and social context)*		
23. Inclusion criteria		
24. Exclusion criteria		
25. Method/s of recruitment of participants		
26. Notes:		

4. Methods

	Descriptions as stated in report/paper	**Location in text** ***(pg & ¶/fig/table)***
27. Aim of study		
28. Design *(e.g. parallel, crossover, non-RCT)*		
29. Unit of allocation *(by individuals, cluster/groups or body parts)*		
30. Period of follow-up clinic (weeks after discharge)		

(*Continued*)

31. Period of data recording (weeks after discharge)		
32. Start date		
33. End date		
34. Duration of participation *(from recruitment to last follow-up)*		
36. Notes:		

5. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	**Location in text (pg & ¶/fig/table)**
37. Total no. randomised (n) *(or total pop. at start of study for NRCTs)*		
38. Clusters *(if applicable, no., type, no. people per cluster)*		
39. Baseline imbalances		
40. Withdrawals and exclusions *(if not provided below by outcome)*		
41. Age (Median, IQR)		
42. Sex (n, %)		
43. Race/ethnicity (n, %)		
44. APACHE II, SAPS II		

(*Continued*)

45. Duration of sedation		
46. Presence of ARDS		
47. Reason for ICU admission		
48. Co-morbidities		
49. Incidence of delirium (CAM-ICU) (%)		
50. Other treatment received *(additional to study intervention)*		
51. Other relevant sociodemographics		
52. Subgroups measured		
53. Subgroups reported		
54. Notes:		

6. Intervention groups

Copy and paste table for each intervention and comparison group

Intervention group 1

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
55. Group name		
56. No. randomised to group *(specify whether no. people or clusters)*		

(*Continued*)

57. Description *(include sufficient detail for replication, e.g. content, dose, components; if it is a natural experiment, describe the pre-intervention)*		
58. Remote or direct clinic		
59. Method of contact		
60. Physician led or nurse led		
61. Duration of treatment period		
62. Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
63. Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
64. Co-interventions		
65. Economic variables *(i.e. intervention cost, changes in other costs as result of intervention)*		

(*Continued*)

66. Resource requirements to replicate intervention *(e.g. staff numbers, cold chain, equipment)*		
67. Notes:		

7. Control group

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
68. Group name		
69. No. randomised to group *(specify whether no. people or clusters)*		
70. Description *(include sufficient detail for replication, e.g. content, dose, components; if it is a natural experiment, describe the pre-intervention)*		
71. Type of alternative care		
72. Method of contact		

(*Continued*)

73. Duration of treatment period		
74. Timing *(e.g. frequency, duration of each episode)*		
75. Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
76. Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
77. Co-interventions		
78. Economic variables *(i. e. intervention cost, changes in other costs as result of intervention)*		
79. Resource requirements to replicate intervention *(e.g. staff numbers, cold chain, equipment)*		
80. Notes:		

8. Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
81. Outcome name		
82. Time points measured *(specify whether from start or end of intervention)*		
83. Time points reported		
84. Outcome definition *(with diagnostic criteria if relevant and note whether the outcome is desirable or undesirable if this is not obvious)*		
85. Person measuring/ reporting		
86. Unit of measurement *(if relevant)*		
87. Scales: upper and lower limits *(indicate whether high or low score is good)*		
88. Is outcome/tool validated?		

(*Continued*)

89. Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
90. Assumed risk estimate *(e.g. baseline or population risk noted in Background)*		
91. Notes:		

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

For randomised or non-randomised trial - dichotomous outcome

	Description as stated in report/paper		**Location in text** *(pg & ¶/fig/table)*
92. Comparison			
93. Outcome			
94. Subgroup			
95. Time point *(specify whether from start or end of intervention)*			
96. Results *Note whether: post-intervention OR change from baseline And whether*	**Intervention**	**Comparison**	

(*Continued*)

Adjusted OR Unadjusted			
	No. participants	No. events	No. participants
97. Baseline data	**Intervention**	**Comparison**	
	No. participants	No. events	No. participants
98. No. missing participants and reasons			
99. No. participants moved from other group and reasons			
100. Any other results reported			
101. Unit of analysis *(e.g. by individuals, health professional, practice, hospital, community)*			
102. Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*			
103. Reanalysis required? *(if yes, specify why, e.g. correlation adjustment)*			

(*Continued*)

104. Reanalysis possible?		
105. Reanalysed results		
106. Notes:		

For randomised or non-randomised trial - continuous outcome

	Description as stated in report/paper					**Location in text** *(pg & ¶/fig/table)*
105. Comparison						
106. Outcome						
107. Subgroup						
108. Time point *(specify whether from start or end of intervention)*						
109. Post-intervention or change from baseline?						
110. Results *Note whether: post-intervention OR change from baseline and whether Adjusted OR Unadjusted*	**Intervention**		**Comparison**			
	Mean/median	No. participants	Mean/median	SD (IQR)	No. participants	
111. Baseline data	**Intervention**		**Comparison**			
	Mean/median	No. participants	Mean/median	SD (IQR)	No. participants	
112. No. missing participants and reasons						

(*Continued*)

113. No. participants moved from other group and reasons		
114. Any other results reported		
115. Unit of analysis *(e.g. by individuals, health professional, practice, hospital, community)*		
116. Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*		
117. Reanalysis required? *(if yes, specify why)*		
118. Reanalysis possible?		
119. Reanalysed results		
120. Notes:		

For randomised or non-randomised trial - other outcome

	Description as stated in report/paper	**Location in text** ***(pg & ¶/fig/table)***
121. Comparison		
122. Outcome		
123. Subgroup		
124. Time point *(specify whether from start or end of intervention)*		
125. Type of outcome		

(*Continued*)

126. Results	Intervention result	SD (or other variance)	Control result	SD (or other variance)	
	Overall results		SE (or other variance)		
127. No. participant	Intervention		Control		
128. No. missing participants and reasons					
129. No. participants moved from other group and reasons					
130. Any other results reported					
131. Unit of analysis *(e.g. by individuals, health professional, practice, hospital, community)*					
132. Statistical methods used and appropriateness of these methods					
133. Reanalysis required? *(if yes, specify why)*					
134. Reanalysis possible?					

(*Continued*)

135. Reanalysed results		
136. Notes:		

For controlled before-after study

	Description as stated in report/paper			**Location in text** *(pg & ¶/fig/table)*
137. Comparison				
138. Outcome				
139. Subgroup				
140. Timepoint *(specify whether from start or end of intervention)*				
141. Post-intervention or change from baseline?				
142. Results	SD (or other variance)	Control result	SD (or other variance)	
	Overall results	SE (or other variance)		
143. No. participants	Intervention	Control		
144. No. missing participants and reasons				
145. No. participants moved from other group and reasons				

(*Continued*)

146. Any other results reported		
147. Unit of analysis *(individuals, cluster/ groups or body parts)*		
148. Statistical methods used and appropriateness of these methods		
149. Reanalysis required? *(specify)*		
150. Reanalysis possible?		
151. Reanalysed results		
152. Notes:		

For interrupted time series or repeated measures study

	Description as stated in report/paper	**Location in text** ***(pg & ¶/fig/table)***
153. Comparison		
154. Outcome		
155. Subgroup		
156. Length of time points measured *(e.g. days, months)*		

(*Continued*)

Total period measured			
157. No. of participants measured			
158. No. of missing participants and reasons			
159. No. of time poi measured	160. Pre-intervention	161. Post-intervention	
162. Mean value *(with variance measure)*			
163. Difference in means (post - pre)			
164. Percent relative change			
165. Result reported by authors *(with variance measure)*			
166. Unit of analysis *(individuals or cluster/ groups)*			
167. Statistical methods used and appropriateness of these methods			
168. Reanalysis required? *(specify)*			

(*Continued*)

169. Reanalysis possible?				
170. Individual time point results				
171. Read from figure?				
172. Reanalysed results	**SE**	**Change in slope**	**SE**	
173. Notes:				

10. Applicability

174. Have important populations been excluded from the study? *(consider disadvantaged populations, and possible differences in the intervention effect)*	*Yes/No/Unclear*
175. Is the intervention likely to be aimed at disadvantaged groups? *(e.g. lower socioeconomic groups)*	*Yes/No/Unclear*
176. Does the study directly address the review question? *(any issues of partial or indirect applicability)*	*Yes/No/Unclear*
177. Notes:	

11. Other information

	Description as stated in report/paper	**Location in text** ***(pg & ¶/fig/table)***
178. Key conclusions of study authors		

(*Continued*)

179. References to other relevant studies		
180. Correspondence required for further study information *(what and from whom)*		
181. Further study information requested *(from whom, what and when)*		
182. Correspondence received *(from whom, what and when)*		
183. Notes:		

Appendix 3. Modified 'Risk of bias' tool

Domain	Description	Review authors' judgement
Sequence generation		
Allocation concealment		
Blinding of participants and personnel		
Blinding of outcome assessors		
Incomplete outcome data		
Selective reporting		
Other sources of bias		
Baseline outcomes		

(*Continued*)

Contamination		
Baseline characteristics		
Intervention independent? (ITS)		
Appropriate analysis? (ITS)		
Shape of effect prespecified? (ITS)		
Effect on data collection? (ITS)		
Blinding (ITS)		
Incomplete outcome data (ITS)		
Selective reporting (ITS)		
Other sources of bias (ITS)		

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: PA

Designing the protocol: OSR

Coordinating the protocol: OSR

Designing search strategies: OSR, SL

Writing the protocol: OSR, SL

Providing general advice on the protocol: PA, AS, JM

Securing funding for the protocol: AS

DECLARATIONS OF INTEREST

- Oliver Schofield-Robinson: Nothing to declare
- Sharon Lewis: Nothing to declare
- Andrew F Smith: Nothing to declare
- Joanne McPeake is the chief investigator on a Health Foundation study on rehabiliation after ICU stay. The study is funded by the Health Foundation, under the grant number 7672, and is run through NHS Greater Glasgow and Clyde. There are no additional interests to declare.
- Phil Alderson: Nothing to declare

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NOTES

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