Evaluation of a Health and Social Care Rehabilitation Programme for Survivors of Critical Illness and their Families

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Abstract

Post-Intensive Care Syndrome (PICS) has been defined as new or worsening physical impairments, mental health problems, and/or cognitive dysfunction after a critical illness. PICS-Family (PICS-F) has been described as new or worsening mental health problems in the relatives and close friends of patients who have experienced intensive care. The Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE) programme is a complex outpatient health and social care intervention designed to address the common problems that encompass PICS and PICS-F. The InS:PIRE intervention is delivered by a complex Multidisciplinary Team (MDT), with patients and caregivers treated together in groups through repeated visits, usually over five weeks. The intervention is designed for both patients and their caregivers and incorporates peer support throughout the programme. This thesis has taken advantage of an InS:PIRE 'scaling-up' project during which the programme was being expanded from the original single InS:PIRE site to a further five sites across Scotland.

Before evaluating the effectiveness of InS:PIRE, a scoping review identified that there were no definitive treatments for PICS or PICS-F. Furthermore, there was a paucity of literature on the effects of complex outpatient interventions for critical illness survivors and their families. Having identified a gap, this thesis conducted three studies of the effectiveness and adaptability of the InS:PIRE intervention.

The first study was a multicentre evaluation that compared the Health-Related Quality of Life (HRQoL) of 137 patient participants who attended the InS:PIRE programme (intervention cohort) with 115 patient participants who were treated in hospitals that had no intensive care follow-up service (usual care cohort). After covariate adjustment, HRQoL, measured using the EQ-5D Health Utility Score, was statistically significantly higher in the intervention cohort compared to the usual care cohort (0.12, 95% CI: 0.04 to 0.20, p=0.01) one year after hospital discharge. Self-efficacy was also significantly higher and there were 62% lower odds of screening positively for depression (odds ratio: 0.38, 95% CI: 0.19 to 0.76, p=0.01). There was no difference in the odds of anxiety. Overall, attendance at InS:PIRE appeared to be associated with better HRQoL and emotional outcomes for patients.

The second study compared 81 caregiver participants who had attended the InS:PIRE programme (intervention cohort) with 89 caregivers recruited in parallel with the usual care cohort, as described above for the patient outcomes. After covariate adjustment, the intervention cohort had lower odds of screening positively for anxiety (odds ratio: 0.42, 95% CI: 0.20 to 0.89, p=0.02), caregiver strain (odds ratio: 0.39, 95% CI: 0.16 to 0.98, p=0.04), and clinically significant insomnia (odds ratio: 0.36, 95% CI: 0.17 to 0.77, p<0.01). There was no significant difference in the odds of depression between these cohorts. The intervention was therefore associated with a reduced burden on the caregiver from the problems relating to PICS-F.

The final study assessed the implementation of the InS:PIRE intervention at a specialist Cardiothoracic Intensive Care Unit (CICU). This study did not have a usual care cohort and as such was conducted as a quality improvement project. Over the course of five cohorts, 27 patients and 23 caregivers participated in InS:PIRE. Over 90% of patients had problems in at least one HRQoL domain and 57% of caregivers had features of anxiety, while 35% had depression. The InS:PIRE programme adapted well to the needs of this specialist quaternary referral CICU. The intervention appeared feasible, with 96% of participants completing the programme. In conclusion, the InS:PIRE intervention appeared to identify and address unmet health and social care needs for this group of patients and their caregivers; it was well tolerated and appeared to offer significant utility for this population.

This thesis describes in detail the literature relating to PICS, PICS-F, and specifically through a scoping review, outlines the outpatient interventions that have been described in the literature. Following on from this, the thesis documents the evolution and conduct of the InS:PIRE intervention and the framework under which the three studies were conducted. Finally, the detailed results of all three studies are described and the importance of this work to the literature is discussed.

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Author's Declaration

I declare that this thesis is my own composition and that the research contained within it is entirely my own unless stated otherwise. No part of this thesis has been submitted for another degree or professional qualification. The publications resulting from this thesis have been stated and explained in the text.

The work presented herein was undertaken when I was employed as an Anaesthetic and Critical Care research fellow at the University of Glasgow. This work continued as I completed my clinical training in Anaesthesia and Intensive Care Medicine and finally while employed as a substantive consultant in Greater Glasgow and Clyde. The research was conducted between February 2019 and October 2023. Data collection for the intervention (InS:PIRE) cohort was collected by the local teams delivering InS:PIRE and I was responsible for the transcription of all data onto a data collection tool. As such, I am the guarantor of this data. I was solely responsible for the further data collection (background characteristics, usual care cohort), statistical analysis, and interpretation of findings.

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Table of Contents

List of Tables

List of Figures

Publications directly resulting from the work of this thesis

1. **Henderson, P**, Robinson, C, Quasim, T. Socio-Economic Reintegration After Critical Illness. In: Haines, K.J, McPeake, J, Sevin, C.M. (eds) Improving Critical Care Survivorship. Springer, Cham. 2021. DOI: 10.1007/978-3-030-68680-2_18. Springer Nature (license number: 5646401077762). Link: https://link.springer.com/chapter/10.1007/978-3-030-68680-2_18.
   Book chapter; thesis chapters 1 & 7[1].

2. **Henderson P**, Quasim T, Asher A, Campbell L, Daniel M, Davey L, Devine H, Gall M, MacTavish P, Mcgroarty K, Nolan F, Purdie C, Quasim I, Sharp J, Shaw M, Iwashyna TJ, McPeake J. Post-intensive care syndrome following cardiothoracic critical care: Feasibility of a complex intervention. J Rehabil Med. 2021 Jun 3;53(6):jrm00206. DOI: 10.2340/16501977-2825. Published under creative commons license; CC BY-NC 4.0; https://creativecommons.org/licenses/by-nc/4.0/.
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   Journal article; thesis chapters 3 & 4[4].

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1. **Henderson P**, Quasim I, Asher A, Campbell L, Shaw M, Quasim T, McPeake J. P344 Caregiver burden after prolonged cardiothoracic critical care. 40th International Symposium on Intensive Care & Emergency Medicine: Brussels, Belgium. 24-27 March 2020. Crit Care. 2020 Mar 24;24(Suppl 1):87. DOI: 10.1186/s13054-020-2772-3.

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3. C Purdie, P MacTavish, T Quasim, **P Henderson**, J McPeake, M Shaw. P403 Predicting medication related problems in a post-ICU population using demographic and in-ICU clinical data. 40th International Symposium on Intensive Care & Emergency Medicine: Brussels, Belgium. 24-27 March 2020. Crit Care. 2020 Mar 24;24(Suppl 1):87. DOI: 10.1186/s13054-020-2772-3.

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Definitions / Abbreviations

6MWT	Six-Minute Walk Test
APACHE II	Acute Physiology and Chronic Health Evaluation Two
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Respiratory Failure
ASD	Acute Stress Disorder
BPI	Brief Pain Inventory
CABG	Coronary Artery Bypass Graft
CART	Categorical and Regression Trees
CBT	Cognitive Behavioural Therapy
CCI	Charlson Comorbidity Index
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Confidence Interval
CICU	Cardiothoracic Intensive Care Unit
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COVID-19	Coronavirus Disease 2019
CR	Cardiac Rehabilitation
CReDECI 2	Criteria for Reporting the Development and Evaluation of Complex Interventions in Healthcare: Revised Guideline
CSI	Caregiver Strain Index
CT	Computed Tomography
DS	Digit Span (memory test)
EQ-5D	EuroQol Five-Dimension Survey (EuroQol Quality of Life Group)
EQ-HUS	EuroQol Health Utility Score (EuroQol Quality of Life Group)
EQ-VAS	EuroQol Visual Analogue Scale (EuroQol Quality of Life Group)
FICM	Faculty of Intensive Care Medicine
GDP	Gross Domestic Product
GJNH	Golden Jubilee National Hospital
GP	General Practitioner

GPICS	Guidelines for the Provision of Intensive Care Services
GRI	Glasgow Royal Infirmary (NHS Greater Glasgow and Clyde)
GSE	Generalised Self-Efficacy
HAC	Heteroskedasticity and Autocorrelation Consistent
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS-Anxiety summary score
HADS-D	HADS-Depression summary score
HDU	High Dependency Unit
HRQoL	Health-Related Quality of Life
ICNARC	Intensive Care National Audit and Research Centre
ICON	Intensive Care Outcome Network
ICU	Intensive Care Unit
ICU-AW	Intensive Care Unit-Acquired Weakness
IES-6	Impact of Events Scale–6
IES-R	Impact of Events Scale-Revised
InS:PIRE	Intensive Care Syndrome: Promoting Independence and Return to Employment
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IQR	Interquartile Range
ISI	Insomnia Severity Index
MCID	Minimal Clinically Important Difference
MCS	Mental Component Summary (SF-36 summary score)
MCT	Minimised Controlled Trial
MDT	Multidisciplinary Team
MEDLINE	National Library of Medicine's Medical Literature Analysis and Retrieval System (online)
MI	Myocardial Infarction
MICE	Multivariate Imputation by Chained Equations
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment

MOS	Medical Outcome Survey (RAND group)
MRC	Medical Research Council
MRP	Medication Related Problems
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NNT	Number Needed to Treat
OLS	Ordinary Least Squares
OOHCA	Out of Hospital Cardiac Arrest
PCI	Percutaneous Coronary Intervention
PCL-C	Post-Traumatic Stress Disorder Checklist - Civilian
PCS	Physical Component Summary (SF-36 summary score)
PICS	Post-Intensive Care Syndrome
PICS-F	Post-Intensive Care Syndrome-Family
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Extension for Scoping Reviews
PTSD	Post-Traumatic Stress Disorder
QALY	Quality Adjusted Life Year
QI	Quality Improvement
QoL	Quality of Life
QQ-plot	Quantile-Quantile plot
RAND	RAND corporation (also see medical outcome survey, MOS)
RAVLT	Rey Auditory Verbal Learning Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomised Control (or Clinical) Trial
ROCF	Rey-Osterrieth Complex Figure
SALT	Speech and Language Therapist
SCCM	Society of Critical Care Medicine

SD	Standard Deviation
SF-36	36-item Short Form Health Survey (also see MOS and RAND)
SICSAG	Scottish Intensive Care Society Audit Group
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation
SNAHFS	Scottish National Advanced Heart Failure Service
STEMI	ST-Elevation Myocardial Infarction
TMT	Trail Making Test
TTM	Targeted Temperature Management
UHC	University Hospital Crosshouse (NHS Ayrshire and Arran)
UHM	University Hospital Monklands (NHS Lanarkshire)
UHW	University Hospital Wishaw (NHS Lanarkshire)
VAD	Ventricular Assist Device
VA-ECMO	Veno-Arterial Extra-Corporeal Membrane Oxygenation
VFT	Verbal Fluency Test
VH	Victoria Hospital (NHS Fife)
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale

Chapter 1 Introduction: Understanding outcomes after critical illness

> "The success of intensive care is not, therefore, to be measured only by the statistics of survival, as though each death were a medical failure. It is to be measured by the quality of lives preserved or restored."[5]
>
> Reverend Professor Gordon Dunstan, 1984, Intensive Care Society meeting

The birth of intensive care medicine is credited to Björn Ibsen when he and his team delivered positive pressure ventilation through tracheostomies to patients with polio[6]. This was the first time that a group of patients requiring life support were treated together outside of an operating theatre. The technology at the time was in its infancy with lung insufflation being delivered manually by squeezing an oxygen and air-filled bag, often by medical students. Despite this, important improvements in polio mortality rates were observed. Furthermore, the concept of the Intensive Care Unit (ICU) was established. It was seen as feasible and advantageous to deliver complex organ support to multiple patients in one location.

Intensive care has developed significantly over the past seven decades with improvements in the patient important outcome of mortality during this time[7]. However, commentators have equally questioned what sort of life or problems survivors of ICU are left with. The question of the over-reliance on mortality was raised by moralist Reverend Professor Gordon Dunstan at a meeting of the Intensive Care Society in 1984[5]. Despite this early recognition that Quality of Life (QoL) may be an important concept, it would be another 19 years before the intensive care community started to take recovery and measuring long-term outcomes seriously[8]. The purpose of this thesis is to understand how a complex intervention after hospital discharge could improve the lives of patients and families who have been critically unwell in ICU. Before assessing interventions, it is important to understand the problems that patients and their families face after a life changing critical illness. This chapter will explore these problems before the possible solutions and impact of a complex health and social care intervention are evaluated through the remainder of this thesis.

1.1.1 Contemporaneous organisation of intensive care

Critical care units today treat the most unwell patients in the hospital. Definitions of intensive (or critical) care have been standardised to include patients having, or at risk of, life-threatening organ disfunction[9]. In the UK, critical care is usually delivered in an ICU, a High Dependency Unit (HDU), or a mixed unit which delivers both ICU and HDU care[10]. The majority of ICUs, HDUs, and critical care units are general units admitting patients from any hospital specialty who require increased monitoring, nursing care, or organ support compared to a typical hospital ward. There are, however, some specialist units treating single disease processes or specialty case mixes. Some examples would include Cardiothoracic Intensive Care Units (CICU), Coronary Care Units (CCU), Neuroscience ICUs, or other specialist units (e.g. liver critical care units or trauma ICUs)[11,12].

UK admission criteria for ICU is generally reserved for patients requiring invasive mechanical ventilation or those with multiple (≥ two) organ failures[10]. This could include, as an example, patients requiring non-invasive ventilation alongside cardiovascular support in the form of vasopressors. Furthermore, the ICU is usually the only location outwith a renal unit to deliver renal replacement therapy (e.g. haemofiltration or haemodialysis). On the whole, patients requiring, or treated in, an ICU are considered to be receiving level 3 care[10].

HDU admission is generally reserved for patients requiring the support of a single organ system, or those requiring advanced monitoring, who are at risk of deterioration. This could include those receiving vasopressors to treat hypotension or post operative patients at risk of deterioration (e.g. following a laparotomy)[10]. In the UK this is known as level 2 care.

The term critical care unit is less well defined in the UK and can be applied to any area that can deliver a higher level of care than standard ward therapies or monitoring and could apply to any ICU, HDU, or mixed area. In practice, hard definitions tend to be less precisely applied and some patients in an ICU may be receiving HDU level treatment. There are also some regional, and international, variations determined by the healthcare structures in each area, although the specifics of these are beyond the scope of this thesis.

1.1.2 Scale of intensive care

In the UK, two central national registries collate data on ICU care. Data from all NHS adult ICUs, HDUs, and mixed units in Scotland is collated and reported by the Scottish Intensive Care Society Audit Group (SICSAG) in conjunction with Public Health Scotland[11]. In England, Wales, and Northern Ireland, these data are collated and reported by the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme[12]. Both datasets focus on adult critical care services and do not include paediatric critical care, which is not considered in this thesis.

When considering the data from both registries (i.e. the whole UK dataset), there were a total of 338 units in 2021, which is the last complete year from which both registries reported[11,12]. Of these, 276 units were described as ICUs or mixed / combined units and therefore capable of delivering level 3 care. The remaining 62 units were standalone HDUs which could deliver level 2 care. The total number of admissions during this year was 234,000 (to ICUs and HDUs) with 164,000 admissions from general ICUs (this included mixed ICU / HDUs but excludes standalone HDUs and some specialist units). Once readmissions were excluded, this resulted in over 125,000 patients being discharged from hospital alive after being critically unwell and experiencing ICU. COVID-19 likely had a significant impact on these 2021 figures, with slightly fewer total admissions and discharges than the annual average. As such, future non-pandemic years are more likely to be similar to 2019 when over 145,000 patients were discharged from hospital alive after a critical illness and treated in an ICU. These figures also exclude some specialist units (CICU and Neurosurgical ICUs in England, Wales, and Northern Ireland); if these patients were included, the total numbers would be around 180,000 patients discharged from hospital alive after treatment in an ICU in the UK each year. The standalone HDU numbers are not well reported and not included in this figure.

Other international comparisons can be complex with differing access to intensive care, total bed numbers, admission criteria, and staff to patient ratios[13]. Despite this, it is evident that substantial numbers of patients experience and survive intensive care every year. In the USA it is estimated that over five million patients are admitted to ICU every year[14,15]. While in Manitoba, Canada, it was estimated that between 0.5 and 1% of their population were admitted to ICU every year[16].

This figure increased to over 2% in those aged 60 years old or greater. These figures are similar, although slightly higher, than the UK numbers. Regardless of the exact figure, it is clear that both nationally and internationally, the number of people experiencing a critical illness and intensive care treatment is substantial. As such, any issues experienced by this group of critical illness survivors are likely to represent a significant epidemiological issue and form part of the rationale for this thesis.

1.1.3 Definitions of survivorship

Critical illness literature frequently uses the term 'survivor' to describe those who have been through a critical illness. However, some patients and families may not identify themselves as survivors. The term can be useful from a medical perspective as it can differentiate those who are in intensive care (the patients) with those who have recovered from the life-threatening part of their critical illness and are discharged from hospital (survivor). It is therefore worthwhile examining the definitions of survivor and survivorship.

The Oxford English dictionary defines survivorship as "the state or condition of being a survivor" or a "body of survivors" [17]. The simplicity of this description, however, belies the importance of this term to many who have been through critical illness. The concept of survivorship relating to health, illness, and recovery originated from those surviving a cancer diagnosis[18]. For both cancer and critical illness, the process of becoming a survivor suggests that the individual has been through a difficult or challenging event and there is likely to be a shared lived experience among a group of survivors[18-23]. While experiences are unique, it is in the overlapping hardships and challenges that allow critical care survivors to come together and support one another. Ultimately, the use of this term should be directed by the person who has recovered from critical illness, with many wishing to move on and not refer to survivor or survivorship. They may simply be a person who has been through critical illness. Others will see this label as acknowledging their experience and its effects on their lives after hospital discharge. Lastly, it allows recognition of the critical care experience on an individual's life while moving beyond the term patient.

1.1.4 Definition of Post-Intensive Care Syndrome

The physical consequences after critical illness, particularly the decline in respiratory function after Acute Respiratory Distress Syndrome (ARDS), have been documented since the 1970s[24-29]. It was not until the turn of the century that a greater understanding of the longer-term effects, including extra-respiratory effects, were more fully described[8,23].

The significant work assessing the problems after critical illness, particularly at the start of this century, culminated in a meeting of key stakeholders organised by the Society of Critical Care Medicine (SCCM) in 2010[30]. The two-day meeting, involving 31 experts in intensive care recovery, collated and discussed relevant literature. The overarching aim was to develop recommendations to improve long-term outcomes after critical illness for patients and their families. While there were several recommendations, by far the most significant and lasting contribution to the field was to define Post-Intensive Care Syndrome (PICS) and Post-Intensive Care Syndrome-Family (PICS-F).

Their definition of Post-Intensive Care Syndrome was:

> "New or worsening problems in physical, cognitive, or mental health status arising after a critical illness and persisting beyond acute care hospitalization. The term could be applied to either a survivor or family member."[30]

Figure 1-1 is a reproduction from the original paper by Needham et al that first introduced the concept of PICS. Importantly this figure summarises the domains of PICS and PICS-F. It also attempts to summarise examples of worsening or new impairments that belong to each domain[30].

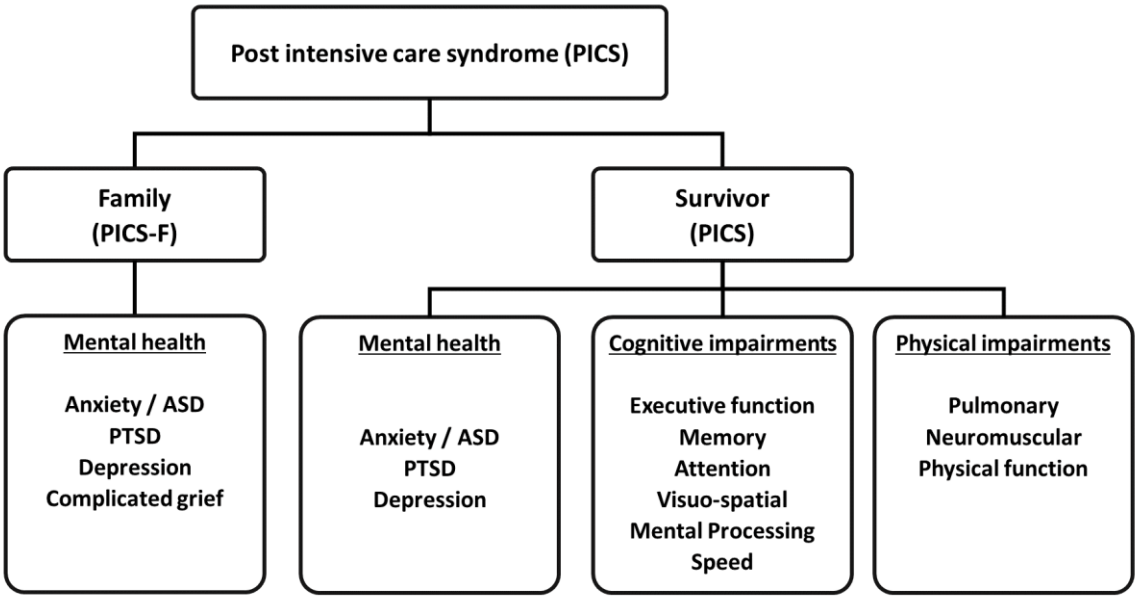


Figure 1-1: Post-Intensive Care Syndrome its problems and domains

PICS: Post-Intensive Care Syndrome; PICS-F: Post-Intensive Care Syndrome-Family; ASD: Acute Stress Disorder; PTSD: Post-Traumatic Stress Disorder. Reproduced with permission from Needham et al (licence number: 5644250614527; Wolters Kluwer Health, Inc.)[30]

PICS can, therefore, be considered an overarching term for all impairments, new or exacerbated, after discharge from hospital where there was a period of critical illness. From this umbrella term arises sub terms. Within this thesis PICS will, unless specified otherwise, refer to the new or exacerbated problems the patient or survivor experiences after critical illness. PICS-F will describe the new or exacerbated problems experienced by the loved ones, family members, informal caregivers, or friends of the patient or survivor.

1.1.5 PICS and PICS-F incidence

Before considering the specific domains of PICS, PICS-F, and the rates of problems in each subsection, it is worth first considering the scale of the problem overall. As can be expected with a heterogeneous cohort, such as ICU survivors, there has been substantial variation in the rates of PICS. One of the most robust studies of incidence of new problems after critical illness was reported by Marra et al[31]. This study reviewed 406 participants from five centres in the USA. The results demonstrated that in this cohort of ICU patients, with very low rates of comorbidities or preexisting problems, the incidence of new onset cognitive impairment, disability, or depression, was 64% at three months and 56% at one

year[31]. This study was methodologically very robust, with excellent background data and good follow up rates (≥80% of those eligible). However, the results should only be extrapolated to all ICU patients carefully as patients with any pre-existing problems were excluded. Furthermore, there was no evaluation of anxiety, PTSD, or social issues. As such, these figures could be considered as a best-case scenario (or lowest incidence).

Other studies have assessed a broader range of patients looking for rates of any problems with activities of daily living, mental health, or pain. Using this definition it has been demonstrated that up to 90% of patients have at least one problem that is new or worse after critical illness[32]. This estimate could therefore be considered an upper estimate, or worst-case scenario.

When these rates of PICS are considered within the context of the overall rates of ICU discharges, the total number of people experiencing PICS is likely to be substantial. In the UK a best-case estimate would be that 70,000 people every year experience PICS for the first time. However, this figure could be as high as 160,000 people per year. Furthermore, 20 to 80% of ICU survivors' families are estimated to experience PICS-F[33-35]. This range is wide and clearly more work is required. However, even the lowest estimates, combined with the high numbers of patients surviving critical illness every year, suggest that PICS and PICS-F combined represent a significant epidemiological problem. Together these issues, and their incidence, are the basis and justification for conducting the work of this thesis.

1.1.6 PICS and PICS-F domains

As is evident from the conceptual diagram (Figure 1-1), PICS and PICS-F are made up of elements which are known as domains. Further, the description offers an idea of the problems that can be expected within each domain, this includes[30]:

- Mental health: anxiety; Acute Stress Disorder (ASD); Post-Traumatic Stress Disorder (PTSD); depression.

- Cognitive impairments: executive function; memory; attention; visuo-spatial; mental processing speed.

- Physical impairments: pulmonary; neuromuscular; physical function (deficits in global physical performance)

- PICS-F mental health: anxiety; ASD; PTSD; depression; complicated grief.

One of the most important factors missing from the original description are the socioeconomic impacts of critical illness on patients and families[36]. Since the original publication in 2012, many commentators and review articles have considered that the socioeconomic consequences of critical illness and intensive care are significant[37-39]. Within paediatric critical care this has been formalised and is considered the fourth domain for children recovering from critical illness[40]. The socioeconomic consequences will be reviewed towards the end of this chapter after first considering the original domains of PICS and PICS-F.

1.1.7 Understanding long-term outcome measures from critical illness and the experience of acute respiratory failure

While the problem of PICS and PICS-F have been well defined, the best methods for measuring these problems remains unclear despite significant work to resolve this issue. Therefore, before considering the extent of the problems relating to PICS and PICS-F, it is worthwhile considering what outcome measures have been utilised or recommended for critical illness survivors generally. It is evident from the literature that the early work on long-term outcomes was centred around patients with Acute Respiratory Failure (ARF) and ARDS[8,30]. PICS was then conceptualised in 2010 partly due to the recognition that patients without ARF or ARDS were also experiencing similar long-term difficulties. It is therefore useful to consider recommendations for measures of long-term outcomes for ICU survivors and ARF research before considering any PICS or PICS-F recommendations.

However, the first challenge when considering the medium- and longer-term outcomes after intensive care (particularly ARF/ARDS) is the variety of outcome instruments used. This was demonstrated when a scoping review of 425 studies by Turnbull et al in 2016 identified 250 different measurement tools assessing outcomes from ICU survivorship[41]. This heterogenicity makes pooling results very

difficult, increases the incidence of selective reporting of results, increasing bias, and can result in outcomes that have little relevance to key stakeholders[42].

Following on from this work, Needham et al carried out two studies looking at patient important outcomes[43,44]. This culminated in a modified Delphi consensus process with the aim of recommending a core outcome set to assess long-term outcomes after critical illness in survivors of ARF[43-45]. The Delphi process involved 77 participants comprising clinical researchers, clinicians, patients, caregivers, and representatives from United States federal research funding organizations. Clinicians and researchers were recruited internationally with 55% of the entire panel coming from outside of the USA, representing 16 countries in total. After evaluating 38 measurement tools through three rounds, there were three tests that met the strongest criteria to be recommended towards a core outcomes set[45]. These were:

- EuroQol EQ-5D to assess Health-Related Quality of Life (HRQoL) and to assess pain (a sub element of the EQ-5D) but not specifically for physical functioning

- Hospital Anxiety and Depression Scale (HADS) to assess mental health

- Impact of Events Scale–Revised (IES-R) to assess metal health or PTSD

There were a further two recommendations, the 36-item Short Form Health Survey (SF-36) version 2, which compliments the EQ-5D, and should be considered as an addition if more detail is required regarding HRQoL. The Montreal Cognitive Assessment (MoCA) received the highest scores for tests of cognition, however, it failed to meet the a priori definition for inclusion, achieving only 55% agreement.

Perhaps the most noteworthy parts of the paper are the elements that did not achieve agreement, specifically, there were no physical measures that reached agreement, although the Six-Minute Walk Test (6MWT) was closest. The process was unable to recommend any tools for assessment of survival, muscle and / or nerve function, physical function and symptoms, pulmonary function, or pain. A significant weakness of this paper was that it gave a consensus statement of 77 stakeholders, rather than a vigorous validation of each tool. However, the breadth

of groups represented, and the methodology give this the mantle as one of the strongest papers to have recommended a core outcome set for long-term outcomes after ARF.

As previously discussed, this process was for a core outcomes set for ARF rather than specifically for PICS. Although there is significant overlap with long-term outcomes and PICS, the Delphi process cannot be described as the PICS core outcomes set. At the time of writing there is no core outcomes set for PICS and researchers have to choose carefully which outcomes to measure, but can be guided by the existing intensive care, ARF, and ARDS literature.

1.1.8 Synthesising PICS definitions and outcome measures

Almost a decade after the original meeting defining PICS, PICS-F, and its domains there was another two-day meeting, again involving 31 international experts, who were charged with assessing factors for predicting and identifying long-term impairments after critical illness[46]. With substantial literature reviews, including a systematic review, alongside presentations from experts in the field, the conference developed several recommendations. These included continuing use of the term PICS with its three domains (physical, psychological, and cognitive). There was also 100% agreement on increasing the emphasis on the social aspects of recovery. Other recommendations that directly relate to outcomes are the timing of patient assessments (recommended as serial assessments beginning 2-4 weeks after discharge), and which assessments should be carried out. Specifically, strong recommendations were made for the use of HADS to screen for anxiety and depression, and MoCA to screen for cognitive disfunction. Weak recommendations were for the use of EQ-5D and 6MWT for physical function and IES-R or abbreviated Impact of Events Scale–6 (IES-6) for PTSD. Notably, these recommendations were for "default" assessments of patients and families post-ICU, rather than a recommendation for the measurement of outcomes as part of research studies.

These recommendations, however, are very similar to the Delphi process from Needham and colleagues relating to ARF outcomes. It should be noted that some delegates contributed to both reviews, although the processes were significantly different. There were different numbers of delegates at each review. Also the role and input from patients was less well defined for the consensus conference,

although it states they were involved and their names appear on the authorship list[46]. However, the Delphi process of ARF outcomes was much more explicit in the involvement of multiple different stakeholder groups including ICU survivors[45].

While neither process was specifically designed to guide researchers assessing PICS and PICS-F long-term outcomes, these inter-related recommendations are as close to a core outcomes set as is currently available. This is, however, a research gap and more work needs to be done to create a definitive care outcomes set.

These developments, alongside the increasing emphasis on socioeconomic wellbeing highlight that the original conceptual framework from 2012 (Figure 1-1) merits updating. For this thesis Figure 1-2 synthesises these advancements over the last decade to highlight the important patient and family outcomes, the importance of socioeconomic wellbeing as a domain, and where outcome measures fit into the conceptual framework.

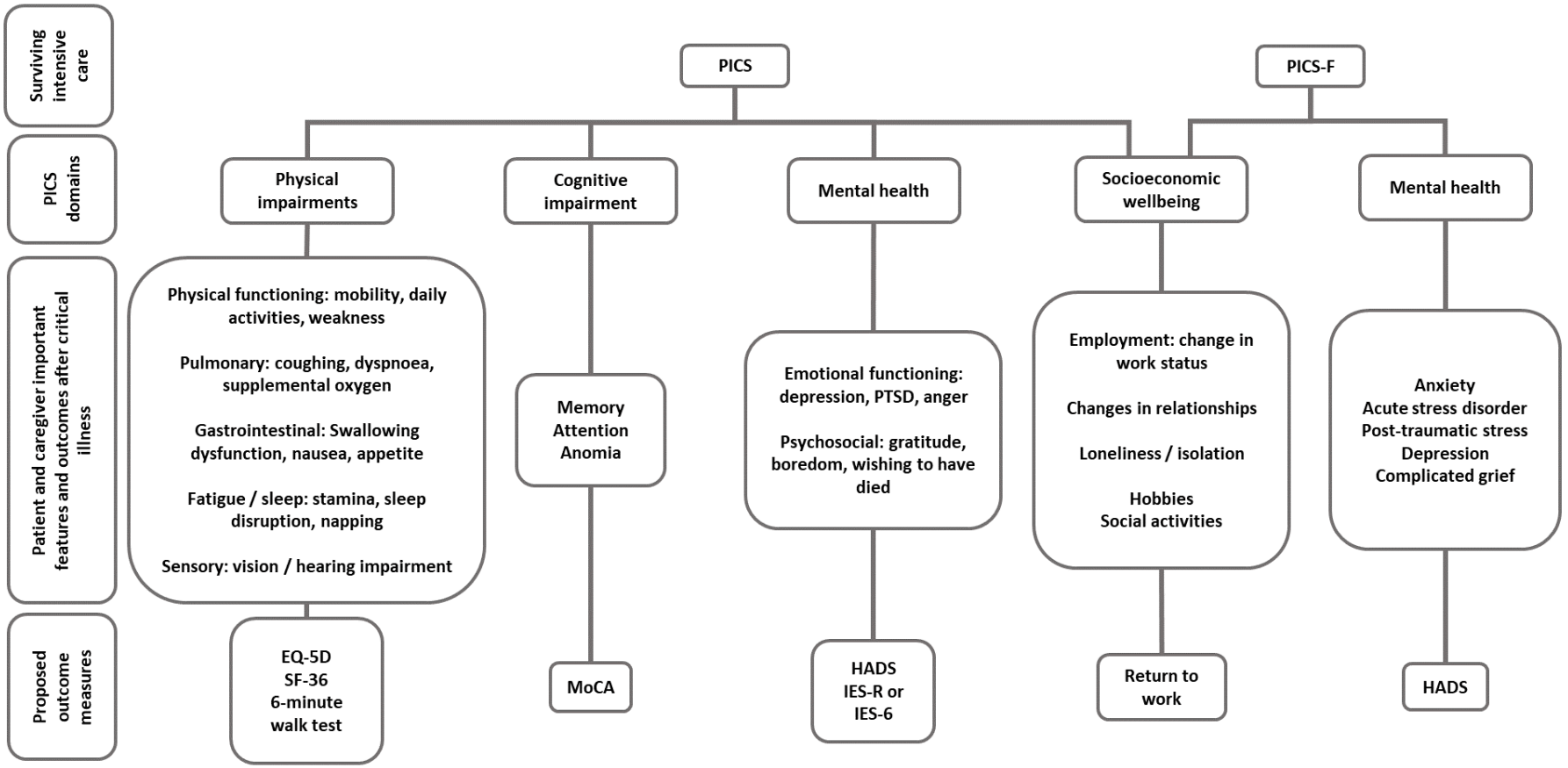


Figure 1-2: An overarching PICS framework for this thesis

Original diagram created for this thesis incorporating PICS definitions, important outcomes, and proposed outcome measures. PICS: Post-Intensive Care Syndrome; PICS-F: PICS-Family; PTSD: Post-Traumatic Stress Disorder; EQ-5D: EuroQol 5-dimension survey; SF-36: Short-Form 36 health survey; MoCA: Montreal Cognitive Assessment; HADS: Hospital Anxiety and Depression Scale; IES-R: Impact of Events Scale-Revised

1.2 PICS biological plausibility: a description of two critical illness disease states

Before exploring the longer-term physical effects of critical illness and its treatment it is worth considering two common intensive care disease states: ARDS and Intensive Care Unit-Acquired Weakness (ICU-AW). These have been chosen as any critically unwell patient can suffer from these conditions regardless of admission diagnosis and they are well studied within the intensive care literature. Finally, they may offer a biological explanation as to how critical illness could lead to new or worsening impairments as defined by PICS. While other disease states could have been chosen (e.g. sepsis, delirium, or cardiac arrest), ARDS and ICU-AW appeared in the literature as the most likely to offer biological plausibility for the problems of PICS. Furthermore, the purpose of this section is not to offer a comprehensive analysis of these disease processes, instead this is to generate insights into how the events in ICU could lead to problems (particularly physical problems) after critical illness.

1.2.1 Acute Respiratory Distress Syndrome

ARDS is a respiratory condition almost exclusive to intensive care medicine defined as hypoxaemia with a PaO_2/FiO_2 (arterial partial pressure of oxygen to fraction of inspired oxygen) ratio ≤300 mmHg, non-cardiac bilateral pulmonary infiltrates, low respiratory system compliance (≤40 mL/cm H_2O), and occurring within one week of a known clinical insult[47,48]. The definitions of ARDS are constantly evolving with the most recent updates in 2023 recommending the inclusion of patients receiving high flow nasal oxygen[48]. These updates likely reflect the fact that ARDS is not one single pathological condition. However it is difficult to overstate the importance of ARDS to intensive care, the patients treated in ICUs, and to the critical care research community[49]. It is likely that Ibsen and Lassen first described some features of ARDS in 1952, however, it was not until the turn of this century that the first trials demonstrating a positive outcome were published[50-52]. Specifically, low tidal volume positive pressure ventilation and prone positioning, together with the judicial use of neuromuscular blockers are the cornerstones of ARDS management[51-54]. Mirroring the overall changes in critical care, in North America, mortality from ARDS has improved from 50% in 1988-1992 to 33% in 2006-

2010[55]. Unfortunately, there are long-term effects from this heterogenous disease. For example, up to 87% of patients have persistent changes on chest Computed Tomography (CT) between six and 10 months post hospital discharge, although the main lasting respiratory abnormality is a reduced diffusion capacity of the lung for carbon monoxide[8,56,57]. More significantly these studies demonstrate greater effects on survivors' overall QoL and more global measures of physical functioning[8,57].

These findings help to link, directly, events occurring in the ICU to long-term outcomes after critical illness. While this is important on its own, considering ARDS, and having some knowledge of this syndrome is useful when attempting to answer the question of, what are the persisting physical effects after critical illness? Many studies focus primarily on ARDS as this offers a better-defined population than all patients admitted to ICU. As such, we must remain careful when extrapolating these data to all ICU survivors, even though there is much overlap. Some of the features and treatments of ARDS can involve:

- Reduced physical activity, often including prolonged periods of bed rest
- Endotracheal intubation with direct pressure areas and problems with mouth care, oral hygiene, and vocal cord dysfunction
- Mechanical ventilation, with resultant barotrauma, volutrauma, atelectotrauma, biotrauma, and the toxic effects of oxygen
- Use of sedation and neuromuscular blocking agents, which may have direct effects but also result in issues relating to patient positioning, including pressure areas to skin, nerves, and muscles
- Nutritional deficits including pre-intensive care poor nutritional states, inadequate caloric intake during acute illness, and the high metabolic demands of acute illness

Many of the above features are common to ICU patients without ARDS also. The overlap with these issues and the multisystem nature of ARDS and its treatments

can make fragmentation of intensive care into individual disease states less desirable. Furthermore, ARDS is defined by having a known clinical insult and therefore, must co-exists with many other critical care related diagnoses[47]. Even if the reason for admission is a non-ARDS related process, many patients will have occult ARDS or develop the syndrome later in their disease course [58]. As such, many of the issues relating to ARDS will also occur in non-ARDS (or occult ARDS) ICU patients.

In understanding both the pulmonary and extra-pulmonary effects of ARDS, it is possible to link problems experienced by the survivor of intensive care back to events occurring during the critical illness. While this may not be possible for every pattern seen, it is worth maintaining an awareness of these issues when considering the biological plausibility of PICS.

1.2.2 Intensive Care Unit–Acquired Weakness

Just as ARDS can have long-term consequences, ICU-AW is common in ICU patients and could potentially explain some of the physical problems experienced after critical illness. ICU-AW is an umbrella term that describes a symmetrical limb and respiratory muscle flaccid paralysis[59,60]. The contributing syndromes of critical illness myopathy, critical illness polyneuropathy, or more commonly, a mixed disease process is seldom differentiated in routine clinical practice. Differentiating between ICU-AW subtypes is challenging as this involves technology often not available at the bedside and / or patient active participation, and it is contested whether this level of subtype differentiation changes treatment or outcomes[61,62]. ICU-AW, however, affects between 43 and 46% of all ICU admissions and results in longer durations of mechanical ventilation, ICU length of stay, and hospital length of stay[63]. Studies often have methodological flaws, and it can be difficult to pool results. Despite this, some proposed risk factors include severity of illness, sepsis, systemic inflammatory response, hyperglycaemia, catecholamine use, renal replacement therapy, neuromuscular blocking agents, and aminoglycosides[63,64]. Importantly, the effects of ICU-AW appear to last significantly beyond hospital discharge[65,66]. ICU-AW is unlikely to explain all the physical problems associated with PICS, but an awareness of the issue helps place

into context the direct effects of critical illness and offers a further degree of biological plausibility to any findings within this domain.

1.3 PICS Physical outcomes

Maintaining a focus on patient important outcomes may be most important when considering the physical domain of PICS. It is tempting for the clinician or researcher to retreat to familiar hospital-based tests including spirometry, radiography, CT, grip strength, and nerve conduction studies. While the utility of these tests when diagnosing or managing specific diseases is clear, their usefulness in understanding the longer-term impact of critical illness is less clear. The recommendations explored up to this point have not proposed any of these traditional tests as these are unlikely to match with important patient specific outcomes[38,46,67]. The purpose of considering these tests here is that these are the traditional basis for early follow-up. Furthermore, they are meaningful for many clinicians and can offer insight into the pathophysiological processes, allowing the targeting of possible therapeutic interventions.

1.3.1 Respiratory function

Pulmonary assessment has involved spirometry, lung volumes, diffusion capacity, radiology, and blood gas assessments[68]. These studies have primarily focused on ARDS and acute lung injury (a term not commonly in use now) as it would be expected to find the greatest abnormalities in these groups[57,69-71]. Alongside some sustained changes seen on CT chest scans, early studies suggested that there were impairments in spirometry at one year[69]. Orme Jr and colleagues demonstrated that 80% of patients had reduced diffusing capacity for carbon monoxide, 20% had chest wall restriction, and 20% had airflow obstruction[69]. Importantly, reductions in diffusion capacity are reduced or eliminated if corrected for alveolar volume. This study and others have failed to link these effects to either ventilation strategy; that is, low tidal volume ventilation has not demonstrated improvement in lung function, or improvements in QoL, although it has demonstrated improvements in mortality[51,69,72].

Herridge et al found normal spirometry results and lung volumes among ARDS survivors by six months, although diffusion capacity remained low at one year[8]. They also found that 6% of patients had arterial oxygen saturations below 88% during exercise at one year, with no patients requiring domiciliary oxygen[8]. A subsequent paper then described the outcomes from this same group of patients after five years[57]. This paper described no significant deficits in spirometry (all markers >80% of predicted), with diffusion capacity (carbon monoxide diffusion capacity) improving from 72% at year one to 80% at year five post ICU discharge[57]. The number of patients demonstrating exertional desaturation (arterial oxygen saturations <88%) increased from five (6%) to eight (15%) of those tested at the respective one-year and five-year time points. Despite this, the authors concluded that changes in respiratory function did not explain other markers of deterioration in physical function. This landmark paper in long-term outcomes is noteworthy due to the long period of time for follow-up (five years) and the way in which focal measures of physical function were measured alongside HRQoL.

Others have demonstrated reduced lung volumes with a restrictive pattern as the most commonly observed respiratory abnormalities[73]. This could result from either fibrosis secondary to ARDS or muscle weakness from any ICU related condition. Respiratory muscle strength (defined using maximal inspiratory force compared to non-ICU age corrected populations) has been shown to be reduced in both ARDS and sepsis (non-ARDS) patients at three months (range 72-74%) returning close to baseline at one year (>80%)[70,74]. The lasting effects seen on pulmonary testing in isolation are minimal overall, and the effects on HRQoL appear to last beyond the changes in respiratory function. This is likely to be the reason that no isolated pulmonary marker has been recommended for assessment of long-term outcomes.

1.3.2 Skeletal muscle strength

It is very common for patients to describe a subjective experience of weakness after critical illness[57]. As will be demonstrated, however, outcomes from studies that have quantitatively measured muscle strength during long-term follow-up after critical illness have been mixed.

Focused quantitative measures have included tests of large muscle groups (knee extension or flexion), medium muscle groups (elbow and ankle testing), and small muscle groups (hand grip strength)[66,70,73-77]. These studies largely assess strength with a dynamometer (measuring the torque and rotational speed), or force transducer.

Poulsen and colleagues assessed a small cohort (31 patients total, 16 post intensive care, 15 control volunteers) with a thorough battery of tests, one year after intensive care discharge[66]. Knee flexion / extension and grip strength were assessed for force generation and endurance[66]. Significantly reduced muscle force generation and endurance were demonstrated but once adjusted for muscle volume there were no differences. The unique value of this study is to suggest the underlying mechanisms behind lasting ICU-AW. The muscle mass change entirely explained the reduced force generated, whereas nerve conduction was unchanged. Interestingly ICU corticosteroid use was predictive of weakness at one year. This study contradicted earlier work demonstrating a return to baseline strength at six months[75].

Fan et al reported a larger cohort with 222 participants but relied on normal predicted values rather than a control cohort. ICU-AW was measured on the Medical Research Council (MRC) ordinal scale, which classed strength as 0 to 5 in six muscle groups, with summary range 0-60. ICU-AW was defined as a score of <80% of maximum. Using this criteria one-third of patients had ICU-AW at three months but 9% met these criteria at 24 months. Further, tests of muscle force also improved in this timeframe with a corresponding increase in upper arm circumference[70].

While the muscle power assessment results initially look varied between studies, when the time to follow-up is taken into account the studies appear far more consistent. Those completing follow-up earlier tend to describe lower strength whereas those with follow-up times of one year or greater report better scores. Muscle weakness is usually associated with lower muscle mass while nerve conduction studies have not correlated with power.

While there are some signals of problems in both isolated markers of respiratory and muscle function the natural history of both appears to be resolution over time. These studies also have significant limitations with low recruitment numbers and lack of control group, relying on normal reference values[66,70,73-77]. These factors may be why both core outcome sets for ARF and the consensus statements for PICS tend to include more global assessments of physical function.

1.3.3 Six-Minute Walk Test: Towards a global physical outcome measure

The 6MWT is a more global assessment of submaximal physical function and measures the distance walked, usually in meters, over six minutes on a hard, flat surface[78]. This requires a combination of muscle, respiratory, and cardiovascular reserve to complete. The 6MWT requires a sustained effort from the patient and may be affected by other aspects of HRQoL including mental health.

The most noteworthy studies reporting 6MWT in intensive care survivors have been from Needham et al and Fan et al[70,79]. The unifying features of these studies are the longer follow-up periods (12 and 24 months) and the impressive participant retention numbers (175 and 146 respectively). Results are also consistent with Needham et al reporting a 6MWT distance of 67% (SD +/- 26) of predicted at 12 months and Fan et al reporting 63% (SD +/- 25) of predicted at 24 months. These results have been incorporated into two systematic reviews that confirm persistent reductions in 6MWT distance at 12-month follow-up, including those surviving ARDS and non-ARDS critical illnesses[80,81].

Figure 1-3 demonstrates the progression of 6MWT distances over time. Studies for this figure were chosen if they described multiple measures of 6MWT over time and if they reported the results as a percentage of a reference range or control group. Original values were cross referenced against two systematic reviews of these outcome measures[80,81]. It is notable that in six of the nine studies, there is a similar slope between follow-up at six months and 12 months. The overall trend is that most improvement in 6MWT distances occurred in the first six months after ICU or hospital discharge. There appears to be a plateau effect beyond six months,

with distances walked remaining below predicted or control distances even beyond six to 12 months.

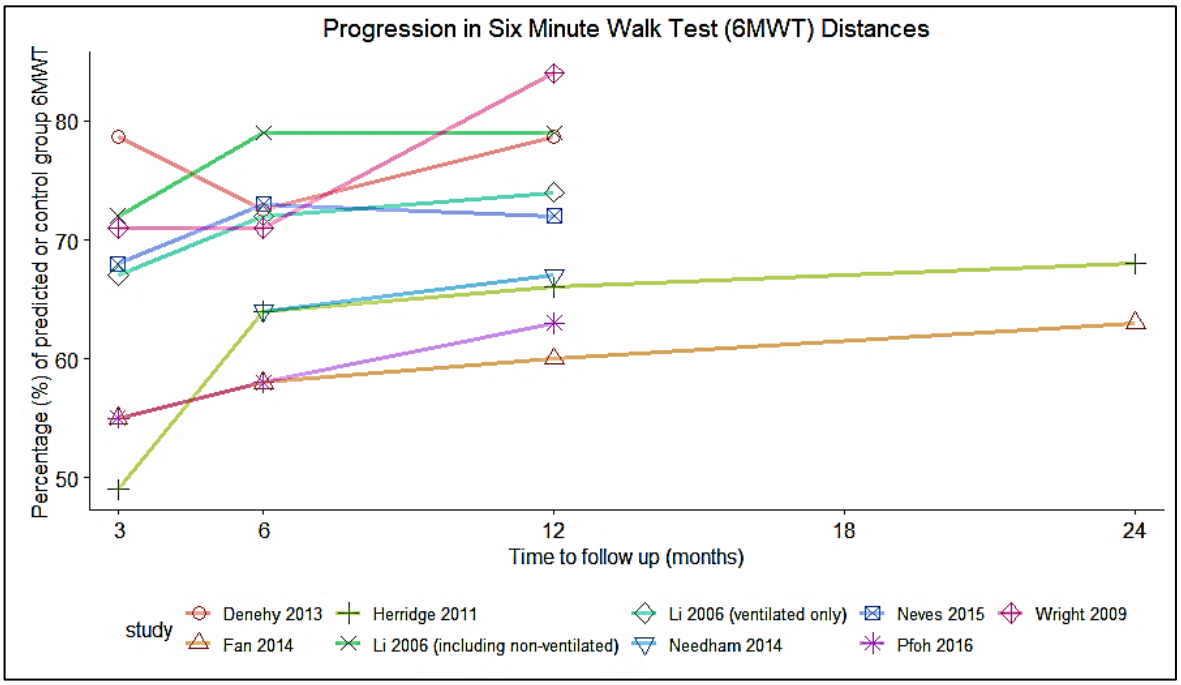


Figure 1-3: Six-Minute Walk Test (6MWT) distances and the change over time.

Studies chosen are those describing multiple measures over time after discharge from intensive care and those reporting 6MWT distances as a fraction or percentage of expected or control group values. Studies included are: Denehy et al 2013[82]; Fan et al 2014[70]; Herridge et al[57]; Li et al 2006[83], note this paper reports ventilated and non-ventilated patients, these are reported separately here; Needham et al[79]; Neves et al 2015[84]; Pfoh et al 2016[85]; Wright et al 2009[86].

1.3.4 Summary of physical measures

The effects of critical illness on the 6MWT moves our understanding forward when considering the problems facing intensive care survivors and offers an insight into where problems lie. Similarities between respiratory function, respiratory muscle function, skeletal muscle function, and 6MWT results are that they all demonstrate some improvement over the first 12 months after critical illness.

Respiratory function largely returns to baseline with some small but lasting effects on diffusion capacity and / or the presence of restrictive lung disease patterns. When correcting for each disease process the results then trend towards normal. Skeletal muscle strength largely returns to baseline and correlates well with an increase in muscle mass over the first year after critical illness. This is where the

6MWT differs significantly. Deficits in 6MWT distances are greater than those seen in skeletal muscle or respiratory function from 12 months and beyond. This suggests that the 6MWT deficits cannot be explained by a problem in one area. The deficits are likely global and multifactorial in nature. This helps understand why the global measures of physical function are more often recommended for use in long-term outcomes and PICS research. These tests are also likely to be more meaningful for patients. This comparison also proposes that the solutions to the problems of PICS are likely to require wider strategies rather than focal therapies.

This exploration has focused largely on indices of skeletal muscle strength, respiratory function, and global measures including the 6MWT. The research community has focused on and developed understanding of these areas more than the manifold other problems that can exist after ICU. An in-depth analysis of every physical symptom is beyond the scope of this review and would limit the exploration of other important areas of PICS and PICS-F. As such, Figure 1-4 is included to summarise most of the physical and organ function problems that can exist after critical illness. Figure 1-4 itself is not exhaustive but highlights the main problems grouped into four thematic areas.

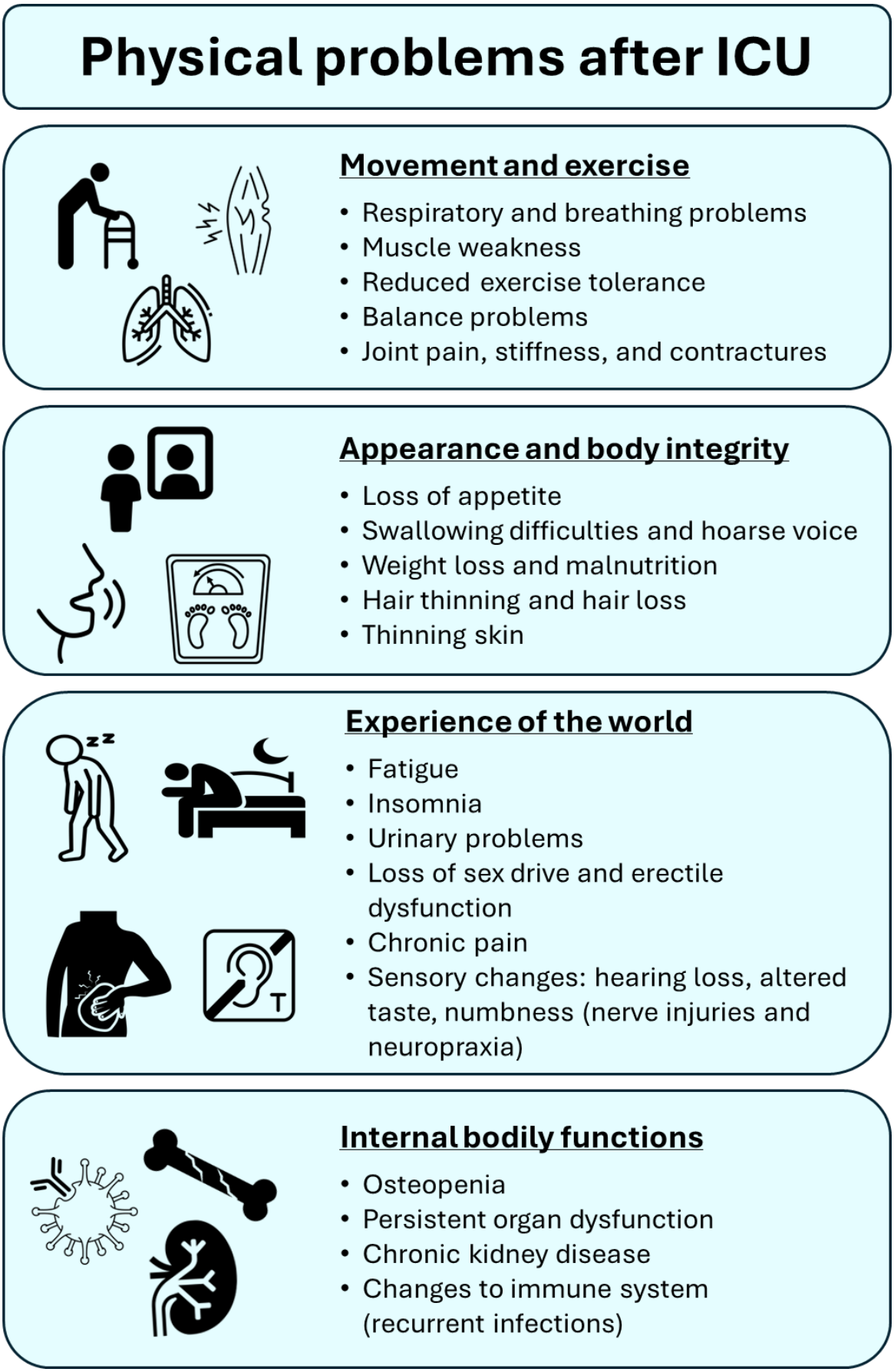


Figure 1-4: Common physical problems after critical illness.

1.4 Mental health outcomes

The largest studies into mental health outcomes after critical illness have been conducted by postal or telephone survey[87-91]. The convenience of these techniques has resulted in very impressive total study numbers. However, it must be recognised that to achieve the high survey response numbers required an even larger number to be invited due to the postal methodology. Frequently between two and ten patients have been contacted for each completed survey[88-91]. It is important to understand this limitation and consider where reporting bias can be introduced.

The most common psychological problems described after critical illness are those of anxiety, depression, and PTSD. Describing the extent of problems can be challenging due to the variety of definitions, timepoints, and surveys used. More recent studies have addressed this with consistent reporting of HADS. This is an ordinal scale survey where participants answer 14 questions, seven questions each on anxiety and depression (questions scored as: 0, 1, 2, or 3). This produces two summary scores, out of 21, where eight or greater is generally considered as screening positive for the respective condition[92]. PTSD is also widely reported although there are a larger variety of surveys used in the literature. The two most studied are the IES-R and the IES-6[93,94]. The IES-R is a 22-item questionnaire, with each item scored from 0 to 4. Various cut-off values to score for PTSD have been proposed where the original studies suggested a score of ≥33/88 (mean score ≥1.5) correlated with 'probable' PTSD[93,95]. However, recent critical care research has proposed a mean score ≥1.6 which corresponds to a total score of approximately ≥35/88[46,93,95]. The IES-6 is a shortened version of the IES-R, where only six items are scored. The generally accepted threshold for PTSD after critical illness on the IES-6 has been reported as a mean score of ≥1.75 or total score of approximately ≥11/24[46,94,96].

1.4.1 Rates of mental health problems after critical illness

The largest and most comprehensive study to date, on mental health outcomes after critical illness, is from Hatch and colleagues[88]. Known as the ICON (Intensive Care Outcome Network) study, this reports the results from 4,943 participants,

recruited from 26 ICUs that contribute to the Intensive Care National Audit and Research Centre (ICNARC) database based in the UK[97]. Every patient receiving ≥24 hours of level 3 treatment was screened. Surveys included the HADS, where a positive case ("caseness") was described as an anxiety or depression sub scale score of ≥8/21, and the Post-Traumatic Stress Disorder Checklist - Civilian (PCL-C), where caseness was defined as ≥45/88.

The methodology changed over time, being described as three phases. The commonality was that all patients received all surveys by post at 3 and 12 months following ICU discharge. The main change was in phase three, where research nurses would approach patients before hospital discharge, this meant that patients could refuse follow-up in phase three, and the research team could not track these patients' mortality through the ICNARC database. This change is unlikely to affect the rates of mental health problems as only returned surveys were included in analyses.

The headline figures are that the proportion of patients meeting the caseness threshold for mental health problems at either 3 or 12 months was: 46% for anxiety; 40% for depression; and 22% for PTSD. Further, 55% of patients met the caseness diagnosis for at least one mental health condition at either 3 or 12 months. These results initially appear very striking and generally higher than that described by other important and recent studies which are summarised in Table 1-1. The main difference is that the definition used is very broad, being a description of positive on testing at either time point. A third of patients met the definition of caseness at one time point but not the other. Some patients also responded at one time point but not the other. The authors attempted to address some of this reporting bias by analysing the results at single time points with rates of anxiety of 36 to 39% and depression rates ranging from 31 to 34%. Similarly, PTSD rates varied depending on analysis method between 16 and 18% at either timepoint. These results are much more in keeping with other primary studies and systematic reviews conducted before and after this study[98,99].

Hatch and colleagues also explored the overlap in symptoms in their study, demonstrating that 18% of patients had all three present (anxiety, depression, and

PTSD). Further, if one condition was present, there was a 65% chance of at least one other being present. Lastly, only 0.7% of patients who tested positive for mental health problems had PTSD in isolation (Figure 1-5). This is very important when considering how patients should be screened and what follow-up to conduct; PTSD screening in isolation will miss many cases of psychopathology, while the addition of PTSD screening to HADS is unlikely to identify many further cases.

This study has clear limitations as it was not a prospectively recruited trial and the postal design can lead to bias from lower recruitment numbers or ratios. Background information from the ICU database (ICNARC) was clearly good at describing the ICU stay but was lacking in comorbidity details. Overall, this study is difficult to ignore and the high numbers, using well recognised surveys, make this the most comprehensive analysis of the epidemiology of mental health after critical illness.

Table 1-1: Summary of important and recent studies reporting mental health outcomes after critical illness.

Study & design	n	Surveys, cut-off values, and outcomes			Notes
		Anxiety	Depression	PTSD	
Teixeira 2021 Telephone survey 10 ICUs Brazil[91]	579	HADS ≥8 Outcomes 6 months: 24.2%	HADS ≥8 Outcomes 6 months: 20.9%	IES-6 >9/24 Outcomes 6 months: 15.4%	The 6-month prevalence of any mental health disorder was 36.2%. Reduced HRQoL in survivors with mental health problems. Good summary of associated factors with mental health problems: age; previous mental health problems; emotional symptoms at ICU discharge; physical dependence / reduced functional status.
Shima 2020 Postal survey Single centre Japan[100]	117	HADS ≥8 Outcomes 3 months: 42% 12 months: 33%	HADS ≥8 Outcomes 3 months: 48% 12 months: 39%	IES-R >25/88 Outcomes 3 months: 20% 12 months: 21%	Low numbers overall but response rates high. Similar or higher rates in this Japanese study compared to UK / USA. Unique element is comparing overlapping psychiatric issues with problems with ADLs. Demonstrates those with ADL problems have high rates of psychological problems.
Karnatovskaia 2019 Telephone survey Single centre but 6 ICUs, USA[90]	174	HADS ≥8 Outcomes 3 months: 23%	HADS ≥8 Outcomes 3 months: 25%	IES-R ≥1.6 Outcomes 3 months: 19%	Single centre but 6 different ICUs within this centre. No difference in rates of psychological comorbidity between specialist ICUs: Cardiac MICU; Vascular/Thoracic; "Heme-onc" or Transplant; MICU; Cardiovascular SICU; Trauma SICU.
Milton 2018 Postal survey 10 ICUs, Sweden, Denmark and Netherlands[89]	404	HADS ≥11 Outcomes 3 months: 10%	HADS ≥11 Outcomes 3 months: 11%	PTSS-14 part B >45 Outcomes 3 months: 13%	20% prevalence of any psychological problems. Other measures included RAND-36 but less comprehensively reported in this study. Other results: high levels of 'psychological problems' (although this term was poorly defined): 70% had single symptoms, 46% two symptoms, and 24% had 3 symptoms. Predictors of mental health problems well described.

Study & design	n	Surveys, cut-off values, and outcomes			Notes
		Anxiety	Depression	PTSD	
Hatch 2018 Postal survey 26 ICUs UK[88]	4,943	HADS ≥8 Outcomes* 3 months: 36-39% 12 months: 38% 46% at either 3 or 12 months	HADS ≥8 Outcomes* 3 months: 31-34% 12 months: 32-33% 40% at either 3 or 12 months	PCL-C ≥45 Outcomes* 3 months: 16-18% 12 months: 18% 22% at either 3 or 12 months	55% had any mental health disorder at 3 or 12 months. 18% had all 3 present (anxiety, depression, and PTSD). 47% increased incidence of death in first 2 years post ICU if depression present. *Range of values offered as 2 analyses completed, either all responders at each time point or linked responses of those responding at both time points. Rates were the same for some measures with single values reported.
Wolters 2016 Postal survey Single ICU, the Netherlands[101]	567	HADS ≥8 Outcomes 12 months: 43%	HADS ≥8 Outcomes 12 months: 45%	IES-15 ≥35/75 Outcomes 12 months: 39%	53% either anxiety or depression. 63% of those who scored positively for one mental health problem had all 3 present. No association between delirium and mental health problems after critical illness.
Jackson 2014 In-person 5 ICUs USA[102]	415	Not assessed	BDI-II score >13 Outcomes 3 months: 37% 12 months: 33%	PCL-S ≥50 Outcomes 3 months: 7% 12 months: 7%	Results from the BRAIN-ICU study (Pandharipande et al)[103]. There are further multiple study reports using or incorporating this data including Marra et al (2018)[31]. Marra et al also describe overlap between problems (cognitive, depression, disability): Single PICS problem in 35% at 12 months; 2 problems: 16%; 3 problems: 4%.
Needham 2013 Telephone survey 41 hospitals USA[87]	525	HADS ≥8 Outcomes 6 months: 45% 12 months: 42%	HADS ≥8 Outcomes 6 months: 37% 12 months: 37%	IES-R ≥1.6 Outcomes 6 months: 26% 12 months: 23%	Combined results from the EDEN randomised trial[104]. Thorough methods, although mental health was a secondary outcome. Impressive numbers and good follow-up rates. Note very similar results from Dinglas et al (2016), but crossover between EDEN and this study and therefore not reported here[105].

Study & design	n	Surveys, cut-off values, and outcomes			Notes
		Anxiety	Depression	PTSD	
Myhren 2010 Postal survey Single site Norway[106]	255	HADS ≥8 or ≥11 <u>Outcomes</u> 12 months: 33% (≥8) 12 months: 18% (≥11)	HADS ≥8 or ≥11 <u>Outcomes</u> 12 months: 27% (≥8) 12 months: 12% (≥11)	IES ≥20/75 or ≥35/75 <u>Outcomes</u> 12 months: 50% (≥20) 12 months: 27% (≥35)	Early study with robust methods. Prospectively recruited. Further analysis found no significant differences between ICU subgroups: medical; surgical; trauma. Evaluation of degree of severe disease also of value.

Studies chosen are those making significant contributions to the understanding of mental health after critical illness, with a preference for recent or most up-to-date reports. n: number included in initial study analysis; PTSD: Post-Traumatic Stress Disorder; ICU: Intensive Care Unit; HADS: Hospital Anxiety and Depression Scale; IES: Impact of Events Scale; IES-R: Impact of Events Scale-Revised; EDEN trial: Initial trophic vs full enteral feeding in patients with acute lung injury, the EDEN randomized trial; BDI-II: Beck Depression Inventory-II; PCL-S: Post-Traumatic Stress Disorder Checklist-Specific; BRAIN-ICU: The BRAIN Intensive Care Unit (ICU) Study: Bringing to Light the Risk Factors (BRAIN-ICU); PICS: Post-Intensive Care Syndrome; PCL-C: Post-Traumatic Stress Disorder Checklist-Civilian; PTSS-14: Post-Traumatic Stress Syndrome-14; RAND-36: open access version of RAND® corporation's medical outcome study contains same elements as the licensed RAND® corporation Short Form-36 health survey (SF-36); MICU: Medical Intensive Care Unit; 'Heme-onc': haematological or oncological; SICU: Surgical Intensive Care Unit; ADL: Activities of Daily Living; HRQoL: Health-Related Quality of Life.

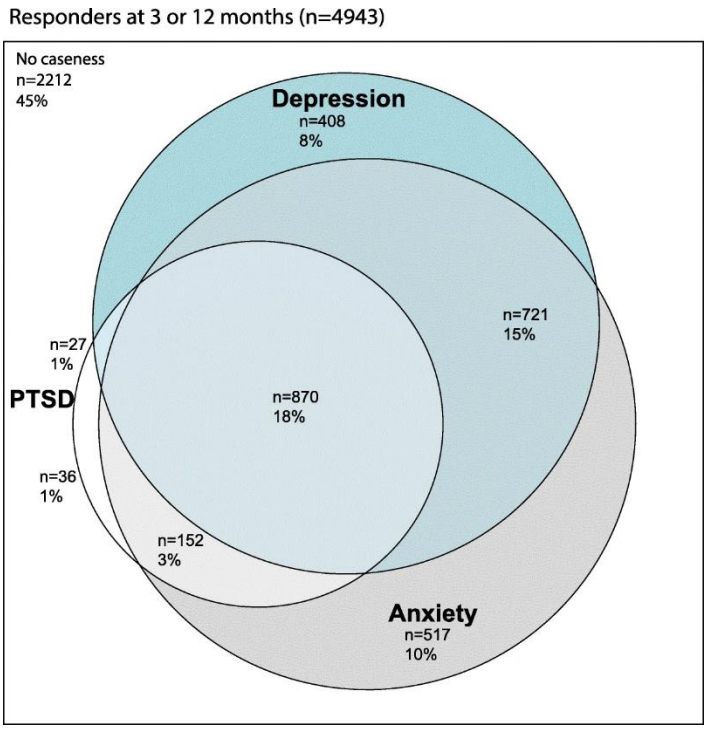


Figure 1-5: Crossover of anxiety, depression, and Post-Traumatic Stress Disorder (PTSD)

Concurrent psychopathology of those meeting the criteria for anxiety, depression, or PTSD through a postal survey of 4,943 critical illness survivors in the UK. Reproduced from Hatch et al under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) with no changes to the original figure[88].

1.4.2 Patterns between studies describing mental health outcomes

On the whole, one third of patients will test positive for anxiety and one third will test positive for depression after critical illness, as demonstrated through assessment of the primary research and through systematic review[98,99]. For PTSD, approximately one in five patients will experience symptoms[107]. There are a few studies that appear to contradict this or suggest lower rates of anxiety or depression. A study from Brazil (Teixeira et al) demonstrated rates of anxiety and depression of 24% and 21% respectively at 6 months[91]. Even more striking is the single study by Tipathy et al (not included in Table 1-1 above) where the outcomes from 322 patients from a single centre in India are reported[108]. They found that no patient met the thresholds for anxiety, depression, or PTSD (using HADS and IES-R) at 6 months, although a third of patients met the threshold for depression at ICU discharge. There are many differences between the patients in this study and those from the other studies included in Table 1-1, including low Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (mean=9.4) and low

rates of ventilation (60% mechanically ventilated). These factors are unlikely to explain all of the differences in the results and sociocultural differences are likely to play a significant role. There may also be differences in who had access to critical care services more widely. The key learning from both studies is that context is extremely important. Any study looking at the incidence of problems or the potential solutions will need to understand these sociocultural factors and what the baseline attitudes and mental health disease prevalence is within their respective communities.

1.4.3 Summary of mental health outcomes

Overall, the mental health burden after critical illness is substantial. Even conservative estimates would suggest the rates of anxiety and depression are at least 10% higher than those seen in the general population in western countries[109-111]. PTSD rates are remarkably similar across studies despite varying definitions and scoring systems, although PTSD seldom occurs in isolation. There is some evidence that geo-cultural differences exist with more research required to understand the extent and reasons behind these differences. All research looking at mental health outcomes should understand and describe the societal and cultural context of the research.

1.5 Cognitive outcomes

In comparison to mental health outcomes, the single greatest challenge to aggregating incidence of cognitive dysfunction after critical illness is the variety of testing measures used[112]. Some of the more commonly used tests are[41,113-123]:

- Consortium to Establish a Registry for Alzheimer's Disease (CERAD)
- Digit Span (DS) memory test
- Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)
- Mini Mental State Examination (MMSE)
- Montreal Cognitive Assessment (MoCA)
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- Rey Auditory Verbal Learning Test (RAVLT)
- Rey-Osterrieth Complex Figure (ROCF)

- Trail Making Test (TMT)
- Verbal Fluency Test (VFT)
- Wechsler Adult Intelligence Scale (WAIS) or Wechsler Memory Scale (WMS)

As highlighted earlier the MoCA was suggested as a default test for PICS though expert consensus[46]. It is not, however, settled that this should be used for all long-term outcomes research in intensive care. MoCA had a strong recommendation from the expert panel, but an earlier Delphi process was unable to recommend a cognitive outcome measure for ARF / ARDS research[45,46]. Part of the appeal of this test is the short time it takes to administer (10 mins) and the sensitivity of MoCA to detect mild dementia or Alzheimer's disease. This section will largely focus on other tests as these have been more prominent in the larger studies, often with professional neuropsychological testing. Further, this recommendation is recent and applies to recommendations for routine follow-up rather than specifically for academic studies of incidence or prevalence[46].

Table 1-2 outlines recent studies examining cognitive dysfunction after critical illness with incidences ranging from 6 to 82%[124,125]. This significant variation will partly be caused by the chosen testing methods with subjective testing methods offering the least reliability and most bias[126,127]. Further variability can be explained through the differences in study population, including age, premorbid cognitive dysfunction, and delirium, all of which have demonstrated effects on incidence of cognitive dysfunction after critical illness[103,124,128]. Overall, cognitive dysfunction appears common with some improvements evident within the first three months after critical care. However, there are lasting and measurable effects detectible at one year.

The landmark study from Pandharipande et al in 2013 is one of the most robust contributions to our understanding of cognitive dysfunction after critical illness. This study prospectively recruited patients from a single ICU. Although follow-up rates appeared low (821 recruited, 382 followed up at 12 months), this is in keeping with much of the literature. There were 510 (62%) patients available for follow-up at 12 months. This study offered a robust figure of the incidence of cognitive dysfunction at one year (34%) with testing carried out by specialists in neuropsychological assessment. Perhaps the most controversial aspect was that

there was no association between cognitive dysfunction and use of sedatives in ICU, although there was an association between delirium and cognitive dysfunction. It seems that this paper challenges the accepted dogma correlating sedation and delirium, or at a minimum, questions a perceived linear connection from sedation dose to delirium to cognitive dysfunction. A recent systematic review has also cast doubt on the strength of connection between sedation choice, dose, and delirium[129].

1.5.1 Cognitive dysfunction and cardiac arrest

Cognitive dysfunction has been specifically studied in Out of Hospital Cardiac Arrest (OOHCA) patients as improvement in neurological function is one of the primary objectives. These studies are often large and utilise robust methodology and offer important insights for OOHCA patients.

The trials studying Targeted Temperature Management (TTM) have produced some interesting results. The rates of cognitive dysfunction after OOHCA (17 to 52%) and after other critical illness appear similar[130-132]. There are clearly many confounders to the rates seen after OOHCA, particularly a significant survival bias. Those surviving are likely to have had the less severe global physiological insult, although this could be said of general critical care patients also. The counter argument is that the OOHCA patients have almost certainly had a period of cerebral hypoxia, while the general critical care patient might not have experienced this. These patterns are simply observations across studies and are not strong evidence. More work comparing OOHCA patients to a general ICU population would be a valid comparison and could help advance the literature about theoretical mechanisms behind cognitive dysfunction.

Another TTM based study compared patients suffering an ST-Elevation Myocardial Infarction (STEMI) without OOHCA arrest to a cohort of OOHCA arrest patients who required temperature management[132]. Again, rates of cognitive dysfunction were very similar between both groups. All the same concerns about survival bias should be borne in mind. However, this study does raise the possibility that the cognitive dysfunction after OOHCA may have mechanisms beyond simply cerebral hypoxia. A global inflammatory or stress response could also be a contributing factor to the new cognitive deficits. If this were to be demonstrated more conclusively it may

also advance our knowledge of the mechanisms behind the deficits seen in the general intensive care population.

Overall, more knowledge is required to understand the mechanisms behind cognitive dysfunction resulting from OOHCA and critical illness.

1.5.2 Summary of cognitive dysfunction

As demonstrated in Table 1-2 overall rates of post ICU cognitive dysfunction appear high, even if only compared to normative values or collateral history about cognitive function before ICU. Follow-up studies, and those embedded in other trials have largely confirmed the high incidence and prevalence of these problems with only a few outlying studies.

However, more work is needed to understand which aspects of critical care or illness led to cognitive dysfunction, or if this is a parallel process. The rate would suggest that there are likely to be causative elements from the critical illness period. However, better understanding of these causative factors would facilitate targeted management during or after ICU, and avoidance of precipitating factors.

Table 1-2: Selection of studies describing incidence of cognitive dysfunction after critical illness

Study	Population	Number included in analysis	Tests	Incidence of cognitive decline	Notes
O. Collet 2020[133]	26 Danish ICUs, all ICU patients, study within a trial	106 of 256	RBANS	6 months: 52%	52% meeting the lower threshold of 1.5 SD below normative mean, 36% meeting higher threshold (2 SD below normative mean)
Bulic 2020[128]	2 Australian ICUs, all ICU patients	60 of 103	MMSE; telephone Interview for Cognitive Status	12 months: 68%	Delirium associated with poor cognitive function after ICU.
Müller 2020[124]	Single centre, Germany, All ICU patients	73 of 108	CERAD-plus-battery and the Stroop Colour and Word Test	9 months: 6%	ICU group had low severity of illness and low rates of delirium (25%). Depression associated with worse cognitive outcome. Study attempted to evaluate risk of dementia pre-ICU (identified vulnerable patients) using IQCODE.
de Azevedo 2017[134]	Single centre, Brazil, all ICU patients, medical or surgical	413 of 724	Battery of testing: 1) Forward and backward digit span; 2) RAVLT; 3) Clock-drawing test; 4) Verbal fluency test; 5) MMSE	11 months: 50%	Specific focus on all ICU patients rather than just the 'sickest of the sick'. Very low prevalence of delirium in this group (10%). 'Severe' cognitive impairment in 20%.
Zhao 2017[125]	Single centre China, all ICU patients (neuro / medical / surgical)	332*	MoCA	3 months: 82%	Included a cognitive intervention, this was an RCT. Note (*) loss to follow-up rate not reported.
Cronberg 2015[131]	Out of Hospital Cardiac Arrest (TTM trial)	445 of 939	MMSE IQCODE	6 months: 17%	Part of TTM trial. No difference in cognitive function between 33°C and 36°C
Lilja 2015[132]	20 of 36 sites as part of TTM trial (Europe). Cardiac arrest patients, included control compared to non-ICU patients (ST-Elevation MI [STEMI] group)	287 of 652 patients from TTM study (ICU after cardiac arrest) and 119 (STEMI)	1) Rivermead Behavioural Memory Test; 2) Frontal Assessment Battery; 3) Symbol Digit Modalities Test	6 months: 51%	Further assessment of TTM trial but different group and compared to control cohort (STEMI). Similar rates of cognitive problems in STEMI i.e. the non-ICU group.

Study	Population	Number included in analysis	Tests	Incidence of cognitive decline	Notes
Pandharipande 2013[103]	Single ICU, USA, Respiratory failure or shock	382 of 821	RBANS	12 months: 34%	"BRAIN-ICU" study. 6% had cognitive dysfunction at baseline. 74% had delirium during ICU, delirium associated with cognitive dysfunction. Many other offshoot studies from same / similar group[135].
Mikkelsen 2012[136]	Multi-site, USA, ARDS patients	75 of 213	WAIS-III, controlled oral word association test, Hayling sentence completion test	12 months: 55%	Study within a trial, adjunct study of the FACTT trial[137]. Large recruitment numbers but low numbers completing cognitive assessments at 12 months.
Iwashyna 2010[138]	Multi-site, USA, Severe sepsis from those involved in the health and retirement study	516 of 623	Those aged ≥65 assessed with 35-point scale for: memory, serial 7 subtractions, naming, and orientation Those <65 years used a 27-point scale	12 months: 11% increase in moderate to severe cognitive impairment	Severe sepsis in older population resulted in higher incidence of moderate to severe cognitive impairment
Jackson 2010[139]	Single centre, USA, Medical ICU, mechanical ventilation	20 of 180	MMSE, trailmaking A & B, verbal fluency, Digit symbol and span, RAVLT, ROCF Rey-Osterrieth Complex Figure (ROCF)	12 months: 70%	Recruited from another study. Reported as 180 in study but only 20 completed follow-up at 12 months.

ICU: Intensive Care Unit; SD: Standard Deviation; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; MMSE: Mini-Mental State Examination; CERAD: Consortium to Establish a Registry of Alzheimer's Disease; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; RAVLT: Rey Auditory Verbal Learning Test; MoCA: Montreal Cognitive Assessment; TTM: Targeted Temperature Management; ARDS: Acute Respiratory Distress Syndrome; WAIS: Wechsler Adult Intelligence Scale; FACTT: Fluid and Catheters Treatment Trial; ROCF: Rey-Osterrieth Complex Figure .

1.6 Delirium and cognitive dysfunction

Causation may be one of the most challenging questions to answer for many illnesses, but especially PICS. Up to this point most aspects of causation have been assumed through an analysis of normative values, alongside the pathophysiological effects of critical care and its therapies. Pandharipande and colleagues made an assessment that only 6% of patients had evidence of cognitive dysfunction before ICU admission, but 34% had evidence at 12 months post ICU discharge. This would certainly point towards the events during critical illness being, at least, correlated with cognitive dysfunction[103]. While delirium was proposed as a significantly associated feature, a more recent study from de Azevedo et al reports a high rate of cognitive dysfunction despite a low severity of illness and low rates of delirium in ICU[134]. A further confounding factor is that the tests for delirium in ICU are likely to be imperfect thus weakening any correlation[140]. It remains unclear, therefore, exactly how the factors of delirium, critical illness, and an ICU admission combine to result in cognitive dysfunction. There is a role for more work assessing the predictors of cognitive dysfunction. Furthermore, studies aiming to address both inpatient and outpatient therapies to reduce the incidence of, and mitigate the effects of, cognitive dysfunction after critical illness are required. These studies would need also to consider comorbidity alongside rates of delirium and the effects of these on cognitive dysfunction.

1.7 Health-Related Quality of Life

Perhaps reflecting the nature or training of intensivists, the data up to this point has focused on very specific metrics of health and the three primary domains of PICS. The clear advantages of these measures are their interpretability and reproducibility. The apparent sense of objectivity, particularly with physical measures such as the 6MWT and muscle strength is appealing. However, whether these are important to the patient is unclear. Furthermore, and contrary to the initial attractiveness of objective physical and isolated markers of outcome, it has been postulated that self-reporting of physical function is more reliable than objective testing[127]. As such, and in keeping with the more general healthcare literature, the concept of Health-Related Quality of Life (HRQoL) may offer a more reliable measure of outcomes after critical illness. Examples of this are offered from the surgical literature, where it has been demonstrated that patients

perceive a reduced HRQoL after emergency general surgery compared to elective general surgery[141]. Similarly, patients also report reduced QoL after intestinal stoma formation compared to those undergoing bowel resection surgery without stoma formation (e.g. with primary anastomosis)[142,143]. These examples demonstrate how clinicians can perceive a successful outcome using biological markers of success (e.g. avoidance of mortality or return to independence), while those living after significant illnesses may perceive a different outcome. This is why HRQoL and patient self-reporting of outcomes through validated measurement tools are critical to understanding long-term outcomes for most, if not all, healthcare interventions.

One significant stumbling block is that the concepts of HRQoL and Quality of Life (QoL) are generally very poorly defined[144]. The literature would suggest that most authors who have described HRQoL have actually reported "self-perceived health status" whereas HRQoL should describe the interaction between health and QoL[144]. HRQoL can then be defined as how health impacts on QoL, although most of the literature uses HRQoL and QoL analogously. For practicality purposes this thesis will use HRQoL in its broadest definition and no specific distinction between self-reported health status, QoL, and HRQoL will be made. While beyond the scope of this thesis, these variable definitions highlight an area of weakness within the current literature. Furthermore, there appears to be no PICS, PICS-F, or critical care specific definition of HRQoL, which could be an area for future study.

1.7.1 Measures of HRQoL

Regardless of definitions, the most widely reported assessment methods of HRQoL in both the general medical literature and the critical care specific literature are the EuroQol 5-dimension (EQ-5D) survey and the RAND medical outcomes 36-Item Short Form (SF-36) health survey[145-147].

The EQ-5D is a relatively simple questionnaire comprising five descriptive questions on: mobility; self-care; usual activities; pain / discomfort; and anxiety / depression. There are two main versions available. The EQ-5D-3L has three levels for each domain, and the EQ-5D-5L which has five levels for each domain[145,146,148-150]. Both can generate the same output summary scores. There is then a sixth question asking the participant to rate their health on a scale of 0 to 100, this is

known as the EuroQol Visual Analogue Scale (EQ-VAS)[146]. The survey can be summarised by offering a breakdown of the five dimensions, describing what problems participants have, alongside a summary of the mean or median values of EQ-VAS. Finally, and most powerfully, the five dimensions can be summarised into a Health Utility Score (EQ-HUS) which has been validated in hundreds of countries, is the most popular assessment for health economics assessments, and is recommended by the National Institute for Health and Care Excellence (NICE)[151]. The EQ-5D is, therefore, simple to implement, uses health descriptors, has a patient-focused subjective measure of health (EQ-VAS), and allows the assessment of health against a national standardised dataset (EQ-HUS). This is likely the reason why this has been proposed as a default survey through the previously discussed Delphi process and SCCM consensus statements[45,46].

The SF-36 on the other hand allows for a more granular description with 36 items or questions. This survey allows for the generation of eight dimension scores, and two summary scores[147]. The two summary scores are the Physical Component Summary (PCS) score and the Mental Component Summary (MCS) score. The SF-36 can be described as a non-preference based survey and as such this does not generate a health utility state[152]. It can, however, be converted to a health utility state known as the SF-6D, but this has not been as widely adopted when compared to the EQ-HUS, and the SF-6D has not been recommended by NICE[151,153,154]. The SF-36, therefore, creates a more granular picture of individual patients or participants, but has generally not been the first choice when a preference summary (health utility score) has been desired. This increased granularity comes at a cost as the 36 questions of the SF-36 is a more time-consuming survey to complete compared to the EQ-5D.

1.7.2 EQ-5D and SF-36 after critical illness

The ubiquitous nature of both the EQ-5D and SF-36 make summarising all the work of the last two decades challenging. The seminal paper from Herridge et al in 2003 demonstrated that at one year post ICU, ARDS patients had a reduced QoL compared to age and sex matched controls[8]. The five-year follow-up of the same patient group using the SF-36 survey demonstrated that the physical outcomes (PCS) remained one standard deviation below population norms but mental health outcomes (MCS) had returned to age and sex population norms[57]. These papers are

noteworthy due to their originality, the comprehensive assessments of this population, and the long follow-up period (five years)[8,57]. However, as is common with this type of research, the number of participants was low and the loss to follow-up was high[8,57].

More recently a systematic review from Gerth and colleagues in 2019 attempted to quantify the change in HRQoL after critical illness[155]. The authors report a summary of 48 studies, with 30 studies using the SF-36 or similar 'short form' type survey. There were 20 studies that used the EQ-5D and it is noted that this was most used after 2010, indicating the increasing popularity of this measure in post-ICU studies. The results across all domains of the SF-36, and EQ-5D demonstrated remarkably similar results. That is, all QoL domains (excluding bodily pain) appeared to remain below population-matched scores from hospital discharge to five years after hospital discharge. There were some differences in rates of improvement between the surveys, with improvements in SF-36 during the first six months but limited improvements in EQ-5D. This may reflect the more granular nature of the SF-36. This also reflects the findings discussed earlier from the physical measures (e.g. 6MWT) and cognitive dysfunction, where improvements were most rapid in the first six months.

Beyond the systematic review, the larger stand-alone studies have consistently demonstrated lower values of HRQoL after critical illness compared to population norms using both the EQ-5D and SF-36[36,156,157]. The results from five-year follow-up studies are more difficult to interpret as these generally have higher loss to follow-up rates and have a significant survival bias. Regardless, the current best estimate would suggest that on average those surviving critical illness are likely to have lower HRQoL when compared to population age and sex norms.

There appear to be few recent observational studies reporting HRQoL from Western or English-speaking countries in formal journals. This may be due to researchers and journal editors considering this study type as less novel or unique. HRQoL has been used as an outcome measure for interventional studies rather than as a primary observational outcome. However, there have been large studies from countries that have not traditionally published in the intensive care literature. In particular a recent study by Kang et al assessing EQ-5D in a South Korean population (n=534; 2022)[32]. This study confirmed very similar results from

an earlier systematic review and brought the HRQoL outcomes up-to-date, while also offering insights into HRQoL in less well studied populations. The authors demonstrated that, of participants who were ventilated for 48 hours or greater, 92.1% had problems in at least one domain of the EQ-5D 12 months after critical illness.

The issue of correlation vs causation in ICU follow-up studies will continue. However, it can be stated with reasonable certainty that ICU survivorship is associated with a HRQoL status that is substantially lower than the general population.

1.8 Family or caregiver outcomes

1.8.1 Nomenclature for this thesis

For the remainder of this thesis, family member and caregiver are used interchangeably. The term family will be used in the most liberal application, meaning anyone the patient or ICU survivors deems to be family will be family. This is in keeping with other studies within the literature and could refer to a spouse, partner, other relation, or a friend with no legal or genetic connection[158]. The term caregiver will similarly have just as broad a remit. In some (rare) cases an ICU survivor (patient) may be the caregiver, but for consistency the ICU survivor will keep this description and the family member may be referred to as a caregiver or family member. As this thesis is focused on survivorship, caregiver will be used more often but this is not deliberate, and family could easily be replaced for any occurrence of caregiver.

1.8.2 Caregiver outcomes

Family outcomes for those surviving intensive care have been less well described in the literature. As may be expected, studies have often been designed to collect ICU survivor outcomes and the caregiver outcomes have been of secondary concern. This understandably has been done for reasons of practicality as recruitment has often come from the patient in ICU. It has also been difficult to aggregate results with a similar heterogeneity in reporting of outcomes as has been demonstrated in the patient literature. Furthermore, if caregiver results are reported as secondary outcomes, then electronic searches are less likely to find

these studies as the caregiver may not feature in the title or abstract. Systematic reviews have suffered from being very broad where paediatric outcomes or in-hospital outcomes are included, which are beyond the scope of this thesis[159,160].

A systematic review by Johnson and colleagues from 2019 reported an enormous range in prevalence for mental health problems in the families of ICU patients[160]. The reporting included an analysis of in-ICU and post-hospital discharge mental health outcomes together for caregivers from 40 studies. The authors report rates of depression from 4 to 94%, anxiety from 2 to 80%, and PTSD from 3 to 62%[160]. The review did include 16 studies of outcomes beyond hospital discharge but the incidence or prevalence from this time point is not individually reported. Rather, it was simply noted that for depression, anxiety, and PTSD there was an improvement over time, although in a few studies mental health worsened over time. Similarly, another systematic review from 2015 was only able to aggregate rates of depression after hospital discharge as other outcomes were poorly reported[161]. This study from Haines et al concluded that the rates of depression one year after ICU in informal caregivers are between 23 and 29% which is similar to the rates of depression in caregivers of patients with dementia[161]. The range of mental health outcomes described in these systematic reviews suggests that there remains a significant degree of uncertainty around what rates of problems can be expected in families after critical illness. It also suggests a need for both further studies into long-term caregiver outcomes and the need for updated systematic review.

A final review article identified for this chapter was from van Beusekom et al where a broad range of long-term outcomes and timepoints were assessed and published in 2016[33]. This review used a systematic technique to summarise the caregiver burdens after intensive care and they included a risk of bias assessment alongside dual reviewing, although they described this as a literature review. The review included 28 papers that reported caregiver mental health, employment, lifestyle, and HRQoL outcomes[33]. Anxiety rates ranged from 42 to 80% during the relatives hospital admission, reducing to 15 to 24% by six months post discharge[33]. The rates of depression appear less certain with a range of 16 to 90% during hospital admission and a reduced range by one year of 23 to 44%. PTSD rates are the most striking with an estimate of 57% (no range offered) during hospital

admission and a range of 32 to 80% at one year, signifying a huge burden of problems for caregivers even at one year after ICU. The authors also note that 50% of caregivers reduced their working hours which likely impacts significantly on psychosocial outcomes[33].

This review also attempted to assess HRQoL in caregivers after critical illness and noted that there were significant decreases in mental health, but limited or no changes in physical outcomes. Finally, almost 50% of caregivers had quit activities (of any description) to facilitate care of the ICU survivor one year after ICU discharge.

Together the figures demonstrate a significant burden for caregivers across the entire spectrum of recovery and survivorship after critical illness up to one year after discharge. The results and reporting are not granular enough to map an exact trajectory and there are some nuances in the reporting within the three review papers reported here. An example from the van Beusekom paper is that the lowest scores for depression occurred at three to six months and then were higher again at one year[33]. It may be that this is the natural progression, but this also highlights the difficulty in synthesising outcome measures at various time points. The reporting and loss to follow-up biases are likely to be significant. Fundamentally, it is difficult to ascertain whether this observation is simply an artefact or a genuine effect. The authors note that the quality of studies was very poor, confirming the hypothesis that this area of long-term outcomes, PICS, and PICS-F needs much more work[33].

These findings have been confirmed by larger standalone studies, in particular by a landmark new England Journal of Medicine study from Cameron et al[34]. This large study (n=280) describes the mental health outcomes of caregivers of ICU survivors up to one year after critical illness with a specific focus on depression. The headline result demonstrated that two-thirds (67%) of caregivers experiences depressive symptoms within three months of survivor discharge. This did reduce over time to 43% by one year but clearly remained a significant burden to caregivers and the family unit. The authors then created a multivariable regression demonstrating that no patient factors were associated with improvements in depression. However, several caregiver factors including younger age, higher depression scores at first assessment, higher degrees of strain, and

lower family income were all associated with worse mental health outcomes at one year. This study was robust in demonstrating the rates of depression but also added significantly to our understanding on the factors that can influence mental health recovery.

More recently (2021) a study from Naef and colleagues, analysed HADS scores from 214 family members of both survivors and non-survivors within four weeks of ICU discharge or death[35]. They noted very high rates of PTSD at 67.6% whereas just over a third (38.9%) experienced anxiety (HADS-A subscale scores ≥8/21) and approximately a fifth (22.4%) experienced depression (HADS-D subscale scores ≥8/21). The very early time point of the survey (within four weeks) alongside the inclusion of non-survivors, where 19.7% of the caregivers' family members died, added some confounding[35]. Regardless of exact interpretation, these figures appear significant, but perhaps not unexpected. What is not known, however, is whether the type of psychological distress changes over time. More work is required to understand if high rates of PTSD and anxiety (high stress states) are then replaced during the first year after ICU with depression. There is not enough detail in the literature to understand this and this is an area where more work is required.

In conclusion, the rates of mental health problems of anxiety, depression, and PTSD appear significant for caregivers in the first year after a family member has been in intensive care. There are significant gaps in our knowledge, and this is an area that researchers should focus on.

1.9 Socioeconomic consequences of intensive care

The socioeconomic burdens of critical illness and intensive care are substantial. While the definitions of PICS and PICS-F are appropriate, there is emerging evidence demonstrating the social and financial impact of critical illness. The literature appears to be ahead of the definitions from the learned societies, although the most recent statement does mention the importance of psychosocial outcomes on mental health[46]. The following section formed the basis of a book chapter which was published as part of the work of this thesis. The content has been significantly adapted and redacted to fit in with this thesis but the themes and background research remain the same[1]. Reuse and the creation of derivative

works from the published book chapter for this thesis have been approved by Springer Nature (license number: 5646401077762).

1.9.1 The financial burden

The term "financial toxicity" has been applied to the family unit after critical illness, although this was originally described in association with cancer survivorship[162]. The term includes both an objective measure of financial distress (e.g. reduced income or more debt) alongside subjective measures (e.g. perception of being less well off)[163]. The causes of this financial toxicity can be direct and obvious, and this is frequently the case in private medical systems. An example is the finding that 17% of all bankruptcy applications in the USA in 2007 cited medical costs as a main cause[164].

Even in publicly funded or mixed (part public, part insurance) systems there can be significant hidden, but direct costs, which may include travel expenses for family members, including parking, bus or train expenses. These issues become more apparent for the critical illness survivor once discharged from hospital[165].

After discharge from hospital, the ICU survivor's financial situation can deteriorate further, with additional hidden costs for adaptations to housing that, even in a publicly funded system, is frequently paid for at an individual level[8,166]. Other adaptations to increasing frailty and life after intensive care may include more costly travel expenses (e.g. taxi vs bus), and this may all play out on the backdrop of trying to catch up on unpaid bills during the period of hospitalisation.

1.9.2 Employment

As with all healthcare areas, the critical care literature tends to gravitate towards binary, reproducible, and ostensibly objective measures of outcome. For the socioeconomic consequences this is return to employment post critical illness[37]. This has been the subject of two large systematic reviews. The first from McPeake et al described a return-to-work rate of 54% by one year after intensive care. Notably, only patients employed before ICU were included and therefore the more powerful converse description is that 44% of people who were employed before ICU were out of work at one year post discharge[37]. The second study from Kamdar

and colleagues included 52 articles (one more than McPeake et al) and described the return-to-work rate as 60% at one year[167]. This study also attempted to define return-to-work rates between 42 and 60 months, with a pooled estimate of 68%. These very long-term follow-up periods are clearly more at risk from confounding and external factors (e.g. death), but it appears fairly certain that up to one-third of patients are highly unlikely to return to work after ICU for up to five years. This effect is consistent across multiple countries (notably all high-income) and the end effect is often job loss after ICU (20 to 36%).

This only considers ICU survivors themselves. As previously reported up to half of caregivers are likely to be working fewer hours after their loved one's critical illness[33]. Other studies have reported that 20% of relatives have to give up work completely after family member critical illness with a huge component of this due to informal caring duties[168]. Another metric is that one-third of families report losing their major source of income[168]. The combination of lost earnings alongside the additional costs of illness both overt and hidden, can lead to significant financial problems for entire family units.

1.9.3 The social consequences

Loneliness and social isolation are two similar and overlapping concepts. Social isolation is the absence of contact with other people; whereas loneliness is the psychological experience when the desired level of social contact (or engagement) is not achieved[169,170]. The patient recently discharged from ICU is at risk of both. It is likely that the pre-existing relationships between survivor and caregiver will have changed. Similarly, just as the patient and caregiver are likely to have changes to their employment status, their ability to return to their previous social roles is likely to be limited. Combined, these effects of changing roles, relationships, a tendency towards social isolation, and loneliness are likely to lead to significantly negative effects on HRQoL and even mortality post hospital discharge[170-174].

While the financial and economic burdens after critical illness are clear, measurable, and reproducible, much more work is required to understand the rates and impacts of social isolation, loneliness, and failure to return to pre-illness

roles and interests. This is early work and the exact rates of failure of social reintegration after critical illness is unknown.

1.9.4 Defining socioeconomic reintegration

The work of this literature review identified that there was no clear definition for socioeconomic reintegration after critical illness. As such, the work of this thesis alongside a review of definitions relating to military personnel has revealed that a new definition may be useful. By combining both the financial and social consequences of critical illness the suggested definition of socioeconomic reintegration is:

> "The resumption of relationships, roles, and financial income after a period of critical illness. This should include family, friends, nurturing and supportive roles, reclaiming interests, as well as returning to work (if of employment age)."[1]

As far as can be ascertained, socioeconomic reintegration after critical illness has not previously been defined. This definition offers a working platform to consider how the potential socioeconomic aspects of PICS and PICS-F can at least be assessed from a holistic point of view. This does not, however, describe what should be done to mitigate these issues and the remainder of this thesis will consider what interventions after critical illness can help improve all aspects of PICS and PICS-F.

1.10 Summary and aims of thesis

This chapter has explored the definitions of survivorship, PICS, and PICS-F. It has assessed the role of the SCCM in creating the original definitions to explain the problems after critical illness. Furthermore, an exploration of how these problems have been measured over the past two decades has also been described. An in-depth analysis of the three main domains of PICS (physical health, mental health, and cognitive health) and PICS-F using traditional and focused measures has been offered. Thereafter, HRQoL has been defined and the possible measurement tools as well as the expected outcomes have been discussed. The caregiver outcomes and the limited research base, alongside the research knowledge gaps in caregiver outcomes has also been identified. Finally, an exploration of the socioeconomic

consequences has been discussed, concluding with a new definition of socioeconomic reintegration after critical illness.

Before defining the aims of the thesis, it is worth noting the inspiration and preliminary work that this thesis was based on. The Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE) programme was designed and delivered by the work of Prof. Joanne McPeake and Prof. Tara Quasim alongside a complex multidisciplinary team (MDT). The primary paper for this early work described the programme and its implementation at a single site[175]. The team were able to demonstrate improvements in HRQoL measured using the EQ-5D for those attending the complex intervention combining an MDT with social support and peer support as well as involving caregivers. This was a small study (n=40), and the control was an historical one, therefore the generalisability was limited. However, this pilot study did demonstrate the programme's potential. Alongside this paper, new funding to expand InS:PIRE to multiple sites in Scotland formed the platform from which this thesis could evolve.

The thesis aims are therefore generated based on the understanding of the manifold problems faced by ICU survivors and their families and the opportunity resulting from the expansion of the InS:PIRE programme to multiple sites throughout Scotland.

I therefore aim to address the following questions:

1. **Within the formal literature, what has been included in outpatient follow-up services for ICU survivors and their families?**

To better understand the landscape from which the InS:PIRE programme was being implemented it is of value to have a broad appreciation of what has already been described in the literature. The starting impression from this less formal literature review (Chapter 1) was that the aftercare services for PICS and PICS-F are at an early stage and there was not a standardised model of care. The following formal scoping review (Chapter 2) will evaluate who staffs these follow-up services, when the services are delivered after hospital discharge, and what other components have been included.

2. **What is the impact of the InS:PIRE intervention on HRQoL for ICU survivors?**

With the absence of any clear international guidance on how to ameliorate PICS after hospital discharge, is there an observed association with attending the InS:PIRE programme and a change, or improvement, in HRQoL? This question will aim to use the multicentre roll-out of InS:PIRE as a platform to compare those who attend InS:PIRE with those treated at non-InS:PIRE sites. This offers the opportunity to conduct a multicentre study of a treatment cohort for a very complex intervention compared to a usual care cohort. The aim will be to assess multiple markers of HRQoL and mental health outcomes to establish if attendance at InS:PIRE is associated with changes, improvements, or reductions in HRQoL.

3. **Is caregiver participation in the InS:PIRE programme associated with a reduction in PICS-F symptoms?**

The family members of ICU survivors experience significant mental health and other negative QoL outcomes. Furthermore, the family unit is interconnected and the traditional model of treating just the individual patient may not reflect real life strain. Therefore, can the InS:PIRE intervention, with the inclusion of caregivers in the programme, demonstrate a measurable change or reduction in caregiver PICS-F symptoms, mental health problems, and strain?

4. **Do PICS and PICS-F affect those who have been treated in a specialist cardiothoracic ICU and how can the InS:PIRE intervention be adapted to meet their needs?**

Less is known about the specialist ICU and the presence of PICS and PICS-F in this group. Furthermore, there are already services in place for many of these patients and their experience of recovery may be different from the general ICU population. Through the implementation of InS:PIRE at a specialist cardiothoracic centre, the aim is to better understand the effects of PICS and PICS-F in this population. Furthermore, this also affords the chance to understand how the InS:PIRE intervention can be adapted to different groups and different healthcare models. This process of adaptation will also be assessed.

Chapter 2 Scoping review: Who staffs ICU recovery clinics and what outpatient services have been studied?

2.1 Introduction

The previous chapter established that the problems patients and their families face after critical illness are significant, so it is essential to understand what has been done to mitigate and treat these problems. It was evident from this review that the literature continues to evolve and that there did not appear to be one settled solution for PICS. The overall impression was that studies describing benefits were lacking and the literature was still in a reasonably early phase.

As such, it was decided that the best solution to understand the literature relating to post-hospital discharge solutions for PICS was to conduct a scoping review alongside a narrative discussion of some of the techniques and approaches taken. This chapter will contain two distinct sections.

The first section will be a scoping review with the following questions:

- Which professionals have been described in the formal literature as contributing to ICU follow-up services after hospital discharge?

- What other components or personnel have been studied? This may include whether caregivers were involved, written or digital information provided, or other non-professionals, e.g. volunteers.

- The scoping review will also describe the size of the studies, when follow-up was commenced, and finally offer an insight into the overlap between different components.

The second section will use a narrative approach and explore the different outpatient follow-up services described in the literature. This section will not be constrained by the results of the scoping review, allowing a broader understanding of the literature.

2.2 Methods

A complete literature search was conducted which included Randomised Clinical (or Control) Trials (RCTs), cohort studies, case-control studies, observational studies, mixed methods studies, Quality Improvement (QI) projects, and qualitative studies. Studies were excluded if they had involved fewer than 10 participants. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) method was followed, with the one exception that a single reviewer conducted this review[176]. This approach was decided on for reasons of pragmatism relating to this thesis. It became clear that completing this review with multiple reviewers would significantly detract from the time available for the remaining work of this thesis. The single-reviewer approach also allowed the review to be sequentially updated as the literature developed throughout the complete research programme.

2.2.1 Literature search

A comprehensive search of MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) was conducted.

The completed searches with outputs can be found in Appendix 1. The searches had three broad components, and these were: 1) descriptors of critical illness, intensive care, and related diseases; 2) descriptors of condition after critical illness or intensive care, including survivorship and post-intensive care; 3) descriptors of follow-up, clinics, aftercare, rehabilitation, and other related terms. Retrieved articles met all three criteria.

Databases were searched from database inception and were sequentially updated from June 2019 (first search) until the last search which was completed on 22nd May 2023. Results were limited to English as there was no available interpreter service. The search strategy and the outputs from this were peer-reviewed by the professional library service at the University of Glasgow (Dr Paul Cannon) during the design phase in June 2019.

2.2.2 Study selection

Included studies met the following criteria: 1) there was an intervention after hospital discharge following a stay in ICU — this could be a general or specialist ICU; 2) there was a clear description of who was involved in delivering the intervention; 3) it was clear that the intervention had been delivered — if the study included a design phase there had to be a description of implementation alongside this.

Studies excluded from this review were: 1) duplicate reporting or secondary analyses from a previously reported study; 2) diary interventions were excluded as these were primarily deemed to be in-hospital interventions, however, if a programme or clinic included a diary as part of an outpatient follow-up service this was included; 3) if the intervention was not directed specifically at ICU or critical care patients, an example might be a study on sepsis that included ward patients with sepsis rather than just ICU patients; 4) single case studies and any studies including fewer than 10 participants were excluded; 5) conference proceedings, abstracts, and trial protocols were excluded.

The first exclusion reason above (duplicate reporting or secondary analyses) was an area that required further review during the full text screening. There were some studies that had tested a slight variation of an intervention on a new population, these were included once it was ascertained that participants did not crossover between the studies. Similarly, if a study involved caregivers but did not report the number attending in one report then had a separate focused caregiver paper, then this was included as a separate study. Once more the reported number was assessed to make sure there was no crossover. These decisions were made to prioritise study inclusion over exclusion to capture as much of the published literature as possible.

As previously stated, all screening was completed by a single reviewer (thesis author).

2.2.3 Data extraction

The following data were extracted from the full texts: first author; year published; country; study design; number of participants recruited or initially approached; number of participants completing final follow-up; number of centres delivering the follow-up; time from hospital discharge to first follow-up contact; intervention type; whether a control group was used, and what this involved; the population involved; and the clinic components.

The clinic or follow-up components collected were: ICU nurse; ICU doctor; physiotherapist; pharmacist; psychologist or therapist; other nurse; other doctor; social care specialist; other professional group (free text descriptions of other groups included in the studies were collated and summarised during statistical analysis); volunteers; digital input; written information; peer support; signposting to other services; critical care debrief; caregiver involvement.

In keeping with recommendations from PISMA-ScR risk of bias assessment was not undertaken[176]. A critical appraisal of the overall quality of the corpus of literature reviewed is offered in the discussion section.

2.2.4 Statistical analysis

The studies were summarised using two key metrics. Firstly, the summaries were generated at a 'per-study' level. That is, the number of studies describing certain interventions or components. Secondly, summaries were generated at a 'per-participant' level using the number of participants that the paper reported as completing follow-up. It was decided to include the number completing follow-up as this was more reliably reported throughout the literature rather than another measure of participant recruitment and retention (e.g. number consented).

Summaries were all created as simple counts and percentages to assess the trends in the literature and understand the overall landscape. Significance testing between groups was not done to avoid erroneously attaching certainty to individual outcomes which would be beyond the remit of this methodology. Data were collated using Microsoft Excel[177]. Summaries, descriptive statistics, outputs, and graphs were generated using R version 4.3.1[178,179]. Overlapping domains were

generated using the UpSetR package and all other graphics generated through the ggplot2 package[180,181].

2.3 Results

2.3.1 Study numbers and selection

The initial database search revealed 16,875 possibly relevant studies. After deduplication, 10,393 articles required title and abstract screening. Figure 2-1 demonstrates the number of studies retrieved by the electronic database search compared to the year of publication. There was a significant upward trend around 2010 which is the date when PICS was originally defined[30]. The year-on-year increase in the number of studies in this field has been substantial over the course of this programme of research; the search identified 5,054 articles between January 2009 and December 2018 (10 years), whereas 4,007 articles were identified between January 2019 and May 2023 (4 years, 5 months).

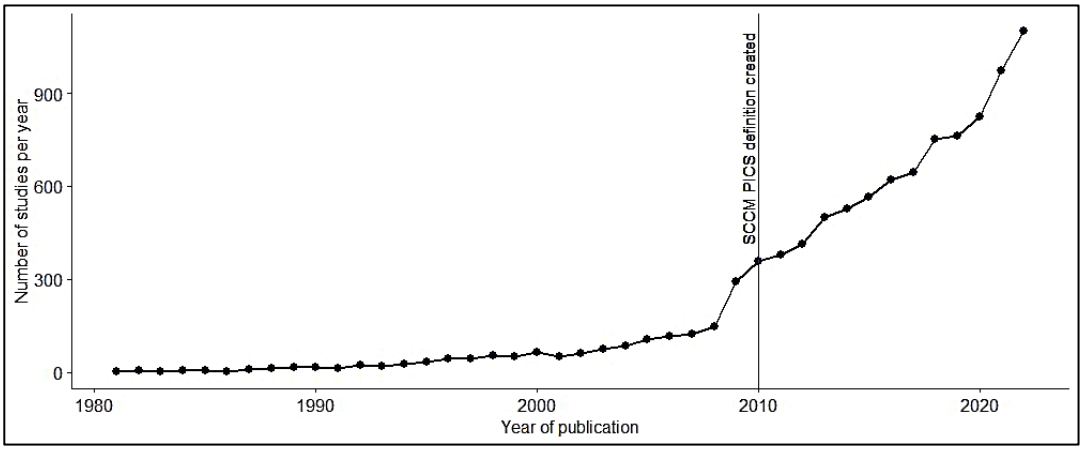


Figure 2-1: Number of studies retrieved per year

Studies retrieved from the database search and published between 1980 and 2022 after removal of duplicates. SCCM: Society of Critical Care Medicine; PICS: Post-Intensive Care Syndrome

The complete study selection process is outlined in Figure 2-2 (PRISMA flowchart). After title and abstract screening 795 studies remained requiring full text review. A total of 734 were excluded, the most common reason for exclusion was that the article was a conference proceeding rather than a full text article (n=305). There were a substantial number of studies (n=175) which did not describe any intervention and were simply observational studies; this was the second most common reason for exclusion. Most of these studies described clinic follow-up but

did not actually contain an intervention, rather the purpose of the clinic was simply to measure outcomes rather than modify outcomes. Figure 2-2 further outlines the rationale for exclusions at full text review.

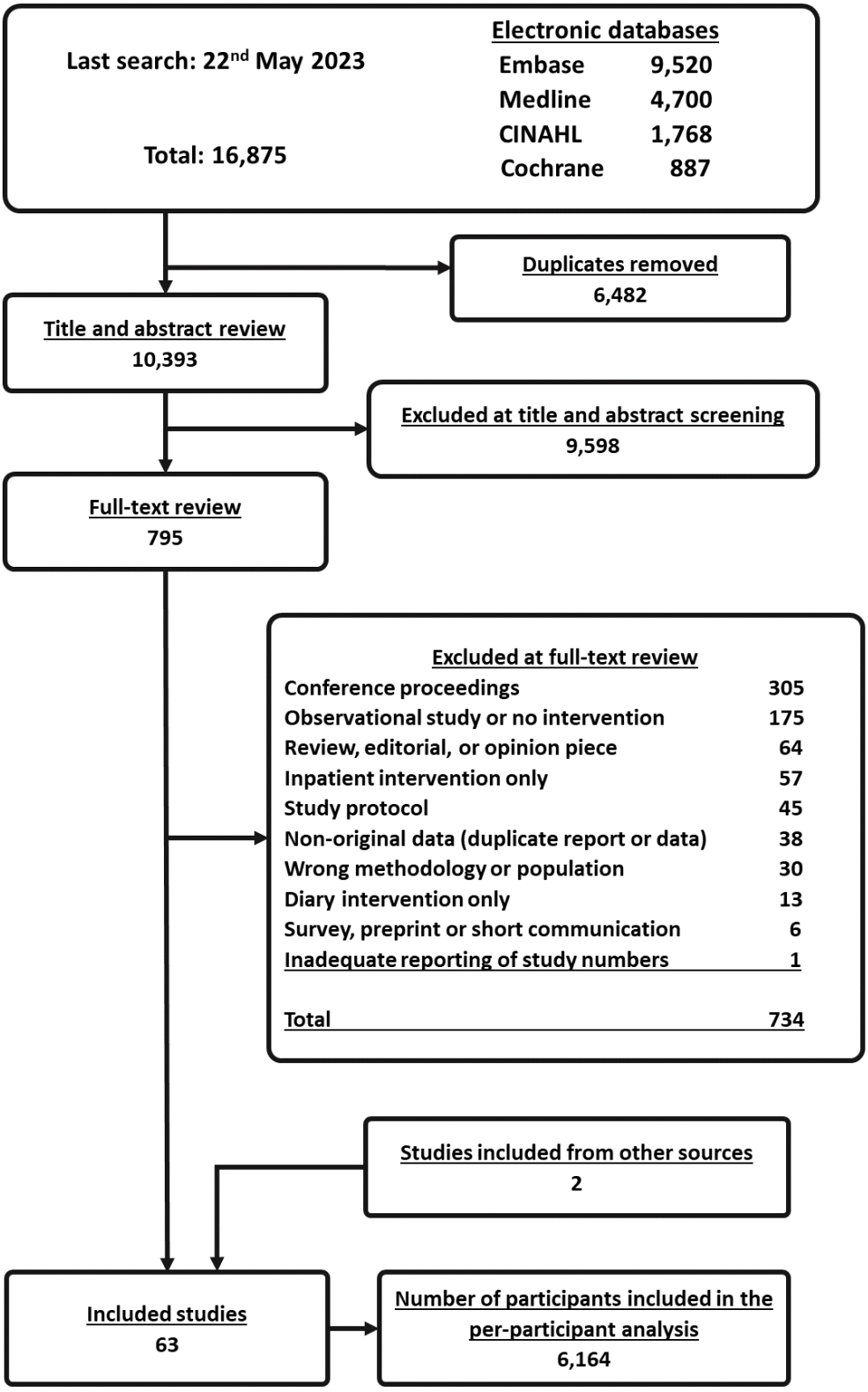


Figure 2-2: PRISMA flowchart of study selection

There were two studies identified that were not retrieved by the electronic search[182,183]. These studies were both case management interventions and met the pre-defined inclusion criteria and were added to those requiring data extraction. The final number of studies that were included in data extraction was 63, which corresponded to 6,164 participants completing the follow-up as planned across all of the included studies[175,182-243]. The study characteristics for all 63 studies can be found in Appendix 2. The median number of participants per study was 62 (Interquartile Range [IQR]: 32 to 109) with a skewed distribution; 21 studies had 100 participants or greater completing follow-up. There were only four studies with over 250 participants, and the largest study (n=688) included was a retrospective cohort analysis by Duarte and colleague describing an MDT follow-up service based in Brazil[226]. No RCTs had over 250 participants, and only nine RCTs had over 100 participants.

All of the studies included a description of the number of participants completing follow-up, however, not all studies had reliable data on the numbers initially consented, approached, or attending. A follow-up completion rate or fraction (number completing compared to the number initially attending or consenting) was therefore only available for 53 studies resulting in a median rate of 71.1% (IQR: 52.6 to 81.7). As may be expected the median follow-up rate for RCTs (n=23) was higher at 79.5% (IQR: 69.1 to 82.5) whereas cohort studies with reliable data (n=23) had a median follow-up completion rate of 56.7% (IQR: 37.7 to 76.2).

2.3.2 Study design, locations, and populations

Of the 63 studies retrieved, 28 (44.4%) were cohort studies and 23 (36.5%) were RCTs (Table 2-1). There was one minimised controlled trial (MCT) and the remaining 11 (17.5%) studies comprised qualitative, mixed methods, QI, and case series. In the per-participant analysis, 3,218 (52.2%) participants were reported from cohort studies while 2,346 (38.1%) were reported from randomised trials. The studies involving the remaining 600 (9.7%) participants included qualitative / mixed methods, case series, QI projects, and minimised controlled trials (Table 2-1).

More studies had a comparator group (54.0%) than not. While RCTs and MCTs by definition have a control group, there were seven cohort studies, two QI projects,

and one mixed methods study that also had a control or usual care group. Combined, the studies containing a comparator group from cohort, mixed methods, or QI designs accounted for 857 participants which was 26.5% of all participants where a comparator group was included.

Table 2-1: Study design, locations, and populations

Study characteristic	Per study analysis (n = 63)	Per participant analysis (n = 6164)	Median number of participants per study grouped by characteristic
	n (%)	n (%)	Median (IQR)
Study type			
Cohort	28 (44.4)	3218 (52.2)	57 (32 to 108)
RCT	23 (36.5)	2346 (38.1)	77 (35 to 177)
Qualitative / mixed methods	5 (7.9)	110 (1.8)	21 (12 to 32)
Case series	2 (3.2)	146 (2.4)	73 (59 to 87)
QI project	4 (6.3)	314 (5.1)	77 (46 to 110)
Minimised controlled trial	1 (1.6)	30 (0.5)	30 (*)
Usual care or control group			
Present	34 (54.0)	3233 (52.4)	69 (34 to 137)
Absent	29 (46.0)	2931 (47.6)	46 (28 to 101)
Location of intervention			
USA	21 (33.3)	1924 (31.2)	66 (32 to 106)
Continental Europe	18 (28.6)	1658 (26.9)	60 (36 to 104)
UK and Ireland	16 (25.4)	930 (15.1)	38 (30 to 77)
Australia	3 (4.8)	212 (3.4)	26 (26 to 94)
Other (one each of): Brazil; combined USA/UK; Japan; Iceland; India)	5 (7.9)	1440 (23.4)	133 (119 to 472)
Study population			
General ICU (including ARDS and sepsis)	46 (73.0)	5225 (84.8)	76 (34 to 130)
Exclusively COVID-19	12 (19.0)	678 (11.0)	34 (27 to 45)
Other specialist population	5 (7.9)	261 (4.2)	42 (26 to 70)
Time to first follow-up intervention appointment			
Under 1 month	23 (36.5)	2034 (33.0)	48 (26 to 129)
From 1 to 2 months (inclusive)	21 (33.3)	1773 (28.8)	63 (33 to 101)
After 2 months	14 (22.2)	1445 (23.4)	46 (29 to 74)
Not accurately reported	5 (7.9)	912 (14.8)	111 (106 to 119)

ARDS: Acute Respiratory Distress Syndrome; COVID: Coronavirus Disease; IQR: Interquartile Range; (*): IQR not reported for single studies. All median values rounded to whole numbers when required. For comparison the median number of participants across all studies was 57 (IQR: 32 to 104).

As may be expected from research involving intensive care, the locations of studies were predominantly from high GDP countries. Specifically, the developed, predominantly English-speaking countries of USA, UK, Ireland, and Australia accounted for two-thirds (n=41) of all the included studies. These figures included a single study comprising 472 participants that recruited from both the UK and USA[190]. Continental Europe represented the largest group outwith the English-speaking block (n=18), with Sweden (n=5) the largest component of this group followed by the Netherlands (n=4) and then Belgium (n=3). The only studies based in Asia were single studies from Japan and India with a single study from Brazil, although this was the largest study in the review as mentioned previously[203,225,226].

In keeping with the design of the search strategy the majority of the studies were from a general ICU population (73.0%). The events of the last 3 years with the Coronavirus Disease 2019 (COVID-19) pandemic are clearly represented as 19.0% of studies were in a COVID-19 specific cohort. However, these studies were generally smaller with a median number of participants of 34 (IQR: 27 to 45) and only 11.0% of the participants overall were represented by the COVID-19 group. Some specialist populations were also included as they met the inclusion criteria. These specialist populations comprised one neurological critical care study, two surgical and trauma-based studies, one cardiac ICU study, and one multicomponent intervention for diabetic patients after general ICU.

The reporting of the precise timing of the intervention after hospital discharge was variable and could not be summarised for five studies. Follow-up was most commonly commenced within 2 months of hospital discharge with 69.8% of studies commencing within this timeframe which corresponded to 3,807 (61.8%) participants.

On the whole the proportions in both the per-study summaries and the per-participant summaries were similar, as demonstrated in Table 2-1. The median number of participants column signposts where studies are generally larger or smaller than the overall median (62 [IQR: 32 to 109]). Some of the characteristics associated with fewer participants per study include qualitative studies, those without a comparator group, and COVID-19 studies.

2.3.3 Staff and professional involvement

Table 2-2 summarises all of the components described in the studies and included in data extraction. When considering the staff involved in the follow-up services, ICU nurses have been described in just under half of the studies (n=31; 49.2%). The number of participants who have been studied involving an ICU nurse is proportionally larger at 3,392 (55.0%). This therefore suggests that the average number of participants per study was generally larger for those that involved an ICU nurse compared to the overall study participant average. This is further represented by the higher median number of participants within this subgroup (median=77; IQR: 35 to 115) compared to the overall median for all studies.

There were six studies that described the involvement of nurses that were not ICU nurses. Often these would be trained study nurses or case managers (and counted as both case managers and nurses) and no study had both an ICU nurse and another nurse. As such, there was no overlap and in total nurses (ICU or non-ICU) were involved in 37 (58.7%) studies which included 3,951 (64.1%) participants.

Similarly, ICU doctor (or physician) involvement was described in 30 (47.6%) studies, however, this corresponded to a proportionally lower number of participants (n=2,675; 43.4%). The relatively lower median number of participants in the ICU doctor group further supports this observation. The remainder of the professionals involved and reported in the studies are fully described and included in Table 2-2. Physiotherapists have been involved in 41.3% of the studies but this only included 32.8% of participants. These numbers could be interpreted as being low given the significant contribution physical impairments play in the definitions and morbidity of PICS.

Table 2-2: Summary of staff and components of retrieved studies

Summary component	Per study analysis (n = 63)	Per participant analysis (n = 6164)	Number of participants per study per component
	n (%)	n (%)	Median (IQR)
Professionals involved in follow-up			
ICU nurse	31 (49.2)	3392 (55.0)	77 (35 to 115)
ICU doctor	30 (47.6)	2675 (43.4)	44 (32 to 101)
Physiotherapist	26 (41.3)	2020 (32.8)	34 (25 to 71)
Pharmacist	15 (23.8)	1640 (26.6)	62 (32 to 112)
Psychologist or therapist	19 (30.2)	1943 (31.5)	40 (22 to 109)
Dietician or nutritionist	6 (9.5)	1247 (20.2)	108 (42 to 246)
Occupational therapist	3 (4.8)	160 (2.6)	36 (30 to 69)
Speech and language therapist	2 (3.2)	720 (11.7)	360 (196 to 524)
Other nurse (non-ICU)	6 (9.5)	559 (9.1)	37 (22 to 164)
Other doctor (non-ICU)	4 (6.3)	280 (4.5)	26 (25 to 71)
Social care specialist	8 (12.7)	1376 (22.3)	105 (35 to 160)
Case manager	8 (12.7)	969 (15.7)	91 (44 to 213)
Other follow-up components			
Caregivers included	22 (34.9)	2211 (35.9)	84.5 (41 to 117)
Written information	13 (20.6)	1404 (22.8)	90 (66 to 161)
Critical care debrief	9 (14.3)	823 (13.4)	77 (40 to 119)
Peer support	6 (9.5)	262 (4.3)	33 (29 to 38)
Digital component	6 (9.5)	671 (10.9)	71.5 (38 to 167)
Volunteers	2 (3.2)	146 (2.4)	73 (57 to 90)
Clergy	1 (1.6)	106 (1.7)	106 (*)
Signposting to other services	1 (1.6)	40 (0.6)	40 (*)

ICU: Intensive Care Unit; (*): IQR (Interquartile Range) not reported for single studies.

A psychologist (or therapist) was involved in 30.2% of the studies and the per-participant summary demonstrated a similar total proportion (31.5%). Once more, this could be considered low given the high rates of emotional and cognitive problems after intensive care, however, this may be explained by the fact that psychologists are not routinely part of the day to day running of most ICUs[244].

Although only two (3.2%) studies have included Speech and Language Therapists (SALT), the participant count is proportionally much higher at 11.7% (n=720). This is primarily due to a large study by Duarte et al from Brazil that describes the experiences of 688 participants being treated three months after hospital discharge[226]. This large study describes the involvement of seven different healthcare specialists at their single centre follow-up clinic which includes dietetics as well as SALT thus accounting for 688 participants in the dietician or nutritionist summary also[226].

Figure 2-3 offers a bar chart summary of all the professionals involved in the ICU follow-up services identified by this review. Note the difference between the top bar chart which describes the per-study analysis and the lower bar chart which is the per-participant summary.

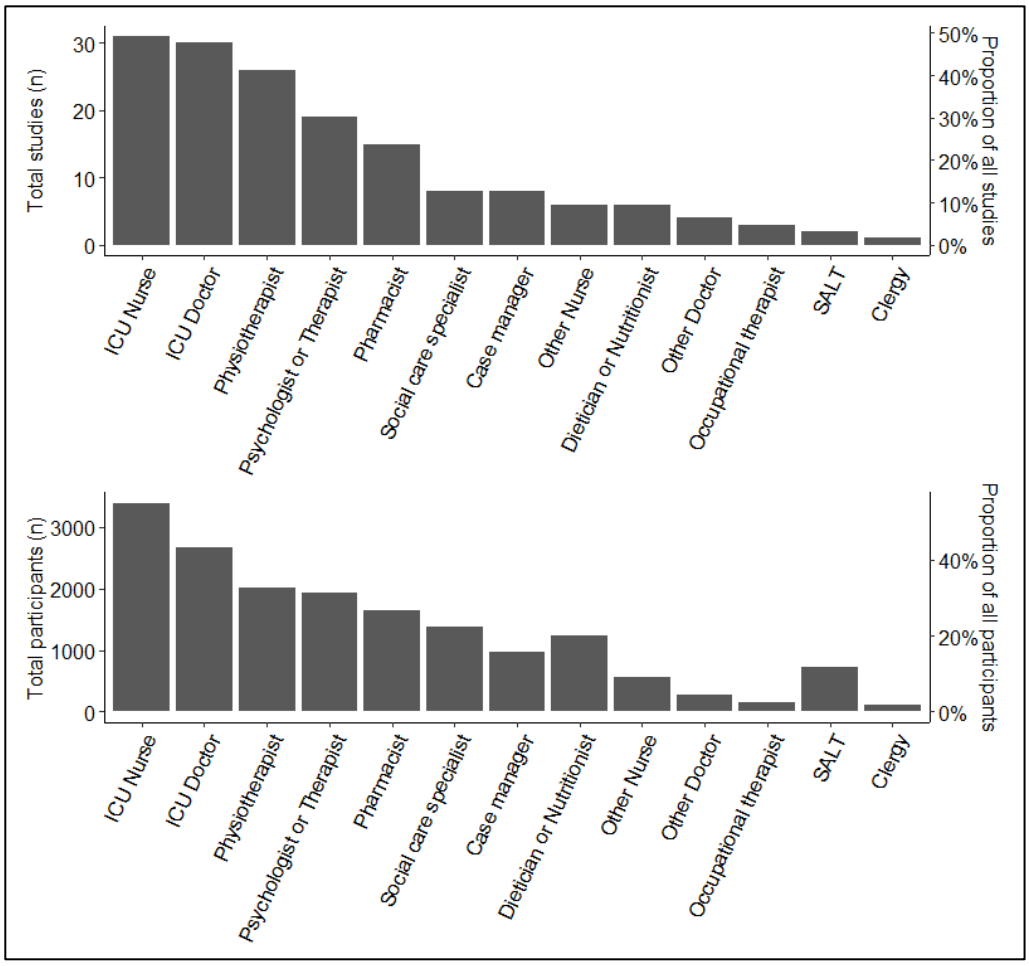


Figure 2-3: The numbers of professionals, volunteers, and third sector members of ICU follow-up services as described in the literature.

The upper bar chart summarises the number of studies describing each member of the ICU (Intensive Care Unit) follow-up service and the lower bar chart counts the total number of participants. SALT: Speech and Language Therapist.

2.3.4 Additional follow-up components

Beyond the professionals involved in each clinic the most common component to be described and studied was the inclusion of caregivers in the follow-up service. This was present in 22 studies (34.9%) and involved a very similar proportion of participants (35.9%). The largest study including caregivers was a registry study of a nurse led clinic from Glimelius-Petersson and colleagues (n=372)[204]. This study invited caregivers or family members to the follow-up service but the caregivers were not the specific target of the intervention and outcomes from caregivers were not measured. This is common for the vast majority of studies that included caregivers.

The remainder of the component summaries can be found in Table 2-2 and in the bar chart summary in Figure 2-4. These outline the numbers of studies and participants involved in studies describing the use and implementation of written information, a critical care debrief, a digital component, peer support, and volunteers. The peer support component merits further inspection as this is a well described form of support, however, both the number of studies (n=6; 9.5%) and the total number of participants (n=262; 4.3%) appeared very low. It could be that this search strategy did not have the fidelity to find studies that involved peer support. However, the alternative explanation that this component has been underutilised as part of multicomponent follow-up after critical illness is equally possible and is supported by other review articles[245].

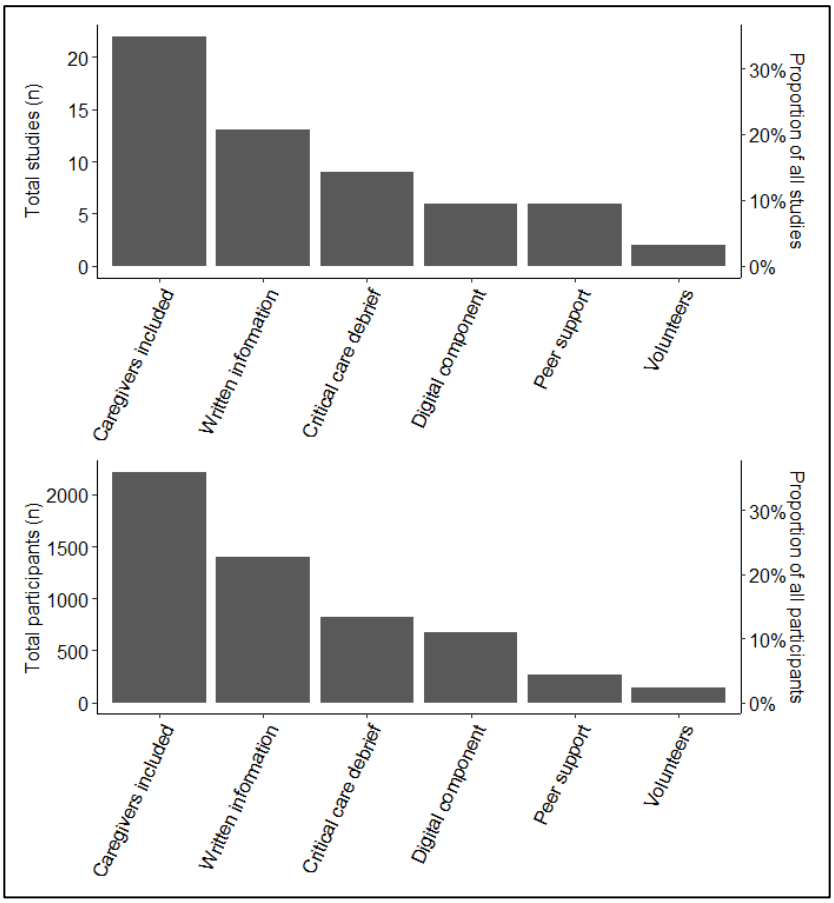


Figure 2-4: Additional follow-up components described in the literature.

The upper bar chart summarises the number of studies describing each component of the follow-up service and the lower bar chart counts the total number of participants.

2.3.5 Multicomponent interventions

The numerical summaries up to this point have simply considered whether specific people and components are involved in follow-up services. However, given the complexity of PICS and the manifold problems involved it is equally valid to consider the complexity of the interventions described in the literature. To address this question the six most common follow-up components identified through the earlier work were included in a "component count". The six summarised components (or professionals) included in this component count were: nurses (ICU nurse or other nurse); ICU doctor; physiotherapist; pharmacist; psychologist or therapist; and caregivers. This revealed that every study included at least one of these components, which resulted in every study being assigned a value between one and six.

Table 2-3 summarises the component count data and demonstrates that the majority of studies only included one or two components (n=39; 61.9%). There were 19 studies that had one component and 20 studies that had two components. However, there were proportionally more participants in the two component studies (39.1%) compared to the single component studies (26.0%). This is also reflected in the higher median number of participants (102; IQR: 43 to 193) in this group.

Table 2-3: Component counter of the six most common professionals or components used in ICU follow-up studies

Component count	Per study analysis (n = 63)	Per participant analysis (n = 6164)	Number of participants per study
	n (%)	n (%)	Median (IQR)
1	19 (30.2)	1602 (26.0)	49 (32 to 77)
2	20 (31.7)	2410 (39.1)	102 (43 to 193)
3	10 (15.9)	764 (12.4)	83 (39 to 103)
4	11 (17.5)	1254 (20.3)	32 (22 to 84)
5	2 (3.2)	94 (1.5)	47 (40 to 55)
6	1 (1.6)	40 (0.6)	40 (40*)

The six components included in the component count are: nurse (ICU or other); ICU doctor; physiotherapist; pharmacist; psychologist or therapist; caregivers. The top row describes the studies and participants that only contained one component, and the bottom row are the studies and participants including all six. Every study included at least one of these components. ICU: Intensive Care Unit; (*): IQR (interquartile range) not reported for single studies.

Figure 2-5 offers a graphical summary of the component count data and demonstrates that there is almost a stepwise reduction in the number of studies as the number of the key components increases. Thus, exactly one-third of studies had three or four components (n=21; 33.3%) and only three (4.8%) involved five or six components. The number of participants follows a similar pattern except for a spike in two and four component studies but a similar stepwise reduction when considering in pairs.

It is worth repeating that this component count only included the six most common components. As such, some components are not counted and some of the studies would have more components if all of the 'other' components were counted (e.g. SALT). Therefore, if there were a total component count including every component there would be more studies with four or more components. The focus on the main six components (or professionals) is an attempt to remove some of the heterogeneity that is seen throughout this research.

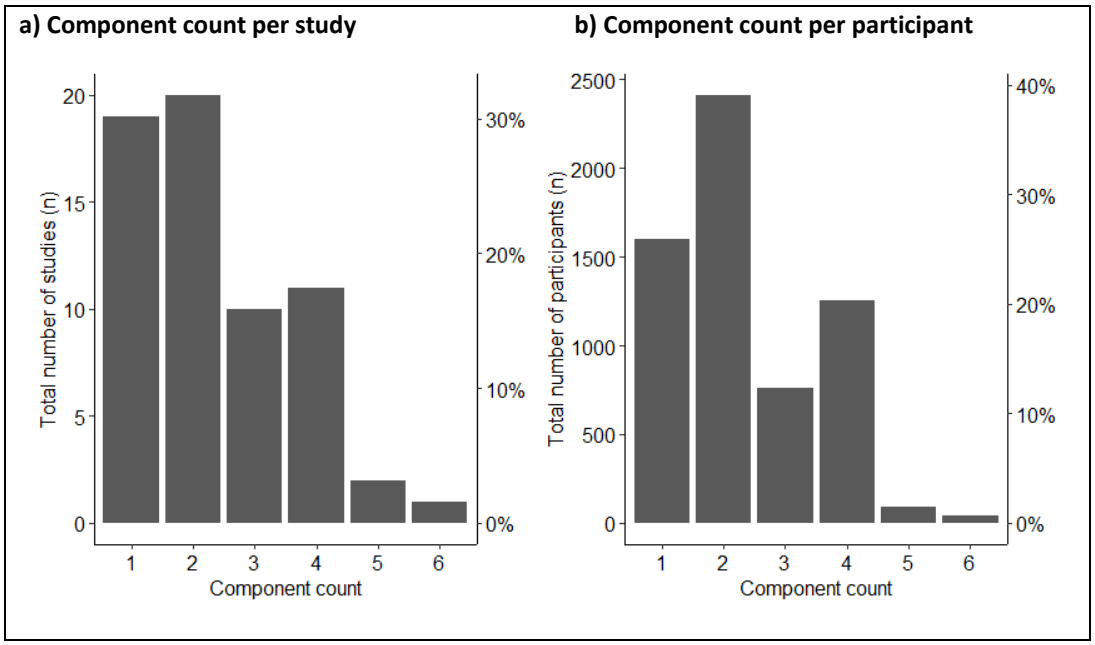


Figure 2-5: Component counter bar charts

a) Component count per study; b) Component count per participant. Totals are a count of the six most commonly included components of follow-up services. These include: nurse (ICU or other); ICU doctor; physiotherapist; pharmacist; psychologist or therapist; caregivers.

2.3.6 Intersecting and overlapping components

A final exploratory analysis was carried out to better understand the overlap between interventions and components. The five main healthcare professionals involved (nurse; ICU doctor; physiotherapist; pharmacist; psychologist or therapist) were plotted using bar charts but split into their separate overlapping components. This can be viewed in Figure 2-6. This allows a more granular breakdown to understand what different combinations of professionals have been involved in follow-up studies. This analysis confirms that as the complexity increases the number of participants that have experienced the specific follow-up components reduces. Once more, the nurse (ICU or other nurse) is the most likely professional to be involved in a follow-up service with the nurse being the most common professional for interventions involving one, three, four, and five professional groups. The one place this is not true is for follow-up involving two professionals, where the most common combination described is an ICU doctor and a pharmacist. There were three studies that described this combination with a total of 417 participants from the three studies [193,218,223].

After the stand-alone nurse intervention, the next most common combination was four professionals together involving nurse, ICU doctor, physiotherapist, and psychologist as part of an MDT. The largest study contributing to this component was a paper from 2017 by Duarte et al, which was the largest single study (n=688) in this review, has been referenced a number of times above, and involved a diverse MDT[226]. They did not, however, involve a pharmacist in the MDT and caregivers or family members were not involved except in a discussion with the patient about transport to the clinic and a discussion about income[226]. The focus in this study was multiple individual reviews from each professional rather than an embedded team approach.

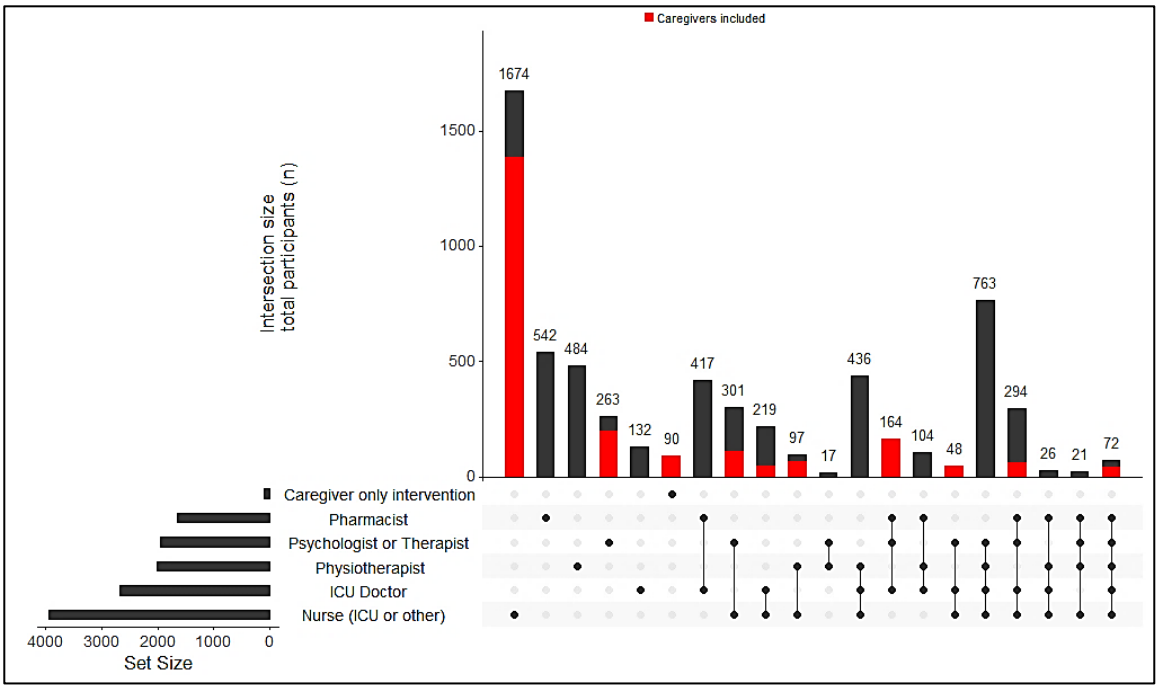


Figure 2-6: Upset graph of the overlapping follow-up components per participant.

The five main professionals with or without caregiver involvement are described. The circles and joining lines below the bar chart indicate which combined components are being described. The vertical bar height demonstrates the total number of participants in each combined component with the number (of participants) on top. The red bar heights are the total participants of the specific intersection that includes caregivers. The 'Set Size' bar chart at the lower left demonstrates the total number participants with each component, whether occurring individually or combined (i.e. across all intersections).

The last layer of Figure 2-6 is whether caregivers were involved in the follow-up service, and this is represented by the red bar. To be included the caregiver will not necessarily have been the direct target of an intervention, but the study or paper had to describe that caregivers were invited to attend at a minimum. As the interventions become increasingly more complex, caregivers were less likely to be involved. The largest group involving caregivers was once again the single nurse follow-up intervention where 10 of 12 studies involved a caregiver. There was only one study that primarily targeted caregivers where the main intervention was self-help guidance as written information[241]. This was included as this was a definitive intervention delivered after critical illness and improved the understanding about both caregiver involvement and the use of a self-help strategy.

The number of participants included in multi-professional interventions which also described caregiver involvement was very low. There were 10 studies that had caregiver involvement and at least two of the main five professionals also

involved. The 10 studies together only included 538 participants or 8.7% of the total participants. Given the importance of PICS-F and the importance or treating the family unit, this number appears low. Furthermore, there were only seven studies and a total of 360 participants that were studied as part of services that included an ICU doctor and caregivers.

2.4 Discussion: understanding the scoping review results

2.4.1 Study type and design

This scoping review has demonstrated the exponential growth in studies relating to critical illness recovery in the last 10 to 15 years. From the 63 retrieved studies the total participant count was impressive (n=6,164). However, the median number of participants per study appeared low (median=62; IQR: 32 to 109). These figures underpin the overall impression that this literature is in an early phase and there are significant gaps in the knowledge base with many small studies reported in the literature.

The two additional studies included (from other sources) both involved case management after hospital discharge by specialist nurses[182,183]. One study from Schmidt et al was discovered as the protocol was found as part of the electronic search but the original paper was not; this was then retrieved[182]. The other study was discovered by examining a systematic review that assessed long-term outcomes after ICU but also included inpatient treatments[183,246]. The similarity in these studies perhaps suggests that the search strategy could have been widened to include more primary care and case management studies. However, this review did use well recognised techniques to search and cross reference the literature alongside a thorough evaluation of the retrieved papers. Similarly, it is not uncommon for review articles to include other studies beyond those from electronic databases.

The studies included in this review varied in quality and the loss to follow-up rates are likely a marker of this. The precise reporting of recruitment numbers and

completion of (or lost to) follow-up was variable and could only be summarised for 53 studies. This resulted in an overall median loss to follow-up rate of over a quarter (28.9%). For cohort studies the median loss to follow-up rate was even higher at 43.3% and this was lower for RCTs (20.5%). The high loss to follow-up rate is an important marker of potential bias although there is no agreed cut-off within the ICU literature[247]. The social sciences propose follow-up rates of 70 to 80% to be the minimum acceptable level, however, the ICU population have specific problems including cognitive dysfunction that can result in very experienced teams failing to achieve this rate of follow-up[247]. This is an important reminder that when designing any study, the issue of reliable follow-up is important to address and resource appropriately.

The variety of studies included in this review is substantial with cohort studies representing the most commonly studied type. Cohort studies clearly have their limitations and are at much higher risk of bias when compared to RCTs[248]. It is also more difficult to assign causation from a cohort study and careful consideration needs to be given to selection bias and confounding. Similarly, the number of studies without a control or usual care group was high (46.0%), these were included to understand the breadth of the formal literature, but these studies cannot assess the effectiveness of interventions. For cohort studies this was even higher where the vast majority (75.0%) of the cohort studies did not have a control or usual care group.

The final area considered in the study design section was the timing of delivery of the post hospital discharge intervention. This data were often difficult to extract as the reporting was very mixed. Furthermore, there were a number of timepoints reported and it may be that the intervention was delivered one month after discharge, but follow-up complete at one year. In this example the follow-up timeframe was recorded as one month rather than one year as the former number was more reliably reported. Using this methodology, it was clear that most interventions were delivered within two months of hospital discharge. The heterogeneity in reporting of these datapoints limited more granular understanding of the timing. There was not enough consistency to differentiate between when the intervention was intended to be delivered and when it was actually delivered. The variability in reporting limited other understanding and

this study was unable to assess whether loss to follow-up rate increased as the time from hospital discharge to intervention delivery increased. Similarly, it was not possible to consider loss to follow-up rates compared to intervention complexity. As the literature matures there may be the possibility to repeat this and consider follow-up rates compared to intervention timing and / or complexity.

2.4.2 Staff: nurse and doctor involvement

2.4.2.1 Nursing staff

Nursing staff were involved in more studies than any other group. Combined nurses (ICU nurses and other nurses) were involved in the care of 64.1% of all participants described in this review. The ICU nurse made up the largest proportion of nurses (31 studies) whereas other nurses were included in six studies with no overlap; there were no studies with both an ICU nurse and another nurse.

Despite the large proportion of studies involving nursing staff there is limited evidence of the effectiveness of follow-up involving nurses. The largest RCT (n=232) involving ICU nurses reported in this scoping review was from Bloom and colleagues and involved a broad MDT[216]. This feasibility trial included ICU nurse, ICU doctor, pharmacist, psychologist, and case manager. The conclusion of the study was that for those who were readmitted to hospital after discharge home, the time to readmission was greater in the treatment arm. While on the surface this appears positive (patients stay out of hospital longer), there was no statistically significant difference between the numbers readmitted (within 30 days), and this could suggest that follow-up simply delayed readmission rather than prevented it. Other studies involving ICU nurses as part of a smaller MDT or as a single professional intervention have similarly failed to demonstrate a definitive signal of benefit, some of which include: Schmidt et al, the PRaCTICaL trial from Cuthbertson et al, Jonasdottir et al, and Jones et al[182,220,239,242].

The most common role of the non-ICU nurse was case management, where this was described in 2 studies, another study described the nurse as a coordinator[183,206,214]. These will be considered later in this discussion but it is clear that none of these three studies described the nurse as having any background or training in ICU. There were two studies describing the nurses as having completed

psychological skills training[228,234]. The larger of these two studies was the RAPIT trial by Jensen et al[228]. This trial invited participants to a structured nurse-led debriefing session that was based on structured narratives and Cognitive Behavioural Therapy (CBT). The nurses were described as trained study nurses and the training included 10 study days with no description that the nurses were specifically from an ICU background. The study failed to demonstrate any benefit from this intervention, and it also highlights a key question of what training individuals should have when delivering interventions after intensive care? It is unclear whether it is of greater importance to have specific training in psychology or whether the experience and depth of understanding about care delivered in the ICU is of primary importance. The optimal strategy may be to involve ICU nurses that have undergone specific training, however, this is time consuming and likely to be more expensive.

Another question may be why nurses rather than other groups have been studied more than any other staff group. Part of the rationale may be availability, there are simply more nurses than any other group, especially in ICU when care is often delivered on a one-to-one basis. Furthermore, in delivering the one-to-one care the nursing staff are directly exposed to and able to empathise with the patient recovering from critical illness resulting in a personal motivation to be involved in follow-up. There are also likely to be financial considerations with lower average salaries for nurses compared to other groups, particularly doctors. Finally, in some healthcare settings there may be a greater ability to relieve a nurse from their other clinical commitments. Whatever the rationale, it is evident that nursing involvement in post discharge follow-up interventions is more well studied than any other single component within the formal literature.

2.4.2.2 Doctors

The ICU doctor involvement has also been better studied than most other groups, with 30 studies describing the involvement of an ICU doctor. However, the ICU doctor has not been studied in isolation to any extent with only 132 participants involved in studies where the ICU doctor was the only professional (of the main five professionals) as demonstrated in Figure 2-6. Of studies assessing the ICU doctor in isolation the largest was a report about the feasibility of a follow-up consultation in Belgium (n=42)[187]. This study reported low feasibility and offered

no concrete effectiveness from this intervention. Similarly, the other studies that focused primarily on an ICU doctor as the main professional delivering follow-up have been small and inconclusive[185,211,225].

None of these studies were from the UK, with most UK studies that involved an ICU doctor also involving other components of the MDT. The largest was a case series by Crocker from 2003 describing outcomes from 101 patients who visited a traditional MDT involving nurse, doctor, physiotherapist, and occupational therapist[243]. Feedback was overall good but there was no comparison group and outcomes were largely qualitative and therefore no treatment effect could be ascertained. There were only four other UK studies that involved an ICU doctor as part of the follow-up service and only two of these had a comparison group[175,192,208,209]. A study from McPeake et al involved 40 participants, including an historical control, and was the inspiration for this thesis[175]. As such this is described elsewhere, but this study had a signal that a complex MDT (including ICU nurses and doctors) could have measurable effects on improving HRQoL for ICU survivors. This study was very small, and the strength of correlation was confounded by the use of an historical control.

Overall, evidence is lacking that demonstrates effectiveness from an ICU follow-up service which involves ICU doctors. In the UK this is likely compounded by the absence of specific learning outcomes relating to ICU follow-up for doctors in intensive care medicine training programmes[249]. This may also contribute to the low number of studies involving ICU doctors as an independent intervention from the UK and is perhaps why there are relatively more studies from countries outwith the UK. This is particularly true of the USA where intensive care (or critical care) training is frequently combined with pulmonology, which has a significant outpatient component[250].

Very few studies have utilised doctors other than ICU physicians. There were three that involved other specialists and these accounted for only 73 participants[184,206,211]. A small paper from the USA treating a COVID-19 specific group by Sayde et al (n=21) involved a dually qualified internist-psychiatrist as part of a wider MDT (physiotherapist, pharmacist, and case manager). This paper reported high rates of psychiatric problems but as a cohort study without a control group it could not estimate outcome effects. It certainly suggested that the

internist-psychiatrist can feasibly be involved in follow-up although in other countries this combined training does not exist[251]. It does suggest that other medical specialties could be involved in follow-up services. However, the current state of knowledge on these approaches is very limited and it is likely that much more feasibility work would be required before embarking on a large study in this area. The other two studies would confirm this sentiment with low numbers reported from specialist surgical follow-up from Bottom-Tanzer et al, and low feasibility of an endocrinologist lead diabetes focused intervention (the SWEET-AS trial) from Abdelhamid and colleagues[206,211].

2.4.2.3 Summary of nurse and doctor involvement

It is clear that nurses (ICU and other nurses) alongside intensivists (ICU doctors or physicians) represent the largest and most common professionals at an ICU follow-up service. There were a total of 1,858 (29.8%) participants who were involved in studies that had both professionals present (Figure 2-6). It is evident, however, that those who design services and implement studies involving these groups value the contribution from both. More work is therefore required to better understand the effectiveness of nurse and doctor interventions (with or without a wider MDT) after hospital discharge.

2.4.3 Staff: physiotherapist, psychologists, and pharmacists

2.4.3.1 Physiotherapy

Physiotherapy input was present in 26 (41.3%) studies involving a total of 2,020 (32.8%) participants. This could be considered low, given the significant contribution physical impairments make to the definition of PICS. Furthermore, the median number of participants for studies involving physiotherapists was also low at 34 (IQR: 25 to 71). This could be explained by the more hands-on physical work of physiotherapy, resulting in a tendency towards smaller study sizes for those that involved this treatment. There were nine studies in total primarily focused on physiotherapy and six of these were RCTs. The largest was a 2011 RCT from Elliot and colleagues (n=161) which randomised participants to an individualised eight-week home exercise programme with three visits from a physical therapist or usual care[237]. Measuring outcomes using the 6MWT, SF-36, and a sleep scale they report no difference between cohorts. Conversely Jones et

al (2015) report an RCT that involved a factorial design (2x2 study) comparing control groups to nutritional supplementation, physiotherapy, or both[230]. Given there were four arms in this study, the completed follow-up of 72 participants appears low. Furthermore, the study had to be extended by one year and despite this it only achieved half the pre-planned participant recruitment numbers (92 recruited vs 180 planned, both before loss to follow-up). However, the results did show a significantly increased improvement in the supplementation plus physiotherapy groups for 6MWT distances, SF-36, and anxiety rates. Although it should be noted that the baseline anxiety rate for the intervention arms was much higher than controls. This study is unlikely to form the basis for a change in clinical practice as the numbers and results appear to have a high degree of fragility. It has also been demonstrated that studies which are stopped early should be interpreted with caution and they may inflate the treatment effect[252]. Positives from this study are that combining physiotherapy with other treatment modalities is possible and could be part of the solution to improve long-term outcomes after critical illness.

Other randomised trials have been small and failed to give a conclusive signal of benefit for post hospital discharge physiotherapy and its effects on QoL[217,224,227]. A systematic review from 2019 also found that there was no consistent effect from enhanced physiotherapy starting after ICU discharge (either in-hospital or at home)[253]. Furthermore, the authors conclude that more work needs to be done to better understand the optimal physiotherapy approach after ICU discharge[253].

The other consideration for physiotherapy is how this treatment fits within multicomponent services. This scoping review has demonstrated that a physiotherapist featured alongside at least one of the other four main professionals in studies involving 1,536 participants, whereas physiotherapy as the primary (or only) component involved 484 participants (Figure 2-6). Despite this ratio it is very difficult to aggregate and find an overall effect from studies involving a physiotherapist as part of a multicomponent study. Even more noteworthy is the absence of caregivers in physiotherapy studies, with only two studies involving physiotherapy and caregivers (regardless of other components) with a total of 109 participants[175,231]. Figure 2-6 clearly highlights this absence of overlap. This may stem from the way in which physiotherapists work within a

hospital, patients may be taken away from their family to the hospital gym for assessment and therapeutic interventions. Although physiotherapy is generally integrated into the ICU MDT, it may be that studies that have had a narrow focus on physical outcomes have not considered caregivers as part of these interventions[10]. While there may be some rationale why the single component physiotherapy interventions would not involve a caregiver, it is far less clear why this mutual exclusivity would be present for the multicomponent interventions. A possible explanation may be that the multicomponent interventions involving a physiotherapist are designed and focused more on the biological model of healthcare and perhaps place less emphasis on the psychological and social aspects of recovery. The presence of a physiotherapist may essentially act as a selection bias for these biological models. This may also help to explain the limited efficacy from the stand-alone physiotherapy interventions.

2.4.3.2 Psychology

A psychologist (or therapist) was involved in 19 (30.2%) studies which included 1,943 (31.5%) participants, representing the fourth largest professional group described in the literature. Cox and colleagues have assessed the impact of a psychologist and other psychological therapies in three studies identified through this review[215,219,234]. The initial study was a combined development and feasibility study reported in 2012[234]. The aim was to develop a telephone based coping skills programme which also included caregivers. After interviewing 44 participants (21 patients; 23 caregivers) the intervention was then designed and delivered for 14 participants (7 patients; 7 caregivers). They report that ineffective coping strategies are common in both patients and caregivers. The study continues by describing a well-tolerated, feasible intervention that could have measurable, beneficial effects for psychological wellbeing if this methodology was expanded to a larger trial.

Following on from this Cox et al conducted an RCT to understand the effects of a combined six-week telephone (the intervention designed c.2012) and web-based coping skills programme after hospital discharge[219]. Fundamentally the outcomes reported for the 197 participants (131 patients; 66 caregivers) at three and six months did not support the hypothesis that the skills training programme improved psychological or HRQoL outcomes. Perhaps the most significant aspect of this trial

was the control group. The authors note that a usual care approach was not possible as during the design phase (c.2013) the patient and family stakeholder groups expressed that an approach of "no attention" would be "unacceptable"[219]. As such a control group intervention was designed that involved six training videos that discussed important aspects of critical illness, omitting any material about psychological distress. This control group also received two phone calls from study staff to discuss material or answer questions. This trial was, therefore, an RCT comparing two different educational or treatment approaches. It was not a study of effectiveness of a psychological intervention against no follow-up. It cannot be assumed therefore that the programme had no effect.

There are two clear learning points from this trial. Firstly, there are many different approaches to outpatient interventions, and specifically the use of technology is worth considering. The 2018 trial from Cox et al is the largest RCT that involved a digital component[219]. Secondly, those involved in the design and implementation of the study clearly did not perceive equipoise with no intervention. The key stakeholders felt that some sort of follow-up was the minimal acceptable standard. This is despite the absence of clear evidence for the effectiveness of psychological interventions after critical illness. It is likely, with the increasing interest in intensive care aftercare, more stakeholders will begin to consider that no follow-up does not have equipoise compared to some (or any) follow-up. As such it may be that studies involving usual care (without follow-up) will not be possible in the future despite the absence of empirical evidence.

The final study from Cox et al was reported in 2019 and is a pilot RCT involving 66 participants and describes three interventions: a mindfulness mobile app, a telephone consultation with a psychologist, or a self-help guide (written information only). The study concludes that the app is feasible however the study was not powered to assess a treatment effect.

The absence of any treatment effect from psychological interventions is unexpected given the significant contribution that mental health and cognitive impairments play as part of PICS and PICS-F. A recent systematic review concluded that mental health interventions for caregivers were beneficial, however, they included neonatal, paediatric, and adult critical care[254]. They also include both inpatient and outpatient psychotherapies, which is beyond the scope of this

review. Much of the benefit described in this review was from the inpatient interventions[254]. It is unclear, therefore, exactly what model or type of psychological intervention should be prioritised after critical illness for both patients and caregivers.

2.4.3.3 Pharmacist

Pharmacist involvement was only described in under one-quarter of the studies (n=15; 23.8%). This included the involvement of 1,640 (26.6%) participants with a median participant size per study involving pharmacy of 62 (IQR: 32 to 112), which was very similar to the median study size across all studies.

The most significant study to be included in the pharmacy component was from Stollings et al[190]. This study describes an international multicentre collaboration which collected data from 12 multicomponent ICU recovery clinics. The work of a pharmacist at these clinics is described, reporting that pharmacists intervened in 84% of 472 participants reviewed. Although recently published (2023), this paper is likely to become a seminal piece of work for ICU recovery and the involvement of pharmacists. This paper alone accounted for 28.8% of all participants with whom a pharmacist was involved. The report also describes in great details what medication interventions were undertaken, highlighting that proton pump inhibitors and anticoagulants were discontinued most frequently[190]. This highlights that there is significant utility in pharmacy interventions after critical illness.

This study raises some important issues about how research in the field of multicomponent interventions after ICU may be conducted in the future. If there is a general move towards offering every patient some form of follow-up, then the only option to understand effectiveness may be to break the components into their constituent parts. All 12 recovery clinics described followed their own programme and had their own mix of specialists, professionals, and other components. Perhaps due to the measurable work that a pharmacist does it was possible to place a meaningful metric on outcomes that are likely to be important to the patients (using fewer medications) and the healthcare systems (lower cost). The results are impressive, however other professional groups and components are less likely to have such quantitatively measurable outcomes.

It is also worth highlighting that inclusion of this paper from Stollings and colleagues was considered carefully before forming part of this scoping review's numerical summary[190]. This was treated as a standalone pharmacy intervention, and it highlights some of the differences in the formal literature and clinical practice. All of the interventions were multicomponent, but this was variable between the 12 different services. The simplest was a nurse, doctor, pharmacist, and the most complex involved combining health and social care with healthcare professionals. Given that the focus was entirely on pharmacy intervention it was deemed not appropriate to count this as a multicomponent intervention. Regardless, this study adds to both the literature and this review significantly.

The paper clearly demonstrates substantial utility for pharmacist involvement alongside a description of many different clinic models that have utilised pharmacy services. This raises the question of why pharmacists have not been involved in more studies. While there will always be financial constraints when more skilled staff are involved there could be several other factors that have contributed. It may be that the original definition of PICS (problems with physical, cognitive, and mental health) does not propose or suggest a clear target for the pharmacist. There could also be cultural differences in how and when a pharmacist is used as part of the ICU MDT, and it may be that this is seen as more of an inpatient role or intervention. Similarly, in some areas pharmacy may have subspecialised into outpatient (community) and inpatient (acute) services[255]. More studies should be done to understand the barriers to pharmacy involvement in outpatient follow-up.

There were four studies that included some form of comparator group and involved pharmacists[175,193,195,216]. The most significant study was from Bloom et al, as has previously been described, which did demonstrate a delay to readmission but no difference in overall hospital readmission when attending a clinic[216]. This also highlights the difficulties in measuring endpoints or very downstream effects (hospital readmission) in multicomponent studies. It would appear that Bloom et al failed to capture the value of a pharmacist as part of their intervention, although this was not the purpose of the study[216].

In summary, although there were fewer studies involving a pharmacist, the effectiveness of the pharmacist as part of a multicomponent intervention has a

better overall signal of benefit than many of the professionals described in the literature. It seems clear that pharmacy involvement should be strongly considered as part of post ICU interventions.

2.4.3.4 The "three Ps" combined: physiotherapists, psychologists, and pharmacists

There were only three studies that involved a physiotherapist, a psychologist, and a pharmacist which included 93 participants (Figure 2-6)[175,184,208]. One study was focused on the pharmacy intervention but described a clinic involving all three, and the other two were multicomponent observational / QI projects. There were no randomised trials, and it is difficult to discern any treatment effect from services involving all three professionals.

Figure 2-6 also allows more granular detail of the intersecting points of these three specialists. When considering studies with only two of physiotherapists, psychologists, and pharmacists, it is demonstrated that: there were five studies involving a psychologist and physiotherapist (n=780); five studies involving a psychologist and pharmacist (n=458); and only two involving a physiotherapist and pharmacist (n=130).

This review has demonstrated that those designing studies appear to value the input from physiotherapists, psychologists, and pharmacists although there is variation in reported results. The most significant gap in the literature is in the effects of all three together as part of multicomponent interventions. Given the extent and problems of PICS it would appear logical, at least from first principles, to involve these professionals in future follow-up studies.

2.4.4 The wider hospital Multidisciplinary Team

The results described in Table 2-2 and Figure 2-3 include the other professionals who have been described in the literature as contributing to the aftercare of ICU survivors. Among these, the members of the traditional acute hospital MDT are: dieticians or nutritionists (n=6); occupational therapists (n=3); and speech and language therapists (n=2). No studies had all three of these professionals and nine studies had at least one.

2.4.4.1 Dietician or nutritionist

The role of dieticians during the critical illness and hospitalisation is well established, particularly in the UK[256]. There have been correlations between more dietician involvement in intensive care and improvement in outcomes[256,257]. However, these are only associations, and it is conceivable that dietician input is simply a marker of a higher resource setting. Regardless of the precise rationale for dietician input, the Guidelines for the Provision of Intensive Care Services (GPICS) UK standards propose that a suitably trained and experienced dietician should be involved in critical care[10,258].

When it comes to the outpatient setting and follow-up after hospital discharge the precise role of the dietician is less clear. There was only one RCT in this review that involved nutritional support and that was the study from Jones et al which combined physical therapy and nutritional supplementation[230]. This demonstrated important statistically significant mean differences in 6MWT distances and anxiety levels. The concept of combining nutritional support with physiotherapy (for all, including control groups) using this methodology is novel yet rational. The significant catabolic insult of critical illness frequently results in weakness, an inability to meet basic nutritional intake requirements, and a subsequent negative impact on QoL. However, the results have not been integrated into routine clinical practice. The reasons for this are manifold but certainly the small numbers may have contributed to this limited translation into clinical practice. The crossover design resulted in fewer than 20 participants completing the three-month follow-up in each group. Regardless of exact reason, this intervention would benefit from a further, larger trial, before widescale adoption of this intervention.

The largest study to describe nutritional support as part of a multicomponent intervention and include a comparison group (usual care) was from Weidman and colleagues, assessing a COVID-19 specific cohort[193]. This report does not describe the exact approach from the nutritionist but does state that they did participate. There were no significant signals of efficacy, and this highlights how little is known about the dietician (or nutritionist) involvement in follow-up aside from the inherent logic in this type of support.

2.4.4.2 Speech and language therapy

Speech and Language Therapy (SALT) were involved in only two studies in this review. Ward et al mention this input but did not describe this further as their main focus is the pharmacist input as part of a wider outpatient MDT[208]. Similarly, the very large observational study from Duarte et al failed to describe the specific role for SALT in the clinic or how often their input was required[226]. The incidence of post extubating dysphonia may be as high as 63% and it seems logical that SALT could contribute to the treatment of these patients after hospital discharge, however, the effectiveness of this intervention remains unknown[259]. A significant study from Brodsky and colleagues demonstrated that dysphonia persists in 23% of patients at six months but is fully resolved by five years[260]. A key metric for SALT may therefore be the rate of improvement but at the time of writing this is only hypothesis generating.

2.4.4.3 Occupational therapy

The final professional that is frequently involved in both inpatient and outpatient care in most acute hospitals and included in this review was the occupational therapist. Despite having the potential to bridge the gap between inpatient and outpatient care, this group was only mentioned in three studies. This could be explained by the fact that the exact involvement of the occupational therapist in the ICU itself is poorly studied or understood[261]. However, it may be at the transitions of care and downstream care where this input is of greatest importance[261]. The largest study that involved occupational therapy was a case series of 101 participants by Crocker et al and published in 2003[243]. They offer a robust and well thought through argument for occupational therapy input to start before ICU discharge and continue through hospital discharge with follow-up as an outpatient. They cite important roles for the therapist to review activities of daily living after a period at home. It is also highlighted that although walking on the flat surfaces of a hospital may be manageable, once home the uneven surfaces encountered in everyday life may present difficulties that the patient was not able to face beforehand.

Given this early and clear description of the role of the occupational therapist in ICU follow-up, there has been little research since 2003. Bates and colleagues

assessed a technological approach to recovery and involved occupational therapists[192]. Unfortunately, the exact role of the therapist was not clear, and the study was primarily focused on feasibility. There may have been some signal of improvement in the intervention arm, but this result was not robust and more work is needed. Similarly, a small study by Parker and colleagues failed to demonstrate benefits for the intervention group and although an occupational therapist was involved in the follow-up, their precise role and involvement was unclear[209].

It is evident that patients after critical illness consistently fail to return to the function and roles that they had previously, with a clear marker of this being the low return to work rates (54%)[37]. It is surprising, therefore, to see such scant evidence of involvement of occupational therapy in the formal literature of ICU follow-up services. It could be that these services are designed around the inpatient ICU model and therefore miss certain aspects of recovery that may be expected in other more outpatient focused disciplines.

2.4.5 Beyond the healthcare MDT: integrating social care

The two key professionals discussed in the literature beyond the traditional hospital-based MDT are social care specialists and case managers. There is likely to be significant overlap in the roles of both of these specialists and it is worth considering these factors together.

There were 15 studies that had either a social care specialist or case manager present. Of these, eight involved social care with 1,376 (22.3%) participants and eight had involvement of a case manager with a total of 969 (15.7%) participants. Clearly one study had both social care specialists and case managers and this was from Wang and colleagues[212]. This study describes the first critical care recovery centre in the USA and importantly for this section, the case manager could be a social worker or a nurse with experience in case management. The crossover between social care and case management appears to be significant and possibly highlights the artificial separation of both in this review. However, there are important differences, and both roles can contribute to care after critical illness regardless of who delivers the service.

2.4.5.1 Social care specialist

A social care specialist is a poorly defined term but is used to encompass all professionals who are involved in this aspect of care. Clearly, and especially in the UK, the most common professional to focus on social care is a social worker[262]. However, this belies the breadth of disciplines that encompass social care. Not only do many professional groups fit into this role, but social care is delivered from incredibly diverse organisations and funding models[263]. This could involve aspects of healthcare, publicly funded care or support, privately funded care, and the third or voluntary sector.

Given the significant social problems that have been identified after critical illness it is reassuring that there has been some focus on social reintegration after critical illness. However, there is no definitive approach yet identified to address these problems. Duarte et al was the largest study to involve a social worker. This observational study from Brazil, without a control group, describes the social problems after ICU and describes that a social worker was involved in follow-up. The key role of the social worker was to administer questionnaires about income, living arrangements, and whether there was any governmental funding or benefits being received. This identified that there were significant financial issues after intensive care but did not specifically describe how these were addressed. It is perhaps assumed that when the social worker discovered a problem then they could address that issue, but how this was addressed was not specifically described. Similarly, none of the studies identified in this review described the interventions delivered by a social worker, instead focusing on the review process. This included studies from Weidman et al (cohort study n=280), Wang et al (QI project, n=120), and Boehm et al (QI project, n=106)[193,212,213]. The rationale for this could be due to the medical model of follow-up and perhaps there should be a new approach with a greater focus on social care in the future. More work is required to better understand the role of the social care specialist after ICU.

2.4.5.2 Case manager

The case manager role is even more poorly defined. This is true of case management generally (i.e. outwith the ICU population). Even for the general population a case manager could be a nurse, a social worker, or anyone with

relevant experience[264]. What constitutes a good outcome for case management is also difficult to define and where measurement has been attempted the most robust outcome appears to be the assessment of self-efficacy[264]. In these situations, a good outcome is when the patient or caregiver are supported to navigate a system and then become more independent when dealing with future problems. This aspect of case management may be a realistic and achievable aspect to incorporate into the biological model of ICU follow-up. The ICU physician and nurse are both comfortable with the concept of the MDT and multisystem problems. Having an additional person overseeing and organising care is likely to work well alongside this traditional healthcare MDT. Case management may also be a way to bolt on some of the social aspects as part of holistic care. Certainly, the approach of combined health and social care is evolving for the general healthcare literature and this approach for ICU patients may be a crucial part to improve long-term outcomes after critical illness[265].

There have been two randomised controlled trials assessing the role of case management specifically[182,183]. The first was from Douglas and colleagues and reported in 2007[183]. This study involved an advanced practice nurse engaging with a patient before hospital discharge and then contacting the patient eight times over eight weeks. The primary goals for the intervention group were to establish case management and improving interdisciplinary communication. The study demonstrated important predictors of death but did not show any benefits for the intervention in the utilisation of services or QoL. There was some suggestion that there was a shorter duration of readmission but this was not a robust result given the other non-significant outcomes[183].

Similarly, Schmidt et al report the outcomes from an RCT that compared a group of patients receiving follow-up from a specially trained ICU nurse compared to usual care[182]. The ICU nurses received eight hours of training to become outpatient case managers. The study involved nine centres in Germany and the nurses worked with the patients' primary care physicians to improve the medical care after discharge. After an initial one hour face-to-face meeting the nurses contacted the patients monthly for the first six months and then every three months until one year after hospital discharge. The primary outcome was the mental health component (MCS) of the SF-36 and there was no difference between groups.

Case management has also been studied as part of multicomponent studies with the most significant contribution from Bloom and colleagues[216]. In this study, 232 participants were randomised either to a follow-up service (which was delivered in the first 30 days after hospital discharge) or usual care. Case management was delivered by a "registered nurse case manager". The key roles in this study were a review of the living situation, healthcare needs, a financial review, and onward referral if any needs were identified. This intervention appears to be more holistic than the previous two, and certainly involved more staff. Effectively the patient review was assessing the key intersections between health and social care, and this is probably what most would think of as case management. This was a pilot study that confirmed more interventions were delivered to the treatment arm and this was likely due in part to the case management approach. However, as previously discussed there were statistically significant differences (time to readmission) but few clinically significant differences (readmission rate). This study, however, is a valuable resource in how services can be integrated. The written article is also of a high standard and demonstrates how a complex intervention can be reported and easily understood as the description of case management is exceptionally succinct. The authors appear to report all elements of the CReDECI 2 (Criteria for Reporting the Development and Evaluation of Complex Interventions in Healthcare: Revised Guideline) although there is no reference to this in the publication[216,266]. This approach to writing is of value to all staff groups but particularly those engaging in case management as the exact role is not as well defined as some other professionals.

The remaining five studies involving case managers were small and failed to demonstrate significant or meaningful outcomes[184,189,212,214,222]. There are many unanswered questions regarding case management after ICU. Specifically, who should deliver this care, when should it start, and how can this be integrated with other aspects of care?

2.4.5.3 Summary: what is missing in social care?

It is evident that there is growing interest in the roles of both the social care specialist and case manager. These roles can be fulfilled by multiple professionals, although social care mostly involves a social worker; case management can be delivered by anyone involved in health and social care. Regardless of who delivers

the services, the post critical care states of PICS and PICS-F offer clear targets for integrated health and social care. Patients and their families are likely to need help to navigate the increasingly complex health and social care landscape after critical illness. Evidently, this type of support is likely to be location specific. A very tangible example would be the significant differences between insurance-based health and social care systems compared with those that are primarily publicly funded. Fundamentally, the profound financial and social strain experienced by the entire family unit will have very different solutions depending on the local cultural, financial, and social environments[164,267]. Furthermore, the low rates of returning to work may be a crucial piece of the puzzle to help with this, although approaches will certainly need to be locally developed[37]. Despite these challenges, there is inherent logic that the complex syndromes of PICS and PICS-F are likely to require complex solutions. These solutions should equally involve social support alongside healthcare support. It remains unclear who should deliver this support. This could involve community groups, social care specialists, or healthcare specialists with additional training. Nevertheless, this inherent logic is currently hypothesis generating and remains largely untested. To test these hypotheses, services will need to be designed that have the competing demands of being adaptable to local needs while having enough reproducibility to allow testing of effectiveness. If successful, however, this could be the missing element for the success of post hospital discharge ICU recovery services.

2.4.6 Caregiver involvement

This review has shown that there were 22 studies that included caregivers. These involved a total of 2,211 (35.9%) participants between them. The median number of participants per study involving caregivers was higher than the overall median size and this could point towards larger trials involving caregivers. When considering the overlapping areas (Figure 2-6) it is evident that the largest area of study involving caregivers is when this was combined with nurse only follow-up. The largest study that involved caregivers was from Glimelius-Petersson et al[204]. This study was a registry study and was therefore retrospective. It described the outcomes of 372 participants and involved an ICU nurse delivered (single operator) follow-up clinic. During the follow-up at two and six months post discharge, the next-of-kin was encouraged to also attend. This study was not specifically targeted at family; however, their participation was strongly encouraged. The

majority (70%) of patients were accompanied by their family members or close friends with 90% of the family choosing to revisit the ICU. This suggests that there is a relatively high engagement from family when their involvement in rehabilitation and follow-up is encouraged. The authors also comment that there was an important therapeutic role of having both patients and family present at the same clinic. They observed that there was linking between the patient and family member's narratives relating to the critical illness. This area certainly warrants further exploration and the effect on caregiver outcomes or strain from their involvement appears relatively unknown.

The largest RCT to involve caregivers was from Douglas and colleagues. This particular study failed to demonstrate any meaningful outcomes for patients in their primary description of a case management programme after critical illness[183]. This study also had a separate report specifically describing the caregiver outcomes that was not included in the analysis of this scoping review[268]. The report describes 290 caregivers and their mental health outcomes at two months post-acute hospital discharge, although in most instances (for the caregiver report) this was to an intermediate care facility or similar. The authors describe significant utility for a case management approach, effectively a professional patient and caregiver advocate during key decision-making junctures around discharge planning. Unfortunately, there was no signal of improvement for mental health outcomes with the programme. This also highlights the complexity of family studies. This study aimed to catch all caregivers, whether the patient survived or not, which was the justification for the exclusion of the specific caregiver report in this scoping review. There clearly may be differential outcomes for families (or caregivers) of those who survive and those who do not. This thesis is focused on the survivors but more work in the future should consider whether common approaches to both family of survivors and non-survivors are appropriate.

Of the studies with a specific focus on caregiver or family outcomes an early study from Jones and colleagues is one of the most significant[241]. This study describes a rehabilitation programme that started before hospital discharge but involved an ICU clinic visit at two and six months post discharge[241]. The focus of the study was the effectiveness of a six-week self-help manual on post-traumatic stress in

relatives of patients following critical illness. This RCT involved 90 relatives and described high rates of stress in both control and intervention arms, with 49% scoring >19 on the impact of events scale[241]. There was, however, no difference between groups and this intervention did not appear to attenuate the experience of PTSD six months after hospital discharge for relatives (family of caregivers). This study was effectively a comparison of additional information for relatives about ICU and the common problems afterwards. Given that PTSD is a complex condition frequently requiring psychotherapy, it was perhaps ambitious to expect a relatively simple intervention to meaningfully reduce the experience of PTSD[269]. This study clearly demonstrates that interventions will have to evolve beyond simple information strategies to improve mental health outcomes for family, relatives, or caregivers after critical illness.

Vranceanu and colleagues described the implementation and feasibility of an RCT for both patients and informal caregivers after neuro-ICU. This intervention involved technology to help patients and caregivers develop resiliency. The intervention involved a mobile phone and web-based application with a focus on mindfulness. There then was a follow-up component that was more patient and family (dyad) focused with specific targeted interventions delivered by a therapist, but through the video technology. This study demonstrated a statistically significant difference in the rates of improvement of important mental health outcomes (PTSD and depression), however, the baseline rates of mental health problems were higher in the treatment group. This study was only powered to be a pilot study and overinterpretation should be avoided. It does suggest promise that there could be value in treating both the patients and caregivers together and technology may have a role for future interventions.

Considering caregiver outcomes, there is not one clear strategy or way to involve families. On the whole, caregivers have been treated alongside the patients but specific treatment effects for caregivers are lacking. There is some evidence that treating both patients and family together is achievable and may be effective, but definitive treatment effects are lacking.

2.4.7 Other components

Table 2-2 outlines the other components that have been described in the literature. The largest was written information which was only studied as a standalone intervention by Jones et al as part of two studies but failed to demonstrate significant benefits for patients or caregivers[241,242]. These studies have been discussed previously throughout this review.

The inclusion of the other components was entirely exploratory and demonstrates a large variety of interventions that have been described. The literature lacks detail on effectiveness of these interventions and this lack of specificity makes recommendations for what components should be included in any future interventions difficult. However, many of the interventions focus on the delivery of information and improvement of understanding of what critical care involves and its effects. The main limitations for these studies are the heterogeneity which would make more focused work, such as systematic reviews or meta-analyses of these components difficult to perform.

It would appear understandable, from first principles, to target an improvement in survivors' and caregivers' understanding and knowledge of critical care, their illness, and the common problems after ICU to improve psychological outcomes. Certainly, improving knowledge of the traumatic event has been an approach that is described for trauma PTSD patients[270]. However, the effects of this approach within critical care recovery remain poorly studied and understood. Within the ICU literature this type of intervention, with the goal of increasing the survivors' knowledge of their own critical illness narrative, has focused on ICU diaries. These studies were not included in this review as much of the intervention occurs in hospital. However, there are some signals of benefits, particularly for rates of depression, although existing systematic reviews highlight the uncertainty of their effect and that more work is required to better understand the ICU diary intervention[271,272].

2.4.7.1 Peer support

There were six studies that included peer support, all of which were small studies with the range of participants from 23 to 106 (median=33; IQR: 29 to

38)[175,189,192,199,207,213]. The only study to specifically focus on peer support was the largest (n=106) from Boehm and colleagues based in the USA[213]. This was also the single study that included clergy (a chaplain). It also involved input from ICU nurses, social workers, volunteers (previous patients), and included caregivers / family. The study was designed as a QI study where the key focus was on service implementation rather than the effectiveness of the intervention. The report included results from surveys of those attending and the feedback was overwhelmingly positive, with 85% stating that they would recommend friends in a similar situation to attend. The authors also describe in a qualitative way how the peer support group improved care in the ICU and generally improved the empathy and understanding staff had towards their patients and caregivers.

There were no interventions that directly compared peer support to no peer support. Where there was a control or usual care group the peer support element was part of a package for a more complex intervention as described by McPeake et al and Ahlberg et al[175,207]. Conversely, peer support formed part of usual care for a feasibility RCT conducted by Bates at al, where peer support was part of their usual practice and the team compared this to an eye movement desensitisation and reprocessing protocol[255]. These studies demonstrate that peer support can be integrated into other forms of support but do not help us to understand the effectiveness of standalone peer support.

It is evident that this review was not designed to specifically address peer support as a standalone intervention, and this explains why the peer support has largely been an integrated approach with other interventions. This has been the subject of systematic review by Haines and colleagues who identified eight studies describing peer support but none of these studies were suitable to be included as part of a meta-analysis[245]. They concluded that peer support had some effects on psychological and social outcomes but the results were not robust and that more studies are required. The failure to be able to collate data as a meta-analysis, as was planned, also points to the heterogeneity in these studies.

The lack of literature relating to peer support may be because this type of intervention, by its very nature, is often patient and caregiver designed and delivered. Patients and families are less likely to be familiar with research methodology and are more likely to be driven by informal qualitative feedback.

In order to capture some of the real world practices of peer support Groves and colleagues sent questionnaires to 163 ICUs and received responses from 56% of those surveyed[273]. Of those responding 48% (46 ICUs) had access to a support group and 25 (27%) had access to both a support group and ICU follow-up. These results should be interpreted with caution as under half of those surveyed responded, but it can be concluded that peer support appeared to have a growing popularity in the UK. This report also described the survey responses from 30 participants who attended peer support with positive feedback overall. This is not empirical evidence of benefit but does demonstrate that there is perceived value in peer support in the UK.

Fundamentally, and this is a recurring theme from this review, peer support does not appear to have a strong evidence base. There have been signals of growing popularity of peer support. Finally, there is the need for more studies into peer support, both as a standalone intervention and as part of more complex follow-up processes.

2.4.8 Complex interventions

The final aspects that this review attempted to understand were the overlapping components and the complexity of interventions that have been assessed. Table 2-3 describes the complexity / component count for the six most common professionals or components. These were nurse (ICU or other), ICU doctor, physiotherapist, psychologist (or therapist), pharmacist, and caregiver (or family) involvement. This descriptor was led by the data and designed for this review to help classify study complexity focusing on the most commonly appearing elements. This highlighted that very few studies (n=3) had five or six of these elements and the participant count was very low, with only 134 (2.2%) participants[175,208,222].

None of these studies were randomised trials and only one had a comparison group (McPeake et al, historical control)[175]. Sevin et al described an observational cohort involving the completed follow-up of 62 participants[222]. The clinic did not involve a physiotherapist but involved the other five components and a case manager. The authors described a median of four interventions per participant, which appeared high alongside very low rates of returning to work (15%). Perhaps the most

noteworthy aspect of this study, however, was the very low uptake rates as only 62 patients were seen from 218 who were discharged alive from ICU. There is likely therefore to be a significant selection bias in this study and this may explain the high intervention count and low rates of returning to employment. Similarly, Ward et al described a multicomponent intervention but did not describe caregiver involvement[208]. The main focus of this COVID-19 study was the pharmacy interventions, but a reasonable description of the other components was included. Once again, no comparator group was described.

The only intervention that included all six components was from McPeake et al and, as stated previously, this was the inspiration for this thesis and demonstrated how unique this approach was[175]. This multicomponent intervention, delivered over five consecutive weeks, involved the main healthcare professionals alongside caregivers, and other third sector organisations. This complex intervention aimed to also include peer support with deliberate 'downtime' to allow patients and caregivers time to share experiences. The study involved an historical control group and demonstrated important differences in the control group and intervention group for HRQoL and self-efficacy. It is recognised that the methodology had significant limitations, specifically the small size (n=40) and the use of an historical control[175]. This study could be considered effectively a pilot study and demonstrated promise that the rehabilitation programme could be delivered and that a larger study should be feasible.

The only RCT with more than three components was from Bloom et al who described ICU nurse, ICU doctor, pharmacist, psychologist, and a case manager[216]. As previously discussed, this study failed to demonstrate practice changing outcomes with readmission rates similar between groups but time to readmission longer in the intervention arm. The only other study with four or more components and a comparison or control group was from Snell et al[214]. This study was small (n=48) but described a novel approach in attempting to assign efficacy to interventions after critical illness. The control group of this QI project was a population-based dataset. The intervention involved ICU doctor, a nurse case manager, psychologist, and caregivers. The nurse organised all of the interventions. Outcomes for those attending were compared to those who declined to attend. The remarkable outcome was that the mortality rate for those

attending was statistically significantly lower than for those who did not. The way the cohorts were divided is a clear limitation of this study. This result could simply represent that those who attended may have been more engaged with their health and this may explain the mortality outcome. Furthermore, readmission rates were not different between the groups, suggesting that patients died at home, or at least not in hospital. This approach warrants more work but this evidence is not strong enough to recommend widescale implementation based on this study alone. It does, however, add some evidence to the feasibility and possible utility of interventions involving four or more components.

The component counter described also has its limitations. It has the potential to overly simplify clinics or services that have other components beyond the six main areas included in this counter. The standout example is the study from Duarte and colleagues[226]. This very large (n=688) retrospective observational study counted as including four components although others were included. The authors describe a single visit clinic where patients were seen by an ICU nurse, ICU doctor, physiotherapist, psychologist, social worker, nutritionist, and SALT. The total components were therefore seven, but the clinic did not include pharmacists or caregivers. It is difficult to assign effectiveness from the retrospective observational nature of this intervention, but the authors described a well-established and consistently delivered clinic from a large single centre. The patients and staff clearly valued the service, and the structure allowed for recording of problems and patient important outcomes. This study highlighted that there are many other professionals who can be utilised for follow-up and can be integrated alongside some of the more common interventions.

2.4.9 A note on effectiveness

The primary purpose of this review was to understand the landscape of who and what is involved in ICU follow-up as described in the formal literature. Effectiveness was a secondary consideration, but the breadth and depth of studies included in this review has been useful in attempting to find interventions that demonstrate measurable benefits for ICU survivors and their families. This has also allowed a consideration of the different methodologies employed in the formal literature to study the effects of outpatient interventions after critical illness. The overwhelming conclusion from both considerations is that a single clear

approach cannot be recommended based on this review. None of the nine RCTs that had over 100 participants demonstrated any statistically significant or meaningful benefits for survivors or their families[182,183,216,219,221,228,237,239,242]. These studies have been described under the relevant sections throughout this review.

Two physiotherapy interventions by Jones et al and McWilliams et al have demonstrated some benefits although both were small RCTs and their results are overshadowed by the larger trials[227,230]. It is difficult to form practice recommendations based on these studies alone.

The pharmacy interventions described by Stollings et al were some of the most impressive and clearly demonstrated the function of a pharmacist at ICU recovery clinics[190]. Although this study could be used as a blueprint for other international collaborations of other clinic components, the study did not have a control or usual care group and causation cannot be assigned to these interventions. It is unknown whether the pharmacy interventions would have been delivered by other means if the participants were not reviewed by an ICU pharmacist (e.g. by community pharmacists).

The effectiveness of interventions would best be addressed through systematic review. However, the current state of the literature identified by this scoping exercise would suggest that this type of review would be highly unlikely to identify a single intervention to ameliorate the effects of PICS or PICS-F. The heterogeneity between studies was very high. The studies were also small overall, and the outcomes were not consistently reported. It would be difficult to design a systematic review to reliably account for all of these factors. This was also the conclusion from a 2018 Cochrane review[274]. Based on the evidence in this thesis, it would appear unlikely that this Cochrane review would find a different result if this were to be repeated today[274].

A review of non-pharmacological interventions both in ICU and after hospital discharge was conducted by Geense and colleagues in 2019[246]. This review included 36 studies and concluded that the evidence base was thin at best. There was some evidence for exercise programmes (including inpatient interventions) but little evidence for other interventions, particularly those after hospital discharge. The authors recommended further studies. This adds weight to what

has been described in this review. There have been few interventions which have demonstrated benefit and the priority should be to conduct well-designed studies that aim to measure the treatment effects of outpatient interventions. The areas that have been least well studied are complex multicomponent interventions. Further review articles are unlikely to produce definitive results to help the clinician or researcher who is developing post hospital discharge interventions for PICS and PICS-F.

2.5 What is missing from this review?

2.5.1 Beyond ICU studies

There was a single study from Taylor et al that described a case management approach post sepsis. The specific focus was on care transitions during recovery and convalescence post sepsis[275]. This study was excluded from the review as most of the participants were not treated in ICU, with only 41.8% being ICU patients. This large RCT, however, demonstrated benefits for the case management approach with a specific focus on transitions between phases of care. The case management approach demonstrated improved outcomes for a composite endpoint of death or hospital readmission in the first 30 days after hospital discharge. This large trial (n=691) offers some insight that this type of intervention can be successfully completed and that positive outcomes may be achievable. However, the composite outcome, at a relatively short follow-up period (30 days) does not offer the most compelling benefits to encourage a clinician to embark on this approach. Similarly, the patient characteristics demonstrated a very comorbid group with high Charlson Comorbidity Indices (CCI) and multiple complex comorbidities. The rate of participants with coexistent malignancies was particularly high at 19.5%. Although not directly applicable to the general ICU population, this study may suggest that the case management approach could be of value for the patient with a greater burden of comorbidity although future studies would be best to include a longer follow-up period and address broader HRQoL outcomes.

2.5.2 Does the literature reflect contemporaneous practice?

This review has been entirely focused on the formal literature of studies describing an intervention after critical illness. A key drawback from this methodology is that contemporaneous practice may evolve with alternative local evidence. This could include patient and caregiver feedback, local evaluation of needs, and other service based qualitative outcomes. This review, and indeed most of the formal literature, will fail to capture this.

Within the UK, NICE recommends that patients should receive follow-up after critical illness[276,277]. This guideline specifies that patients should be reviewed after two to three months post hospital discharge with a focus on physical and functional assessment. Follow-up is also recommended by the Faculty of Intensive Care Medicine (FICM) in their GPICS guidelines[10]. The GPICS guidance recommends follow-up at two to three months also, but emphasises that patients should have access to a post-ICU recovery service involving intensive care consultant, intensive care nurse, clinical psychologist, physiotherapist, dietitian, and occupational therapist. This advice is therefore similar but more specific and overall stronger. However, both recommendations are broad, lack specificity, and state that follow-up should be patient targeted, depending on needs. This is likely to be a reflection of the limited evidence base on the precise interventions that should be delivered after critical illness.

To better understand the current delivery of follow-up services in the UK, Connolly and colleagues undertook a national survey of current practice[278]. The survey was conducted between June and August 2020. Each ICU in the UK was requested to describe the follow-up services that were in place before the COVID-19 pandemic, which corresponded to the services available before January 2020.

Return rates were reasonable involving 72.7% of all ICUs in the UK (England, Scotland, Wales, and Northern Ireland). Of those responding, 130/176 (73.9%) ICUs stated that their patients had access to an outpatient ICU follow-up service. The ICU nurse was involved in 93.1% of outpatient clinics, the ICU doctor was involved in 76.9% of clinics and a physiotherapist was involved in 50.0% of clinics. These figures are similar to what has been described in the formal literature in this review. Conversely psychologist involvement was low at 27.7% and pharmacist

involvement was rarely described and only formed part of 10 clinics (7.7%). This is a significant departure from the literature included in this review.

The most common combination described by this survey involved an ICU nurse and ICU doctor (22.3%) followed by three professionals (ICU nurse, ICU doctor, and physiotherapist) included in 14.6% of clinics. This is similar to the component count described earlier and it may be that the literature largely reflects real world experience or vice vera. Peer support was available at approximately half the ICUs surveyed. There was a mention in the survey that the peer support involved (or could involve) caregivers or relatives but this was not described in any granular detail. Furthermore, there was no description of caregivers of family members being involved in the formal clinic or professional parts of follow-up which is a significant limitation of this survey. With the significant burdens on caregivers, alongside their importance in the recovery trajectories of patients, it would be of value if future surveys included this in more detail.

Contemporaneous practice in the UK would generally appear to mirror the literature, with the exception of pharmacist, and to a lesser extent, psychologist involvement. This survey also shows a substantial increase in the availability of outpatient follow-up over the last ten years. A similar study completed a decade previously demonstrated that only a quarter (27.3%) of ICUs had access to ICU specific follow-up[279]. This could be considered progress for ICU recovery services. However, there remains a significant knowledge gap in the understanding of the effectiveness of these interventions despite the substantial increases in service delivery over the past 10 years[279].

While the formal literature lacks definitive solutions or approaches for outpatient services, much of the current practice may be based on local feedback or service evaluations (grey literature). However, without robust empirical evidence the heterogeneity seen in the formal literature is equally reflected in the contemporaneous practice. Finding robust and reproducible interventions would help reduce variation in practice across trusts and health boards and would give more consistency for patients and caregivers regardless of their geographical location.

Further mirroring the lack of clear treatment strategies, other international surveys demonstrate variable use and delivery of ICU follow-up programmes or outpatient services. Denmark appears to have one of the highest rates of outpatient ICU follow-up services as demonstrated by a survey from 2017[280]. This survey reported that 84% of ICUs were delivering some form of outpatient follow-up service[280]. Conversely, a survey from Australia as recently as 2020 only identified two ICU follow-up clinics and only one of these clinics had formal funding[281]. Finally, a survey from the Netherlands in 2019 reported that 52% of ICUs had an outpatient follow-up service[282]. Given the state of the current evidence base for outpatient services after critical illness this variation is not surprising. The international community should focus on establishing standardised evidence, pathways, and guidelines on the best approach to delivering outpatient follow-up services for survivors of critical illness and their families.

2.5.3 Contemporaneous practice vs usual care

From the survey evidence, contemporaneous practice in the UK could be considered as including ICU outpatient follow-up for most patients. However, most of these services do not have specific funding and it has been demonstrated that 71% of these clinics are "funded at risk"[283]. Thus, overall, this funding is from general ICU budgets and there is no specific guarantee that funding will be recurring. As such, despite the survey evidence and the work of NICE to recommend ICU follow-up, the definition of usual care at the time of writing this thesis cannot be considered to include specific outpatient ICU follow-up.

Instead, usual care in the UK, should be considered as no formal outpatient critical care follow-up or review. This means that usual care will mostly be the responsibility of the General Practitioner (GP) or the specialist (medical or surgical) outpatient department if this is part of the disease specific follow-up. As such, for the remainder of this thesis, usual care will be defined as no specific post critical care follow-up and is considered to be primarily delivered by GP services.

2.6 Strengths and limitations

A key strength of this scoping review (with narrative discussion) is that this has offered a comprehensive summary of the formal literature describing outpatient services after critical illness. The search strategy was comprehensive and was reviewed by professional library services at the University of Glasgow (Dr Paul Cannon). The electronic search was repeatedly updated throughout the period of research and therefore remained current at the time of writing this thesis. This review has, therefore, offered insights into the most up-to-date evidence of follow-up services after critical illness. Further strengths included the comprehensive summaries offered for the professionals, staff, and components described in the literature. These summaries were novel and made greatest use of the scoping review methodology. This methodology was also appropriate to the literature that was included. The heterogeneity in study designs would have made any attempt to formally aggregate treatment effects inappropriate. As such, this review has offered a more comprehensive overview of the literature than would have been offered by a narrower technique such as a systematic review. By including a broader range of studies, including those without a control group, this review has offered a more complete summary of the contemporaneous literature.

The scoping review also offers a structure to discuss the impacts and effects of different components, including review of seminal and important studies in this field at an individual study level. By comparing this to existing systematic reviews this scoping has been able to benchmark the narrative discussion with the previously reported systematic reviews.

There are key limitations for this review. Firstly, this was conducted as a single operator scoping review. Although some reviews take this approach, it is generally best to have two independent reviewers to help minimise any bias. This was a pragmatic decision for this thesis and the scoping review approach will be less susceptible to bias than a systematic review or meta-analysis. Similarly, if there were small errors in the data extraction processes, these are unlikely to significantly change the meaning of the numerical summaries. The narrative review further limits any errors as the data were cross referenced when studies were being reviewed as part of the discussion. Finally, the key decisions relating to what studies were included and why, are described throughout the review to

make these processes as transparent as possible within the methodological limitations. An advantage of the single operator review is that this could be repeatedly updated during the life of this thesis as previously discussed. This review therefore shares some aspects of a rapid review and has been a living document over the last four years[284].

Other limitations relate to the search strategy. There were two case management studies that were included from other sources[182,183]. This may suggest that the search strategy was not optimised for these types of studies. However, the electronic search identified another six studies that included case management and therefore the search strategy was able to find at least some of this type of intervention. Furthermore, it has been demonstrated that hybrid search techniques, which include manual searches alongside snowballing references, may be superior to the over reliance on just the electronic database searches[285].

This review has deliberately excluded diary interventions. These have been studied extensively elsewhere and their effects are better understood compared to outpatient interventions[271]. Furthermore, these interventions are also not exclusively delivered after hospital discharge and as such they did not meet the inclusion criteria for this review; diaries were not considered as specific outpatient interventions on their own. To make sure appropriate interventions were included, the presence of a diary in a study report did not automatically exclude the study. Instead, if there was a description of at least some outpatient intervention, then the study was included in the review.

Finally, this review of the formal literature has not necessarily captured contemporaneous clinical practice. To help compare the literature to contemporary clinical practice a discussion of key international surveys was offered to attempt to bridge this gap.

2.7 Conclusion

This scoping review with narrative discussion has demonstrated that, on the whole, studies of outpatient interventions after critical illness are small. There has been a tendency towards simpler interventions. This review has also highlighted significant gaps in the knowledge base relating to the efficacy of interventions for PICS and PICS-F after hospital discharge. There is a need for more well conducted RCTs and cohort studies (with a control group) involving multiple follow-up components. It is unlikely that further systematic review or meta-analysis will bridge this knowledge gap. Researchers should focus on undertaking high quality studies to better understand the effectiveness of outpatient interventions after critical illness. Fundamentally, this review supports the goals of this thesis to better understand how a multicomponent complex intervention can help patients and their families after critical illness.

Chapter 3 Methods: one-year multicentre outcomes studies

3.1 Overview

This chapter describes the background and methods for the Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE) studies presented in Chapter 4 and Chapter 5. The two key outcomes of interest are the measurable effects of the InS:PIRE intervention on one-year patient outcomes (Chapter 4) and one-year caregiver outcomes (Chapter 5). Given that the InS:PIRE intervention was designed to benefit both patients and caregivers and the significant overlap in design of the patient and caregiver outcomes studies, the methods for both chapters are presented together.

3.1.1 Objectives: patient outcomes

The primary outcome for the patient one-year study was to understand the impact of the InS:PIRE intervention on Quality of Life (QoL). The time point was defined as one year after discharge from hospital, following hospitalisation that involved treatment in an ICU or High Dependency Unit (HDU). Precise timings will be described in the relevant results section (Chapter 4).

Specifically, the areas assessed were:

1. Objective measurement of QoL
2. Subjective measurement of QoL
3. Experience of mental health
4. Confidence in problems solving and self-determination; self-efficacy
5. Experience and severity of pain

3.1.2 Objectives: caregiver outcomes

The primary outcomes for the caregiver one-year study were to understand the impact of the InS:PIRE intervention on the mental health and strain placed on the family of survivors of critical illness. The time point was once more defined as one year after the patient was discharged from hospital, following an illness that involved treatment in an ICU or HDU. Precise timings are once more offered in the relevant results section (Chapter 5).

The specific areas assessed were:

1. The experience of mental health problems (anxiety and depression)

2. The strain (or burden) placed on the family member related to the caring role

3. The extent of sleep problems and insomnia

3.1.3 Ethical approval

Ethical approval was granted by the Northwest (Liverpool Central) Research Ethics Committee (reference number: 17/NM/0119). A substantial amendment was completed to increase the recruitment, particularly for those not attending the InS:PIRE intervention and allowed for reminders to be sent to participants. This was critical for the development of this thesis and approval was granted on 10th June 2019 (Appendix 3). Every participant provided written informed consent (Appendix 4). Patients (ICU survivors) and caregivers each consented separately. Appendix 5 includes the letter of invitation and the participant information sheets outlining the details given to patients and family members regarding the study conduct.

3.1.4 Summary of study design

Both studies were multicentre prospective cohort studies comparing participants attending the InS:PIRE intervention with those who did not, one year after hospital discharge. Multivariable regression was used to correct for covariate differences in the cohorts.

3.2 Study setting

3.2.1 Background and design of the InS:PIRE intervention

The InS:PIRE intervention started as a QI project, funded by a small grant from the Health Foundation (Shine 2014)[286]. Recognising the burden of survivorship after critical illness for both patients and their caregivers, a team based at Glasgow Royal Infirmary (GRI) co-designed a programme with patients and caregivers / relatives / friends. The target treatment group were those perceived to be at highest risk of PICS and PICS-F. The involvement of these ICU survivors and families in the programme design was facilitated through focus groups. Those attending the focus groups were also involved in the choice of outcome measures.

This phase of the project was delivered as a QI project at a single site (GRI) between 2014 and 2016. The programme evolved over this period with continual review, it was delivered in five-week cohorts of patients and family (or caregivers), with the inclusion of week-six 'learning sessions' after each cohort. The results of this phase have been reported extensively[175,287].

Importantly, there was a signal of benefit in HRQoL for ICU survivors from the intervention, although the results were limited by small numbers and the use of an historical usual care cohort[175]. This formed the basis for the expansion of the programme and this work was complete before conceptualisation of this thesis.

3.2.2 Scaling up

The scaling up phase was delivered between 2016 and 2019 and involved the expansion of the intervention to a further four health boards. Funding was delivered again through the Health Foundation by their "Scaling Up Improvement programme"[288,289]. Of note, during this phase of the programme the decision was made to expand the programme to all patients rather than just focus on those who were of working age before their critical illness.

The primary purpose of this part of the project was to assess the feasibility of the intervention when delivered by multiple sites. Applications were taken from many ICUs and there was a selection process lead by the GRI team who sought diversity to understand spread and scale. Specifically, sites were chosen to represent the

variety of hospitals and areas across Scotland. Some of the goals in the selection process included: covering a wide geographical area; a mix of urban and rural populations; large and smaller hospitals; a variety of medical and surgical specialties within the hospitals; and consideration for specialist ICUs. As described, and due to the fact that this was a QI project to assess the feasibility of scaling up, there was no randomisation to this process. The sites chosen to run the intervention (including the original site at GRI) comprised six hospitals from five health boards. One of the health boards delivered a joint programme from two hospitals. The intervention was therefore delivered from the following sites:

1. Glasgow Royal Infirmary (GRI), NHS Greater Glasgow and Clyde: ongoing delivery of the existing intervention from this site.

2. University Hospital Crosshouse (UHC), NHS Ayrshire and Arran: new intervention set-up and delivery at this site.

3. Victoria Hospital (VH), NHS Fife: new intervention set-up and delivery at this site.

4. University Hospital Wishaw (UHW) and University Hospital Monklands (UHM), NHS Lanarkshire: combined clinic set-up and delivered between the two sites. Location of intervention delivery alternated between both sites, but patients treated by either ICU could also attend the intervention at the other site.

5. Golden Jubilee National Hospital (GJNH), NHS National Waiting Times Centre: set-up and delivery of the intervention at this site. This specialist NHS health board is unique in Scotland and the ICU primarily delivers critical care for specialist cardiology, cardiac surgery, and thoracic surgery. The hospital is a quaternary referral centre without an emergency department. The purpose of inclusion at this site was to assess the implementation of the intervention in this specialist population. As such, the experience, and outcomes from this part of the project are described in further detail as a standalone study and can be found in Chapter 6 of this thesis.

The focus of this methods chapter (Chapter 3) and the subsequent two results and discussion chapters (Chapter 4 and Chapter 5) will be on the InS:PIRE programmes that were delivered from the five general ICUs based at GRI, UHC, VH, UHW, and UHM.

The choice of sites, and the expansion of InS:PIRE to these sites commenced before the design of this thesis. This context, however, is important to understand the methodological design of the following studies, and the evolution of the project up to this point. The funding and design of the expansion phase was primarily as a feasibility project with a focus on qualitative interviews with learning days built into the programmes. The qualitative work fed into learning events where programme developments were discussed and disseminated between the InS:PIRE sites. However, on the whole this qualitative work was not published, and this work is not included in this thesis.

The intention and design of this thesis was to quantitively assess the effectiveness of the intervention on aspects of QoL for ICU survivors and their families. The goal was to compare the intervention to a usual care cohort, that is, participants recruited from hospitals / sites with no ICU follow-up service. The ICU survivors and caregivers who participated in the intervention and included in this thesis attended InS:PIRE during the scaling up phase between May 2016 and October 2018.

3.3 The InS:PIRE intervention

The following section describes what the InS:PIRE intervention is and how it was conducted during the period of study for the patient and caregiver outcomes (Chapter 4 & Chapter 5).

3.3.1 The programme setting

InS:PIRE is a complex multidisciplinary, multi-professional programme with involvement from patients and caregivers in the design and delivery of the service. The intervention is specifically designed to be flexible and allow adaptation to local services and needs. Each site conducted focus groups involving patients and

caregivers before setting up their programme. A conceptual overview of PICS, the InS:PIRE intervention components, and its aims is offered in Figure 3-1.

The core 'InS:PIRE team' at each site were all professionals from the local ICU, comprising: nurse; doctor; physiotherapist; and pharmacist. A consultant clinical psychologist provided input determined by local need at each site.

InS:PIRE was delivered in cohorts. Patients and caregivers were sent invitation letters by post, from the local ICU team, between 4 weeks and 12 weeks after hospital discharge. The letters were followed up with a phone call to confirm if the patient would be attending the intervention and whether they would have a caregiver attending with them.

On the whole, a group of patients and caregivers attended weekly for five weeks. Most sites conducted this as half day sessions (e.g. three to four hours). The same group attended for the 'five-week course'. It is notable that the five week programme was rather arbitrary, and since the end of the study period some sites have reduced this, usually to four sessions. The key intention was to have repeated visits by the same group to the same team over a short period of time rather than to dictate a programme length.

3.3.2 Core reviews

During the first three weeks of the intervention each patient and caregiver dyad received one-to-one reviews together (one per week) from the: 1) critical care nursing and medical team; 2) critical care pharmacist; and 3) critical care physiotherapist. The order was not set, but simply each dyad received one review per week and would complete all three by the end of the third week. Therefore, completion of all three reviews guaranteed attendance at three of the five planned InS:PIRE weeks. The patient / caregiver were then considered to have completed the programme for the purposes of the outcomes studies. The conduct of each of the three reviews is described below.

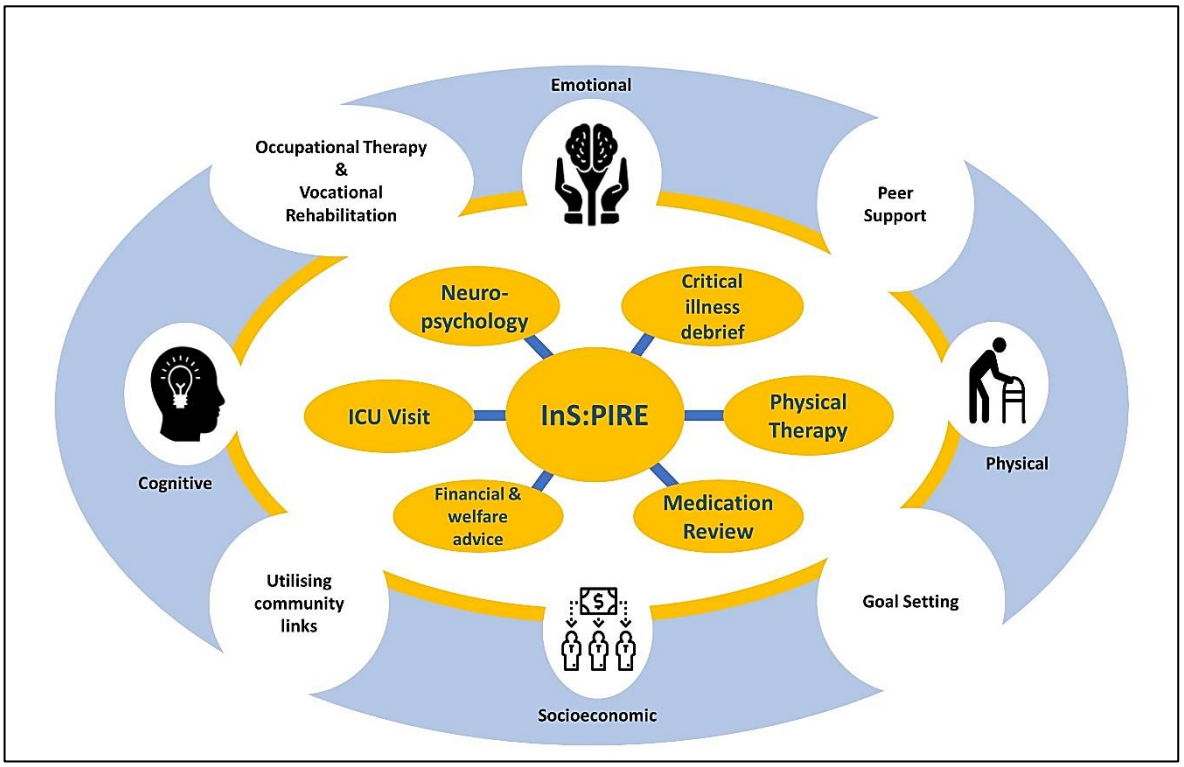


Figure 3-1: InS:PIRE conceptual diagram

Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE) conceptual diagram. Four domains of Post-Intensive Care Syndrome (PICS): Emotional, Physical, Cognitive, and Socioeconomic. InS:PIRE direct multidisciplinary input (yellow ellipses) alongside broader InS:PIRE community elements (white circles / ellipses) facilitating patient self-management and social reintegration following critical illness.

3.3.2.1 Critical care medical and nursing review

The patient and their caregiver (if attending the programme) met the critical care nurse and doctor together. A lay summary of the patient's critical care journey was given as a letter. A verbal summary or description was also offered and depending on patient / caregiver preference there was the opportunity to discuss the contents of this in detail. Questions and clarifications were encouraged to facilitate better understanding of the critical illness, associated treatments, and the recovery afterwards.

Alongside the review of the preceding events, a discussion about the patient's contemporaneous health and wellbeing was encouraged. This facilitated discussions about future ambitions and goal setting. Personal goals were then co-created and set between patient, caregiver, nurse, and doctor. These goals could relate to any element of health and wellbeing, as determined by patient

preference. They could also be immediate; short; or long-term goals. Some clinics separated the critical illness debrief and goal setting reviews, while others delivered these aspects simultaneously.

The medical and nursing team were also able to assess for ongoing unmet healthcare needs. The patients and caregivers could then either be signposted to the relevant area of healthcare. This may include the General Practitioner (GP) or referred directly to a relevant specialist service (e.g. addiction services), depending on the specific needs, expertise of the clinicians involved, and the local services available.

Finally, the patient and caregiver were offered a visit of the local ICU. Depending on team preferences, and local logistics, this could be offered on the day of this review, on another week, or a separate appointment outwith the InS:PIRE weeks.

3.3.2.2 Pharmacist review

Individual review by a critical care pharmacist was undertaken. A full medicines reconciliation was completed and documented. Drug review was completed and advice was offered on: restarting previous medications; the discontinuation of existing, no longer indicated medications; dose optimisation and titration; and ongoing medicines surveillance. The primary physician (GP) was informed about all recommended changes by letter and the patient and caregiver were involved in all medicine decisions.

3.3.2.3 Physiotherapist review

Of the three core reviews, the physiotherapy intervention was the most heterogeneous. However, every site delivered an individual, complete physical assessment and personalised exercise programme. This assessment also facilitated onward referral to community or specialist (e.g. cardiac rehabilitation) physiotherapy if required.

One site (the combined InS:PIRE clinic from two ICUs at UHW and UHM) chose to continue to deliver a group physiotherapy session, on top of the individual appointments. The remaining three sites (GRI, UHC, VH) decided that the group session did not provide any additional benefit after this was reviewed by their

focus groups. This group session was therefore, not considered a 'core intervention' but relevant to mention and should be included as a point of discussion in any other focus groups prior to new InS:PIRE sites being set up.

3.3.3 Further sessions

Alongside the core reviews, every InS:PIRE service integrated three key components to help address important aspects of PICS, PICS-F and recovery. These were: 1) psychology support; 2) social and financial advice; and 3) an education programme. These elements of InS:PIRE broadened the multi-professional approach. Moving beyond the confines of hospital medicine, these elements particularly helped to differentiate InS:PIRE from other critical care follow-up clinics.

3.3.3.1 Psychology

This session was delivered in a number of different ways. Usually facilitated by a clinical psychologist, the majority of sites had two separate sessions: one for patients; the other for caregivers. Some sites delivered a presentation on the common problems faced after critical illness, while at other sites the session was a facilitated discussion. Regardless of precise format, all sessions allowed a discussion of common problems and for participants to share their lived experience of intensive care and its recovery with professionals and peers. Goals of the sessions were understanding common reactions to critical illness, development of coping strategies and an appreciation of when more focused help was required.

The separation of patient and caregiver allowed a different focus for each group, and possibly facilitated more open discussion. The caregiver sessions, in particular, allowed the focus to move away from being entirely patient centric, which was the natural tendency whenever both groups were part of the same session. The time spent apart also promoted independence for both patients and caregivers, this was seen as a particular benefit for the caregiver group.

Individual psychology sessions were only available at some sites. However, all sites were able to screen for ongoing mental health problems throughout the programme, referring on for individual support if required.

3.3.3.2 Social, financial, and economic support

Towards the end of each five-week programme there was a focus on social, financial, and economic issues. Each site developed their own links with community organisations, but all offered financial advice. This was particularly important for those suffering cognitive and mental health issues after critical illness as these participants often found engagement with financial issues difficult.

Citizens Advice Scotland (https://www.citizensadvice.org.uk/scotland/) offered help at most sites[290]. Examples included, a drop in session for patients and caregivers to discuss ongoing financial issues, a presentation session describing the services on offer, or individual appointments on request by InS:PIRE participants.

Other social and financial care specialist groups were involved in the development of InS:PIRE at each site. These varied significantly between each site, were determined by local patient needs identified through the focus groups, and community availability. The common themes for these interventions were: return to work (if employed before critical illness) including access to vocational rehabilitation; access to available financial support, including help with the completion of forms; and return to previous social roles, which overlapped with the goal setting earlier in the programme.

3.3.3.3 Education sessions

Education sessions were developed at each site to address the common problems faced after critical illness, once again directed by the results of the focus groups and participant feedback. The target was to have no more than one education session per week, with the aim of avoiding cognitive overload. These short sessions were either delivered by the core InS:PIRE team or by a relevant professional from the hospital or community. Examples of education sessions included:

- Pacing of activities
- Dietary advice
- Sleep hygiene

3.3.3.4 Peer support and volunteer involvement

Peer support occurred throughout all five weeks. The three main mechanisms for delivering peer support were:

- Built into the programme, with ‘downtime’
- Volunteer facilitation and the ‘social café’
- Group sessions

The embedded peer support started with having all participants attending together for the five-week course while ‘downtime’ was built into the programme. This encouraged mixing and discussion between the patients and caregivers. Thus peer support was allowed to evolve more naturally than may occur with traditional peer support formats. The goal was for all participants to have some involvement or experience of peer support but at their own pace. In particular, this was seen as valuable for participants who were willing to attend a more traditional follow-up clinic but were less likely to participate in stand-alone peer support groups.

Every clinic utilised volunteers. These were patients and / or caregivers who were further along the recovery trajectory. Often, but not exclusively, the volunteers had attended previous InS:PIRE clinics. The volunteers facilitated discussion and offered support and insight from those further along the recovery continuum. These volunteers also managed the ‘social café’, offering refreshments for participants. This contributed to the informal nature of peer support further embedding this into the programme and extending its reach. The volunteers did not receive formal training for this role but were selected by either offering their help or being approached by the InS:PIRE team. There were members of the InS:PIRE team present throughout the programme and could therefore offer help and support if required at any stage.

There were no specific peer support sessions, but discussion was encouraged and facilitated throughout the education and group sessions that have been previously described. The psychology sessions were particularly suited to this form of indirect

peer support. When delivered as two separate sessions (patients and caregivers) they also offered space for subgroup peer support with a different focus.

Figure 3-2 summarises the programme components, the five-week timeline and offers an outline of how a typical programme was delivered during the intervention and study period.

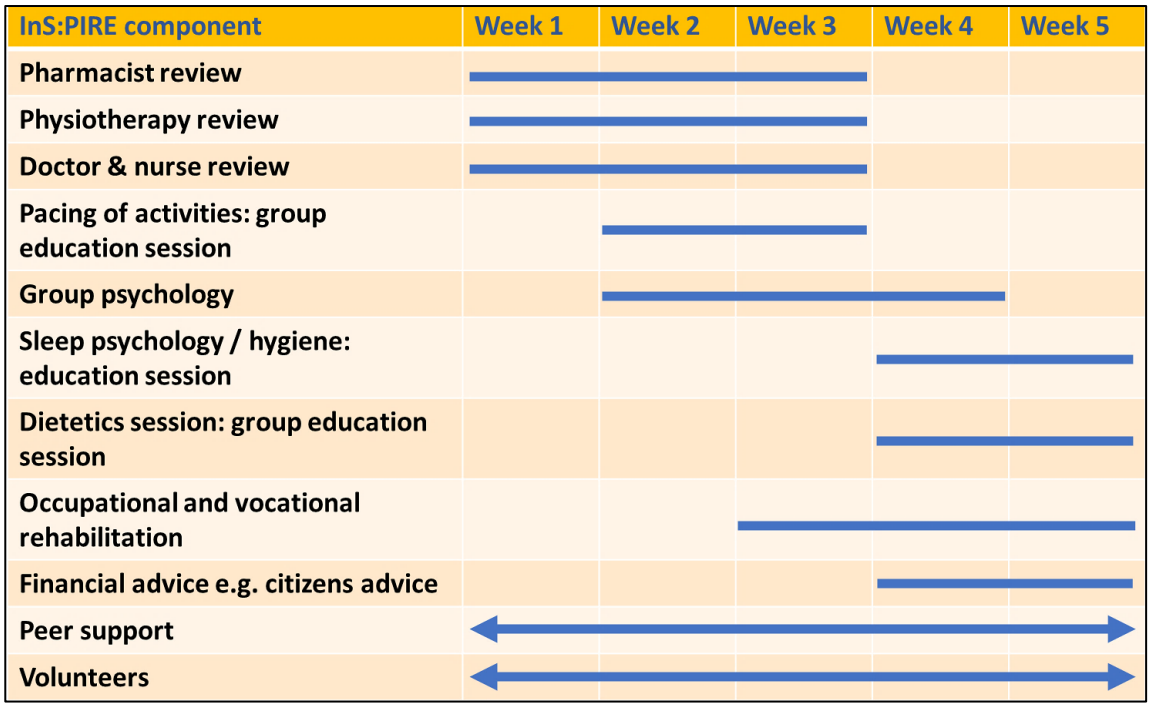


Figure 3-2: Example of a typical InS:PIRE five-week programme
Where: occurs in one of these weeks
occurs in every one of these weeks

3.3.4 Programme close

After each five-week programme there was a learning session held locally at each site. The InS:PIRE team discussed the conduct of the intervention and reviewed participant feedback, which was given both informally (verbally) and formally (written). They discussed what went well and what could be improved. Plans were then made on how to conduct the next five-week programme.

3.3.5 Follow-up

Participants were invited to return at three months and 12 months after the initial clinic attendance. There was no formal structure to this follow-up. Progress on health, wellbeing, and personal goals were generally discussed. Review, advice, or onward referral were offered if required. Peer support continued during these visits, and the 'social café' continued. This also formed the basis of the quantitative studies.

3.3.6 Costs of InS:PIRE programme delivery

The estimated cost of delivering a single cohort of InS:PIRE is £10,000 (c. 2023). Appendix 6 outlines a breakdown of the staff costs alongside the time commitments for each of the core staff members required to deliver InS:PIRE. The staff costs constitute most of the expenses (Appendix 6: basic staff pay costs of £6,600; total employer cost of £9,700). There are small amounts of sundry and administrative costs (e.g. letter printing, phone calls, clinic stationary, including patient and caregiver name badges / stickers). Every clinic also provided tea, coffee, cold drinks, biscuits, and snacks for the 'downtime' and peer support elements. Finally, most programmes offered to pay for patient transport (usually a hospital taxi) for patients and caregivers who had difficulty attending (typically up to two patients per cohort) and this was included in the total figure. None of the sites required to pay the hospitals for outpatient accommodation to deliver the programme, with delivery of these services being done from available existing spaces (e.g. hospital or ICU education and outpatient suites). If other services were to duplicate this, then these costs may have to be considered if applicable to the local area.

Based on the above, the cost to treat a single patient and caregiver unit at InS:PIRE was £1,250. This is based on a typical attendance of eight patients per cohort (anticipated range: 5 to 12).

3.4 Outcomes studies: participants and recruitment

3.4.1 Inclusion and exclusion criteria

Inclusion and exclusion criteria were the same for those receiving the intervention (intervention cohort) and those who did not (usual care cohort).

Inclusion criteria for the studies were any patient, or the caregiver of any patient, who had received level 3 treatment (multiple organ support and/or invasive respiratory support) or more than 7 days of level 2 treatment (single organ support or postoperative care).

Exclusion criteria were any patient, or caregiver of any patient, who was terminally ill, had suffered a traumatic brain injury, was an inpatient under psychiatric services, or was a prisoner.

All participants were treated in adult critical care units and were 18 years old or greater, but there was no upper age limit. This was, therefore, not confined to those employed prior to critical illness.

3.4.2 Intervention cohort

Each new site completed an initial five-week InS:PIRE programme without consenting participants. Subsequently participants were consecutively recruited to the studies during clinic attendance at any one of the five general ICU based InS:PIRE programmes (GRI, UHC, VH, UHW, UHM). Combined, this group of participants will now be referred to as the ‘intervention cohort’ and were recruited during InS:PIRE attendance between May 2016 and October 2018. Participants completed questionnaires (outcome measures) at baseline clinic attendance, three-month, and 12-month review. Patient participants were recruited directly and then caregivers were simultaneously recruited if willing to participate. Caregivers were not recruited if the patient refused consent as the patient details would be required for study analysis. Thus, there were some patient participants without associated caregivers (if the caregiver did not attend the clinic or declined consent), conversely there were no consented caregiver participants without an associated patient participant.

3.4.3 Usual care cohort

Usual care for both the patient and caregiver studies was defined as no specific ICU or critical care follow-up and was almost entirely delivered by the patient's own GP. In many cases there would also have been specialist, disease specific follow-up through hospital outpatient departments. However, none of this would have been focused specifically on the critical illness and did not involve any of the ICU MDT. This is in keeping with usual care as defined in Chapter 2.

Participants in the usual care cohort were recruited by postal survey between 10- and 16-months post-hospital discharge, from 8 hospitals in Scotland. This matched the one-year follow-up window of the intervention cohort.

The four new InS:PIRE hospitals involved as part of the scaling up project recruited a very small number of usual care participants (15 patient participants in total from UHC, VH, UHW, UHM) before commencing InS:PIRE. These participants were contemporaneous with participants recruited from the original InS:PIRE site (GRI) as this site commenced recruitment to the intervention cohort first. Once InS:PIRE was established at each new site then no further usual care recruitment occurred at these sites. After a major amendment to ethics (Appendix 3) a further four usual care sites commenced recruitment to the usual care cohort. These sites were:

1. Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde
2. Royal Alexandra Hospital, NHS Greater Glasgow and Clyde
3. Inverclyde Royal Hospital, NHS Greater Glasgow and Clyde
4. University Hospital Hairmyres, NHS Lanarkshire

In keeping with the studies definition of usual care only sites which did not have any critical care follow-up services were included, although this did limit the choice of sites significantly. The included sites for this part of the study matched those in the intervention cohort for size, geographical location, and mix of specialties. The sites were also pragmatically chosen to maximise recruitment to

this cohort as soon as was possible. Therefore, the three sites from NHS Greater Glasgow and Clyde were included alongside University Hospital Hairmyres which is part of NHS Lanarkshire.

For all participants recruited to the usual care cohort, questionnaire packs and pre-paid envelopes were sent to those meeting the inclusion / exclusion criteria identified through the local electronic patient record, in this case, WardWatcher (Critical Care Audit Limited, Yorkshire). A single pack was sent to patients requesting participation from both themselves and a caregiver / relative / loved one. Thus, both patient and caregiver consent forms and questionnaire packs were posted simultaneously in one envelope. This ensured caregivers were recruited only if the patient also participated which allowed the required data linkage and mirrored the intervention cohort.

Reminder questionnaire packs were sent if the pack was not returned after one month. Participants were given the opportunity to call to discuss issues or the recruitment and study processes with researchers.

Questionnaires were sent between July 2017 and March 2020, to mirror the one-year follow-up window for the intervention cohort, ensuring both groups were contemporaneous. Although ethical approval was in place to continue beyond March 2020, the impact of the COVID-19 pandemic was unknown, and this study was closed at this time to minimise any confounding effect.

3.5 Patient background data

Background demographic and health data were critical to this project for a number of reasons. This data allowed the understanding of the baseline characteristics to ensure that the populations studied represented ‘typical’ critical illness survivor populations. More importantly, due to the lack of blinding or randomisation in the study designs, correction for important confounders was critical in balancing the cohorts, particularly since the follow-up design was different for intervention and usual care cohorts.

The information offered here is very specific to the systems used and available in Scotland at the time of these studies. However, if these studies were to be

repeated in other countries with different systems, it is the data collected that are important, rather than the specific systems used. The overall goals were to obtain information describing the ICU stay (e.g. severity of illness, length of stay); the pre-ICU admission comorbidities (e.g. cardiovascular disease, mental health diagnosis, and alcohol or drug addictions); and descriptors of social deprivation.

3.5.1 Critical care data

Scotland has a national system for data collection, and every intensive care in these studies is part of this system. The Scottish Intensive Care Society Audit Group (SICSAG) supply every unit with software known as WardWatcher (Critical Care Audit Limited, Yorkshire). Once the patient participants were consented, the local WardWatcher database was interrogated, and the relevant information was collected. The key information gathered from this system described the date of intensive care admission and discharge; severity of illness, as measured by the APACHE II score; gross comorbidities, as measured by APACHE II; description of organ support levels, including days intubated, days of complex cardiovascular support, renal support; and patient postcode[291].

3.5.2 Electronic patient record

Although the SICSAG WardWatcher data is a rich source describing the ICU stay, the comorbidity data is based on the APACHE II score, which on the whole describes severe organ insufficiency[291]. This comorbidity list is very strict and misses a significant number of comorbidities that were likely to be important to this study. Crucially it is not possible to generate a Charlson Comorbidity Index (CCI) or a total comorbidity counter, required to describe multimorbidity, from the WardWatcher dataset[292-294].

A separate search for every participant using the local electronic patient record was undertaken. The system used in all of the study sites was Orion Health Clinical Portal system. Each site uses this system in slightly different ways. The system was searched in the following order:

1. Summary comorbidity page: this is not available in all sites, but if available, coded comorbidities were recorded.

2. Previous GP referral letters: a search for any GP summary letters with coded comorbidities was included. One off, historical episodes (e.g. resolved reactive depression) were not included. Other diagnoses, if coded by the primary care physician, were included.

3. Discharge letter: if available, hospital discharging letters with coded diagnoses were included in the comorbidity list.

4. ICU discharge letters: comorbidities from this source were included if available.

The time point to include comorbidities was on discharge from intensive care. This offered a clear reproducible reference point for all participants, and removed the need for repeated searches of the clinical record that would be impractical. This would also allow for significant new critical care discharge diagnoses to be included in the comorbidity count (e.g. new cancer diagnosis).

3.5.3 Deprivation

Scottish Index of Multiple Deprivation (SIMD) is used to describe deprivation, where Scotland is divided into 6,976 small areas, known as data zones, with all having roughly the same size of population[295]. These are then ranked from one (most deprived) to 6,976 (least deprived). Rankings have been generated from the assessment of 30 different indicators, which are grouped into 7 deprivation domains. The deprivation domains are: income; employment; education; health; access to services; crime; and housing.

The recommended way of reporting this relative measure of deprivation in Scotland is to split the summary rankings into groups of either deciles or quintiles. In order to minimise the degrees of freedom used in the modelling process, and maximise the inclusion of clinical variables, quintiles were the chosen reporting measure for both the patient and caregiver outcomes. The numerical scale was one to five with SIMD quintile one representing the most deprived 20% of the population and SIMD quintile five representing the least deprived 20%.

The period of study was covered by the 2016 publication of SIMD. The patient data zones were linked from their postcode, from WardWatcher data. This would correlate with the patient's address at ICU admission. Caregivers were asked if they lived with the patient during the consenting process, if they did then the patient postcode was used, and if they did not, they were asked to supply their own postcode to calculate the SIMD-2016 quintile.

3.5.4 Caregiver additional data

Alongside the question about where the caregiver lived (and their postcode), at recruitment, caregivers were also asked to complete a short survey of additional demographic data. This included the relationship to the patient, age, sex, and employment.

3.6 Outcome measures

Outcome measures were chosen during the set-up of the original InS:PIRE clinic (at GRI) with involvement of patients and caregivers. Feedback from participants alongside the information gathered through the focus groups guided the choice of surveys. This evolved during the conceptualisation for the scaling up project and was finalised before recruitment began. Importantly this occurred before any recommendations on standardised outcome measurements had been recommended by the SCCM[45,46]. This explains the differences between the outcomes described here and the default surveys described by the SCCM. Reassuringly, there was significant overlap. The target was to measure outcomes at one year following hospital discharge to allow the comparison between intervention and usual care cohorts. The outcome measures are summarised in Table 3-1. All outcome measures (and the caregiver demographics data) were collected on paper proformas before being transcribed into Microsoft Excel by the thesis author[177]. This choice was made for pragmatic and practicality reasons to guarantee every site was able to administer the surveys in the same way. This accounted for some missing data as described in the subsequent chapters (Chapter 4 and Chapter 5). The caregiver age demographic was particularly poorly completed due to this methodology.

3.6.1 Patient outcome measures

The following areas were assessed to evaluate patient HRQoL and PICS; the results are reported in Chapter 4:

1. HRQoL measured by the EQ-5D-5L (EuroQol group 2009)[145,146]

2. Self-efficacy, measured by the General Self-Efficacy (GSE) scale questionnaire[296,297]

3. Emotional and mental health outcomes measured with the Hospital Anxiety and Depression Scale (HADS)[92]

4. Pain outcomes were measured by the Brief Pain Inventory (BPI) short form[298-303]

3.6.2 Caregiver outcome measures

The following areas were assessed to evaluate caregiver burden, strain, emotional health, and extent of PICS-F; the results are reported in Chapter 5:

1. Emotional and mental health outcomes measured with the Hospital Anxiety and Depression Scale (HADS)[92]

2. Caregiver strain using the Caregiver Strain Index (CSI)[304]

3. Experience of insomnia was measured using the Insomnia Severity Index (ISI)[305]

3.6.3 Health-Related Quality of Life: EQ-5D-5L

The primary outcome for the patient study was HRQoL at one year measured by the EQ-5D-5L (EuroQol – 5 dimension– 5 level survey, 2009)[145,146]. This survey comprises two pages and was completed in paper format. The first page is the EQ-5D descriptive system; the second page is the EQ-5D Visual Analogue Scale (EQ-VAS).

3.6.3.1 EQ-5D descriptive system

The EQ-5D descriptive system asks participants to answer five questions each assessing a different aspect of QoL. The questions ask the participant to rate their experience of problems with: mobility; self-care; usual activities; pain or discomfort; and anxiety or depression. Each question has five possible responses and participants choose the best response. This generates a number from one to five for each domain area, one being the best descriptor (e.g. “I have no problems in walking about” for mobility) and five being the worst descriptor (e.g. “I am unable to walk about” for mobility). Each response is then summarised with a five digit code known as the health descriptor with “11111” being the best possible score and “55555” being the worst health possible.

Although the extremes of the value set can be interpreted, every other summary health descriptor has no arithmetic value. This means these values cannot be interpreted directly (e.g. it cannot be assumed that a health state of “31111” is better or worse than “22222”). They must be converted with the help of a value set before any comparison between patients.

Countries have their own value sets to convert the health descriptors to a single number known as the health utility score (EQ-HUS). On this scale a value of 1.0 is considered the best health possible and a value of 0.0 is a health state equivalent to death. Values can be negative, representing a state worse than death[148]. For this thesis, the UK ‘crosswalk’ value sets are used as recommended by NICE[148,149,306,307]. The Minimal Clinically Important Difference (MCID) for EQ-HUS is 0.08[308,309].

3.6.3.2 EuroQol Visual Analogue Scale (EQ-VAS)

The second page of the EQ-5D-5L is the Visual Analogue Scale (EQ-VAS). This records participants self-rated health, on the day of testing by marking on a continuous vertical scale from 0 (worst health) to 100 (best health) with an MCID of 8[308,309]

3.6.4 Self-Efficacy: Generalised Self-Efficacy (GSE)

Self-efficacy was used as a secondary outcome for the patient chapter (Chapter 4). It was measured in an attempt to understand the mechanisms behind any changes in HRQoL. This does not form part of any recommended outcome measures for ARF, ARDS, or PICS[45,46]. Self-efficacy was suggested as a possible mechanistic hypothesis for improvements in patient's HRQoL through the InS:PIRE clinic during the design phases of the study. It was proposed that an improvement in a patient's sense of agency and self-determination, alongside the skillset to self-manage their own health and social wellbeing, may deliver the desired improvements in HRQoL.

To measure this the GSE was utilised. This is a ten-item questionnaire generating a score with 31 levels (minimum 10 to maximum 40)[296,297]. An MCID has not been well described for this survey, especially in post ICU populations. The best estimate for an MCID for GSE within the literature is a 6% change (1.86 points absolute change)[297]. This will be the MCID for this thesis, although it should be highlighted that this was produced for a specific group of patients with chronic obstructive pulmonary disease and should be interpreted with caution[297].

3.6.5 Mental Health outcomes

HADS was used to evaluate mental health outcomes for both patients and caregivers. For patient outcomes this was a secondary outcome and in keeping with recommendations from expert opinion and ARDS recommendations[45,46]. This outcome was considered the primary outcome for the caregiver chapter (Chapter 5) as mental health problems have been the best described features of PICS-F[45,46].

HADS is a questionnaire with 14 items (statements or questions). Each one has four possible responses or level of agreement, scored 0, 1, 2, or 3. Half of the items contribute to the summary score for anxiety (HADS-A) and the other half contribute to the depression summary score (HADS-D). Thus, two output scores are generated, each ranging from 0 to 21. The cut-off values for scoring for anxiety or depression are well established in general and critical care populations. A score ≥8/21 is required to meet the survey's definition of anxiety or depression. Scores of ≥11/21 defines moderate symptoms, and ≥15/21 severe symptoms [45,46,92]. For

the purposes of analysis, a score ≥8/21 was used to define a case of anxiety or depression for each sub score. Both outcomes were therefore described individually for patients and caregivers.

3.6.6 Pain outcomes

Pain is not specifically recommended as part of expert recommendations as previously discussed[46]. However, this was a feature highlighted by many patients during focus groups, the pre-consenting phases of the study, and in pharmacy datasets[310-313]. Pain also features in many studies of HRQoL, and is part of the EQ-5D-5L. As such it was felt a valuable area to explore further.

The Brief Pain Inventory (BPI) short form was used to measure patient pain outcomes at one year[298-303]. This comprises four sections.

1. Experience of pain in previous 24 hours, with a binary yes/no response.

2. Body areas where pain is experienced (pictorial summary), participants are asked to shade the areas where they experience pain, and to mark an 'X' where pain is at its worst.

3. Pain severity scores, four items are scored from 0 (no pain) to 10 (worst pain), the areas asked are: worst pain (past 24 hours); least pain (past 24 hours); average pain; and pain right now.

4. Pain interference. Which aims to quantify the effects of pain on both daily activities and quality of daily interactions, over the preceding 24 hours. Each area is scored from 0 (does not interfere) to 10 (completely interferes). The seven areas scored are: general activity; mood; walking ability; normal work; relations with others; sleep; and enjoyment of life.

In order to summarise the pain outcomes from this complex survey, the standard approach is to summarise the scores into two summary scores. A mean pain severity score is the mean of the total of the four severity scores, while the mean pain interference score is the mean of the total of the seven interference scores[298-303]. Also considered in the analysis were average pain (single question),

worst pain (past 24 hours), pain interference on work, and pain interference on enjoyment of life[314-317]. The decision to include the two standalone pain interference scores was that this may reflect how InS:PIRE is delivered and the possible mechanisms behind the programme.

As an exploratory outcome measure, MCIDs for BPI are not well established, especially after critical care. For this study a change of 2/10 will be considered clinically significant, in keeping with other pain interventions, e.g. those for fibromyalgia[318].

3.6.7 Caregiver strain

The CSI is a 13-item questionnaire which measures strain relating to care provision from the perspective of the caregiver. The 13 questions cover areas of emotional adjustment, social issues, physical strain, and financial strain. Each question is answered 'yes' (scoring one point) or 'no' (scoring no points). Addition of the 13 responses give a total score from 0 to 13. A score of 7 or greater is the suggested cut off for a high level of strain or stress[304].

CSI is not included in any recommended outcome measures for critical care research. Inclusion here was guided by the earlier focus group work and to better understand the impact of the InS:PIRE intervention.

3.6.8 Insomnia Severity Index

The ISI questionnaire is a validated screening tool for clinical insomnia[305]. This questionnaire has 7 key items, which ask the participant to rate specific aspects of sleep problems on a scale of 0 (no problems) to 4 (severe or extreme problems). The first three questions describe the severity and frequency of sleep problems. The subsequent four questions aim to describe the effects on insomnia on the participants' lives and relationships.

Addition of the 7 items generates a summary score range from 0 to 28. Guidelines suggest that the summary result should be interpreted as:

- 0 to 7: No clinically significant insomnia
- 8 to 14: Clinically significant insomnia
- 15 to 21: Moderate clinical insomnia
- 22 to 28: Severe clinical insomnia

For this study a cut-off value of eight or greater was used to define a case of clinical insomnia in caregivers. There are a further three questions that are not used as part of analysis but are better suited to using the tool on an individual basis. These ask about the number of nights per week where insomnia occurs or medication is required. For this reason, these questions are not used in the outcomes analysis.

Although the ISI is not a recommended survey, insomnia was a recurring theme during the early phases of InS:PIRE, and is seen as a key determinant of HRQoL[319]. Inclusion of this outcome measure for the caregiver outcomes was seen as making an important contribution to understanding the effectiveness of InS:PIRE.

Table 3-1: Summary of outcome measures used for both patient and caregiver outcomes

Survey	Outcome measures reported	Outcome scale	Clinical significance or cut-off value	Group surveyed
EQ-5D-5L (EuroQol: Quality of Life Group)	Health Utility Score (HUS); UK crosswalk scores.	Continuous; range for UK: -0.594 to 1.0	MCID: 0.08	Patient
	Visual Analogue Scale (EQ-VAS)	Continuous; range 0 to 100	MCID: 8	Patient
Generalised Self-Efficacy (GSE)	Summary score	Continuous; range 10 to 40	MCID: 6%; 1.86 points	Patient
Hospital Anxiety and Depression Scale (HADS)	Depression	Binary; screened as depression present or absent	Cut-off value of ≥8/21 to screen positive for depression	Patient and Caregiver
	Anxiety	Binary; screened as anxiety present or absent	Cut-off value of ≥8/21 to screen positive for anxiety	Patient and Caregiver
Brief Pain Inventory – short form (BPI)	Pain scores: Mean of all four pain scores; Average pain (single question);Worst pain (past 24 hours)	Continuous; range: 0 to 10	MCID: 2 points / 20%	Patient
	Pain interference scores: Mean pain interference (average of 7 scores); Enjoyment on life; Normal work	Continuous; range 0 to 10	MCID: 2 points / 20%	Patient
Caregiver strain Index	Caregiver strain	Binary; strain present or absent	Cut-off value of ≥7/13 to screen positive for caregiver strain being present	Caregiver
Insomnia Severity Index (ISI)	Presence of Insomnia	Binary; insomnia present or absent	Cut-off value of ≥8/28 to screen positive for insomnia being present	Caregiver

MCID: Minimal Clinically Important Difference

3.7 Statistical analysis

Participants who had not completed any outcome measures at 12-month review were excluded from analysis, defined as 'lost to follow-up'. The critical care data (WardWatcher data), comorbidity data (from the electronic patient record search), SIMD data, caregiver additional data, and the outcome measures were all linked with a unique, non-identifiable code.

Separate demographic and participant characteristics tables were generated for both patients and caregivers. Differences in the baseline characteristics between the usual care and intervention cohorts were assessed using Wilcoxon rank-sum, Pearson's chi-squared test, and Fisher's exact tests. These differences, alongside core domain knowledge influenced the covariate adjustment and modelling strategies. R version 4.0.4.26 was used throughout[179].

3.8 Modelling workflow

Given the non-randomised nature of this cohort study, bias correction for important and significantly different baseline demographics were required. Furthermore, the challenges of conducting one-year follow-up in this patient group, alongside the multiple questionnaire surveys, had the potential to result in a significant number of missing data points. To account for these issues the following workflow was chosen a-priori: firstly, multiple imputation accounted for missing data; secondly, multivariable regression to correct for possible confounders; lastly, propensity score matching, with further multivariable regression.

A power calculation was not carried out as the concept and design of this study was embedded in the QI methodology. It was decided that a post-hoc power calculation would not add meaningful information to these studies. For significance testing the standard value of $p<0.05$ was set for all significance testing throughout this thesis.

The overall recruitment target for both combined studies was 400 to 500 participants. The exact model workflow was not specified a-priori, that is, it was not decided if propensity score matching would occur before model generation or

after model generation (as a sensitivity analysis). Due to the final recruitment numbers and loss to follow-up rates, it was decided that the primary outcome would be the effect of the intervention determined by regression modelling. Propensity score matching was therefore used as a sensitivity analysis for the patient outcomes study only. This helped to ascertain the robustness of the model and results.

3.8.1 Multiple imputation

Most of the missing data were considered to be missing at random. The one exception was the pain questionnaire (BPI), where participants consistently missed out data when they were not experiencing pain. If this was the case, the pain scores and pain interference were scored as zero to facilitate analysis of this outcome. All other missing data was imputed using Multivariate Imputation by Chained Equations (MICE) using the Categorical and Regression Trees (CART) technique[320].

Patient and caregiver data were imputed separately. The imputation process was reviewed and iteratively modified. Output convergence and distribution were considered during this process. The final imputed datasets were created using 5 imputations and 30 iterations for the patient data, and 5 imputations and 10 iterations for the caregiver datasets.

3.8.2 Model generation and covariate adjustment

Continuous outcomes (EQ-5D, GSE, BPI) were modelled using multivariable linear regression. Binary, or binomial, outcomes (HADS, CSI, ISI) were modelled using multivariable logistic regression. A brief description of both are offered here.

3.8.2.1 Multivariable linear regression

Simple linear regression in its most basic form describes the line of best fit between two continuous variables. The variable being predicted is known as the dependent variable, usually denoted by the letter ‘Y’, whereas the prediction variable is known as the independent variable, denoted by the letter ‘X’. An intercept describes where the line of best fit crosses the y-axis, described when X=0. An associated error term (‘ε’) is also included[321].

Multivariable linear regression is also the line of best fit, but includes multiple independent variables. Thus, the equation would be written as:

$$Y = \beta_0 + \beta_1 X + \beta_2 X + \beta_3 X + \beta_4 X \ldots + \varepsilon$$

Where: Y=dependent variable; β_0=intercept; $\beta_1 X$ to $\beta_4 X$…= independent or explanatory variables, β represents the coefficient for each independent variable, described as the magnitude of change (increase or decrease) in Y given a one unit increase in X; ε=residual error value.

It is, therefore, possible to account for multiple different confounding factors simultaneously, as part of the explanatory variables. There are numerous different approaches to model building, however, for the studies in this thesis, the priority was to find the best estimate of treatment effect. The models were generated by choosing important variables known to influence outcomes after critical illness and correcting for these.

The residual is the distance from a single value to the regression line. When calculating the line of best fit the usual technique is to minimise the total of the square of the residuals, which is known as Ordinary Least Squares (OLS). The function of squaring the residual ensures all values are positive and simply give an arbitrary scale of magnitude of actual points vs the line of best fit.

All statistical tests rely on assumptions, and regression models are no different. The assumptions underpinning multivariable linear regression are: a linear relationship between the dependent and independent variables; absence of collinearity; constant variance of residuals i.e. presence of homoskedasticity, or absence of heteroskedasticity; independence of observations; multivariate normality i.e. normal distribution of residuals. Plots were used to assess these assumptions, firstly, a ‘QQ-plot’ of residuals was primarily used to look for the normality of distribution of the residuals (see Figure 3-3). The residuals are plotted and compared to a theoretical distribution which has a completely normal distribution. Secondly, the residuals were fitted against the predicted values allowing the assessment of the spread of the residuals across the range of outcome variables (see Figure 3-4). A systematic widening, narrowing, or ‘pinch point’, in

spread of points would suggest the presence of heteroskedasticity, and the model should be reviewed and / or interpreted with caution[322,323].

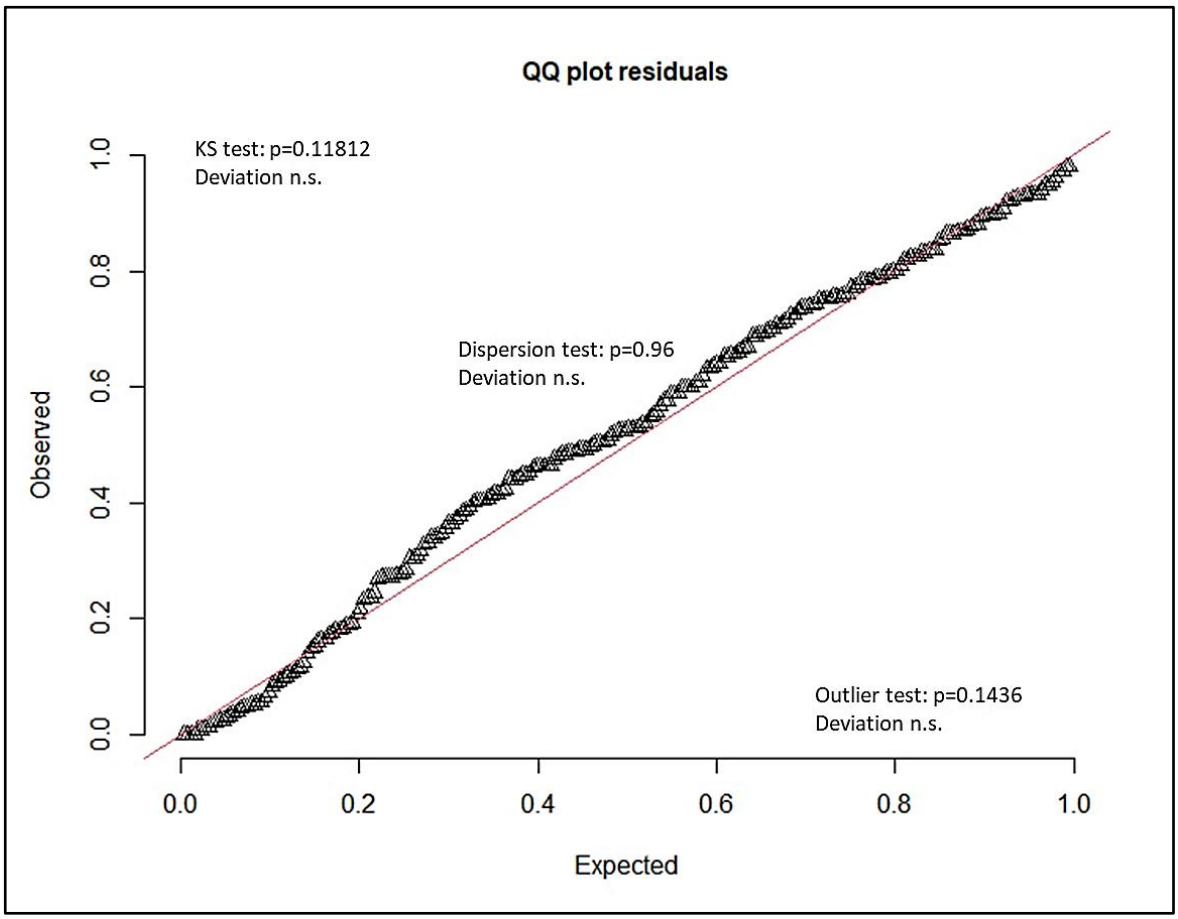


Figure 3-3: QQ-plot of observed residuals against expected values.

Red line is the line of a perfectly normal distribution. KS test is a test of distribution. Dispersion and outlier tests also included. In this example all of the tests are not significant, with plotted residuals roughly matching to the ideal normal distribution.

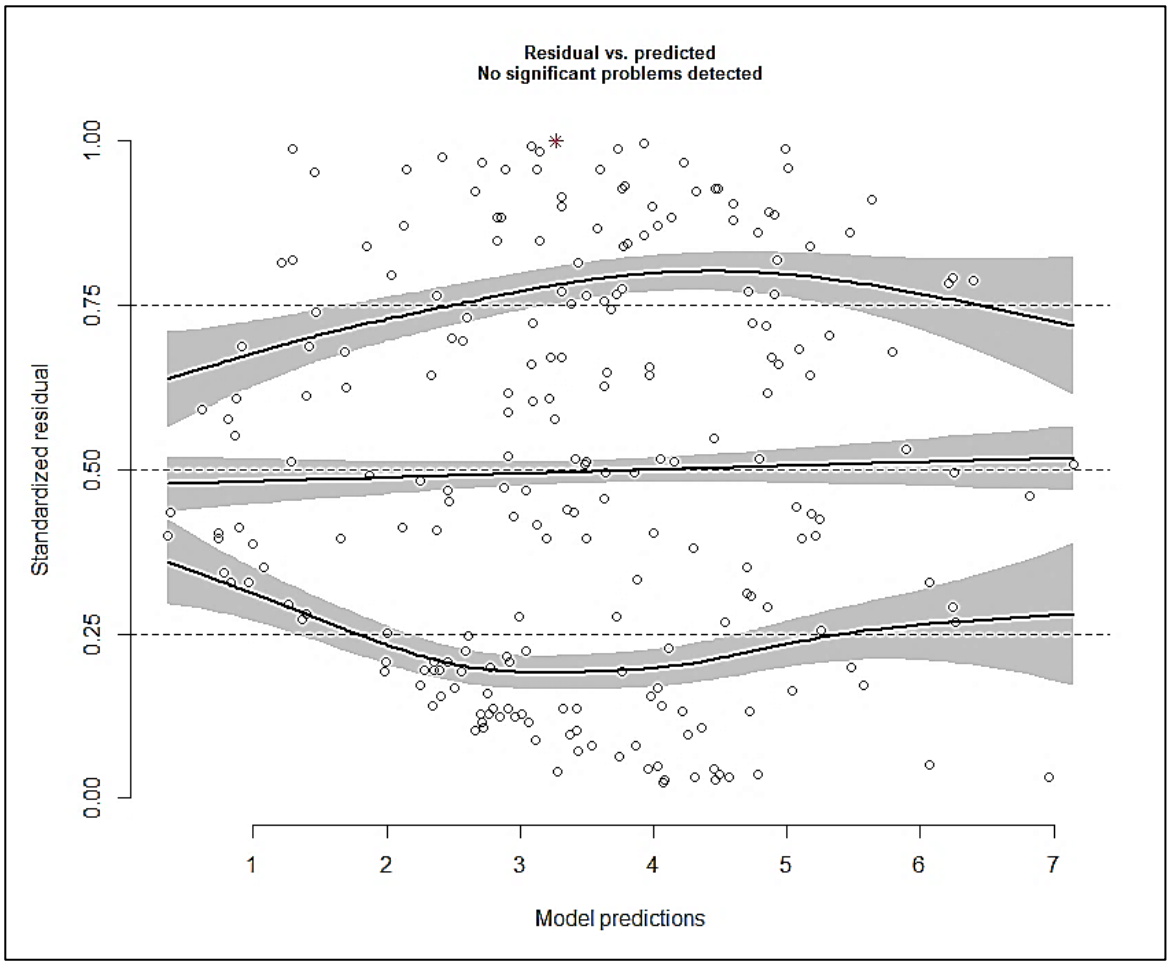


Figure 3-4: Residuals vs predictor plot to assess for heteroskedasticity.

Data points outwith the expected simulation values are highlighted as a red star (*). Parallel lines suggest that the residuals are homoskedastically (i.e. not heteroskedastically) distributed and model assumptions are met. In this case significant heteroskedasticity is not present.

3.8.3 Sandwich estimator

To further minimise any effects from heteroskedasticity a sandwich estimator was used to generate the coefficients and confidence intervals, this was suggested during peer review for the patient outcomes paper (Chapter 4). This protocol is a variation on the OLS method (for linear regression) and is more robust to systematic errors. It may also be referred to as robust modelling. For these models the heteroskedasticity and autocorrelation consistent (HAC) estimator was used[324,325].

3.8.4 Multivariable logistic regression

Multivariable logistic regression was used to assess the binomial or binary outcome measures (HADS, CSI, and ISI). The log-odds of an event occurring is known as the logit. The logit effectively transforms the binary data into a sigmoid curve that estimates the log-odds of the probability of an observation belonging to either one of two categories[326]. An example in this study would be calculating the log-odds of a participant meeting the cut-off value for depression or not, as scored by the HADS survey.

The logit equation can be written as:

$$Logit = \frac{1}{1 + e^{-x}}$$

Once the model is generated, the coefficients are exponentiated to report odds ratios, rather than the log odds. The assumptions for logistic regression are not as strict as, and less testable than, linear regression. Overall, however, the transformed output (log values) should still be linear[326].

3.8.5 Final models

3.8.5.1 Patient outcomes models

The primary outcomes for Chapter 4 (patient outcomes) were adjusted for: patient sex; ICU length of stay; APACHE II score; time to follow-up; deprivation index (SIMD quintiles); surgery at admission or in the first week of ICU; Charlson Comorbidity Index (CCI); history of alcohol or drug use; history of pain; and history of pre-existing psychiatric diagnosis.

3.8.5.2 Caregiver outcomes models

The primary outcomes for Chapter 5 (caregiver outcomes) were adjusted for: relationship with the patient; caregiver age; caregiver sex; time to follow-up; deprivation index (SIMD quintiles); patient hospital length of stay; patient age; and patient pre-existing psychiatric or mental health diagnosis.

3.8.6 Sensitivity analyses: patient outcomes

Clearly the patient model was much more complex, with more variables and a much greater number of alternative covariates to choose from during model generation. Alongside the higher number of participants, this results section and the outcomes were suitable for several sensitivity analyses **(Chapter 4).**

3.8.6.1 Propensity score matching and doubly robust modelling

Doubly robust modelling involves regression modelling (outcome prediction) after propensity score matching (input prediction). The latter models which participants should be included in the analysis[327]. For the patient outcome measures, this technique was carried out as a sensitivity analysis, effectively to determine if the outcomes held up to the propensity score process. This technique was not chosen as the primary outcome as there was likely to be a significant loss of participants, particularly in the intervention cohort.

3.8.6.2 Propensity score matching methodology

After imputation with Multivariate Imputation by Chained Equations (MICE), propensity score matching was undertaken[328]. Participants in the intervention cohort were propensity matched to the usual care cohort, using Nearest Neighbour Calliper Matching (calliper = 0.1)[328]. Balance between covariates was reviewed between the intervention and usual care cohorts using Mann-Whitney U test for continuous variables and Pearson's chi-squared test for categorical variables. Baseline characteristics were reviewed, each with their associated significance values, with the goal of balancing the baseline characteristics in the two groups.

Covariates were iteratively included in the match until balance was achieved. This process was completed before considering any outcome variables. The following covariates were included in the propensity score: surgery at admission or in the first week of ICU; time from hospital discharge to follow-up; age; hospital length of stay; advanced respiratory support; ICU length of stay; history of harmful alcohol or drug use; and pre-existing psychiatric diagnoses. Close to two-thirds (65.2%) of the usual care cohort were successfully matched to the intervention cohort.

After matching, the patient outcome measures of EQ-HUS, EQ-VAS, GSE, HADS-D, HADS-A, and mean pain score (BPI) were tested for differences between the intervention and usual care cohorts using the Mann-Whitney U test.

After simple testing, the outcome measures underwent the same modelling and adjustment strategies used in the primary analysis. This was considered the main outcome for the sensitivity analysis or the doubly robust technique.

3.8.6.3 Nomenclature: Unmatched and Matched cohorts

For convenience during the results and discussion sections the "matched" cohorts will refer to the patients remaining after the propensity score matching process. Thus, any reference to matched will be a direct reference to the sensitivity analysis involving propensity score matching.

This will be combined with adjusted or unadjusted with the following meaning:

- **Unadjusted matched** cohort (or analysis): This references the sensitivity analysis which uses the data generated from the propensity score matching process and assesses the effects between the groups using simple (unadjusted) inferential statistics (e.g. Mann-Whitney U test or Pearson's chi-squared test).

- **Adjusted matched** cohort (or analysis): This references the sensitivity analysis which uses the data generated from the propensity score matching process and assesses the effects between the groups using multivariable (adjusted) linear or logistic regression. This has also been called doubly robust analysis as described above.

Any references to an "**unmatched**" cohort will reference the primary analysis which did not involve propensity score matching.

3.8.6.4 Mixed effects analyses: hospital site cluster effects

A further sensitivity analysis was carried out on the patient outcomes to assess the clustering effects of hospital site, focusing on the size of the treating hospital. This analysis measured the variability of the random effects from hospital site, divided between large tertiary referral hospital or medium acute general hospital (in the UK known as a district general hospital).

3.8.6.5 EQ-5D domain analysis

A final exploratory analysis of the five EQ-5D-5L domains (mobility; self-care; usual activities; anxiety and depression; and pain and discomfort) was undertaken. This was to assess whether attendance at InS:PIRE was associated with differences in the odds risk ratios of having moderate (≥3/5) problems or greater in each domain at one-year follow-up. Logistic regression was used on the unmatched data and the same modelling strategy was undertaken with a separate model (result) reported for each individual domain.

3.8.7 Sensitivity analyses: caregiver outcomes

As recruitment numbers were lower for the caregiver study, this data were not suitable for a propensity scoring or doubly robust analysis technique. However, missing data were higher for this dataset. As such, two sensitivity analyses were undertaken to account for this missing data. Firstly, the same outcomes and models were created but using a different imputation strategy with 30 imputations to better account for missing data. The final sensitivity analysis was conducted with caregiver age removed from the model to remove any risk of collinearity occurring between patient age and caregiver relationship. Both sensitivity analyses were reported together to fully explore the effects of these modelling strategies.

3.9 Methods summary

This chapter has described the background to the InS:PIRE intervention and how it was conducted during the period of study from 2016 to 2019. The design and creation of two cohort studies comparing the one-year outcomes for both patients and caregivers who attended InS:PIRE (intervention cohort) with those who did not (usual care cohort) have been summarised. The statistical methods underpinning the analysis of the outcomes alongside the use of covariate adjustment to reduce the effects of bias in this non-randomised study have also been discussed.

The one-year outcomes for both studies are reported in Chapter 4 and Chapter 5 of this thesis.

Chapter 4 Results: Effectiveness of InS:PIRE on one-year patient outcomes

4.1 Overview

The purpose of this chapter is to compare the outcomes between patients who attended InS:PIRE (intervention cohort) and those who did not attend InS:PIRE (usual care cohort) one year after hospital discharge. The methods for this are fully outlined in Chapter 3. As a reminder the outcome measures used for this section are:

- EQ-5D-5L Health Utility Score (EQ-HUS) and Visual Analogue Scale (EQ-VAS)
- Generalised Self-Efficacy (GSE) scores
- Hospital Anxiety and Depression Scale (HADS) scores for depression (HADS-D) and anxiety (HADS-A)
- Brief Pain Inventory, short form (BPI) pain scores and pain interference scores

All of the outcomes were modelled using linear regression (for continuous outcome variables) or logistic regression (for binary or dichotomous variables generated from the HADS questionnaire). The models used to generate the adjusted outcomes (unless stated otherwise) included the following covariates: patient sex; ICU length of stay; APACHE II score; time to follow-up; deprivation index (SIMD quintiles); surgery at admission or in the first week of ICU; Charlson Comorbidity Index (CCI); history of alcohol or drug use; history of pain; and history of pre-existing psychiatric diagnosis.

Finally, a discussion about the meaning behind the results, what this adds to the literature, and the limitations of these results is offered.

4.2 Study period, participants and their characteristics

4.2.1 Study recruitment period and initial enrolment

The study involved patients who were discharged from ICU between August 2014 and May 2019. The total recruitment to both intervention and usual care was 321 patient participants. By necessity the InS:PIRE clinical teams focused on setting up the programme at each site and therefore recruitment was slow during the early phases of the study; only 12 participants (6 intervention, 6 usual care) were recruited from those discharged from ICU between August 2014 and January 2016. As stated, these dates represented when participants were discharged from ICU, although some had a long in-hospital rehabilitation and were therefore eligible to be recruited to this study. The vast majority of patients (96.3%; 309/321), however, were discharged from ICU between February 2016 and May 2019.

4.2.2 Participant recruitment and retention

In the intervention cohort 570 patients were invited to attend InS:PIRE and 253 (44.4% of those invited) attended the programme. The final total consenting to participate from this were 206 (81.4% of those attending). During the follow-up period 6 participants died. Finally, 63 were lost to follow-up and 137 (68.5%) participants completed one-year follow-up surveys.

In the usual care cohort, 643 patients were screened, 191 were deemed ineligible, therefore, 452 were sent invitations and questionnaire packs. Of these, 115 (25.4%) consented and completed the questionnaires. Figure 4-1 demonstrates this patient flow, recruitment, and retention for both the intervention and usual care cohorts; and Appendix 7 includes a table of the characteristics of responders vs non-responders in the usual care postal survey. The characteristics between postal survey responders vs non-responders are generally similar with the exception of deprivation (SIMD) where responders had a higher proportion from the least deprived SIMD quintile five (18.8% vs 9.0%). Baseline critical care demographics were similar but responders were older (median age: 64 years for responders [IQR: 50 to 72] vs 54 years for non-responders [IQR: 42 to 65]). Full details are available in Appendix 7.

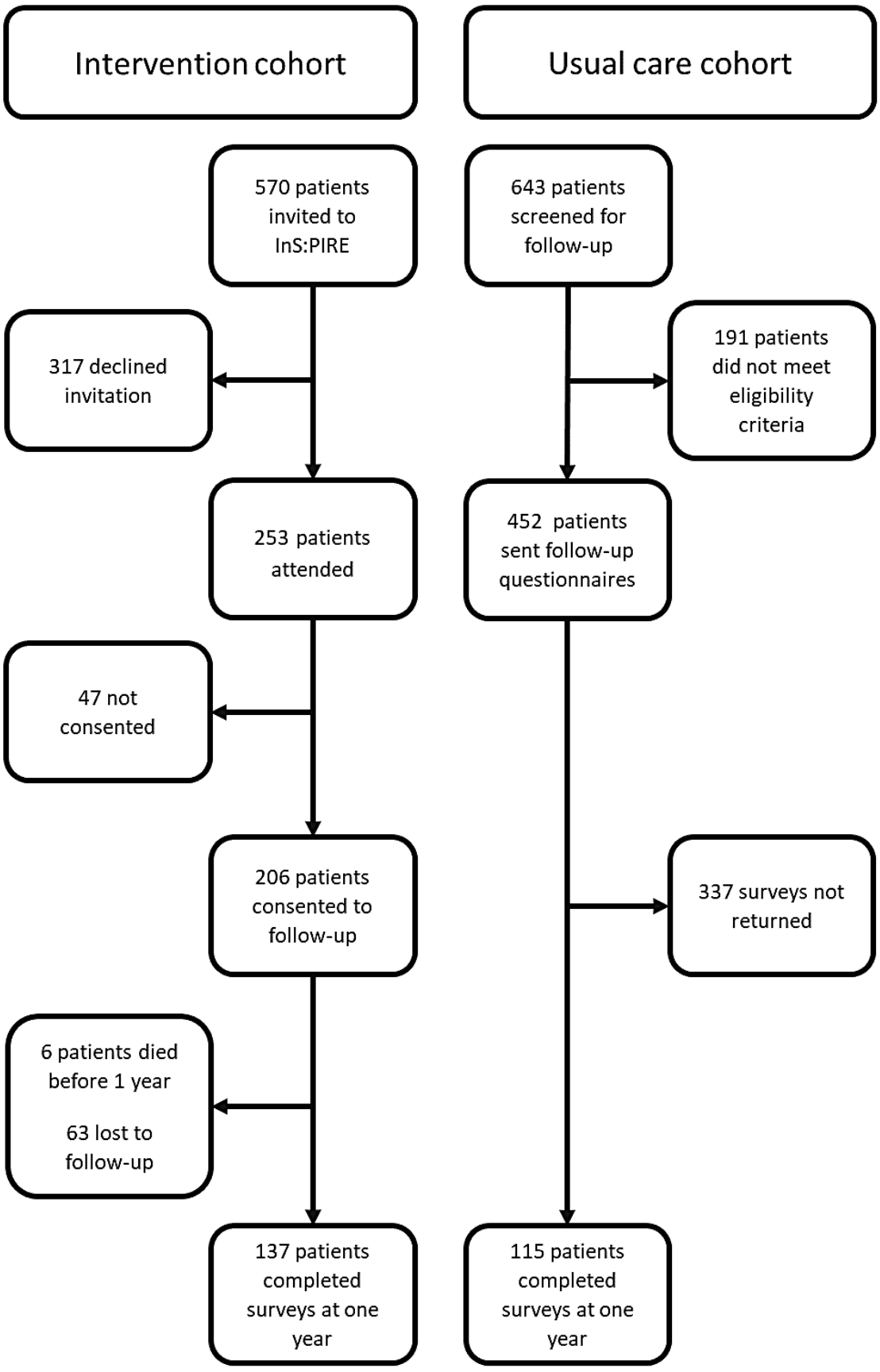


Figure 4-1: Patient flow, recruitment, and retention: intervention and usual care cohorts

The completion rates between both cohorts were very similar when comparing the number of surveys returned at one-year follow-up with the total number invited. Of those invited to attend InS:PIRE, 24.0% (137/570) completed surveys at one year, while 25.4% (115/452) of those sent recruitment packs in the usual care cohort completed the one-year follow-up.

Due to the data collection processes, it was possible to review the characteristics of the responders and non-responders to the postal survey, but not in the intervention cohort.

4.2.3 Participant characteristics

Full details of the baseline participant characteristics for those completing one-year outcome measures can be found in Table 4-1. Most of the participant characteristics were similar between the cohorts. The median age was 63.5 years in the usual care cohort (IQR: 49.5 to 71.5) vs 58.7 years for the intervention cohort (IQR: 50.8 to 67.6) with p=0.06 when testing with the Mann-Whitney U test. Severity of illness defined using the APACHE II scores were 19 for the usual care cohort (IQR: 14.2 to 25.0) vs 20 for the intervention cohort (IQR: 15.0 to 25.3), Mann-Whitney U test p=0.28. In the usual care cohort 67 (58.3%) participants were male vs 73 (53.3%) in the intervention cohort, Pearson's chi-squared test p=0.43.

The level of organ support that the participants had received during their respective ICU admissions were also similar with just under 90% of each group having received advanced respiratory support (87.0% in the usual care cohort vs 88.3% in the intervention cohort, Pearson's chi-squared test p=0.81). Rates of other organ support were similar including renal replacement therapy and complex cardiovascular support.

There were no significant differences in the frequency and extent of comorbidities between the cohorts including the proportion of participants with two or greater comorbidities (47.0% usual care cohort vs 43.8% intervention cohort, Pearson's chi-squared test p=0.41). Both groups also had similar Charlson Comorbidity Index (CCI) scores; rates of psychiatric comorbidities; and rates of substance misuse or addiction. Finally the degrees of socioeconomic deprivation across all five SIMD quintiles were similar.

Table 4-1: Baseline characteristics for the intervention and usual care cohorts

Demographic	Usual care cohort (n = 115)	Intervention cohort (n = 137)	P value
Age, Years, median (IQR)	63.5 (49.5 to 71.5)	58.7 (50.8 to 67.6)	0.06
Male sex, n (%)	67 (58.3)	73 (53.3)	0.43
Admitting specialty, n (%):			**0.03**
Medical	52 (45.2)	83 (60.6)	
Surgery	60 (52.2)	54 (39.4)	
Surgery at ICU admission or within one week of admission, n (%)	50 (43.5)	43 (31.4)	**0.01**
ICU length of stay, median (IQR)	4.95 (2.5 to 9.5)	10.5 (6.9 to 17.3)	**<0.01**
Hospital Length of stay, median (IQR)	18.0 (11.4 to 35.0)	30.5 (17.0 to 49.6)	**<0.01**
APACHE II score, median (IQR)	19 (14.2 to 25.0)	20 (15.0 to 25.3)	0.28
Advanced respiratory support, n (%)	100 (87.0)	121 (88.3)	0.81
Complex cardiovascular support requiring multiple vasoactive drugs, n (%)	21 (18.3)	30 (21.9)	0.54
Renal replacement therapy, n (%)	19 (16.5)	32 (23.4)	0.21
Two or greater comorbidities, n (%)	54 (47.0)	60 (43.8)	0.41
Charlson Comorbidity Index (CCI) score, median (IQR)	3 (1 to 4)	3 (1 to 4)	0.53
Pre-existing psychiatric diagnosis, n (%)	28 (24.3)	39 (28.5)	0.60
History of harmful alcohol or drug use, n (%)	15 (13.0)	25 (18.2)	0.33
Pre-morbid history of chronic pain, n (%)	15 (13.0)	18 (13.1)	0.91
Deprivation index, SIMD 2016, n (%):			0.31
Quintile 1 (most deprived)	34 (29.6)	50 (36.5)	
Quintile 2	27 (23.5)	36 (26.3)	
Quintile 3	12 (10.4)	20 (14.6)	
Quintile 4	18 (15.6)	14 (10.2)	
Quintile 5 (least deprived)	21 (18.3)	17 (12.4)	
Time to follow-up, median months (IQR)	15.2 (13.2 to 16.5)	15.9 (14.8 to 17.3)	**<0.01**

ICU: Intensive Care Unit; APACHE II: Acute Physiology and Chronic Health Evaluation Two; SIMD: Scottish index of multiple deprivation; Time to follow-up, months, from hospital discharge; statistical tests: Pearson's chi-squared test for categorical variables, Mann-Whitney U Test for continuous variables.

Although the median time from hospital discharge to completion of one-year follow-up appeared similar, 15.2 months (IQR:13.2 to 16.5) in the usual care cohort vs 15.9 months (IQR: 14.8 to 17.3) in the intervention cohort, these values were statistically significantly different (p<0.01, Mann-Whitney U test). For this reason, Figure 4-2 is presented and gives a better understanding of this variation demonstrating the differences in the distribution in each cohort. Specifically, the number of outliers in the intervention cohort completing follow-up after a very prolonged period after hospital discharge was much greater. There are also a greater number of participants in the usual care cohort completing follow-up between 10 and 12 months after hospital discharge. This emphasises the need to correct for this variation in the modelling process as described in the methods chapter (Chapter 3).

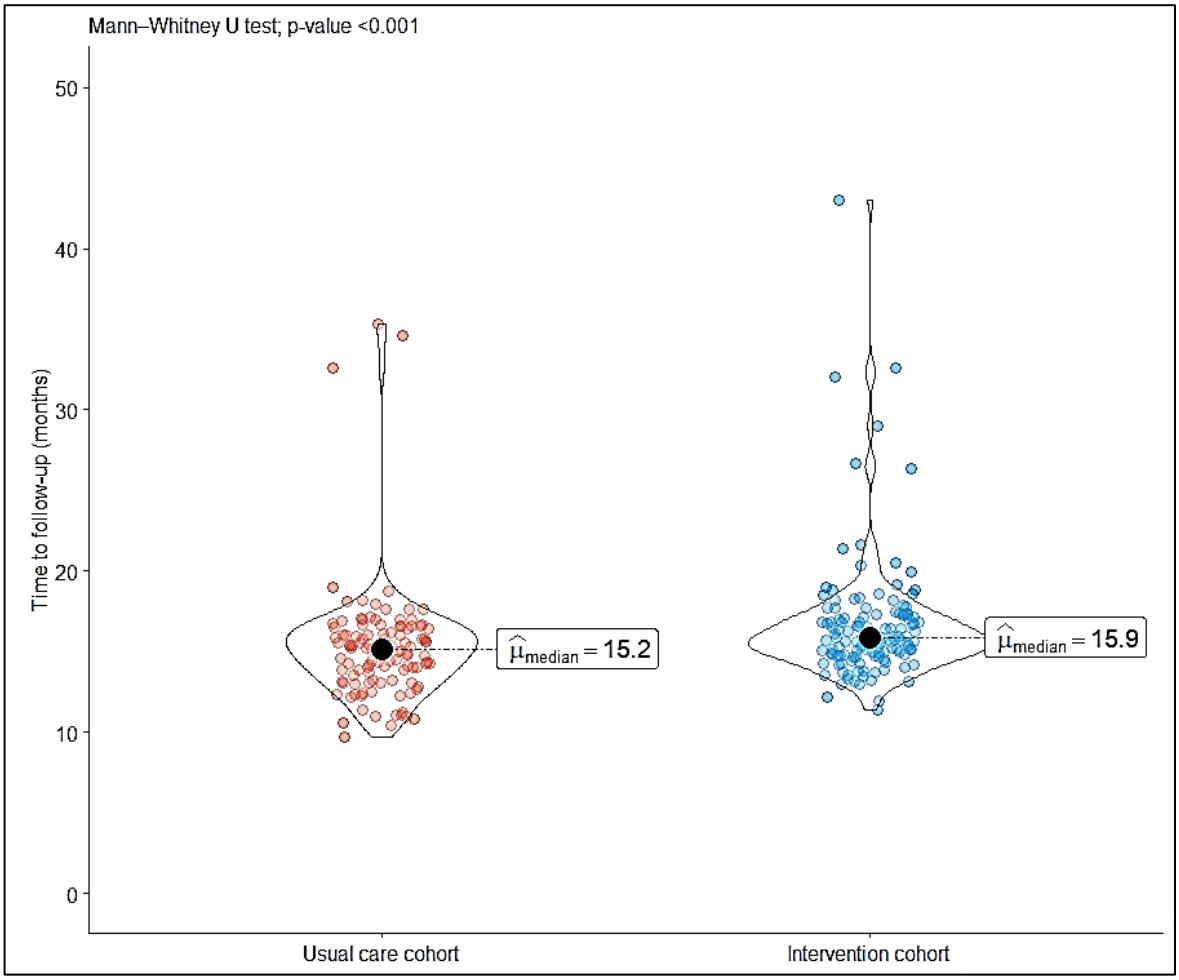


Figure 4-2: Violin plots comparing time from hospital discharge to completion of one-year follow-up.

Time to follow-up was statistically significantly different between the intervention and usual care cohorts. For a description of how to interpret a violin plot please see Appendix 8.

Admission profile was statistically significantly different between the cohorts (Table 4-1), with a higher proportion of medical admissions in the intervention cohort and a correspondingly higher proportion of surgical admissions in the usual care cohort. The number of elective surgical patients was very low in both cohorts, with only 14 (5.6%) patients classed as elective (or scheduled) surgical patients from the entire dataset. This correlated with ten (7.3%) in the intervention cohort and four (3.5%) in the usual care cohort. This is not unexpected given that all of the units were general ICUs and the inclusion criteria was designed to exclude the short stay surgical HDU patients (i.e. only those who required HDU for greater than seven days were included). Furthermore, all the elective patients had unplanned prolonged critical care admissions, in most cases due to complications. Due to the small numbers and confounding factors, no further analysis or comparisons were undertaken between the elective and emergency surgical admissions.

ICU length of stay was shorter in the usual care cohort with a median of 4.95 days (IQR: 2.5 to 9.5) vs 10.5 days (IQR: 6.9 to 17.3) in the intervention cohort; $p<0.01$ (Mann-Whitney U Test). Similarly, hospital length of stay was shorter in the usual care cohort with a median of 18.0 days (IQR: 11.4 to 35.0) vs 30.5 days (17.0 to 49.6) in the intervention cohort; $p<0.01$ (Mann-Whitney U Test).

These imbalances were addressed in the modelling and adjustment processes that have been fully described in the methods chapter (Chapter 3) of this thesis.

4.2.4 Missing data

The total rates of missing data were small, with a total of 2.7% across the entire dataset. This included 1.9% that was missing from the patient characteristics presented in Table 4-1 and 3.4% missing for the outcome data across the four surveys (EQ-5D-5L, GSE, HADS, BPI). The BPI was by far the least well answered survey with 5.6% of the results missing. A full breakdown of the missing data for every variable included in data collection can be found in Appendix 9.

4.3 Primary adjusted outcomes

The primary analysis was a comparison of the intervention cohort and the usual care cohort when adjusted for the variables as set out in the methods chapter (Chapter 3).

4.3.1 Health-Related Quality of Life

After adjustment, using multivariable linear regression, there were statistically and clinically significant differences in the HRQoL measured using the EQ-5D-5L.

The adjusted absolute EQ-5D Health Utility Scores (EQ-HUS) scores were 0.12 (95% CI: 0.04 to 0.20, p=0.01) higher in the intervention cohort compared to the usual care cohort. With EQ-HUS ranging from -0.594 to 1.0, this corresponded to a 7.5% relative increase in the intervention cohort.

Similar results were demonstrated in EQ-VAS, where the intervention cohort reported an adjusted absolute increase of 11.9 (95% CI: 5.9 to 17.9, p<0.001). As EQ-VAS ranges from 0 to 100 this also corresponds to an 11.9% relative increase in the intervention cohort.

Both point estimates for the EQ-5D (EQ-HUS and EQ-VAS) met the well-established MCID of 0.08 and 8 respectively[308,309]. These results, alongside all of the adjusted one-year patient outcomes are summarised in Table 4-2 and Figure 4-3. Full details of the models for HRQoL outcomes alongside all models for the patient outcomes are offered in Appendix 10.

4.3.2 Self-efficacy

After co-variate adjustment (multivariable linear regression), the intervention cohort reported statistically significantly higher self-efficacy scores. The self-efficacy scores were 2.32 points greater in the interventions cohort (95% CI: 0.32 to 4.31, p=0.02). This is equivalent to a relative increase of 7.7% (on the 31 point scale, ranging from 10 to 40) at 12 months, in comparison to the usual care cohort (Table 4-2 and Figure 4-3). The MCID for self-efficacy is less well reported, but this difference is greater than the best estimates used for this thesis of 6%[297].

Table 4-2: Effect of intervention at one-year follow-up (adjusted outcomes)

Outcome measure	Adjusted estimate	P value	95% confidence interval	Relative difference with intervention
EQ-5D summary scores				
Health Utility Score	0.12	**0.01**	0.04 to 0.20	7.5 %
EQ-5D VAS	11.88	**<0.01**	5.91 to 17.86	11.9 %
Generalised Self-Efficacy	2.32	**0.02**	0.32 to 4.31	7.7 %
Brief Pain Inventory scores				
Summary (mean) pain score (across BPI)	-0.62	0.09	-1.35 to 0.11	6.2 %
Average pain score (single question)	-0.75	0.05	-1.50 to 0.00	7.5 %
Worst pain score (single question)	-0.59	0.16	-1.41 to 0.23	5.9 %
Pain interference with enjoyment of life (single question)	-1.00	**0.03**	-1.89 to -0.11	10.0 %
Pain interference on normal work (single question)	-0.69	0.16	-1.66 to 0.28	6.9 %
Mean pain interference summary	-0.73	0.07	-1.52 to 0.06	7.3 %
Hospital Anxiety and Depression Scale (HADS) odds ratios				
HADS depression	0.38	**0.01**	0.19 to 0.76	62 %
HADS anxiety	0.58	0.11	0.30 to 1.13	43 %

Effect of the intervention on quality-of-life outcome measures compared to usual care at one-year follow-up. Linear regression models with absolute effects and scaled relative effects for: 1) EQ-5D-5L, EuroQol five-dimension five-level Health Utility Score; 2) EQ-VAS: EuroQol Visual Analogue Scale; 3) Generalised Self-Efficacy (GSE); and 4) Brief Pain Inventory scores: 3 pain scores and 3 pain interference scores. Logistic regression, with odds ratios for risk of screening for depression (HADS-depression ≥8/21), and anxiety (HADS-anxiety ≥8/21). All models were adjusted for: patient sex; ICU length of stay; APACHE II score; time to follow-up; deprivation index (SIMD quintiles); surgery at admission or in the first week of ICU; Charlson Comorbidity Index (CCI); history of alcohol or drug use; history of pain; and history of pre-existing psychiatric diagnosis.

4.3.3 Mental health outcomes: anxiety and depression

The well-established cut-off value defining depression or anxiety as a score of 8 or greater (≥8/21) for each component of HADS was used during the multivariable logistic regression[45,46,92].

There was a statistically significant, 62% adjusted reduction in the odds risk of screening positive for depression at one year in the intervention cohort (odds ratio: 0.38; 95% CI: 0.19 to 0.76; p=0.01). This would be equivalent to a number needed to treat (NNT) of 4.9 (95% CI: 3.3 to 15.4) if this were repeated in a randomised control trial. This is calculated from the baseline rate of screening positive for depression in the usual care (unmatched) cohort of 42% as outlined in Appendix 11. The remaining unadjusted, unmatched outcomes are also described in Appendix 11.

The differences in the adjusted odds risk ratio for screening positive for anxiety at one year were not statistically significant (odds ratio: 0.58; 95% CI: 0.30 to 1.13; p=0.11).

Therefore, the reported differences were significant when considering rates of depression but not anxiety. HADS has been treated as a binary outcome using logistic regression and as such an MCID value is not well defined. This is why an NNT has been offered simply to place this odds ratio into context and making this outcome more intuitive for the clinician but is illustrative only.

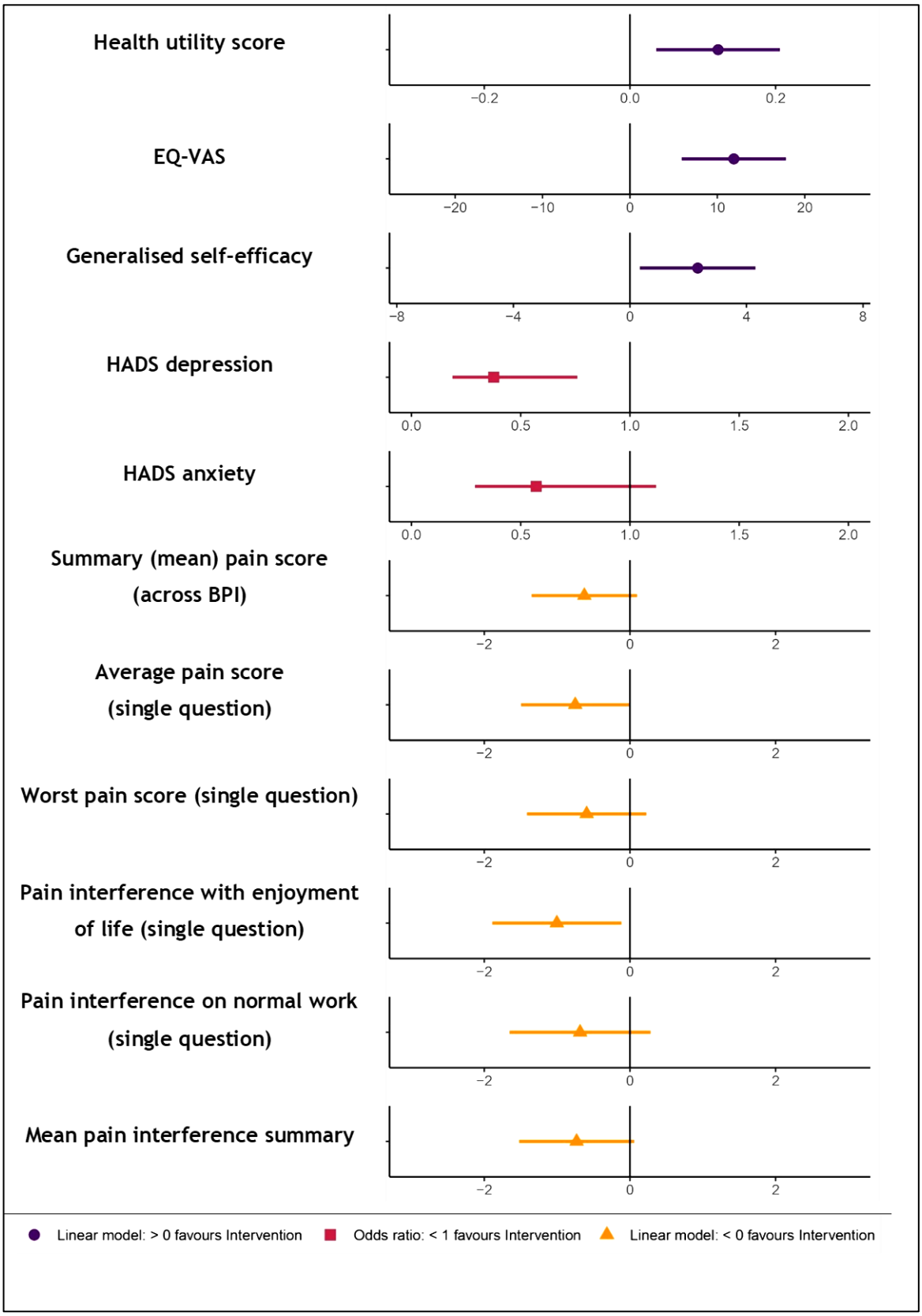


Figure 4-3: Primary patient outcomes forest plot.

Point estimates (circle, square, or triangle) and 95% confidence interval (bars). Linear regression for continuous variables and logistic regression for dichotomous outcomes (HADS depression and Anxiety). EQ-VAS: EuroQol instrument Visual Analogue Scale; HADS: Hospital Anxiety and Depression Scale; BPI: Brief Pain Inventory.

4.3.4 Pain outcomes

Pain appeared to be a significant issue. The BPI demonstrated that those reporting that they experienced pain other than 'everyday kinds of pain' was 149/252 (59.1%) across both the usual care and intervention cohorts.

The modelling and adjustment processes did not demonstrate a consistent effect or statistically significant difference between the intervention and usual care cohorts as scored by the BPI. The effects on the two main outcomes of average pain score (single question) and the mean pain interference scores (the average of all 7 component interference scores) both failed to achieve statistical significance. The point estimate for the relative adjusted average pain score (single question) appeared 7.5% lower in the intervention cohort but this was not statistically significant (absolute difference: -0.75; 95% CI: -1.50 to 0.00; p=0.05). Similarly, the difference in the point estimate for the relative adjusted mean pain interference score was 7.5% lower in the intervention cohort and this too failed to achieve statistical significance (absolute difference: -0.73; 95% CI: -1.52 to 0.06; p=0.07).

The only reported result achieving statistical significance was the change in the interference of pain on the enjoyment in life, which was 10% lower in the intervention cohort after adjustment (absolute difference: -1.0; 95% CI: -1.89 to -0.11; p=0.03).

The other outcomes analysed, which failed to achieve statistical significance, included: summary pain score (mean of all four scores); worst pain score (single question); and pain interference on normal work (single question). All of the reported BPI results are described in Table 4-2 and Figure 4-3. The summary is that the intervention did not demonstrate a statistically significant improvement in the extent or experience of pain, and therefore, it follows that the results were not clinically significant.

4.4 Propensity score matching

The matching process as described in the methods chapter (Chapter 3) was used as a sensitivity analysis to understand how robust the modelling processes and primary outcomes were to alternative approaches. An iterative approach was used to find the best matching formula and the variables included in this final propensity score were: surgery at admission or in the first week of ICU; time from hospital discharge to follow-up; age; hospital length of stay; advanced respiratory support; ICU length of stay; history of harmful alcohol or drug use; and pre-existing psychiatric diagnoses.

4.4.1 The matched cohorts and baseline characteristics

As the usual care cohort was smaller it was matched to the intervention cohort (115 participants vs 137 participants respectively). Using this approach, it was possible to match just under two-thirds (65.2%) of the usual care cohort to the intervention cohort. Table 4-3 outlines a representative dataset of the participant characteristics demonstrating the absence of any statistically significant differences. Specifically, the areas that were significantly different in the original dataset, now have p-values >0.05. The remaining characteristics maintained their similarities across both cohorts. The four area of concern mentioned previously and their completed matched outputs are as follows:

- Time from hospital discharge to completion of one-year follow-up was 15.4 months (IQR: 14.0 to 16.7) in the usual care cohort vs 15.6 months (14.5 to 16.6) in the intervention cohort (p=0.40; Mann-Whitney U Test).

- Admission specialty profile was reasonably matched with surgical admissions representing 48% in the usual care cohort vs 40% in the intervention cohort (p=0.32; Pearson's chi-squared test).

- ICU length of stay was matched resulting in 7.2 days (IQR: 3.9 to 12.8) for the usual care cohort vs 8.3 days (IQR: 5.7 to 12.0) in the interventions cohort (p=0.16; Mann-Whitney U Test).

- Hospital length of stay was matched resulting in a median of 22 days (IQR: 13.2 to 42.0) vs 23 days (IQR: 15.0 to 39.8) in the usual care and intervention cohorts respectively (p=0.68; Mann-Whitney U Test).

One main criticism of the matching approach could be the reliance on the p-value when the reduced sample size is likely to decrease the statistical power to detect differences between the cohorts. To mitigate against this, important variables were also visualised to understand their distribution and spread before and after matching. An example of this, using the previously described time to follow-up is shown in Figure 4-2. This shows that the outlying participants with a prolonged time to follow-up (e.g. >20 months) are more balanced. There remains a greater proportion of participants in the usual care cohort that completed follow-up earlier (e.g. 10 to 12 months) but the difference in the distribution is reduced. Overall this demonstrates the improvements in the balance for this variable while also highlighting the limitations of propensity score matching with this sample size (n=252). That is, the matching process is a relatively crude tool, and justifies the use of covariate adjustment to correct for the final areas of imbalance.

Table 4-3: Propensity score matching participant characteristics

Demographic	Usual care cohort (n = 75)	Intervention cohort (n = 75)	P value
Age, Years, median (IQR)	59.8 (47.5 to 69.8)	59.5 (52.1 to 68.3)	0.75
Male sex, n (%)	48 (64.0)	39 (52.0)	0.14
Admitting specialty, n (%):			0.32
Medical	39 (52.0)	45 (60.0)	
Surgery	36 (48.0)	30 (40.0)	
Surgery at admission or within seven days of ICU, n (%)	26 (34.7)	26 (34.7)	1.00
ICU length of stay, median (IQR)	7.2 (3.9 to 12.8)	8.3 (5.7 to 12.0)	0.16
Hospital Length of stay, median (IQR)	22.0 (13.2 to 42.0)	23.0 (15.0 to 39.8)	0.68
APACHE II score, median (IQR)	19 (15 to 25)	21 (16 to 26)	0.20
Advanced respiratory support, n (%)	64 (85.3)	66 (88.0)	0.63
Complex cardiovascular support requiring multiple vasoactive drugs, n (%)	17 (22.7)	17 (22.7)	1.00
Renal replacement therapy, n (%)	15 (20.0)	15 (20.0)	1.00
Two or greater comorbidities, n (%)	35 (46.7)	32 (42.7)	0.62
Charlson Comorbidity Index (CCI) score, median (IQR)	3 (1 to 4)	3 (1 to 4)	0.87
Pre-existing psychiatric diagnosis, n (%)	24 (32.0)	18 (24.0)	0.28
History of harmful alcohol or drug use, n (%)	11 (14.7)	11 (14.7)	1.00
Pre-morbid history of chronic pain, n (%)	12 (16.0)	10 (13.3)	0.64
Deprivation index, SIMD 2016, n (%):			0.63
Quintile 1 (most deprived)	26 (34.7)	27 (36.0)	
Quintile 2	18 (24.0)	20 (26.7)	
Quintile 3	8 (10.7)	11 (14.7)	
Quintile 4	12 (16.0)	6 (8.0)	
Quintile 5 (least deprived)	11 (14.7)	11 (14.7)	
Time to follow-up, median months (IQR)	15.4 (14.0 to 16.7)	15.6 (14.5 to 16.6)	0.40

Representative dataset of baseline characteristics after propensity score matching. The following covariates were included in the propensity score: surgery at admission or in the first week of ICU; time from hospital discharge to follow-up; age; hospital length of stay; advanced respiratory support; ICU length of stay; history of harmful alcohol or drug use; and pre-existing psychiatric diagnoses. ICU: Intensive Care Unit; APACHE II: Acute Physiology and Chronic Health Evaluation Two; SIMD: Scottish index of multiple deprivation; Time to follow-up, months from hospital discharge. Mann-Whitney U Test used for continuous variables; Pearson's chi-squared test used for categorical variables.

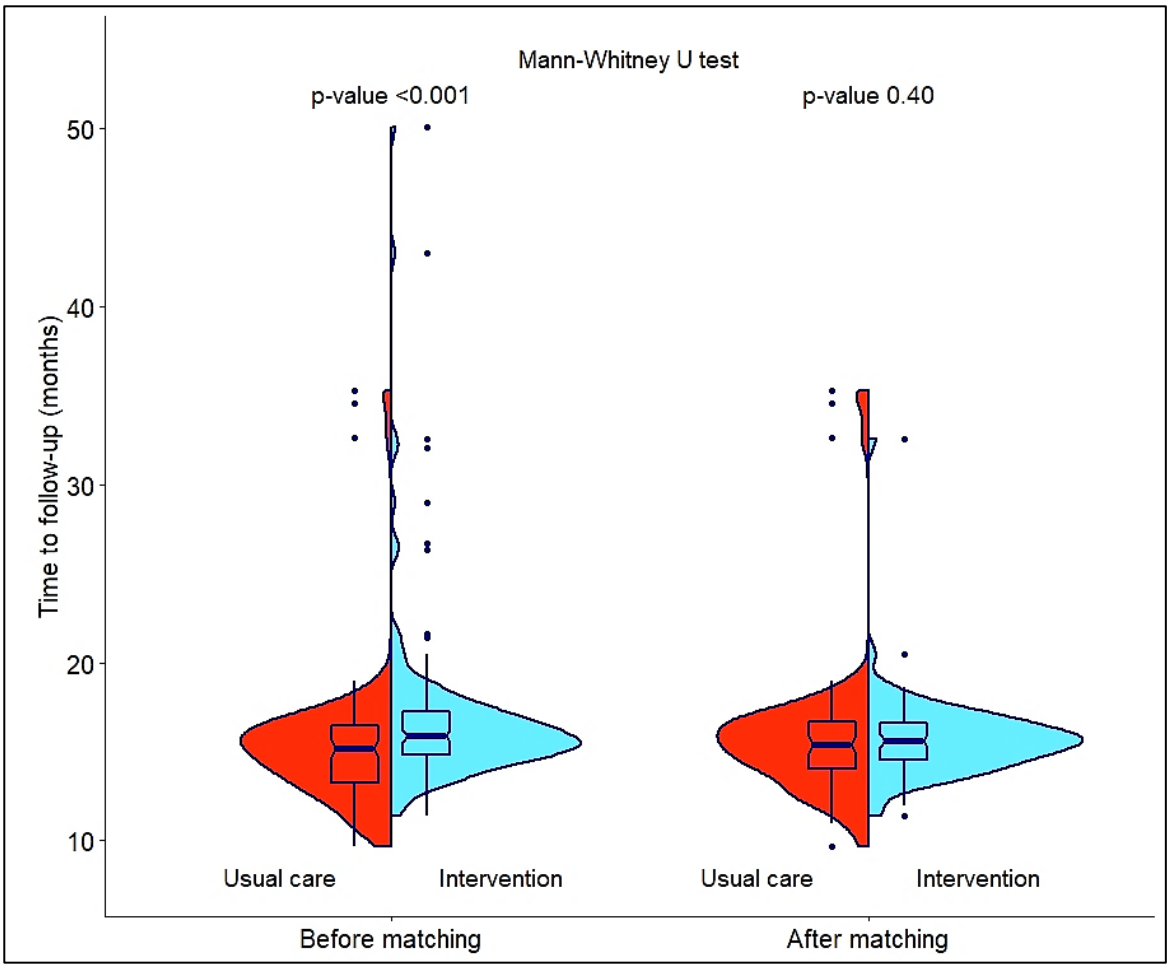


Figure 4-4: Split box-violin plots of time taken from hospital discharge to one-year follow-up, before and after propensity score matching.

Red colour (left) = Usual care cohort; Blue colour (right) = Intervention cohort. The data described as "After matching" are from a representative dataset. For a description of how to interpret split box-violin plots see Appendix 8.

4.4.2 Unadjusted outcomes

Although the propensity score matching process is relatively crude, particularly its use in this dataset, it does lend itself to more conventional statistics, and these are presented in Table 4-4. Broadly the results are similar for the Visual Analogue Scores for HRQoL (EQ-VAS), self-efficacy (GSE), and depression scores (HADS-D) as these passed the threshold of statistical significance. The intervention cohort demonstrated higher scores for HRQoL and self-efficacy, with lower rates of depression.

Table 4-4: Unadjusted outcomes from the matched cohorts

Outcome measure	Usual care cohort (n = 75)	Intervention cohort (n = 75)	P value
EQ-5D summary scores			
Health Utility Score, median (IQR)	0.592 (0.225 to 0.792)	0.639 (0.542 to 0.791)	0.14
EQ-5D VAS, median (IQR)	55 (35.3 to 75.0)	70 (50 to 88.3)	**<0.01**
Generalised Self-Efficacy, Median (IQR)	30 (22.2 to 33.9)	32 (28 to 35)	**0.02**
Brief Pain Inventory scores			
Summary (mean) pain score (across BPI), median (IQR)	3.75 (1.3 to 6.5)	3 (0.3 to 5)	0.13
Average pain score (single question), median (IQR)	5 (1 to 7)	3 (0.2 to 5.8)	0.10
Worst pain score (single question), median (IQR)	5 (2 to 7.9)	4 (0.2 to 7)	0.12
Pain interference with enjoyment of life (single question), median (IQR)	5 (0 to 8)	3 (0 to 7)	0.09
Pain interference on normal work (single question), median (IQR)	5 (1 to 9)	3 (0 to 7.8)	0.18
Mean pain interference summary, median (IQR)	4.4 (0.7 to 7.3)	3.4 (0.1 to 5.9)	0.12
Hospital Anxiety and Depression Scale (HADS)			
Depression score, median (IQR)	8 (4 to 12.8)	6 (3 to 9.8)	**0.02**
Depression, total scoring ≥8/21, total (%)	38 (50.7)	25 (33.3)	**0.03**
Anxiety score, median (IQR)	8 (4 to 13)	7 (4 to 12)	0.32
Anxiety, total scoring ≥8/21, total (%)	41 (54.7)	35 (46.7)	0.33

Unadjusted testing completed with the Mann-Whitney U test for continuous variables and Pearson's chi-squared test for categorical variables. EQ-5D: EuroQol 5-Dimension instrument; IQR: interquartile range; VAS: Visual Analogue Scale; BPI: Brief Pain Inventory. Results are from a representative dataset after multiple imputation and propensity score matching.

The most notable difference between the primary analysis and this sensitivity analysis (which utilised propensity score matching with simple inferential testing i.e. unadjusted-matched) is that the health utility scores (EQ-HUS) achieved statistical significance in the primary analysis but not in the sensitivity analysis. This, therefore, presents conflicting information and the result has not been robust to this sensitivity analysis.

The results for anxiety (HADS-A) and all pain outcomes (BPI) were largely similar, with no results achieving statistical significance. The one difference was the effect of pain on the interference of enjoyment in life, for which a significant difference was demonstrated in the primary analysis, but not in the unadjusted-matched analysis.

Figure 4-5 graphically presents the unadjusted outcomes (simple inferential non-parametric testing, without multivariable regression) for the original dataset (i.e. before matching) and using the propensity score matching datasets. It is notable that the only statistically significant difference in the outcomes before propensity score matching is seen in the EQ-VAS results. No other results achieve significance until after the matching process. The data used to create Figure 4-5 can be found in Table 4-4 for the matched data and Appendix 11 for the data before matching, i.e. the original dataset. These graphs (Figure 4-5) also demonstrate the various clustering, ceiling, and floor effects of the measured outcomes. Ceiling effects are seen in both scores for EQ-5D and self-efficacy, while floor effects are seen with HADS and BPI scores.

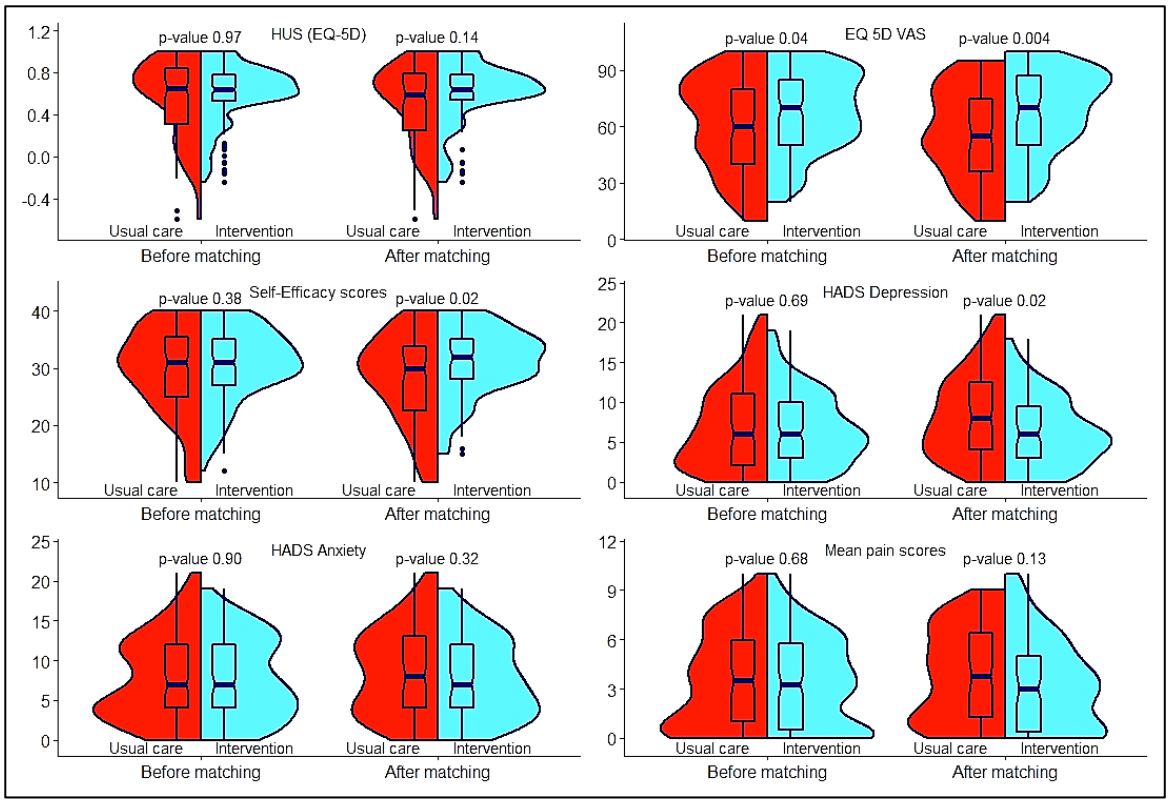


Figure 4-5: Unadjusted outcome measures before and after the matching process.

Differences tested using the Mann-Whitney U test. HUS: Health Utility Score; EQ-5D: EuroQol 5-Dimension Instrument; VAS: Visual Analogue Scale; HADS: Hospital Anxiety and Depression Scale. Data for the matched outcomes are from a representative dataset and can be found in Table 4-4 and the unadjusted unmatched outcomes can be found in Appendix 11.

4.4.3 Matched cohorts: adjusted outcomes

The propensity score matched cohorts were analysed using the same methodology and modelling as used for the primary outcomes. The full details alongside a forest plot showing the results for these adjusted-matched outcomes can be seen in Figure 4-6. This demonstrates that the results for the outcomes of: HRQoL (EQ-HUS and EQ-VAS), self-efficacy (GSE), depression (HADS-D) and anxiety (HADS-A) are similar and robust to this sensitivity analysis. There is no difference in results achieving statistical significance and the clinically important differences also hold true with this analysis. This offers reassurance that despite the reduced power, with the lower sample size, the intervention is significantly correlated with better outcomes for HRQoL, self-efficacy, and rates of depression. Again there was no statistically significant difference in Anxiety scores.

The pain outcomes, however, are statistically different with this analysis. In the primary analysis, it was only the enjoyment in life question that reported a statistically significant difference. In the adjusted-matched analysis, there is a statistically significant difference in five out of six outcomes. The two main outcomes from the BPI were:

- Summary pain score (mean of all four scores) which was 8% lower in the intervention cohort (absolute difference: -0.8; 95% CI: -1.43 to -0.17; p=0.02)

- Pain interference summary was 9.7% lower in the intervention cohort (absolute difference: -0.97; 95% CI: -1.75 to -0.18; p=0.02)

Statistically significant differences were also seen in average pain score, worst pain score, and interference in enjoyment of life but not interference on normal work. The point estimate difference was under one point (1/10) for every pain result except interference on enjoyment in life (absolute difference -1.32; 95% CI: -2.44 to -0.48; p=0.02). The differences themselves are therefore small at approximately one point on a 10-point scale. Furthermore, the two previous analyses (primary analysis and unadjusted-matched) both failed to show a consistent difference between the two cohorts. As such, the results do not support a positive correlation in pain outcomes associated with attendance at the InS:PIRE intervention.

Overall the adjusted-matched sensitivity analysis supports the original reported outcomes and the results are robust to this alternative approach of doubly robust modelling[327]. As already stated, details of all primary patient outcome models can be found in Appendix 10.

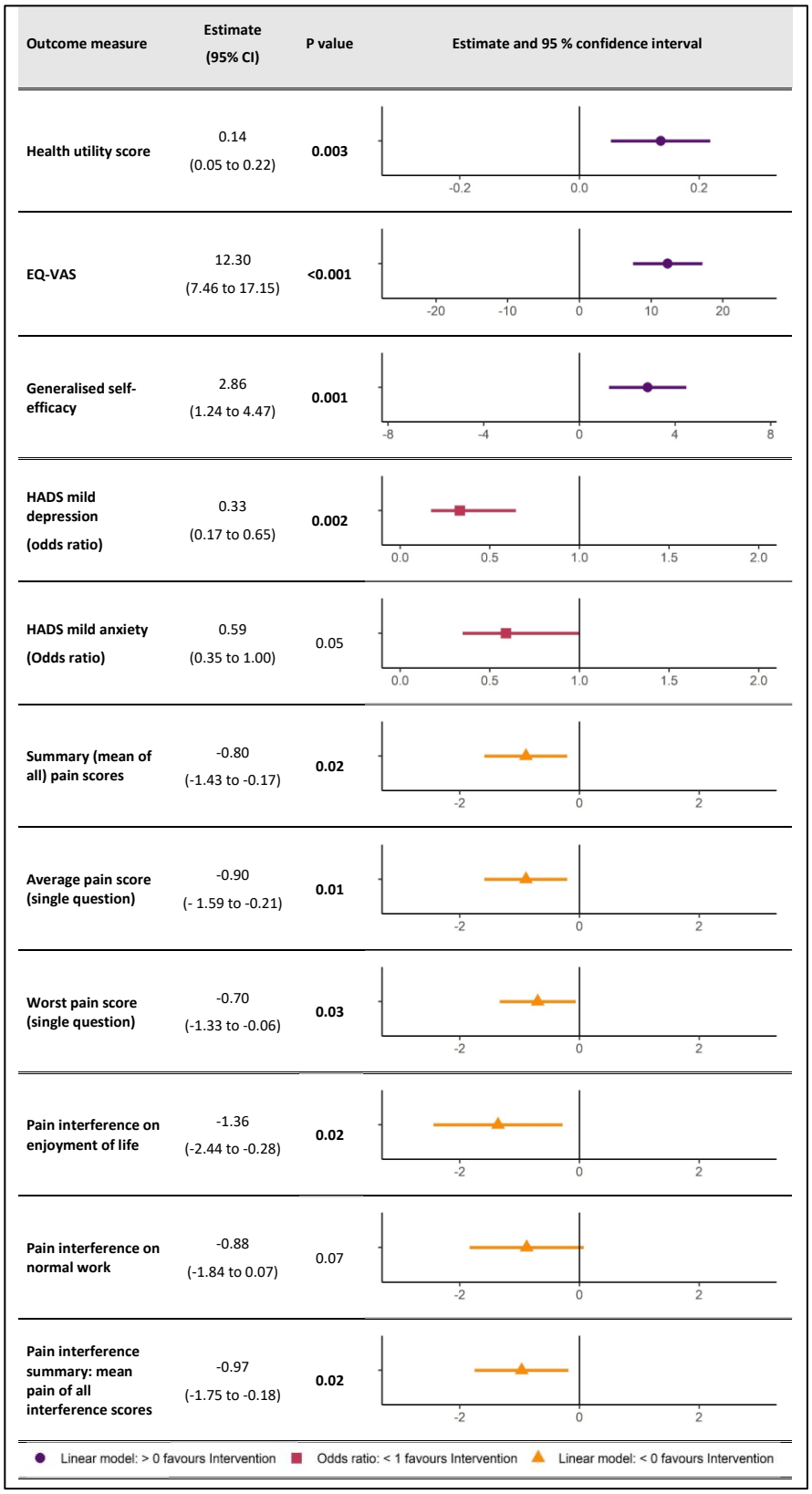


Figure 4-6: Matched and adjusted patient outcomes.

Outcomes table with splines: effects of intervention on all outcome measures alongside coefficient graph of effect size. Absolute change in scores (linear models) and odds risk ratio (categorical outcomes / logistic models) of screening for the condition one year after hospital discharge compared to usual care. Estimate (point) values (circle, square, triangle) and 95% confidence intervals. All models were adjusted for: patient sex; ICU length of stay; APACHE II score; time to follow-up; deprivation index (SIMD quintiles); surgery at admission or in the first week of ICU; Charlson Comorbidity Index (CCI); history of alcohol or drug use; history of pain; and history of pre-existing psychiatric diagnosis.

4.5 Hospital site variation: mixed effects analysis

As previously described (Chapter 3) the intervention was delivered from five sites. The usual care cohort recruited from four primary sites that did not have any ICU follow-up services. The four new intervention sites (i.e. those who delivered InS:PIRE as part of the scaling up project) had initially recruited 15 participants to the usual care cohort before starting to deliver InS:PIRE. Fundamentally, this crossover was minimal (15/252 [6%]) and there remains the possibility that any observed differences in outcomes at one year could be the result of in-built variation between the sites rather than through the intervention. This sensitivity analysis was conducted to help address some of this uncertainty relating to base hospital effects.

The sites for this sensitivity analysis are considered as either medium general acute hospitals or large tertiary referral hospitals. This final sensitivity analysis was conducted while considering both fixed and random effects and for reasons of pragmatism and practicality only the overall HRQoL outcome was considered (EQ-HUS).

4.5.1 Spread of hospital sites

In the intervention cohort 66 (48.2%) participants received the intervention after being treated in one of the four medium general acute hospital, whereas 71 (51.8%) participants had been treated in the large tertiary referral hospital. In the usual care cohort 45 (39.1%) of those recruited had been treated in a medium general acute hospital and 70 (60.9%) participants were from a single large tertiary referral hospital.

Table 4-5 is a contingency of hospital site type and cohort allocation. The differences in spread between groups was not significant on assessment with Pearson's chi-squared test (p=0.19) and would suggest that this variability is unlikely to have influenced the results significantly. The cluster sensitivity analysis was completed as planned to verify this assumption.

Table 4-5: Hospital site type vs cohort group contingency table.

Hospital site type	Usual care cohort	Intervention cohort	P value
			0.189
Medium general acute hospitals	45 / 115 (39.1%)	66 / 137 (48.2%)	
Large tertiary referral hospital	70 / 115 (60.9%)	71 / 137 (51.8%)	

P-value calculated using Pearson's chi-squared test.

4.5.2 Hospital type effects on HRQoL

Firstly, the fixed effects were considered for hospital type and HRQoL; hospital type was added to the original multivariable models (adjusted-unmatched). The reference variable was treatment in the ICU of a medium general hospital, where the relative fixed effects described the correlation with HRQoL and treatment in the ICU of a Large tertiary referral hospital.

The variables included in the model were the same as described throughout this chapter and Chapter 3, including the intervention (vs usual care). There was no significant difference in EQ-HUS at one year for those treated in the large tertiary referral hospital (absolute difference: 0.02; 95% CI: -0.06 to 0.10; p=0.61). The effects on those in the intervention cohort compared to the usual care cohort were also unchanged with this additional variable (absolute difference: 0.12; 95% CI: 0.04 to 0.20; p<0.01).

The mixed effects model included hospital site as a fixed variable (as described above) but also included this variable as a random effect which is one that influences the intercept of the y-axis on the linear regression model. This had no effect on the results and the random effect on the intercept was almost negligible (1.61×10^{-6}).Table 4-6 presents summarises of both the fixed effects model and random effects model, presenting both the intervention and hospital site effects.

Table 4-6: Effects of hospital site on EQ-5D-5L Health Utility Score: fixed and mixed effects models

Covariate and model	Effect estimate	95% confidence interval	P Value
Fixed effects model			
Intervention cohort	0.12	0.04 to 0.20	**<0.01**
Large tertiary referral hospital	0.02	-0.06 to 0.10	0.61
Mixed effects model			
Intervention (fixed effect)	0.12	0.04 to 0.20	**<0.01**
Large tertiary referral hospital (fixed effect)	0.02	-0.06 to 0.10	0.61
Random effects (as part of mixed effects model)	**Variance: random effects on intercept**		
Large tertiary referral and medium general acute hospital	1.61×10^{-06}		

Both fixed and mixed effects models are presented. The intervention results are the adjusted fixed effects differences in the intervention cohort compared to the usual care cohort. The hospital site results are the fixed effects differences in those who were treated in the large tertiary referral hospital compared to those treated in the medium general acute hospitals. The random effects are presented as the variance in the intercept between the two hospital groups. The additional variables included in both models were: patient sex; ICU length of stay; APACHE II score; time to follow-up; deprivation index (SIMD quintiles); surgery at admission or in the first week of ICU; Charlson Comorbidity Index (CCI); history of alcohol or drug use; history of pain; and history of pre-existing psychiatric diagnosis.

4.6 Summary of all sensitivity analyses

Overall, the models were robust to the multiple sensitivity analyses. Differences in EQ-HUS, EQ-VAS, self-efficacy, and HADS-depression were statistically and clinically significant in the primary adjusted models. The differences remained significant in the matched adjusted outcomes for all four measures of HRQoL. The only variation was in the secondary analysis of the matched unadjusted outcomes where EQ-HUS was not significantly different but the other three remained significant. There was also no correlation between the type of hospital and HRQoL (EQ-HUS) at one year after hospital discharge.

The HADS-anxiety outcomes were not statistically significantly different in the primary analysis or any subsequent matched analysis and, therefore, no clinical difference is reported across the two cohorts.

The only consistent difference in pain outcomes was the correlation between the intervention and a reduced effect of pain on the enjoyment of life. This did not reach the threshold of clinical significance but remained present in the unmatched and matched adjusted cohorts. The other pain outcomes failed to demonstrate any significant differences.

4.7 EQ-5D domain exploratory analysis

A final exploration was undertaken to help understand the effects of the intervention on the specific domains of the EQ-5D. As previously stated, there are 5 levels for each domain. To simplify this analysis the domains of the EQ-5D were divided into binary outcomes using 3/5 (moderate problems) as the cut-off threshold. Therefore, scores of one or two (none or mild problems) were considered to represent no problems in the domain, while scores of three, four, or five (moderate, severe, and extreme problems) were considered to screen positively for issues in that domain. A logistic regression was then carried out using the same covariates as the original adjusted regression analyses.

This analysis is summarised in Figure 4-7 which demonstrates that there was a statistically significant 69% lower odds of screening positive for problems in the self-care domain for those in the intervention cohort (odds ratio: 0.31; 95% CI: 0.15 to 0.64; p=0.002). The other four domains (mobility, usual activities, pain and discomfort, and anxiety and depression) all failed to demonstrate a significant difference between the groups. A further visual analysis of the frequency and severity of problems occurring in the matched cohorts is offered in Appendix 12 after the full model specifications.

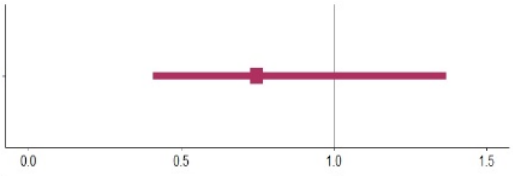
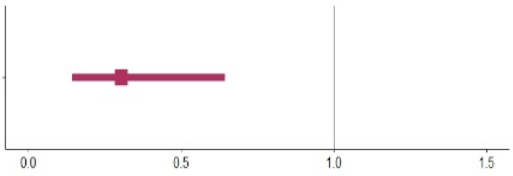
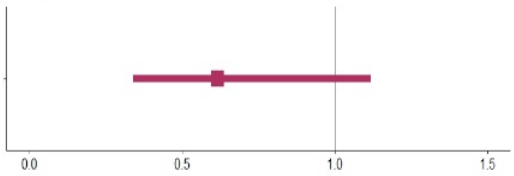
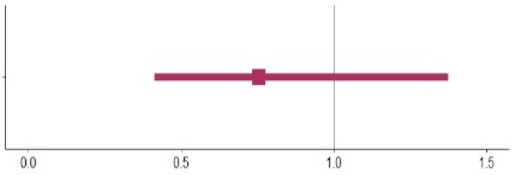
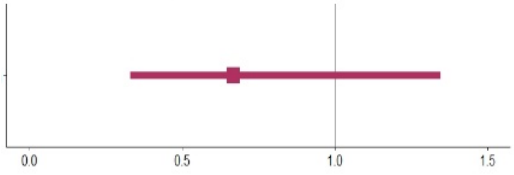
EQ-5D domain	Odds ratio (95% CI)	P-Value	Estimate and 95% confidence interval
Mobility	0.75 (0.41 to 1.37)	0.34	
Self-care	0.31 (0.15 to 0.64)	**0.002**	
Usual Activities	0.62 (0.34 to 1.12)	0.11	
Pain and discomfort	0.75 (0.41 to 1.38)	0.36	
Anxiety and depression	0.67 (0.33 to 1.35)	0.26	

Figure 4-7: EQ-5D individual domain adjusted logistic regression analysis.

Risk of screening positive (≥3/5) for each of the 5 domains of the EQ-5D in the intervention cohort compared to the usual care cohort. Adjustment was for: patient sex; ICU length of stay; APACHE II score; time to follow-up; deprivation index (SIMD quintiles); surgery at admission or in the first week of ICU; Charlson Comorbidity Index (CCI); history of alcohol or drug use; history of pain; and history of pre-existing psychiatric diagnosis. Full model specifications are described in Appendix 12.

4.8 Discussion

4.8.1 Summarising all analyses

This multicentre study, which evaluated a health and social model of care for ICU recovery, demonstrated a significant and clinically important improvement in HRQoL and emotional outcomes for survivors of critical illness. As far as can be ascertained, this is the first multicentre study internationally to report any long-term benefits from any outpatient intervention designed for ICU survivors.

Specifically, these results demonstrate higher scores for both components of the EQ-5D-5L (EQ-HUS, EQ-VAS) and self-efficacy (GSE), alongside lower rates of depression (HADS-D) in the group of patients attending the InS:PIRE programme (intervention cohort) compared to those who did not (usual care cohort). This primary analysis adjusted for important covariates using multivariable regression. Multiple sensitivity analyses were used to explore how robust these results were and overall the results from the primary analyses held true.

An unadjusted matched analysis demonstrated the same outcomes for EQ-VAS, self-efficacy, and depression but failed to demonstrate a statistically significant difference between the cohorts for EQ-HUS. It is not possible to know why this result failed to achieve significance. Some possible explanations include that the reduced sample size may have reduced the power and ability to detect a significant difference. The ceiling effect (as seen in Figure 4-5) of the EQ-HUS crosswalk scores with clustering of results around the upper scores, may also have contributed to this result. It may also mean that this result is less reliable and warrants further testing in future studies.

The adjusted matched cohorts on the other hand replicated the statistically and clinically significant differences that were seen in the original analysis for EQ-HUS, as well as EQ-VAS, self-efficacy, and depression. This ‘doubly robust’ sensitivity analysis increases the confidence that the effects demonstrated here are correlated with attending InS:PIRE; the measured effects are less likely to be due to an imbalance in the groups resulting from the underlying methodology of the study or the differences in the baseline characteristics.

A final sensitivity analysis aimed to assess the impact of hospital site on the outcomes. Using both fixed effects and mixed effects (random and fixed effects together) models there appeared to be little effect on HRQoL (EQ-HUS) at one year correlated with the type of hospital the patient was treated in. This is reassuring that outcomes are consistent between types of hospitals. It also demonstrates that the variation associated with hospital type (the random effects) were small and any effect from these small differences was similarly not represented within the fixed effects outcomes.

No statistically significant differences between cohorts were demonstrated in the rates of anxiety in the adjusted outcomes, whether these were matched or unmatched. There were also no statistically significant differences in anxiety in the unadjusted matched data, whether this was tested as a categorical outcome (Chi-squared testing; HADS-A cut-off ≥ 8), or a continuous outcome (Mann-Whitney U Test). These results would suggest that InS:PIRE was not associated with an improvement in this aspect of emotional health and strategies specifically targeting anxiety warrant further investigation.

Pain was reported commonly one year after hospital discharge in both groups, in approximately two-thirds (59%) of participants. There were mixed results in various aspect of the BPI. The strongest signal of a difference was in the interference of pain on the enjoyment in life which demonstrated lower scores in the intervention cohort in the adjusted-unmatched data (primary analysis) and adjusted-matched data (sensitivity analysis). Other outcomes for the BPI did demonstrate better scores in the adjusted-matched data. Given the reduced sample size in this analysis this is unexpected and statistically noteworthy. The unadjusted analysis (Figure 4-5) demonstrated that there were larger median differences between the cohorts after the matching process for mean pain scores. Given this was the starting point (before adjustment), the adjustment with linear regression has accentuated these differences resulting in the final reporting of the significant results. It is likely, the differences observed after matching have also reduced the variance in the matched dataset and given a significant result. It should also be noted that this result is, perhaps, not so surprising as the point estimates in the primary regression models were universally towards the intervention cohort. It would seem much more likely that there would be a chance

result showing lower scores in the intervention cohort. Despite the statistical interest, none of this gives a statistically robust result and should be interpreted with caution. The overall conclusions of the pain outcomes should be that there were minimal statistically significant differences between cohorts and no meaningful clinically significant differences. The exploration of pain in this study has been noteworthy in highlighting the extent of pain after critical illness which will be valuable for future research.

Lastly, an exploratory analysis identified a lower odds of having moderate problems or greater (≥3/5) in the domain of self-care in the InS:PIRE group compared to usual care. There were no significant differences in the other four domains of the EQ-5D-5L (mobility, usual activities, pain and discomfort, anxiety and depression). The aim of this was to explore mechanistically, how InS:PIRE could improve HRQoL. It is striking that one of the key aims of the intervention is to improve independence and it was the self-care domain where the only statistically significant difference was demonstrated. This could, of course, be a coincidence and simply highlights that more work is required to better understand the mechanisms behind InS:PIRE and the important components of HRQoL that need to be targeted.

4.8.2 The wider context of InS:PIRE and the patient outcomes

Other interventions targeting PICS have demonstrated isolated improvements, such as a reduction in PTSD[329]. However, benefits in overall HRQoL have remained elusive[239,240,329,330]. Existing strategies have largely focused on specific interventions, often with a single healthcare professional group or small MDT[330]. Few studies have targeted complex approaches combining the healthcare MDT with a recognition of the significant financial and social drivers of reduced HRQoL after critical illness. InS:PIRE differs from previous studies by bringing these important concepts together. The MDT involved is not limited to the specific dimensions of PICS or simply the new problems, but instead is directed by what is important to the patient[331]. In this way interventions are focused on both the problems having the greatest impact on each patient's life and the solutions that patients are most motivated to pursue. The adaptability of this approach allows the programme to have relevance and benefits for the diverse groups of patients seen in the general ICU.

InS:PIRE aimed to improve health literacy and access by guiding the patients to existing community interventions through signposting. In practice the MDT would inform the patients about what help, and community organisations were available but encourage them to actively pursue these interventions themselves. Thus, the patients would benefit from both the intervention and by the experience of navigating access to it with support from the clinical teams. The goal is therefore to improve the patients' skillset in navigating the broader health and social care systems. The aspiration is that these effects can last beyond the intervention itself with cascading benefits for each patient's HRQoL and socioeconomic wellbeing.

The overt socioeconomic support that InS:PIRE offers is the greatest and most significant difference from other existing programmes and the contemporaneous literature. The economic support is clear and measurable with the direct contact from specialists in social and financial advice (in this case Citizens Advice Bureau). It is common for issues of benefits, employment, and housing to be raised and addressed during InS:PIRE. This support will frequently have direct, tangible, and prolonged lasting effects on improving the QoL and socioeconomic circumstances for families aiming to live after critical illness. The social support is equally important but more difficult to define. Some of this will be delivered by goal setting from the InS:PIRE team and directed by the participants.

However, the peer support delivered alongside the health and economic evaluations is likely to contribute substantially to the social rehabilitation of these patients. Furthermore, peer support has been reported as being important and valued by survivors as a standalone intervention[332]. The key difference with peer support in the InS:PIRE intervention is that this is an embedded part of the broader programme, rather than a standalone 'self-help' group[332]. This likely resulted in peer support reaching groups of patients who have not normally chosen to access a standalone intervention or group. Alongside the social rehabilitation offered by peer support, this treatment can have further crossover effects, particularly with mental health. Patients are likely to benefit from the normalisation of the shared lived experience which can result in a reduction in anxiety post-ICU[333]. Interestingly, as already noted, there was not a statistically significant difference in anxiety levels between the groups. This may also suggest that it was the social aspects of peer support that resulted in measurable benefits for HRQoL rather

than the mental health aspects. However, more work would be required to better understand the precise mechanisms behind this. Similarly, more work is also required to understand how we can reduce anxiety in ICU survivors and how we can understand the overlap between socioeconomic rehabilitation, mental health outcomes, and HRQoL.

It is likely that improvements in self-efficacy, self-determination, and a general improvement in navigating complex healthcare systems is another driver behind the benefits of the InS:PIRE programme. This enhanced skillset in navigating complex health and social care systems also applies to the entire family unit of ICU survivor and caregiver. The longitudinal nature of InS:PIRE further consolidates these effects. With repeated visits allowing patients the opportunity to incrementally increase independence and consolidate self-management skills. This is in direct contrast to the majority of ICU follow-up services that have been described in the scoping review (Chapter 2) and most services offer a single snapshot intervention or appointment[274,334].

Conversely, the time limited nature of InS:PIRE, occurring repeatedly, but ending after five weeks creates a unique intervention within healthcare. Often patient-healthcare interactions are very brief (visit to the hospital specialist as a single referral) or very long-term (e.g. family physician / GP) that may exist over a lifetime. Few outpatient interventions occur over a medium timeframe. This unique component could have been responsible for some of the effectiveness of InS:PIRE and is certainly an interesting area which merits further exploration.

As stated previously, almost two-thirds (59%) of patients in both the usual care and intervention cohort described pain beyond ‘everyday aches and pains’ at approximately one year after hospital discharge. It cannot be stated that InS:PIRE had a significant impact on pain. As InS:PIRE was never conceived to be a pain management programme this result is unsurprising. The counter argument may be that InS:PIRE inherently has significant crossover with existing pain management programmes[335]. The most obvious examples would be the targeted pharmacy review, the physical rehabilitation components, focus on pacing of activities, and the embedded self-management strategies[313,335-337]. However, despite these shared elements, pain was not the fundamental focus of InS:PIRE and the results reflect this. There is a real need for further studies to better understand the

mechanisms and drivers of pain associated with PICS. This would allow the design of targeted pain interventions for survivors of critical illness.

This study was not designed to understand the mechanisms behind why or how InS:PIRE resulted in lasting benefits for patients at and beyond one year after critical illness. Despite this, this discussion considering the differences between the existing literature and InS:PIRE has highlighted important areas that could explain some of these mechanisms. Most importantly, the socioeconomic rehabilitation that includes direct financial advice and peer support, are the most likely elements which have contributed to the HRQoL outcomes in this chapter. Other elements that may have contributed, or at least had synergistic benefits alongside socioeconomic reintegration are the traditional MDT review, and signposting with its effects on self-efficacy.

4.8.3 Strengths and limitations

Strengths of this study are its multicentre nature and the rigorous and multiple approaches utilised to assess outcomes. Despite this there are obvious limitations. The primary limitation of this study is that it is not an RCT which significantly impacts the ability to attribute causation to the observed effects. There was substantial overlap in baseline characteristics between the intervention and usual care cohorts demonstrated by the baseline demographics tables and the propensity score matching analysis. However, there was no random assignment to groups. Significant steps have been undertaken to address this limitation through the manifold sensitivity analyses including propensity score matching and adjustment for important pre-defined confounders. The significant and meaningful results highlight a strong correlation between multiple areas of HRQoL and InS:PIRE, but as mentioned, causation should not be assumed. A future RCT would therefore be required if the goal was to equivocally demonstrate the causative effects of InS:PIRE.

Missing data could also be an issue with this type of dataset, although the total proportion of missing data was low. The underlying assumption was that data were missing at random rather than systematic, and certainly the comparison on the postal survey results would support this assumption but does not prove this. To further minimise these effects multiple imputation was utilised, although there

could still be some unmeasured confounding which affected the results. Furthermore, the attempts to fully account for confounding with the reduced cohort size in the matched analysis, may have resulted in a particular failure to demonstrate significant effects in important outcomes. The EQ-HUS and the pain outcomes in particular could have been influenced by this. Alternative techniques could have been considered such as inverse probability weighting regression, and propensity score regression, however, there are similar limitations regardless of approach.

A glaring omission is the absence of a cognition outcome measure as described by the SCCM[46]. This study was designed, and recruitment commenced before recommendations on default testing for PICS and before recommended core outcomes existed for ARF research[45,46]. It should also be noted that cognitive outcome measures were not prioritised by the patient and family groups involved in the study design. This, however, could have been due to the selection process involved in the original focus groups. Future work should consider including an assessment of the effects of the intervention on cognitive outcomes given the importance of cognitive dysfunction to the definition of PICS[45].

The recruitment numbers in the usual care cohort were lower than anticipated. Due to the COVID-19 pandemic, recruitment in the usual care cohort was deliberately stopped early to minimise confounding effects on HRQoL during this unpredictable time. This explains the lower than expected total numbers but not the low return rates. Likewise, it could be suggested that those who attended the InS:PIRE programme may have been more engaged with their health. As such, better outcomes would be expected in those participating in the intervention. A counterpoint to this is that the socioeconomic spread was good in both cohorts. Furthermore, the ‘difficult to access’ patients were well represented with a high proportion of those attending InS:PIRE having a history of alcohol excess and drug use.

Overall return rates were low, at a quarter in each cohort, when defined as the proportion completing one-year follow-up after initial invitation to participate. This is not unusual for this type of study and even if the study was repeated as an RCT it is likely that similar limitations would persist. The one modification for future studies would be to embed different modes of contacting participants after

initial enrolment in the programme or study. This would have to be carefully balanced against the important ethical implications of overly harassing participants who have no ongoing desire to complete follow-up. This was part of the consideration during this study design and the reason why multiple repeated requests were not part of the original ethical proposal (e.g. two letters maximum in the usual care cohort). Technology may be able to improve this, and prospective recruitment while in hospital with the participants choosing their preferred contact method may be something to consider for future studies.

This analysis has not included any cost evaluation and given the financial and personnel resource implications of this intervention an economic evaluation would be needed to fully understand any potential benefit. Once more, this would best be done as part on an RCT.

4.8.4 Conclusions

This multicentre study of a complex intervention for survivors of critical illness has shown that attending InS:PIRE was associated with improved HRQoL and emotional health one year after hospital discharge.

Chapter 5 Results: Effectiveness of InS:PIRE on one-year caregiver outcomes

5.1 Overview

5.1.1 Caregiver definition

As stated in previous chapters (Chapter 1 and Chapter 3), a caregiver for the purposes of this thesis, is the individual who the patient identifies as their closest or primary support. This could be a family member of any relation, a friend, or anyone else identified by the patient. In many circumstances there may not be any direct care delivered by this person and in some circumstances the patient may be the carer for their caregiver. This pragmatic approach allowed the definition to be more patient centred and allow the patient to identify who was most likely to be affected by their ICU stay.

5.1.2 Methods

The purpose of this chapter is to compare the outcomes between the caregivers who attended InS:PIRE (intervention cohort) and those who did not attend InS:PIRE (usual care cohort) one year after hospital discharge. The methods for this are fully outlined in Chapter 3. As a reminder the outcome measures used for this section are:

- Hospital Anxiety and Depression Scale (HADS) scores for depression (HADS-D) and anxiety (HADS-A)
- Caregiver strain index (CSI)
- Insomnia Severity Index (ISI)

These surveys generated four outcomes, and each outcome has its own cut-off value to describe the presence or absence of the relevant condition. Table 5-1 describes and summarises the cut-off values and descriptors for each survey.

Table 5-1: Summary of caregiver outcome measures

Outcome measure	Outcome descriptor	Scoring values
Hospital Anxiety and Depression Scale (HADS)	14 item questionnaire, each scored 0 to 3. Separate scores for anxiety and depression (7 items each) scored out of 21.	Total score out of 21 (for each component) 0 to 7: Normal 8 to 10: Mild 11 to 14: Moderate 15 to 21: Severe Anxiety or depression considered present if component score ≥8/21.
Caregiver Strain Index (CSI)	13 item questionnaire. Items relate to: emotional adjustment; social issues; physical strain; and financial strain.	Total score out of 13 Each question is given 1 point for agreement. A score of 7 or greater is considered the cut-off point for a high level of stress.
Insomnia Severity Index (ISI)	7 item questionnaire to help diagnose clinical insomnia. The items are all scores from 0 to 4. Three questions score the severity of sleep problems, while 4 questions score the participants satisfaction with sleep.	Total score out of 28. 0 to 7: No clinical insomnia 8 to 14: subclinical insomnia 15 to 21: moderate clinical insomnia 22 to 28: severe clinical insomnia. Insomnia was considered to be present for scores ≥8/21.

All of the outcomes were modelled using logistic regression. The caregiver covariates included in the primary multivariable logistic regression were: relationship with the patient; caregiver age; caregiver sex; time to follow-up; socioeconomic deprivation index (SIMD quintiles). Important patient factors were also included in the regression models and adjusted for, these included: hospital length of stay; patient age; and the presence of a pre-existing (before hospital admission) psychiatric or mental health diagnosis.

A significant difference between this methodology and the patient methodology was that fewer sensitivity analyses were undertaken. This was primarily due to the lower numbers recruited to this study. The smaller cohort would have meant that a propensity score matching approach would have resulted in a cohort with too few participants to conduct multivariable regression.

After the presentation of results this chapter also offers a discussion of these results placing them in the context of the wider literature.

5.2 Study period, participants, and their characteristics

5.2.1 Study recruitment period

Caregivers were co-recruited when patients were recruited. All the paired ICU admissions occurred between August 2014 and May 2019.

5.2.2 Participant recruitment and retention

In the intervention cohort 206 patients consented to participation, of whom, 136 caregivers consented to participate in the study. The total number of caregivers who were consented and completed survey measures at one-year follow-up was 81 (60%).

In the usual care cohort, 452 patients were approached to participate, of whom 115 consented to participate. From this group, 89 caregivers (77%) completed consent forms and participated in follow-up.

The total number of caregivers who completed follow-up at one year was therefore 170 participants. The flow of participant recruitment for both cohorts is outlined in Figure 5-1.

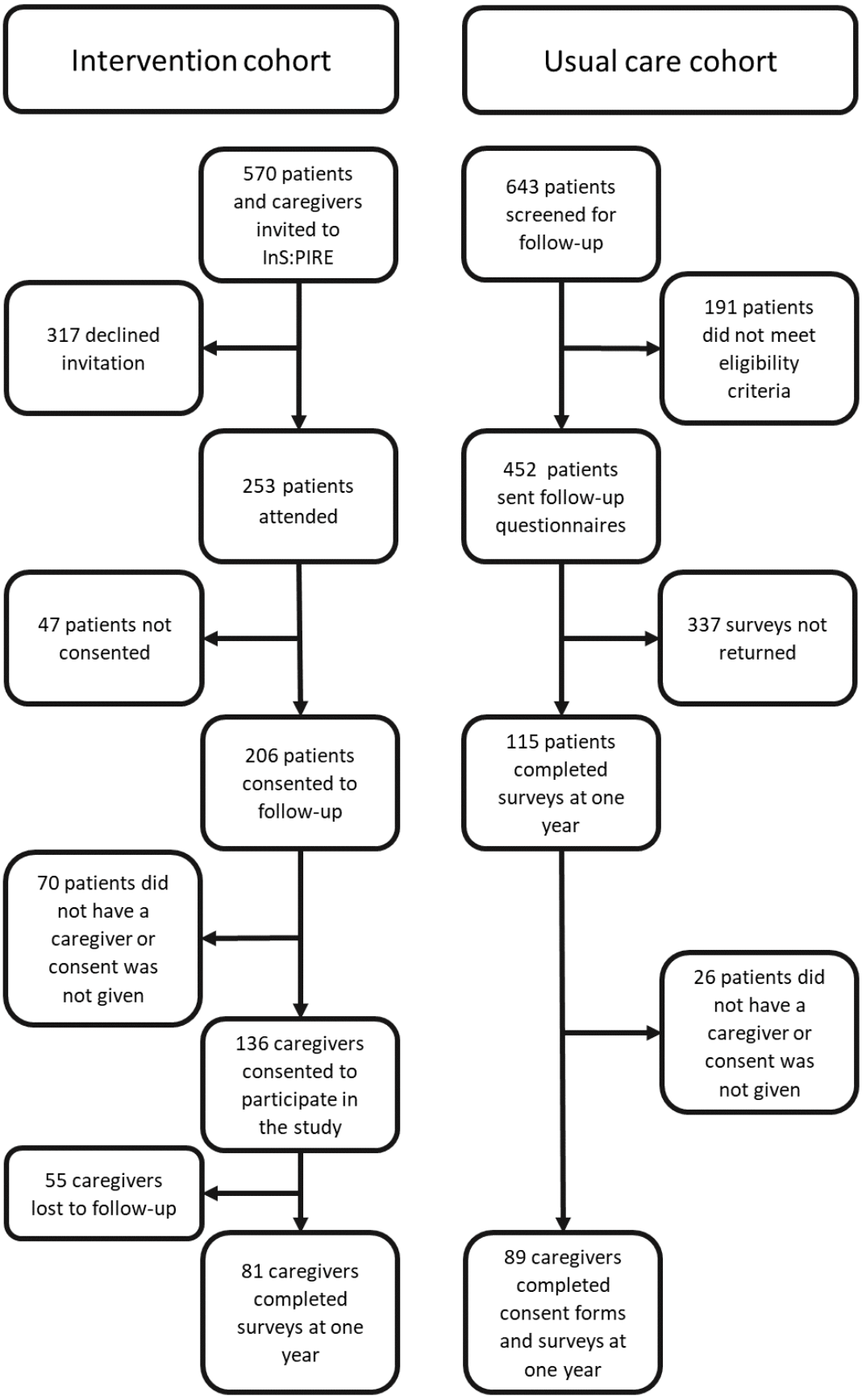


Figure 5-1: Caregiver flow, recruitment, and retention: intervention and usual care cohorts

5.2.3 Participant characteristics

Full details of the participant characteristics for those completing one-year outcome measures can be found in Table 5-2. Most of the participant characteristics were similar between the cohorts.

The relationship the caregiver had with the patient demonstrated a similar spread between the cohorts and did not demonstrate a statistically significant difference between cohorts (p=0.47; Pearson's chi-squared test). The majority of the caregivers were a partner or spouse, with 66 (74.2%) in the usual care cohort and 54 (66.6%) in the intervention cohort described this way. The next most common relationships were those from a younger generation from the family unit with 16 (18.0%) in the usual care cohort vs 13 (16.1%) in the intervention cohort described as a child or grandchild. Few caregivers described themselves as a parent within this study, 11 (6.5%) in total, and only 10 (5.9%) whose relationship was described as 'other'.

Median age for both cohorts was 58 years (usual care cohort IQR: 47.7 to 69.0; intervention cohort IQR: 48.0 to 66.3; p=0.88, Mann-Whitney U test). Sex was similar with 36% male in the usual care cohort vs 37% in the intervention cohort and p=0.79 (Pearson's chi-squared test).

There were no statistically significant differences in the spread of deprivation across quintiles, as measured using the SIMD and Pearson's chi-squared test (p=0.5).

The patient characteristics of the associated caregivers who were included in this study were also largely similar (Table 5-2). Associated patient age was 63.9 years (IQR: 49.7 to 71.4) in the usual care cohort vs 58.7 years (IQR: 51.1 to 67.7) in the intervention cohort (p=0.16, Pearson's chi-squared test). Sex of the associated patient was also very similar with 50 (56.2%) male in the usual care cohort vs 41 (50.6%) in the intervention cohort. Severity of illness described using the APACHE II score was the same in both groups, with a median of 19 (IQR usual care cohort: 14.9 to 25.0; IQR intervention cohort: 15.0 to 26.0). Similarities can also be seen between the paired patients who had pre-existing psychiatric diagnoses, rates of

advanced respiratory support (mechanical ventilation), two or greater comorbidities, and admission specialty (Table 5-2).

The key areas of difference, as identified by formal testing using Pearson's chi-squared test for categorical variables and Mann-Whitney U Test for continuous variables were in the lengths of stay and the time to follow-up. Median ICU length of stay was shorter at 4.75 days (IQR: 2.4 to 9.6) in the usual care cohort compared to 11.3 days (IQR: 7 to 19.7) in the intervention cohort, $p<0.01$. Similarly, the median total hospital length of stay was shorter in the usual care cohort at 19.0 days (IQR: 11.2 to 33.5) compared to 32 days (IQR: 17 to 51.7) in the intervention cohort. $P<0.01$.

Lastly, the time between hospital discharge and the completion of follow-up was statistically significant with a difference of one month. That is, median time to follow-up was 15 months (IQR: 13.1 to 16.5) in the usual care cohort and 16 months (14.8 to 17.5) in the intervention cohort. While the absolute difference appears small the distribution resulted in a statistically significant difference when testing using the Mann-Whitney U Test ($p<0.01$). This distribution is demonstrated in Figure 5-2 highlighting the longer tail and outliers for the intervention cohort. This confirms the importance of correction for this variable in the adjustment and analysis phase.

Table 5-2: Baseline characteristics for the intervention and usual care cohorts

Characteristic Caregiver details and / or paired patient details	Usual care cohort (n = 89)	Intervention cohort (n = 81)	P value
Relationship with patient, n (%)			0.47
Partner or spouse	66 (74.2)	54 (66.6)	
Child or grandchild	16 (18.0)	13 (16.1)	
Parent	3 (3.4)	8 (9.9)	
Other	4 (4.5)	6 (7.4)	
Age, years, median (IQR)	58.0 (47.7 to 69.0)	58.0 (48.0 to 66.3)	0.88
Sex, male, n (%)	32 (36.0)	30 (37.0)	0.79
Deprivation index, n (%)			0.50
SIMD 1 (most deprived)	25 (28.1)	20 (24.7)	
SIMD 2	19 (21.3)	19 (23.4)	
SIMD 3	12 (13.5)	16 (19.8)	
SIMD 4	12 (13.5)	7 (8.6)	
SIMD 5 (least deprived)	19 (21.3)	11 (13.6)	
Paired patient characteristics			
Age at ICU admission, median (IQR)	63.9 (49.7 to 71.4)	58.7 (51.1 to 67.7)	0.16
Sex, male, n (%)	50 (56.2)	41 (50.6)	0.33
ICU length of stay, days, median (IQR)	4.75 (2.4 to 9.6)	11.3 (7.0 to 19.7)	**<0.01**
Hospital LOS, days, median (IQR)	19.0 (11.2 to 33.5)	32.0 (17.0 to 51.7)	**<0.01**
APACHE II, median (IQR)	19.0 (14.9 to 25.0)	19.0 (15.0 to 26.0)	0.49
Advanced respiratory support, n (%)	76 (85.4)	77 (95.1)	0.12
Two or greater comorbidities, n (%)	42 (47.2)	34 (42.0)	0.34
Surgical admission, n (%)	42 (47.2)	31 (38.3)	0.17
Pre-existing psychiatric diagnosis, n (%)	20 (22.5)	21 (25.9)	0.72
Time to follow-up, median months (IQR)	15.0 (13.1 to 16.5)	16.0 (14.8 to 17.5)	**<0.01**

IQR: Interquartile Range; SIMD: Scottish Index of Multiple Deprivation; ICU: Intensive Care Unit; APACHE II: Acute Physiology and Chronic Health Evaluation Two. Statistical tests: Pearson's chi-squared test for categorical variables; Mann-Whitney U Test for continuous variables.

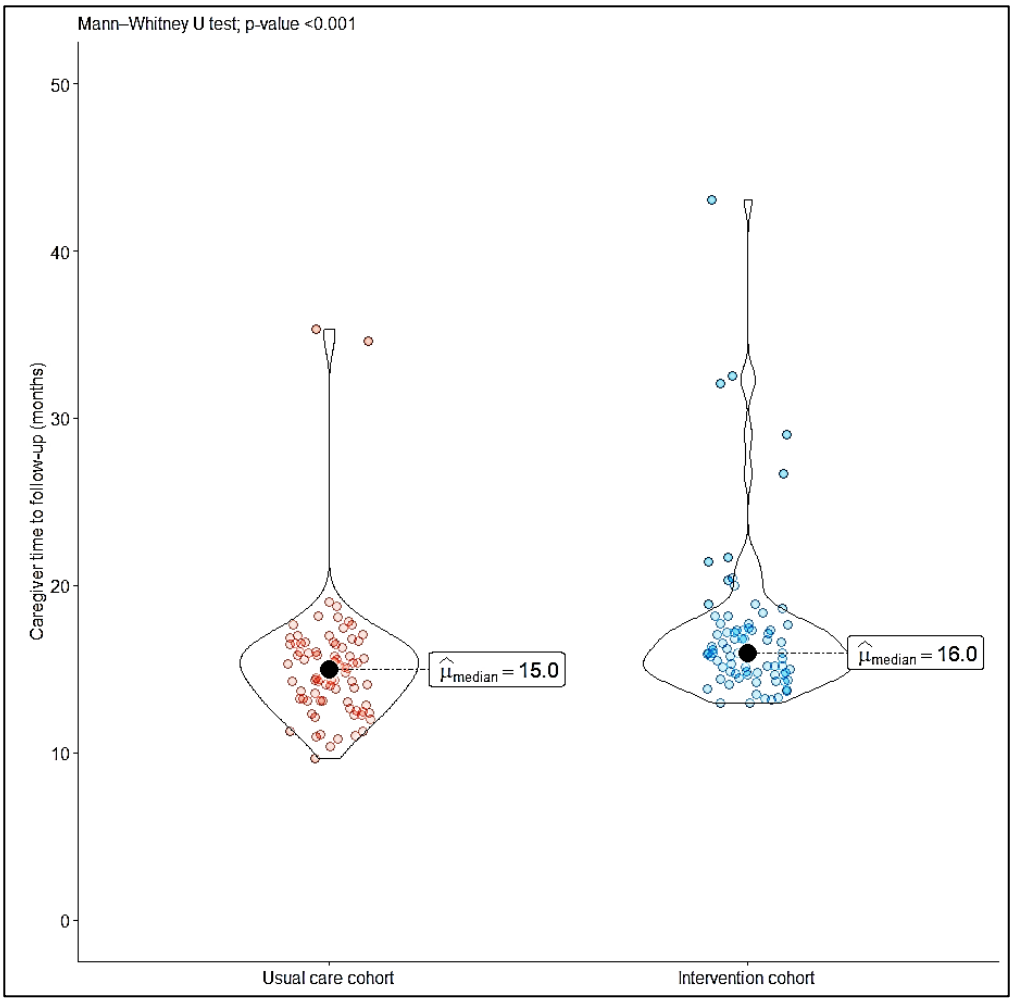


Figure 5-2: Caregiver time to follow-up violin plots.

A comparison of the time from the patient discharge from hospital to completion of caregiver one-year follow-up. Time to follow-up was statistically significantly different between the intervention and usual care cohorts. For a description of how to interpret a violin plot please see Appendix 8.

5.2.4 Patient characteristics of the baseline InS:PIRE cohort with and without a consenting caregiver

There were good quality data on 69 of the 70 patients who consented to participate in the InS:PIRE study but did not have a corresponding consenting caregiver (Figure 5-1). The one consenting patient without a caregiver and without reliable baseline data was lost to follow-up early in the process with no further data collected. The local team did not have any further information on this patient and as such only 69 patients were included in this analysis. The patient characteristics (of the 69) were compared to the 136 patient participants with a caregiver and baseline data (before any loss to follow-up at one year). This was completed to understand the features of patients attending InS:PIRE without a caregiver (or at least without a consenting caregiver).

Appendix 13 offers a table of this comparison. The table highlights that most of the baseline characteristics were similar with a similar age between the groups (patient median age of 57 years vs 59 years, p=0.91), similar distribution of patient sex (male sex of 54% vs 55%, p=0.84); but some statistically insignificant differences in admitting specialty spread with 67% medical admissions in the participants without a consenting caregiver vs 57% medical admissions in the consenting caregivers group (p=0.17).

Most notably, the ICU length of stay was shorter in the participants without a caregiver (median days of 8.9 vs 11.7, p=0.03) although there was no statistically significant difference in total hospital length of stay (median days 28.5 vs 31.0, p=0.22). The group without a consenting caregiver also had a lower rate of advanced respiratory support (non-caregiver group rate of 80% vs 92% in those with caregivers, p=0.01). Comorbidities were similar between the groups, although the rates of substance use (history of harmful alcohol or drug use) was higher in the group without a consenting caregiver. Finally, deprivation was higher in the group without a caregiver.

In summary, characteristics associated with patients who did not have a consenting caregiver were:

- Shorter ICU length of stay (but not hospital length of stay)
- Those who did not receive advanced respiratory support
- A history of alcohol or drug use
- Higher deprivation index

5.3 Missing data

The dataset was 96.2% complete. Table 5-3 gives full details of the missing data and the breakdown of this data per cohort and per variable. The participant (caregiver) characteristics had 5.2% missing in total. A large proportion of this missing baseline demographic data were due to the missing values for the caregiver age which was not recorded for 24 (29.6%) participants in the

intervention cohort. There were fewer missing values in the paired patient characteristics with 2.4% missing from this.

For the outcome measures, 2.9% of HADS responses were missing, 7.0% for the ISI, and 3.6% for the CSI. The effect of this missing data is further explored through sensitivity analyses.

Table 5-3: Number and proportion of missing values per variable for all caregiver participants alongside a per cohort breakdown

Variable	All participants Missingness, n (%), N = 170	Usual care cohort Missingness, n (%), n = 89	Intervention cohort, Missingness, n (%), n = 81
Caregiver demographics			
Relatives' relationship	2 (1.2)	0 (0)	2 (2.5)
Age	24 (14.1)	0 (0)	24 (29.6)
Sex	2 (1.2)	0 (0)	2 (2.5)
SIMD	10 (5.9)	2 (2.2)	8 (9.9)
Time to follow-up	6 (3.5)	6 (6.7)	0 (0)
Paired patient demographics			
Patient age at ICU admission	3 (1.8)	3 (3.4)	0 (0)
Patient sex	3 (1.8)	3 (3.4)	0 (0)
ICU length of stay	3 (1.8)	3 (3.4)	0 (0)
Hospital length of stay	6 (3.5)	6 (6.7)	0 (0)
APACHE II score	7 (4.1)	7 (7.9)	0 (0)
History of pre-existing psychiatric diagnoses	4 (2.4)	4 (4.5)	0 (0)
Advanced respiratory support	3 (1.8)	3 (3.4)	0 (0)
Two or greater comorbidities	4 (2.4)	4 (4.5)	0 (0)
Admitting specialty	3 (1.8)	3 (3.4)	0 (0)
Outcome measures (total missing number of questions or items)			
HADS, depression component, total missing individual responses (7 item survey)	33 (2.8)	13 (2.1)	20 (3.5)
HADS, anxiety component, total missing responses (7 item survey)	35 (2.9)	13 (2.1)	22 (3.9)
Caregiver strain index, total missing responses (13 item survey)	79 (3.6)	18 (1.6)	61 (5.8)
Insomnia Severity Index, total missing responses (7 item survey)	83 (7.0)	26 (4.2)	57 (10.1)

SIMD: Scottish Index of Multiple Deprivation; ICU: Intensive Care Unit; APACHE II: Acute Physiology and Chronic Health Evaluation Two; HADS: Hospital Anxiety and Depression Scale.

5.4 Primary adjusted outcomes

The primary analysis was a comparison between the usual care cohort and the intervention cohort as set out in the methods chapter (Chapter 3). The four outcomes of interest were: anxiety and depression (HADS), caregiver strain (CSI), and caregiver insomnia (ISI). All outcomes were adjusted using logistic regression which generated odds ratios for the association of the outcome in the intervention (InS:PIRE) cohort compared to the usual care cohort. The covariates included in the regression models have been described earlier (Chapter 3).

5.4.1 Mental health outcomes: anxiety and depression

There was a statistically significant 58% reduction in the odds of screening positive for anxiety after adjustment in the intervention cohort (odd ratio: 0.42, 95% CI: 0.20 to 0.89, p=0.02) (Table 5-4). This corresponded to an anxiety rate of 40.7% in the intervention cohort vs 52.8% in the usual care cohort.

There was no statistically significant difference in the odds of screening positive for depression in either group (odds ratio: 0.58, 95% CI: 0.26 to 1.31, p=0.19). Fewer participants screened positively for depression than anxiety. The overall rates of screening positively for depression were 27.0% in the usual care cohort and 22.2% in the intervention cohort. Table 5-4 and Figure 5-3 offer a description of all of the outcomes including both emotional outcomes.

Table 5-4: Effect of intervention on participant caregivers at one-year follow-up: adjusted odds risk ratios

Outcome measure	Adjusted estimate (OR)	P value	95% confidence interval
HADS depression	0.58	0.19	0.26 to 1.31
HADS anxiety	0.42	**0.02**	0.20 to 0.89
Caregiver strain	0.39	**0.04**	0.16 to 0.98
Insomnia	0.36	**<0.01**	0.17 to 0.77

Effect of intervention on participant caregivers at one-year follow-up (after hospital discharge): adjusted odds risk ratios. All logistic regression models adjusted for: relationship with the patient; caregiver age; caregiver sex; time to follow-up; deprivation index (SIMD quintiles); patient hospital length of stay; patient age; and patient pre-existing psychiatric or mental health diagnosis. Outcomes measured using Hospital Anxiety and Depression Scale (HADS) for mental health outcomes, Caregiver Strain Index, and Insomnia Severity Index.

5.4.2 Caregiver strain

There was a statistically significant 61% lower adjusted odds of screening positively for strain in the intervention cohort, defined as a score of 7 or greater on the CSI (odds ratio: 0.39, 95% CI: 0.16 to 0.98, p=0.04). Baseline intervention cohort caregiver strain rates were 18.5% compared to 30.3% in the usual care cohort.

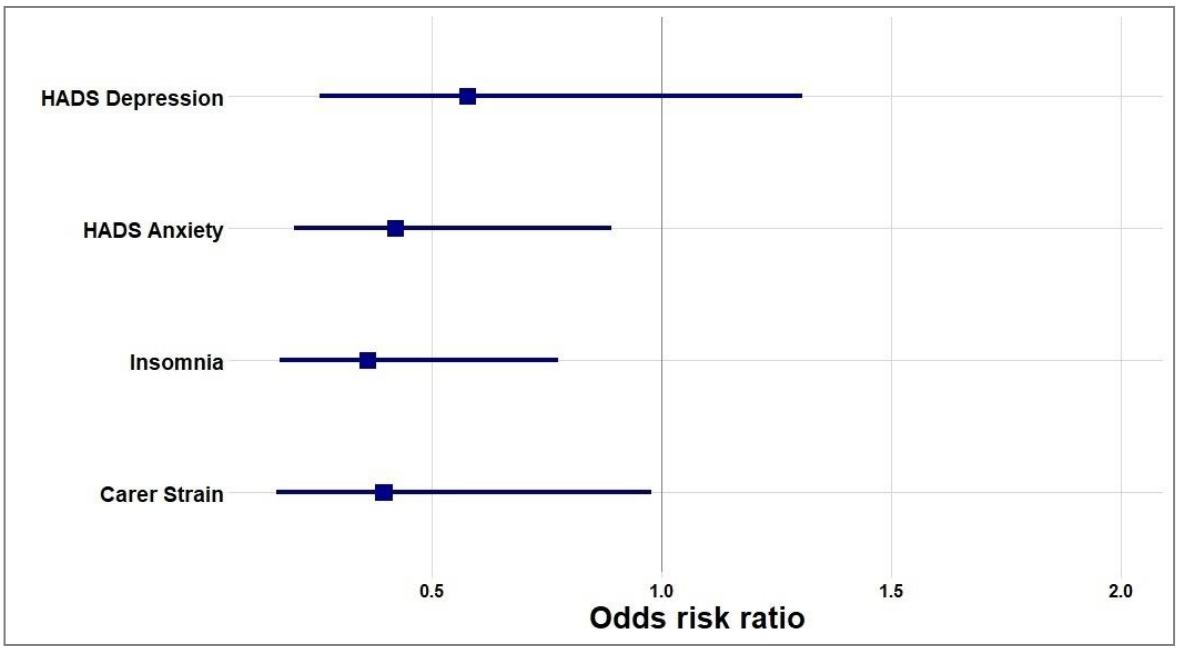


Figure 5-3: Caregiver primary outcomes: adjusted logistic regression forest plot.

Adjusted odds risk ratios of screening positive for each outcome measure in the intervention cohort compared to the usual care cohort. Squares represents the point estimates (odds risk ratios) and splines represent the 95% confidence interval. HADS: Hospital Anxiety and Depression Scale. Insomnia measured using the Insomnia Severity Index (ISI) and carer strain measured using the Caregiver Strain Index (CSI).

5.4.3 Insomnia

The adjusted odds risk ratio of scoring 8 or greater on the ISI was 64% lower in the intervention cohort. The overall rates for insomnia using this measure were 38.3% for the caregiver participants in the intervention cohort and 60.7% in those who received usual care. These results are highlighted in Table 5-4 and Figure 5-3.

Full model specifications of all caregiver outcomes, including sensitivity analyses, can be found in Appendix 14.

5.5 Unadjusted outcomes

The four primary outcomes were also assessed using unadjusted testing utilising the Mann-Whitney U test for continuous variables (where median values are reported) and Pearson's chi-squared test for categorical variables (where rates of screening positive for an outcome are reported). These results are presented in Table 5-5. This demonstrates that the only outcome that achieved statistical significance were the rates of insomnia defined by a score of 8 or greater on the ISI. This achieved statistical significance on testing as a continuous variable where the median values were 10/28 (IQR: 4 to 16) for the usual care cohort and 5/28 (IQR: 1.7 to 12) for the intervention cohort which resulted in a p-value of 0.01 (Mann-Whitney U test). This result held true when considering this variable as a categorical variable and testing using Pearson's chi-squared test highlighted in Table 5-5. The remaining three outcomes of depression, anxiety, and caregiver strain all failed to achieve significance using unadjusted testing.

Table 5-5: Unadjusted outcomes for caregivers in both the intervention and usual care cohorts

Outcome measure	Usual care cohort (n = 89)	Intervention cohort (n = 81)	P value
Hospital Anxiety and Depression Scale (HADS)			
Depression score, median (IQR)	4 (1 to 9)	3 (1 to 7)	0.24
Depression, total scoring ≥8/21, total (%)	24 (27.0)	18 (22.2)	0.59
Anxiety score, median (IQR)	8 (3 to 12)	7 (4 to 11)	0.37
Anxiety, total scoring ≥8/21, total (%)	47 (52.8)	33 (40.7)	0.16
Caregiver Strain Index			
Caregiver strain score, median (IQR)	4 (0.67 to 7)	2 (0 to 5)	0.14
Caregiver strain, total scoring ≥7/13, total (%)	27 (30.3)	15 (18.5)	0.11
Insomnia Severity Index			
Insomnia severity, median (IQR)	10 (4 to 16)	5 (1.7 to 12)	**0.01**
Insomnia severity, total scoring ≥8/28, total (%)	54 (60.7)	31 (38.3)	**<0.01**

Unadjusted testing completed with the Mann-Whitney U test for continuous variables and Pearson's chi-squared test for categorical variables. For categorical variable missing values are treated as a negative response, that is, condition not present. EQ-5D: EuroQol 5-Dimension instrument; IQR: Interquartile Range; VAS: Visual Analogue Score; BPI: Brief Pain Inventory.

5.6 Sensitivity analysis: missing data and caregiver age

Noting that the number of missing values for caregiver age were high in the intervention cohort (29.6%), two sensitivity analyses were undertaken to understand whether this had an impact on the adjusted outcomes. These were:

1. The model was respecified with caregiver age removed using the dataset generated with 5 imputations with 10 iterations. The purpose was to remove any influence from this variable. Given that the original model already specified patient age and caregiver relationship it was anticipated that this technique would also remove any possibility of collinearity occurring between these three variables. This model, therefore, adjusted for: relationship with the patient; caregiver sex; time to follow-up; deprivation index (SIMD quintiles); patient hospital length of stay; patient age; and whether the patient had any pre-existing psychiatric or mental health diagnosis.

2. The original model was again used but the imputation was increased to 30 imputations and 10 iterations. The purpose of this strategy was to help guarantee that the lower number of imputations had not mis-specified any of the missing values. This, therefore, was completed to correct for any errors introduced from the caregiver age variable, but this would also improve the imputation relating to any of the other missing variables.

5.6.1 Models with caregiver age removed

Table 5-6 and Figure 5-4 outlines the results from the sensitivity analyses. This highlights that removal of caregiver age had no significant effect on any of the four outcomes. Specifically, this demonstrates that the adjusted odds risk ratios with caregiver age removed for screening for anxiety (odds ratio: 0.39, 95% CI: 0.19 to 0.81, p=0.01), caregiver strain (odds ratio: 0.37, 95% CI: 0.15 to 0.91, p=0.03), and insomnia (odds ratio: 0.35, 95% CI: 0.16 to 0.74, p<0.01) remain statistically significantly different and lower in the intervention group. Adjusted odds risk ratios for depression were once again not significantly different between the groups (odds ratio: 0.53, 95% CI: 0.24 to 1.18, p=0.12). The modelling process and results have, therefore, held up to this analysis.

5.6.2 Models involving the 30 imputations dataset

The new datasets generated with 30 imputations and 10 iterations were remodelled using the same variables as the original models in the primary analysis. The results are presented in Table 5-6 and Figure 5-4 which once again demonstrate a consistent output with lower odds risk ratios of screening for anxiety (odds ratio: 0.41, 95% CI: 0.19 to 0.87, p=0.02), caregiver strain (odds ratio: 0.40, 95% CI: 0.16 to 0.96, p=0.04), and insomnia (odds ratio: 0.36, 95% CI: 0.17 to 0.78, p=0.01) in the intervention cohort. There was no significant difference between cohorts for the risk of screening positive for depression (odds ratio: 0.57, 95% CI: 0.25 to 1.30, p=0.18). This confirms that the results are not sensitive or reliant upon the specification of the imputation strategy. Direct side-by-side comparison is offered in Figure 5-4.

Table 5-6: Caregiver outcomes sensitivity analyses: original models; caregiver age removed; and original model with 30 imputations

Model	Adjusted estimate, odds risk ratio	P value	95% confidence interval
HADS Anxiety			
Primary (original) model	0.42	**0.02**	0.20 to 0.89
Caregiver age removed	0.39	**0.01**	0.19 to 0.81
Original model with 30 imputations	0.41	**0.02**	0.19 to 0.87
HADS Depression			
Primary (original) model	0.58	0.19	0.26 to 1.31
Caregiver age removed	0.53	0.12	0.24 to 1.18
Original model with 30 imputations	0.57	0.18	0.25 to 1.30
Caregiver strain			
Primary (original) model	0.39	**0.04**	0.16 to 0.98
Caregiver age removed	0.37	**0.03**	0.15 to 0.91
Original model with 30 imputations	0.40	**0.04**	0.16 to 0.96
Insomnia			
Primary (original) model	0.36	**<0.01**	0.17 to 0.77
Caregiver age removed	0.35	**<0.01**	0.16 to 0.74
Original model with 30 imputations	0.36	**0.01**	0.17 to 0.78

Logistic regression models with odds risk ratios of screening positive for the respective outcome. "Primary (original) model" and "original model with 30 imputations" are adjusted for: relationship with the patient; caregiver age; caregiver sex; time to follow-up; deprivation index; patient hospital length of stay; patient age; and patient pre-existing mental health diagnosis; "caregiver age removed" model included the same covariates with the exclusion of caregiver age from the model. HADS: Hospital Anxiety and Depression Scale.

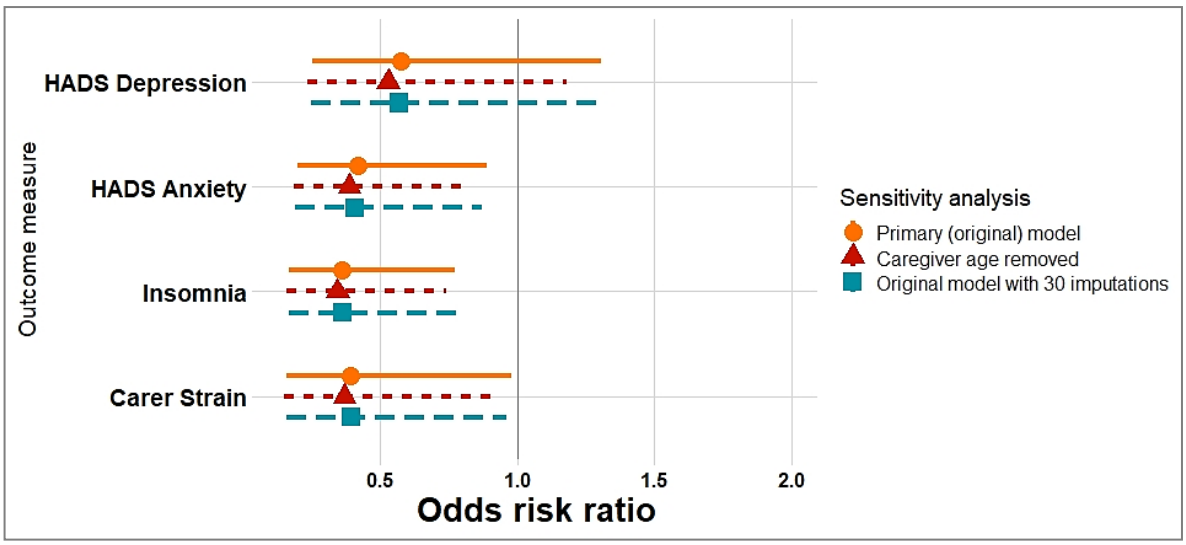


Figure 5-4: Forest plot of sensitivity analyses of caregiver outcomes

Adjusted odds risk ratios of screening positively for each outcome measure in the intervention cohort compared to the usual care cohort. The primary (original) model (circle) alongside two sensitivity analyses: adjustment with caregiver age removed (triangle); and the original model after correcting for missing data using 30 imputations (square). HADS: Hospital Anxiety and Depression Scale.

5.7 Secondary outcomes: caregiver strain subgroups

As an exploratory analysis to better understand the specific areas where caregivers experienced strain the individual responses were analysed from the CSI. The overall rate of strain in each item in the whole population (n=170) was considered, as were the rates of strain observed in each cohort. Testing was then undertaken using Pearson's chi-squared tests to assess whether any difference between the cohorts was observed.

Table 5-7 reports these results demonstrating no significant differences between each group in any item of the CSI. A total of 75 (44.1%) participants indicated that there had been "changes to personal plans". While 42 (24.7%) reported that there had been work adjustments and 44 (25.9%) indicated that it was a financial strain.

Table 5-7: Frequency of problems in each domain of the Caregiver Strain Index

Caregiver Strain Index item	All participants, N = 170, n (%)	Usual care cohort, n = 89, n (%)	Intervention cohort, n = 81, n (%)	P value
"Sleep is disturbed"	53 (31.2)	29 (32.6)	24 (29.6)	0.80
"It is inconvenient"	20 (11.8)	12 (13.5)	8 (9.9)	0.62
"It is a physical strain"	21 (12.4)	12 (13.5)	9 (11.1)	0.81
"It is confining"	46 (27.1)	25 (28.1)	21 (25.9)	0.89
"There have been family adjustments"	54 (31.8)	31 (34.8)	23 (28.4)	0.46
"There have been changes to personal plans"	75 (44.1)	44 (49.4)	31 (38.3)	0.19
"There have been emotional adjustments"	57 (33.5)	35 (39.3)	22 (27.2)	0.12
"Some behaviour is upsetting"	46 (27.1)	27 (30.3)	19 (23.5)	0.40
"It is upsetting to find … has changed so much from his/her former self"	60 (35.3)	33 (37.1)	27 (33.3)	0.73
"There have been work adjustments"	42 (24.7)	24 (27.0)	18 (22.2)	0.59
"It is a financial strain"	44 (25.9)	26 (29.2)	18 (22.2)	0.39
"Feeling completely overwhelmed"	49 (28.8)	31 (34.8)	18 (22.2)	0.10
"There have been other demands on my time"	61 (35.9)	35 (39.3)	26 (32.1)	0.41

Between cohort testing completed using Pearson chi-squared tests (with Yates correction), all variables are categorical variables. Any missing values were treated as a negative response, that is, condition not present.

5.8 Discussion

5.8.1 Summarising all analyses

This multicentre study has evaluated the effects of a complex healthcare intervention, which included targeted input for the caregivers of critical illness survivors alongside interventions for the entire family-caregiving unit. Evaluation was conducted over one year after hospital discharge and has demonstrated improvements in emotional and mental health outcomes, presence of insomnia, and experience of strain.

5.8.1.1 Adjusted outcomes

Specifically, after adjustment, those who attended the InS:PIRE intervention reported lower rates of anxiety scored using the HADS questionnaire, alongside lower rates of strain associated with the caring role using the CSI. A reduced frequency of insomnia was also observed using the ISI. All adjusted outcomes were modelled using multivariable logistic regression using the specific and well-defined cut-off values for each marker of QoL associated with the caring role.

Two important sensitivity analyses were undertaken to identify the effects of alternative approaches to model specification. The first sensitivity analysis removed caregiver age from the adjustment process. This variable had a high level of missing values, particularly in the InS:PIRE intervention cohort where almost 30% of the data points were missing. This sensitivity analysis performed the dual purpose of removing the effects of high levels of missing data on the model as well as any possibility of effects of collinearity between this variable and patient age or relationship. The result was robust to this analysis and there was no meaningful change to the statistically and clinically significant outcomes.

A second approach to dealing with the missing data was conducted where the imputation process was conducted with 30 imputations rather than the original five before using the same primary (original) model specification. Once again the model was robust and the statistically and clinically significant outcomes were unchanged.

The only outcome measure that failed to achieve statistical significance in any adjusted analysis, and therefore no difference between cohorts was observed, was in depression scores (HADS depression). It is noteworthy that the absolute rates of depression were low compared to other outcomes with a HADS-depression rate of 27.0% in the usual care cohort and 22.2% in the InS:PIRE cohort. The corresponding rates of HADS-anxiety and insomnia were much higher. While this result demonstrates that the intervention had no effect on depression between the cohorts it is also possible that the study size (n=170) resulted in an underpowered study to detect differences for this outcome and a type two error. While the rates of carer strain were similar to the rates of depression the absolute difference was greater (30.3% in the usual care cohort compared to 18.5% in the InS:PIRE cohort) and this could explain why a statistical difference was seen for this adjusted outcome but not for depression. Regardless of exact rationale for the failure to detect a difference in the depression rates between the two cohorts, it is clear that this data does not support the hypothesis that attendance at InS:PIRE was associated with an improvement in depression rates during long-term follow-up in the caregivers of critical care survivors.

5.8.1.2 Unadjusted outcomes

The unadjusted outcomes demonstrated a statistically significant lower rate of insomnia (ISI cut-off ≥8/28) in the InS:PIRE (intervention) cohort compared to the usual care cohort. As previously mentioned, the rates of insomnia were far higher than the rates of the other three outcomes measured (anxiety, depression, strain). The usual care cohort had an insomnia rate of 60.7% compared to 38.3% in the intervention cohort and correspondingly the median values were 10/28 (usual care) vs 5/28 (intervention). The combination of the large difference observed between groups and the high prevalence in the entire population likely explains why this result held up to the unadjusted analysis. As such, the insomnia outcome is statistically the strongest result as it held true to the adjusted sensitivity analyses along with unadjusted testing.

The remaining three outcomes failed to achieve statistical significance. The reduced point prevalence alongside the smaller absolute differences clearly affected these results although the adjusted results demonstrated statistically significant differences for anxiety and carer strain outcomes. Whether this

outcome was the result of a type one error could only be answered by conducting a larger study with randomisation.

5.8.1.3 Caregiver strain subgroups

A final exploratory analysis has assessed the rates of strain for each question of the caregiver strain index. This demonstrated no individual question differences between cohorts on unadjusted analysis. This suggests that any reduction in strain correlated with attendance at InS:PIRE was the result of the collective benefit across the multiple areas of strain, rather than one focal area that improved significantly.

The number of caregivers agreeing with each question varied substantially. The question with the fewest caregivers indicating they had problems was “it is inconvenient” with 11.8% of caregivers agreeing to this statement. The question with the highest number of positive responses was “there have been changes to personal plans” where 44.1% of caregivers agreed with this statement.

Other noteworthy caregiver strain statements were: “it is a financial strain” which had 25.9% agreement, and “there have been work adjustments” with 24.7% agreement. Together these results highlight the knock on socioeconomic impacts of an intensive care admission to the entire family unit.

These results merit acknowledgement but do not answer the question of what are the mechanisms behind reducing the impacts of a critical illness on caregivers? A combination of qualitative and quantitative work would likely be required to understand this better.

5.8.2 Understanding caregiver outcomes from InS:PIRE and the wider context

There does not appear to be any other post hospital discharge intervention, specifically involving caregivers, that has demonstrated improvements in caregiver experience, strain, or emotional health. This study, therefore, is the first to demonstrate these outcomes through a quantitative analysis one year after hospital discharge.

The InS:PIRE intervention is unique and brings together a complex MDT, traditional outpatient healthcare services, psychological support, community organisations including the third sector, and socioeconomic rehabilitation. There are specific areas of InS:PIRE that have been developed to target the caregivers of ICU survivors. The peer support that is built into the programme is likely to also have substantial benefits for caregivers of ICU survivors contributing to the social rehabilitation of this group. The proposed benefits of peer support for caregivers are that this improves the experience of anxiety, tempers expectations and normalises the rate of progress alongside allowing the caregiver to support others[332,333,338]. Peer support within InS:PIRE was delivered throughout the programme at multiple levels. Initially ICU survivors and caregivers are brought together in the same space. This part of InS:PIRE fits well with the traditional thinking and existing models of peer support where caregivers could speak to each other allowing a two-way support mechanism to evolve.

InS:PIRE also allows support to cross over between different ICU survivors and caregivers. In this way other relationships and support could form. This may involve a patient supporting another caregiver or vice versa. It has been observed that separate family units may also interact as a group and support one another. Therefore, InS:PIRE is likely to result in differing interactions, and overall more groups that can share lived experience from alternative perspectives offering a greater variety of insights.

Having the patient attending alongside the caregiver could, however, affect the quality of the caregiver peer support if the ICU survivor remains the focus of all discussions. To mitigate this, all InS:PIRE programmes had periods where caregivers and patients were treated separately. This allowed for ‘down-time’, where all patients were receiving a group session (e.g. psychology group session), which would allow the caregivers to interact independently without scrutiny from the staff or the patients / ICU survivors.

This multi-layer approach to peer support is likely to allow caregivers who would not think about attending a separate peer support group to both contribute to and receive this intervention. It also allows the caregivers to observe other family units and normalises aspects of their own individual caregiver-patient relationship. Although this complex, multi-layered approach to peer support is

seen as an advantage overall, an unintended consequence of this design is that it is impossible to know which elements of this peer support are the most effective. For the purposes of the InS:PIRE intervention this needs to be treated as a bundle or package of interventions.

Another key caregiver specific component was the caregiver psychology sessions. Lead by a psychologist, these sessions allowed the caregivers to explore their emotional wellbeing alongside aspects of their life that have had to change due to the critical illness of their family member. This element is complementary to peer support and generally occurred later in the programme (e.g. weeks three or four) after some familiarity with the group when relationships had already been formed. On the whole these sessions would be a facilitated discussion with the key element being the focus on the caregivers without influence from the patient group. Together, the multi-level peer support alongside the focused psychological input are likely to be the key elements that have resulted in the correlation between better emotional health and anxiety outcomes observed in the InS:PIRE cohort.

Other core elements that have been targeted specifically at caregivers are the third sector and community organisations that were involved in InS:PIRE and contributed to the socioeconomic rehabilitation of this group. A core aspect of this was the financial and social care specialists that participated, delivering a session towards the end of each programme[39]. For this intervention, all of these sessions were delivered by Citizens Advice Scotland although the core elements of financial and social care advice and access to services could be delivered in many different ways[290]. The high rates of financial and work-related strain observed in the individual components of the caregiver strain index are a reminder of the importance of these elements as a contributory factor to the experience of carer strain. This crossover and integration are critical to the apparent success of the InS:PIRE programme. This is also supported by the literature which highlights the high levels of financial and employment problems experienced by patients and caregivers after critical illness[37]. The combination of social rehabilitation (peer support) and the direct access to a financial care specialists contributed to the overall socioeconomic rehabilitation of the entire family unit. These unique

elements are the most likely areas that have resulted in the lasting benefits measured and reported for caregivers as discussed in this Chapter.

Finally, every InS:PIRE cohort involved a sleep session. The important and significant results for the insomnia outcomes highlight the value of this session. While it is unlikely that this single session resulted in the much lower rates of insomnia in the intervention cohort, it probably contributed to and complimented all the other components of InS:PIRE.

5.8.2.1 The family unit

All the InS:PIRE areas that are specific and tailored to caregivers have been highlighted and have likely contributed to the statistically and significant outcomes of a reduction in the adjusted rates of anxiety, carer related strain, and insomnia. It is also important to recognise that any benefits in patient outcomes also likely contributed to these benefits. The programme by design treats patients and caregivers together. Separating these elements out could be of benefit to our understanding of the impact of each component from a research perspective. However, downsides of separating patient and caregiver components may be a reduction in the synergistic effects for both with reduced effectiveness overall. Exploring the interaction between patient and caregiver components may lead to a better understanding of the mechanisms behind any benefits offered by the programme.

Aside from the complimentary benefit of improvements in the patient's HRQoL, the caregiver may also experience direct effects from some of the patient focused interventions. With caregiver involvement throughout the programme encouraged, it has been routine for the caregiver to attend many of the patient one-to-one sessions. The ICU doctor and ICU nurse sessions frequently begin with a focus on the patient but there is an acceptance at InS:PIRE that the caregiver is not simply an observer or support for the patient. If there were specific caregiver issues affecting the family unit these would be discussed and explored. This allowed caregiver specific issues to become the focus of a consultation if this was important to the family unit. This has the benefit of reassuring both parties that the other is being cared for and allows a focus on the biggest issues impacting on either group to be explored.

The secondary role this model provided is that it was possible to explore issues that the caregivers, or patients, would not seek help for as a standalone issue. This could broaden the reach of InS:PIRE to pick up and resolve issues that in a more traditional system would not have been addressed. Fundamentally, the family unit approach of InS:PIRE explicitly recognises that recovery of one is dependent on the other. This area of interaction and synergy may have contributed to the effectiveness demonstrated here, but also warrants further study.

5.8.3 Strengths and limitations

Strengths of this work are that this is a multicentre study with assessment of important markers of QoL and burden on caregivers one year after a critical illness. The scoping review (Chapter 2) failed to identify any caregiver based (or included) interventions demonstrating lasting benefits for this group. As such, this is the first study to demonstrate these lasting benefits for caregivers from an outpatient intervention. There are also no effectiveness studies assessing caregiver outcomes as part of a complex or multi-professional intervention (Chapter 2) and the results of this study substantially contribute to this field. Furthermore, the use of a contemporaneous usual care cohort is a significant strength. This meant that any changes in intensive care practice over the study period were accounted for in both cohorts.

The choice of outcome measures is also a strength demonstrating the impacts of the caring role on mental health (anxiety, depression) and a crossover physical / mental health marker of the caregiving role (insomnia). The use of the CSI attempted to describe the overall or total strain but failed to highlight a specific area that was driving the lower incidence of total strain.

The limitations of this study are, however, significant. As with the paired patient outcomes this cohort study cannot assume causation from the intervention as participants were not randomised to the usual care or intervention cohorts. Broadly the baseline characteristics and demographics were similar between groups with the regression adjustment aiming to correct for any known, measured, and anticipated confounding. Despite the thoroughness of this technique, it is not possible to correct for unknown or unmeasured confounding. Of critical

importance, data on pre-existing caregiver mental health diagnoses were not collected. This was a significant omission in the original data collection protocol and if this study was repeated this should be included.

Both attrition rates and missing values had to be considered carefully within this study. The rates of completion from initial recruitment could have been better, even given the fact that attrition is a well-known issue with this type of study[219]. This could not be corrected for during the analysis stage and acts as a reminder that future studies would have to build in appropriate follow-up procedures and consider the use of letters, phone calls, or other digital techniques (e.g. electronic, phone-based applications, or email).

Future work should also consider the caregivers who do not attend or engage with InS:PIRE itself. The results discussed this (also detailed in Appendix 13) to compare patient characteristics of those with consenting caregivers and those without. This highlighted that a shorter ICU length of stay, alcohol and drug use, and increasing socioeconomic deprivation were associated with the patient attending on their own (i.e. without a consenting caregiver). All these patients completed consent (i.e. fully engaged with the programme and the study) and this suggests some of the features associated with caregiver non-participation at InS:PIRE. Future work should aim to understand the caregivers who do not attend InS:PIRE in more detail and specifically target the groups with higher rates of substance use and socioeconomic deprivation. This would be an important area for the service to evolve and optimise uptake. This is also an area where qualitative work may be particularly beneficial.

Within some individual covariates, missing values were significant. Particularly the caregiver age demographic in the InS:PIRE cohort. A primary reason for this was that this data was collected on a paper proforma. This was convenient and reproducible, but it is evident that the recruiting teams did not prioritise completion of this data field. Furthermore, the caregiver details were not cross referenced with other caregiver data, meaning identifiers that could have been used to retrospectively completed this data (e.g. date of birth) were not collected for caregivers. These were all pragmatic decisions made early in the design of the studies aiming to balance the avoidance of unnecessary complexity (e.g. over reliance on computer systems) with robust data collection. Clearly this balance

was lost for the caregiver age component. This missing data reflects this and the clinical teams delivering the intervention did not have the resource required to make sure these surveys were completed in full.

This missing data is also a result of the co-collection of patient and caregiver data together. This data collection strategy has many advantages (e.g. good completion of the paired patient characteristics) but did make the overall data collection process more difficult as the teams completing the paper forms had multiple priorities to balance alongside delivery of the intervention. This missing data may further reflect that the caregivers attending InS:PIRE themselves viewed the patient as the primary focus and completion of their demographics was not prioritised by the family unit. Whatever the cause, it is reasonable to consider that the assumption of missing completely at random cannot be guaranteed for the caregiver age demographic. This is the reason that two sensitivity analyses relating to caregiver age were undertaken to, at least in part, address this limitation. Future studies should use electronic data systems to collect this information, this process should be resourced appropriately, and the collection of other caregiver data should be considered to improve the ability to cross reference and fill in any missing data (e.g. caregiver date of birth and community health index number).

Other sensitivity analyses were considered, but during this phase it became clear that propensity score matching would likely result in small cohorts. There then would be too few observations to complete the adjusted regression as planned. This technique was therefore not included in this analysis. Future work should aim to recruit larger cohorts if multiple and varied analyses are planned.

No data were collected on caregivers who were invited to InS:PIRE but did not attend the intervention. This resulted in an inability to understand the features or characteristics associated with attending the intervention compared to non-attendance. A similar consideration is that it could be argued that caregivers who participated were more motivated and engaged to improve their own health and that of the family unit. A counter to this is that participants with significant degrees of socioeconomic deprivation were high in both cohorts. Likewise, the rates of multi-comorbidity on the paired patients was also high (above 40%) in

both cohorts and more than 25% had pre-existing mental health diagnoses. Therefore, groups that are difficult to reach were included in this study.

Using a postal survey for the usual care cohort vs in-person (or telephone) follow-up in the intervention cohort may have influenced the outcome, although this is very difficult to quantify. Lastly, this study only considers data at one-year follow-up. Future studies comparing this intervention to a usual care or control cohort at multiple time points would give much greater insight into the recovery trajectories of both groups. This would also improve the understanding of when the benefits of any intervention are measurable after critical care discharge and how any benefit is sustained over time.

5.8.4 Conclusions

This multicentre study of a complex intervention has demonstrated that attending the InS:PIRE intervention was associated with lower rates of anxiety, insomnia, and caregiver strain in the families of ICU survivors one year after hospital discharge.

Chapter 6 Results: InS:PIRE after cardiothoracic intensive care – feasibility, outcomes, and process evaluation.

6.1 Overview

The purpose of this chapter is to explain in detail the evaluation and implementation of the InS:PIRE intervention from a specialist quaternary cardiothoracic critical care. The entire focus for this thesis to this point has been on PICS, PICS-F, and the effectiveness of the InS:PIRE intervention for the general intensive care population.

It was proposed that patients who were treated through a specialist intensive care, including different treatment pathways, may have an alternative experience of PICS and PICS-F. Furthermore, their follow-up experiences often follow a disease specific pathway, with more narrow requirements, or may be targeted around a single organ system. There are also explicit challenges in the implementation of a rehabilitation programme within a centralised service, particularly in Scotland. Patients often travel long distances, come from different health boards, or are referred by a variety of pathways including from secondary or tertiary care. Understanding the feasibility of the InS:PIRE intervention for this group and where the programme may fit into existing services was seen as an important step in considering the wider applicability of InS:PIRE. There could also be transferrable learning about the adaptability of the programme to alternative geographical locations and hospitals. This was the rationale for this study and chapter.

The structure of this chapter is as follows:

- The introduction describes the context under which this research was conducted.

- The methods section outlines how the InS:PIRE intervention was implemented, adapted, and measured for this specific service. This section also directly compares InS:PIRE to Cardiac Rehabilitation (CR).

- The outcome measures used to look for markers of PICS will be described.

- The results will explain the evolution of the programme and detail the specific adaptations over the life of the project. The results of the outcome measures will also be reported alongside the service delivery and user feedback.

- The discussion will bring the results into context and how this compares to other services and outline the transferrable learning from this programme for other services and geographical areas.

6.2 Introduction

Overall survival after major life-threatening cardiac events is improving, whether this is post operatively after cardiac surgery or after cardiac arrest[339]. As has been explored in earlier chapters, survival from major life-threatening events involving a stay in intensive care can lead to a significant burden of morbidity[8,23-30]. This earlier discussion highlighted and explained the syndromes of PICS and PICS-F in the general ICU population[46]. For those suffering severe cardiac illnesses the American Heart Association have described a similar spectrum of disease[340]. Most of the evidence behind this guidance is from the study of Out of Hospital Cardiac Arrest (OOHCA) survivors but the language and spectrum of problems is almost identical to that used to describe PICS[340-344]. Specifically, the range of problems experienced by survivors encompasses social, physical, cognitive, and emotional outcomes[340-344]. Furthermore, the timelines for experiencing these problems and for resolution to occur are also comparable[46,340]. Families demonstrate a similar recovery curve between both patients and caregivers as has been seen in the general intensive care population[46,340,344,345].

While the studies and guidance for cardiac patients after severe or critical illness is based on data from OOHCA patients, the patients treated through a Cardiothoracic Intensive Care Unit (CICU) are likely to be far more diverse. The admitting diagnoses as well as the spectrum and severity of illness can vary significantly. Some post CICU patients (either after medical illness or post operatively) follow a standardised pathway with a short ICU length of stay and correspondingly rapid recovery. However, this is likely to contrast significantly

with those who have a longer ICU length of stay and complex recovery trajectory. While some are likely to experience a steady linear improvement after a short CICU stay, others may experience a plateau and possibly even a reduction in QoL after one year[346,347].

This study aims to describe the long-term outcomes of CICU patients and their primary caregivers while also exploring the feasibility of implementing a complex intervention, designed to support problems associated with PICS and PICS-F, in the year following discharge from CICU.

6.3 Methods

6.3.1 Setting

The study was conducted from a single site, the Golden Jubilee National Hospital's (GJNH) CICU. This hospital conducts a large proportion of the adult cardiothoracic critical care in Scotland. The CICU has over 2000 admissions per year. The case mix is diverse including cardiothoracic patients needing both surgical and non-surgical care. The CICU and GJNH also deliver a large range of regional (tertiary) and national (quaternary) services.

Post-operative patients after cardiac surgery are the largest group admitted to the CICU. The most common procedures these patients have undergone are coronary artery bypass grafting (CABG), cardiac valve replacements, or a combination of both. The centre also treats adult congenital cardiac disease with these patients being treated in CICU if required. The GJNH delivers the regional service for cardiac percutaneous revascularisation. While those requiring elective revascularisation are infrequently admitted to CICU, patients requiring admission after Percutaneous Coronary Intervention (PCI) following OOHCA are common. This post OOHCA care forms a significant proportion of the CICU's admissions.

The Scottish National Advanced Heart Failure Service (SNAHFS) is delivered through the GJNH. The CICU is the critical care unit for SNAHFS and as such any patient requiring critical care input from this service will be treated in the CICU. This results in many advanced heart failure therapies being delivered from the CICU including advanced heart failure pharmacotherapy, intra-aortic balloon

pump therapy, Veno-Arterial Extra-Corporeal Membrane Oxygenation (VA-ECMO), and Ventricular Assist Devices (VAD). This is also the only site in Scotland delivering Allogenic heart transplants with all of these patients being treated by the CICU team.

6.3.2 Design

While InS:PIRE is specifically designed to be adaptable and meet the needs of each local ICU, for the studies described in the previous chapters (Chapter 4 and Chapter 5) there were limitations on this adaptability. The intervention was fairly consistent across cohorts and hospital sites, thus allowing the intervention to have enough uniformity to aggregate the outcome data between sites and cohorts. It was decided that relaxing this limitation would allow the team delivering InS:PIRE at the GJNH to iteratively change and improve the intervention to meet their own specific needs. The objectives of this were to understand how the intervention could be adapted for the very specialised, and more narrow spectrum of pathology treated at this critical care site. Perhaps more importantly, the intervention was also likely to deliver the service for a large geographical area given the mix of regional and national services based at the GJNH. Finally, this iterative QI approach also offered some ability to assess the mechanics behind changes to the service, therefore offering insight into a process that would be transferrable to other sites, even if the specific participant outcomes were less generalisable.

This study was, therefore, conducted as a stand-alone, single centre, QI project. This methodology resulted in the need for formal ethics and patient consent to be waived after the initial proposal was reviewed by the research and development department within the GJNH. This project was deemed to be the implementation of a new service and this phase was considered the pilot phase which was part of an ongoing QI process. The research and development department guaranteed overall governance for the project, particularly that pertaining to patient attendance, the collection of data, and all safety approvals.

The MDT delivered five pre-planned cohorts of the InS:PIRE intervention over a 20 month period from January 2017 to September 2018. One-year follow-up was completed in September 2019. The intervention was delivered in five week blocks, similar to the other InS:PIRE sites.

6.3.3 Programme design, set-up, and adaptation

6.3.3.1 What were the similarities with the other InS:PIRE programmes?

As already stated, the funding was to deliver five cohorts. The initial design for the programme mirrored that of InS:PIRE being delivered at the other sites and has been described in Chapter 3. A brief reminder of the key components as well as the specifics relating to this intervention are offered here.

Participants were invited between 6 and 16 weeks after discharge from hospital. The programme treated patients and caregivers together, in cohorts. Each patient and caregiver were reviewed by the doctor, nurse, pharmacist and physiotherapist. An assessment of any unmet medical needs, ongoing physical rehabilitation needs, and a debrief (including a lay person written summary) of their ICU stay was undertaken. The patients also underwent a full medicines reconciliation with the pharmacist. Peer support was embedded into the programme with a 'café' area, and deliberate 'downtime' was built in to encourage discussion and peer support for everyone attending the cohorts. There were also education sessions. The third sector contributed to the programme, including financial advice from local organisations, in this case this was from Citizens Advice Scotland, similar to other sites[290]. Psychology was delivered by group sessions and this evolved over the life of the project. Follow-up visits were offered at three months and one year after completion of the initial cohort.

6.3.3.2 Programme adaptation

Similar to other InS:PIRE programmes there was a learning session after each cohort, the 'week-6 learning session'. This occurred with all of the staff involved present and a 'QI coach'. This session also had some input from healthcare professionals from other sites who were involved in the national collaboration and had more experience of delivering InS:PIRE. The key difference with the implementation of this service was that there was more freedom and flexibility at these sessions to make changes for the following cohort. The focus of each discussion was to evaluate what went well and the areas that needed improvements alongside any feedback received from the participants or service users. The changes to the programme that were planned for the next cohort were noted and evaluated including the practical implications of the proposed changes.

The numbers attending and completing the programme were also recorded to help track the feasibility of the programme and the effects of any changes. This process, involving the learning sessions, formed the main function as the 'plan-study-act' process that often forms the cornerstone of QI methodology, particularly within complex systems including healthcare[348-350]. The staff, however, did not use this terminology and 'week-6 learning session' was the preferred nomenclature for this.

6.3.4 InS:PIRE and Cardiac Rehabilitation

A key criticism of the InS:PIRE clinic in this patient population could be that there is already a great deal of focus on cardiac disease in the UK, and specifically Scotland, and thus services are already in place. The team setting up the GJNH InS:PIRE clinic considered this and reviewed what services were already in place. CR was the main service that patients were referred to after a serious cardiac disease or procedure. On review, however, this service differs significantly from InS:PIRE. Table 6-1 summarises the differences between InS:PIRE and CR broken down into broad elements or programme components and referenced against the most up-to-date national CR guidelines from the Scottish Intercollegiate Guideline Network (SIGN)[351].

Of note, patients and caregivers could attend both InS:PIRE and CR, or may fit into the inclusion criteria for one and not the other. CR is overall more disease focused. There is acceptance that psychosocial health and vocational rehabilitation are important for improving cardiac outcomes and there is screening for mental health with a stepped referral process. However, the overall approach is to address these areas to primarily improve cardiac outcomes rather than a focus on overall HRQoL. Furthermore, the delivery of CR is often more fixed compared to the adaptable platform of InS:PIRE that allows consideration of a variety of presenting complaints or disease processes. Clearly InS:PIRE also specifically addresses the many psychosocial problems unique to PICS. It addresses the altered mentation resulting from delirium and allows the participants to receive a debrief specifically from specialists from intensive care. The approach to addressing psychosocial health, vocational rehabilitation, and the involvement of the third sector is more developed in InS:PIRE. Finally, the specific focus on

involvement of caregivers and the embedded peer support for both patients and caregivers is a significant difference between the programmes.

Table 6-1: Comparison of the InS:PIRE programme and Cardiac Rehabilitation

Component or domain	InS:PIRE	Cardiac Rehabilitation (SIGN guidelines)[351]
Treatment group	Patients treated in intensive care, for any reason, usually those intubated and / or longer intensive care lengths of stay. For this study, invasively ventilated ≥48 hours.	No specific guidance. Largely disease focused e.g. any patient under care of tertiary cardiac / cardiology services who may benefit. Some diseases specifically mentioned including: post-CABG; Post-PCI; Post-MI
Traditional healthcare MDT (e.g. hospital specialists or allied healthcare professionals)	Review by doctor and nurse. Note debrief described below, assessment of any unmet healthcare needs addressed, onward referral if required, and consideration of other problems e.g. comorbidities. Physiotherapy plan, looking not only at exercise activities, but also chronic pain issues. Onward referral to addiction services, speech and language, dietetics, and urology (e.g. for sexual dysfunction) if needed. Analysis of any missed or outstanding care. Pharmacy consultation to undertake education, medicines reconciliation, and address for any patient specific problems.	Individual assessment and care plan. Comorbidities should be taken "into account" but no clear description of what this involves. Lifestyle factors of particular concern: • Smoking cessation interventions and advice • Dietary advice and plan • Individualised exercise assessment and plan
Mental health	Peer support. Psychology session focusing on coping strategies including discussions about anxiety, depression, and PTSD.	Screening test for anxiety and depression with stepped-care pathway to meet psychosocial needs. Onward referral to CBT if required. Relaxation therapies can be considered.
Cognitive impairment	Onward referral from medical team. Coping strategies as part of group sessions alongside peer support. Learning sessions focusing specifically on delirium, PTSD, and cognitive impairment.	Not specifically addressed.
Social	Active peer support (patients and caregivers). Onward referral to community organisations.	Importance highlighted by SIGN but specific approach or strategies not described.

Component or domain	InS:PIRE	Cardiac Rehabilitation (SIGN guidelines)[351]
Financial and economic	Vocational rehabilitation.	Highlighted as an important area but specific strategies not described.
Other	ICU debrief: medical and nursing staff appointment with written lay summary. ICU visit: Patients and caregivers can revisit the unit to help address any mental health issues, PTSD, or confusing thoughts or memories of ICU. Questions about the ICU stay are encouraged. All services extended to family members (outwith physiotherapy and pharmacy).	Information on ongoing support and external organisations.
Family / caregiver involvement	Specifically involved in all aspects except physiotherapy and pharmacy. Caregiver peer support is a specific and particular focus of the intervention.	Recognised as an important element to consider but only where this impacts on the patient's recovery i.e. not a specific target of therapy.

Broad areas addressed ('Component or domain') and a comparison between InS:PIRE and Cardiac Rehabilitation as defined by the Scottish Intercollegiate Guidelines Network (SIGN) recommendations[351]. CABG: Coronary Artery Bypass Graft; PCI: Percutaneous Coronary Intervention; MI: Myocardial Infarction; MDT: Multidisciplinary team; PTSD: Post-Traumatic Stress Disorder; CBT: Cognitive Behavioural Therapy; ICU: Intensive Care Unit

6.3.5 Participants

Patients and caregivers were invited to attend the GJNH InS:PIRE programme at approximately 12 weeks after hospital discharge (range 6 to 16 weeks) and first attendance at the clinic was considered the baseline visit or attendance. Further follow-up was in-person at three months (after the first visit) and one year after the baseline attendance. It was important to the clinical teams to only invite patients who had significant exposure to intensive care. Many patients treated in the GJNH have very short intensive care durations of stay, as they are effectively treated through an advanced post anaesthesia care unit. For this reason, the inclusion criteria was anyone invasively ventilated in ICU for greater than 48 hours, thus only inviting those with a prolonged or complicated ICU stay.

The only exclusion criteria were those treated with palliative care, on an end-of-life pathway, those with significant and ongoing brain injuries, or prisoners.

All patients were encouraged to bring a relative, friend, or caregiver along with them. This person is referred to as the caregiver regardless of what role they fulfilled. These caregivers were included in the programme and a key area of focus for the study.

6.4 Outcome measures and data analysis

6.4.1 Data capture from the learning sessions

The information generated from the QI processes were collated by the thesis author (PH). After the delivery of the five cohorts the information gathered was discussed with each of the local healthcare professionals to check this for accuracy. An individual discussion, or informal interview, with each healthcare group (doctors, nurses, physiotherapists, pharmacists, and psychologist) also allowed each group to reflect on the process as a whole. This also helped capture any other learning that was observed by the teams but not recorded when the programme was being implemented and delivered. This information was synthesised by PH and is presented in the results section describing the cohort-to-cohort adaptation of the programme. The results section also describes the objective outcomes of this process with feasibility defined by the numbers attending and completing each cohort. The more subjective commentary is also synthesised to describe the perceived benefits and outcomes from each cohort-to-cohort iteration.

6.4.2 Quantitative measures

Quantitative data were collected to assess the experiences of both patients and caregivers after cardiothoracic critical care. Specifically, this was to focus on the change over the first year after CICU discharge. Note this change from the other studies which counted the time from hospital discharge. CICU discharge was used as the reference point for this study as this was a more reproducible metric for the quaternary service; it was not uncommon for patients to be repatriated to their local general hospital rather than being discharged home and hospital discharge date was not as readily available or reliable.

The primary measurement tools and questionnaires were the same as those utilised in the larger cohort studies described earlier in this thesis. As the focus

was the change over time, surveys were conducted at baseline InS:PIRE attendance, three-month follow-up, and one-year follow-up. As a reminder the surveys had already been chosen with involvement form patient and caregiver focus groups as important markers of HRQoL after critical illness. As a QI project focusing on the implementation of a new service the data were not, and would not be, compared to those in the general ICU one-year cohort studies. This was deemed inappropriate and beyond the scope of the methodology. While a detailed description of the questionnaires is offered earlier in this thesis (Chapter 3), Table 6-2 serves as a reminder of the outcome measures utilised and how they were specifically used for this study. In addition to the outcome measures previously described, this study also measured some physical outcomes that were not used in the other two studies of this thesis. Specifically, a selection of patients completed 6MWT, grip strength assessment, and had blood pressure measurements taken. This is summarised in Table 6-2.

Table 6-2: Summary of outcome measures utilised for cardiac InS:PIRE

Outcome measure	Components	Descriptors used	Use and timing in this study
Selective Physical measures	A small selection completed 6MWT, grip strength testing, and BP measurements.	Only those completing measures at three time points included.	Patients completing repeated visits.
EQ-5D-5L (EuroQol: Quality of Life Group)	5-question descriptive system, linear scale (EQ-VAS) from 0 to 100, EQ-HUS	Descriptive system summaries for each domain. EQ-HUS and EQ-VAS both reported.	Patients only. At baseline, 3 and 12 months.
Hospital Anxiety and Depression Scale (HADS)	14 item questionnaire, 7 for anxiety and 7 for depression. Score ranges from 0 to 21 for each sub-score.	Condition present if score ≥8/21. 8-10: Mild; 11-14: Moderate 15-21: Severe	Patients and caregivers at baseline, 3 and 12 months.
Caregiver Strain Index (CSI)	13 item questionnaire. Total score out of 13.	≥7/13 scores positively for strain.	Caregivers only at baseline, 3 and 12 months.
Insomnia Severity Index (ISI)	7 item questionnaire. Total score out of 28 points.	0 -7: No insomnia 8-14: Subclinical insomnia present 15-21: Moderate clinical insomnia or greater	Caregiver only at baseline, 3 and 12 months.
Brief Pain Inventory (BPI)	3 components Binary yes/no to having pain Pain severity scores Pain interference scores.	Pain score cut-off values 0: no pain; 1-3: mild pain 4-6: moderate pain; 7-10: severe pain.	Patients only at baseline, 3 and 12 months.

EQ-5D-5L: EuroQol 5-dimension 5-level instrument; EQ-VAS: EuroQol Visual Analogue Scale; EQ-HUS: EuroQol Health Utility Score; 6MWT: Six-Minute Walk Test; BP: Blood Pressure.

The pharmacy intervention was also included in the overall analysis for this part of the project / chapter. There was a specific focus on medication management and Medication Related Problems (MRPs). The senior pharmacist involved in the InS:PIRE clinic recorded every medication intervention that was undertaken to correct a possible or definite MRP. This data were then reviewed by two independent clinicians (the thesis author and another senior pharmacist from a different hospital) and the MRPs were classified on a scale of one (minor significance) to four (catastrophic significance). This classification system is described in Table 6-3 and summarises the approach described by Blix et al[352].

Table 6-3: Classification of intervention severity (pharmacy): Medication Related Problem (MRP) severity scale

Significance score	**1**	**2**	**3**	**4**
Domains	Minor	Moderate	Major	Catastrophic
Clinical Impact	Low risk to patient	Increased therapeutic benefit/avoidance of significant adverse effects	Prevent serious therapeutic failure/avoidance of serious adverse effects	Life or organ threatening event

Classification system as described by Blix et al[352].

Although this study appears towards the end of this thesis, this was the first component to be completed and as such the numerical data were all analysed using Microsoft excel[177].

6.5 Results

6.5.1 Baseline characteristics and attendance

The clinical team at the GJNH delivered five cohorts of InS:PIRE and invited 113 patients to participate. Of these 27 (24%) patients and 23 caregivers attended the programme. The completion rate was 96% with only one patient failing to attend the whole programme due to being readmitted to hospital for reasons unrelated to InS:PIRE attendance. Full details of the patient and caregiver characteristics of those who attended are outlined in Table 6-4 and demonstrate that 18 patients were male (67%) with a median age of 66 years (IQR: 61 to 75). The median ICU length of stay was 13 days (IQR: 9 to 21), the median time spent invasively ventilated was 6 days (IQR: 4.5 to 10), and planned or elective hospital admissions represented 15/27 (56%) of those who attended. The median time from ICU discharge to follow-up at the first InS:PIRE visit was 19.9 weeks (IQR: 14.5 to 25.0).

The majority of patients who attended were admitted to CICU post-operatively and 26% had undergone CABG, 19% had undergone a valve replacement, and a further 19% had undergone both a valve replacement and a CABG. Thus 17/27 (63%) patients in total had undergone CABG, valve replacement, or both.

Of the 23 caregivers attending, 9 (39%) were male. The caregiver relationship breakdown is described in Table 6-4 demonstrating that the majority of caregivers were spouses (78%). The remainder included 2 (9%) adult children, 2 (9%) parents, and 1 (4%) sibling.

Table 6-4: Characteristics of patients and caregivers attending cardiac InS:PIRE

Patient and caregiver characteristics	n = 27 patients
Number of cohorts	5
Patient details	
Male, total (%)	18 (67)
Median age, years (IQR)	66 (61 to 75)
Median APACHE II score (IQR)	17 (14 to 18.5)
ICU length of stay, median days (IQR)	13 (9 to 21)
Days ventilated, median (IQR)	6 (4.5 to 10)
Elective or scheduled admissions, total (%)	15 (56)
Time from CICU discharge to baseline InS:PIRE follow-up attendance, median weeks, (IQR)	19.9 (14.5 to 25.0)
Diagnosis or operation on admission	
Coronary Artery Bypass Grafting (CABG) only, total (%)	7 (26)
Valve replacement surgery only, total (%)	5 (19)
CABG and valve replacement, total (%)	5 (19)
Out Of Hospital Cardiac Arrest, total (%)	4 (15)
Aortic dissection, total (%)	3 (11)
Thoracic surgical procedure, total (%)	2 (7)
Cardiogenic shock, total (%)	1 (4)
Caregivers attended, n	23
Caregivers' sex, total male (%)	9 (39)
Caregivers' relationship to patient	
Spouse, total (%)	18 (78)
Child, total (%)	2 (9)
Parent, total (%)	2 (9)
Sibling, total (%)	1 (4)

IQR: interquartile range; APACHE II: Acute Physiology and Chronic Health Evaluation Two

6.5.2 Feasibility, Quality Improvement, and Learning

A full summary of how the programme evolved over the five cohorts, with a key focus on the data collected from the week-6 learning sessions are presented in Table 6-5 and Table 6-6.

Through an iterative process the team sought to evolve the programme and make it fit the specific needs of the GJNH patients and caregivers. The initial observations from the staff were that patients and caregivers valued the programme highly and this was confirmed with both informal feedback and high programme completion rates (96%). This information was disseminated throughout the team at the week-6 learning sessions. Furthermore, no patient or caregiver was observed to have come to or reported any harm from the intervention.

One area of concern, or a key focus for improvement, from the first cohort was the low uptake rate. Initially only 14% of those invited attended the first cohort. This improved through a series of interventions to between 25 and 30% for cohorts 4 and 5 (Table 6-5). The first change was to phone the patients as well as sending a written invitation letter. A second ICU nurse joined the team before cohort 2 and the two nurses had more resource to call the patients after the invitation letters were sent. This served a dual purpose of reminding the patients about the invitation letter but also as an education moment to inform them on what InS:PIRE involved. The nurses also encouraged the patient to bring a caregiver along with them.

It had also been highlighted from the learning sessions that time to follow-up was very long for the initial cohort. The impression was that those invited a long time after ICU discharge felt that the programme had less relevance. Table 6-5 demonstrates the median time from ICU discharge to follow-up per cohort showing how this reduced significantly from the first cohort onwards.

Table 6-5: Number attending each cohort and time to follow-up from cardiac InS:PIRE

Cohort details	Cohort number				
	1	2	3	4	5
Patients invited, n	28	19	22	20	24
Patients attending, n (% of those invited)	4 (14)	7 (37)	5 (22.7)	7 (30)	6 (25)
Number completing programme, n (% of those who attended)	4 (100)	6 (85)	5 (100)	7 (100)	6 (100)
Time from CICU discharge to follow-up, median days (IQR)	253 (218 to 255)	185 (146 to 210)	84 (67 to 100)	129 (111 to 162)	118 (97 to 142)

ICU: Intensive Care Unit; IQR: Interquartile Range.

Having addressed two significant areas with a perceived benefit in uptake rates it was decided to change the inclusion criteria for cohort 3. The rationale was that there was a younger group of patients that may receive improved peer support and perhaps have different needs from cohorts involving older patients. The programme could perhaps adapt to their needs more readily. It was also thought

that as this centre was a tertiary centre for PCI the numbers of young patients in the ICU, particularly after an OOHCA, would be large. This meant the team targeted a very young group, initially the plan was to only invite those under 40 years, but this would result in very few invitations, and this was expanded to those under 55 years.

On reflecting on this cohort, the team felt that this was a valuable trial but that the programme would have to change even further if they were to continue inviting only the under 55-year-olds. It was observed that invitations after 6 months were particularly problematic for the young age group as they often have other competing demands of being back at work, or family commitments. The peer support also did not work as well as expected. The team thought that having a narrower inclusion criteria would improve discussion but after this trial they perceived the opposite effect. It was the variety of age groups and different mix of experiences that was perceived to facilitate the discussion. The plan moving forwards was then to focus on including all age groups.

Learning from these experiences, the programme at the GJNH changed again for cohorts 4 and 5. To adapt to the specific needs of the GJNH population, it was decided to reduce the number of in-person days for each cohort. Both cohorts 4 and 5 had three in-person days rather than five for each cohort. Patients and caregivers attended for weeks one, three, and five of the cohort and received phone calls on weeks two and four. This built on the confidence and experience of calling patients with reminders during cohorts 2 and 3. The rationale was that those who lived further from the GJNH may be able to attend three rather than five sessions. This was particularly important at the GJNH as the hospital covers both a very large regional area and, for some services, the whole of Scotland. To compensate for the reduced number of days, the in-person sessions were increased from a half day (3-4 hours) to a whole day (5-7 hours). With the longer days, the team decided to offer the patients and caregivers lunch. This had the unpredicted effect of significantly improving the peer support. Patients and caregivers had a fixed time when they sat down together, thus receiving peer support but without a spotlight on this. The team noted that the cohorts bonded better despite attending fewer sessions. The success of cohorts 4 and 5 meant

that the team now considered this the core model for InS:PIRE at the GJNH with fewer plans to modify this further in the future.

Table 6-6: InS:PIRE development through the five cardiac cohorts

Feedback & development notes for each cohort
Cohort 1 • Programme first established, time from hospital discharge to follow-up was generally long. • 5-week programme, reflecting InS:PIRE at other sites at the time. • Follow-up timescale too long for many patients. Those approached more than one year after CICU did not see relevance of the programme or wish to attend. • Reliance on letter invitations only resulted in very low uptake rates. Collation of contemporary patient phone numbers was inadequate, and this needed attention. • Patient feedback from those completing the programme was positive and patients appreciated the input. • Physical and emotional issues encountered from those attending the programme were significant, signalling an ongoing need.
Cohort 2 • During planning, had further discussions with other hospitals running InS:PIRE after general ICU. • InS:PIRE team was expanded to include two nurses rather than one. Extra resource allowed more time to be allocated to patient calls including education about what the programme offers. This was especially important as PICS after CICU is a relatively novel concept. • Greater involvement from caregivers / relatives encouraged in this cohort and discussed in more detail during phone calls. • Uptake improved with this strategy alongside targeting a shorter time from discharge to InS:PIRE attendance. • Informal patient feedback was positive. Similar range of critical illness related problems as seen in cohort one. The team felt those attending had demonstrated a real need.
Cohort 3 • Trial of a younger cohort planned for this stage as this group may have a different spectrum of problems. • Age target was under 55 years; initial proposed cut-off of 40 years was too restrictive and cohort would have been very small. • Timing of programme even more important for this group. Patients had often returned to work if invited >6 months after CICU. • Overall, group did not interact with each other as well. Programme would need more adaptation for this model to continue. Pool of patients meeting criteria was too restrictive and resulted in patients attending 6 months after discharge from CICU.
Cohort 4 • New model introduced, clinic times changed from 3-4 hour, 'half day' sessions, to 5-7 hour 'full day' sessions. Lunch provided, improving patient and caregiver interaction and peer support. Patients and caregivers only attended in-person for three sessions (weeks 1, 3, and 5) and had nurse-led phone call appointments on weeks 2 and 4. This 3:2 split was tolerated well, especially for those who had longer travel times. • Cohort worked very well. Staff and patients / caregivers felt lunch was an 'ice breaker' and facilitated better patient and caregiver peer support. • Staff felt this model should continue and the range of problems facing these patients were, again, significant.

Feedback & development notes for each cohort
Cohort 5 • Model of care consolidated during this cohort. • Continued the 3:2 split, with lunch and cohort ran well. • Staff more efficient at reviewing patients and anticipating problems. • Third sector and community groups more embedded in clinic overall. • Informal positive feedback from patients and caregivers continued. • Feedback from staff and patients / caregivers encouraged continuation of this model.
Learning across all cohorts: • Many patients attended who did not think that they had problems or needed to attend. Most of these patients, when asked directly at follow-up, felt that they had benefited from the clinic. • Longer sessions every second week, with lunch provided, was the best model. • The complex transitions for some patients from CICU to general ICU or hospital, especially those with long CICU/ICU lengths of stay, meant aspects of routine follow-up could be missed. InS:PIRE helped to correct this. • This CICU could identify approximately 20 to 25 patients per quarter meeting the inclusion criteria. Future work may involve extending the criteria to those with shorter ventilation times but long treatment times in high dependency or coronary care areas. • Aiming for patients to attend within 16 weeks of hospital discharge may be the most effective strategy. Those <4 weeks from hospital discharge were not included and it is unclear whether this group would benefit from InS:PIRE.

InS:PIRE: Intensive Care Syndrome: Promoting Independence and Return to Employment; CICU: Cardiac Intensive Care Unit; ICU: Intensive Care Unit; PICS: Post-Intensive Care Syndrome.

Throughout all five cohorts, the team based the clinic at the hospital. This presented its own challenges as InS:PIRE requires both communal spaces for group sessions and private spaces for one-to-one sessions. Similar to many NHS hospitals these types of spaces are at a premium in the GJNH. However, the team also recognised the benefit of being co-located alongside existing services and expertise. These advantages included having other specialist clinicians on-site. It was noted that these patients frequently had specialist follow-up requirements that were often missed due to the complex transitions of care, particularly if the patient was transferred back to a general hospital after a prolonged period in the GJNH CICU. Having the clinic co-located in the hospital allowed the team at InS:PIRE to get more timely input from specialists based at GJNH, especially for issues pertaining to medications. Having ready access to the patient records also facilitated timely answers to specialist enquiries from patients and caregivers.

Finally, having the clinic in the same building as the CICU was particularly useful for facilitating visits back to the unit. This meant the visit could happen at a time to suit the family unit; it could happen early, or allow a few weeks for those

requiring some time to get used to the idea of going back to the unit. This part of the programme was reported to be beneficial for patients, caregivers, and staff.

Initially, psychology was delivered as a single session for both patients and caregivers. It quickly became apparent that this would be best delivered as two separate sessions. The perceived benefits of this were improvements in group discussion and more openness. This was of particular concern for the caregiver group who would often focus on the patient when both were together. By having them separate, the caregivers could focus on their own lived experience and be honest about the challenges of supporting the patient, while also attempting to live their own independent life. The physical separation for these sessions was also noted to be of particular benefit to some patient-caregiver groups. It was frequently noted that these sessions were the first time the caregiver had left the patient's side since hospital discharge. This set-up allowed dyads to experience this in a safe environment, thus encouraging more independence for both groups. The physiotherapy session also replicated this, with the one-to-one sessions being delivered for the patient without the caregiver present thus promoting independence throughout the programme. The physiotherapist also felt this facilitated a more accurate assessment of independent activities of daily living.

6.5.3 Quantitative outcomes

6.5.3.1 Follow-up completion and physical measures

While the programme completion rates were high, the surveys measuring one-year outcomes were less well completed. This likely reflected the competing demands of the team delivering and modifying the intervention while also asking the patients and caregivers to complete surveys. A total of 17 (63%) patients completed the EQ-5D-5L and HADS questionnaires, while only 13 (57%) caregivers completed the HADS survey at one year. The remaining questionnaires were less well completed, with full details offered in Table 6-7 to Table 6-13. A further 11 patients completed a 6MWT at all three time points, while only seven completed grip strength at the three predetermined time points. Table 6-7 demonstrates that distance walked for those completing this was fairly static over the one-year follow-up period with median values ranging from 379 to 401 metres. Grip strength tended to demonstrate an upward trend (Table 6-7). Blood pressure at baseline

was reliably recorded in 16 patients and the median systolic value of 144 mmHg (IQR: 128 to 163) corresponds to stage 1 hypertension[353].

Table 6-7: Cardiac physical outcome measures for those completing all planned measurements at: baseline; three months; and one year

Physical Measures	Baseline	3 months	1 year	Number completing measure
Distance walked, 6-Minute Walk Test, median metres (IQR)	400 (326 to 456)	401 (316 to 457)	379 (336 to 476)	11
Grip strength left hand, median kg (IQR)	41.6 (35.3 to 82.3)	56.2 (39.9 to 90.5)	62.3 (42.6 to 88.0)	7
Grip strength Right hand, median kg (IQR)	48.9 (41.6 to 77.2)	61.7 (48.9 to 82.2)	68.7 (50.3 to 83.8)	7
Systolic BP, median mmHg (IQR)	144 (128 to 163)	Not reported	Not reported	16
Diastolic BP, median mmHg, (IQR)	74 (69 to 79)	Not reported	Not reported	16

6.5.3.2 Patient outcomes: HRQoL, Self-efficacy, and pain

Of those completing the EQ-5D-5L the median values for the Health Utility Score (EQ-HUS) were 0.635 (IQR: 0.533 to 0.819) at baseline; 0.765 (IQR: 0.562 to 0.837) at three months; and 0.795 (0.602 to 0.919) at one year (Table 6-8). Similarly median Visual Analogue Scores (EQ-VAS) were: 70 (IQR: 52 to 85) at baseline; 80 (IQR: 76 to 90) at three months; and 85 (IQR: 65 to 90) at one-year follow-up (Table 6-8). Those expressing any problems in a single domain of the EQ-5D fell from 92% at baseline to 73% at one year and those with severe problems in any domain of the EQ-5D-5L was 22% at baseline and 18% at one year. Table 6-8 offers a full breakdown of the rates of problems at each time point for each EQ-5D-5L domain.

Table 6-8: EuroQol 5-level domain and summary scores

EQ-5D-5L	Clinic baseline	3-month review	1-year review
Number completing questionnaire	25	18	17
Percentage expressing problems in each domain (%)			
Mobility	56	50	45
Self-care	40	33	36
Usual activities	80	61	55
Pain or discomfort	76	72	64
Anxiety or depression	64	39	45
Domain summaries, median scores (IQR)			
Mobility	3 (1 to 3)	1.5 (1 to 3)	1 (1 to 3)
Self-care	1 (1 to 3)	1 (1 to 2)	1 (1 to 2)
Usual activities	3 (2 to 3)	2 (1 to 3)	2 (1 to 2)
Pain or discomfort	2 (2 to 3)	2 (1.3 to 2.8)	2 (1 to 2.5)
Anxiety or depression	2 (1 to 3)	1 (1 to 2)	1 (1 to 2)
EQ-HUS score, median (IQR) (range: -0.594 to 1.0)	0.635 (0.533 to 0.819)	0.765 (0.562 to 0.837)	0.795 (0.602 to 0.919)
EQ-VAS score, median (IQR) (range: 0 to 100)	70 (52 to 85)	80 (76 to 90)	85 (65 to 90)

EQ:5D-5L: EuroQol 5-Dimension 5-Level survey. Percentage of patients experiencing problems in each of 5 domains: mobility; self-care; usual activities; pain or discomfort; anxiety or depression. Median EuroQol Health Utility Scores (EQ-HUS); Median EuroQol Visual Analogue Scale (EQ-VAS) at each time point. IQR: Interquartile Range.

Table 6-9 demonstrates very minimal change over time from those completing the GSE survey and likely suggests that InS:PIRE did not have an impact on self-efficacy for this group.

Table 6-9: Generalised Self-Efficacy scores

Generalised Self-Efficacy	Baseline	3 months	1 year
Number completing survey	24	17	13
Median value (IQR)	32.5 (30 to 36)	31 (26 to 38)	32 (29 to 38)

The BPI demonstrated that 14 (61%) patients had pain worse than their normal pain at baseline (Table 6-10). Completion rates for this survey at three months (n=10) and one year (n=11) were poor. Median scores for 'worst pain' at baseline would be considered as moderate pain (median score = 4 [IQR: 2 to 7]), although other pain score medians would be considered mild pain ('least', 'average', and

'pain right now'). The highest baseline scores for pain interference were on the interference on normal work (median score = 4 [IQR: 0.5 to 7]), and interference on enjoyment of life (median score = 4 [IQR: 1 to 7.5]).

Table 6-10: Summary of Brief Pain Inventory short-form at baseline, three months, and one year

Question	Baseline	3 months	1 year
Number completing Survey	23	10	11
Pain worse than normal: total 'yes' responses (%)	14 (60.9)	6 (60)	9 (81.8)
Pain scores, median (IQR)			
Worst pain	4 (2 to 7)	3 (1.25 to 6.75)	4 (1.5 to 6)
Least pain	1 (0 to 4)	1.5 (1 to 4.5)	1 (0 to 5)
Average pain	2 (1.25 to 5)	2 (1.25 to 5.75)	2 (0.5 to 4.5)
Pain right now	1 (0 to 3.5)	1.5 (0.25 to 5.25)	1 (0 to 4.5)
Pain interference scores, median (IQR)			
Pain Interference on general activity	3 (0 to 5)	1 (0 to 4.25)	2 (0 to 7)
Pain Interference on mood	2 (0 to 3.5)	1 (0 to 3.5)	0 (0 to 4.5)
Pain Interference on walking	3 (0 to 6.5)	2 (0 to 4.5)	1 (0 to 6)
Pain Interference on normal work	4 (0.5 to 7)	1 (0 to 5.25)	1 (0 to 5)
Pain Interference on relationships with others	0 (0 to 3.5)	0 (0 to 0.75)	0 (0 to 2.5)
Pain Interference on sleep	2 (0 to 6.5)	0.5 (0 to 2.5)	0 (0to 5)
Pain Interference on enjoyment of life	4 (1 to 7.5)	1.5 (0 to 4.25)	1 (0 to 6)

6.5.3.3 Mental health: patients and caregivers

As a reminder the standardised cut-off value for anxiety or depression on HADS is a score ≥8/21. At baseline 11 patients scored for mild anxiety or greater which represented 46% of those completing this outcome measure and 6 (25% of those completing the survey) scored positively for moderate anxiety or greater (Figure

6-1 and Table 6-11). Fewer patients scored positively for depression with only 6 (25% of those completing the survey) meeting the HADS depression threshold.

Rates of anxiety for caregivers were 55% for those completing the surveys at baseline and the depression rate was 30%. Table 6-11 gives a full breakdown of mental health outcomes and the changes over time.

Figure 6-1 demonstrates the change in median values for patents and caregivers at the three time points. Median caregiver anxiety scores were 8.5 (IQR: 2 to 11.5) at baseline and appeared higher than patient scores (6 [IQR: 2 to 10.2.5]) although at one year they were similar.

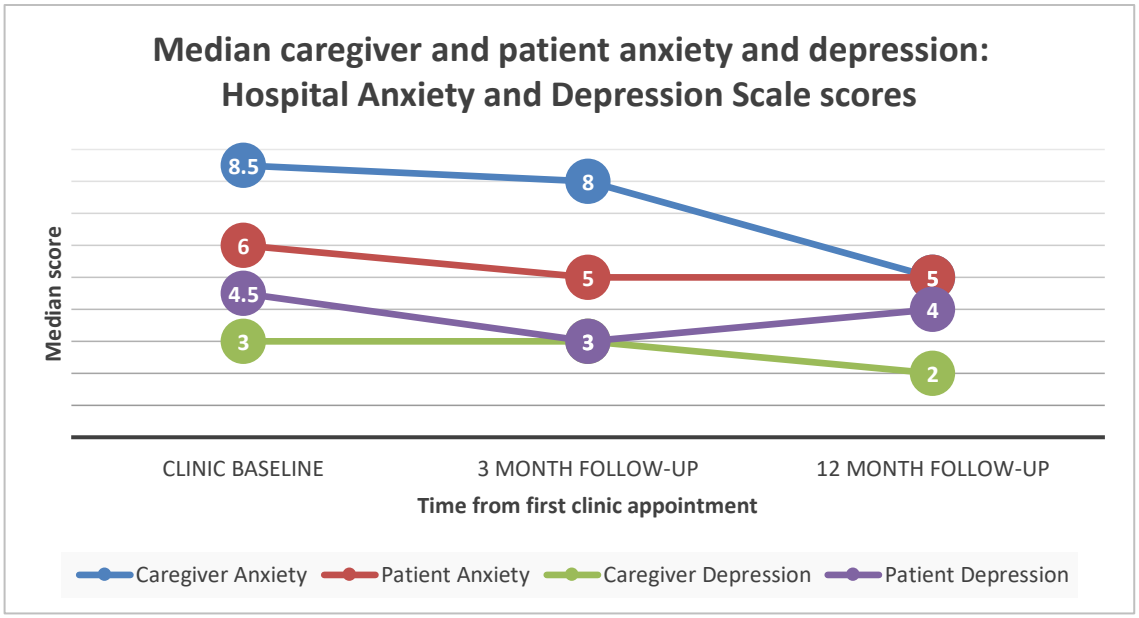


Figure 6-1: Cardiothoracic mental health outcomes.

Median Hospital Anxiety and Depression Scale (HADS) scores for patients and caregivers at first clinic attendance (baseline), 3 months, and 12 months post initial attendance. Numbers completing HADS surveys at each timepoint are: clinic baseline, 24 patients, 20 caregivers; 3-month follow-up, 20 patients, 16 caregivers; 12-month follow-up, 17 patients, 13 caregivers.

Table 6-11: HADS scores for patients and caregivers at baseline, three months, and one year

HADS Summary	Clinic Baseline	3-month review	1-year review
HADS patient outcomes			
Patients completing surveys, n	24	20	17
Anxiety score, median (IQR)	6 (2 to 10.25)	5 (1.75 to 9)	5 (1-8)
Mild anxiety, n scoring ≥8/21 (%)	11 (45.8)	8 (40)	6 (35.3)
Moderate anxiety, n scoring ≥11/21 (%)	6 (25)	3 (15)	4 (23.6)
Depression score median (IQR)	4.5 (2.75 to 7.25)	3 (1 to 8.25)	4 (1-8)
Mild depression, n scoring ≥8/21 (%)	6 (25)	7 (35)	5 (29.4)
Moderate depression, n scoring ≥11/21 (%)	3 (12.5)	2 (10)	2 (11.8)
HADS caregiver outcomes			
Caregivers completing survey, n	20	16	13
Anxiety score, median (IQR)	8.5 (2 to 11.25)	8 (2.75 to 10)	5 (2 to 7)
Mild anxiety, n scoring ≥8/21 (%)	11 (55)	9 (56.3)	3 (23.1)
Moderate anxiety, n scoring ≥11/21 (%)	6 (30)	3 (18.8)	3 (23.1)
Depression score, median (IQR)	3 (0 to 8)	3 (0.75 to 7.25)	2 (1 to 4)
Mild depression, n scoring ≥8/21 (%)	6 (30)	4 (25)	1 (7.7)
Moderate depression, n scoring ≥11/21 (%)	2 (10)	2 (12.5)	1 (7.7)

HADS: Hospital Anxiety and Depression Scale

6.5.3.4 Caregiver strain and insomnia rates: caregivers only

Rates of strain defined as 7 or greater on the CSI did not appear particularly high in this cohort. There were four caregivers (20%) who met this criterion at baseline and rates dropped to 13% at three months and 0% at one year. It should be noted, however, that completion rates were low for this survey with only 50% (10/20) of those who completed the survey at baseline also completed this at one year (Table 6-12). The most common area caregivers experienced strain was in their need to alter their plans, where 8 (40%) reported experiencing this.

Table 6-12: Caregiver strain over time

Caregiver Strain Index	Baseline	3 months	1 year
Number completing survey	20	15	10
Median (IQR)	3 (0.75 to 5.25)	2 (0 to 5)	1 (0 to 1)
Number with strain present (%)	4 (20)	2 (13)	0 (0)

Overall rates of sleep problems in caregivers appeared high, with half of those who completed the ISI met the criteria for insomnia (≥8/28) with a median number of nights of disturbed sleep of 5 (IQR: 1.0 to 6.75). A full breakdown can be found in Table 6-13.

Table 6-13: Insomnia Severity Index outcomes

Insomnia Severity Index	Baseline	3 months	1 year
Number completing survey	22	14	10
Median ISI score (IQR)	8 (1.5 to 14)	7 (2 to 10.75)	4.5 (1.75 to 10.5)
Number scoring positively for insomnia, score ≥8/28 (%)	11 (50)	7 (50)	3 (30)
Number of nights per week of sleep problems, range: 0-7, median (IQR)	5 (1 to 6.75)	1 (0 to 5)	0 (0 to 3)

6.5.3.5 Pharmacy outcomes

All of the 27 patients who attended InS:PIRE received the pharmacy intervention with a one-to-one appointment and full medicines reconciliation. Review of this data demonstrated that 15/27 (56%) patients had at least one MRP; there were a total of 32 MRPs and 27 of these were deemed to be clinically significant (grade 2 or greater, Table 6-3). Cardiovascular medications represented 70% or MRPs with just under a quarter of these (24%) being related to anticoagulation or antiplatelet drugs. The overall impression from reviewing each MRP was that deficiencies in the communication at the transitions of care were the most common area for problems to arise, and this is where preventative interventions could be targeted in the future.

6.6 Discussion

6.6.1 Summary of results

This project has taken the opportunity to carefully examine how the InS:PIRE intervention can be adapted to meet the needs of different patient and caregiver subgroups or local needs. Specifically, it has demonstrated the process involved in changing the intervention to address the issues faced by survivors from a single CICU. Finally, the long-term outcomes experienced by survivors of cardiothoracic critical illness and their caregivers have been described.

The qualitative results from the week-6 learning sessions demonstrated that the InS:PIRE programme is very tolerant to adaptation, and in this specific case, was enhanced by running the programme in different ways. The use of telecommunication, simply a phone call, appeared to improve uptake rates. Furthermore, the use of calls as a replacement for in-person clinic attendance added significantly to the effectiveness of the programme by allowing for longer in-person sessions with perceived improvements in peer support. This approach was also particularly useful as the service covers a very large geographical area. All of this occurred before the influence of the COVID-19 pandemic, before the widespread use of virtual visiting in the NHS, and demonstrates how some of these technologies could be utilised in the future, particularly for centralised services[354].

Other developments were seen as less successful, particularly cohort 3, when younger patients were the focus. The team used this learning to rethink how to maximise the engagement from those attending and further think about the best timing for follow-up which was seen as particularly important in this case. Cohort 3 also allowed the clinical team to re-evaluate the inclusion criteria and work out how to make sure that InS:PIRE could benefit as many CICU patients and caregivers as possible. In effect, the team were considering both the efficiency and effectiveness of this resource simultaneously.

The final areas explored were the patient and caregiver outcome measures. These have quantitively captured the problems experienced by both groups over the one-year follow-up period. These results have highlighted that the extent and range of PICS problems experienced by this group are similar to the general ICU population[31,311,345]. This study has demonstrated that the physical outcomes patients experience and mental health outcomes both patients and caregivers experience, are similar to the general ICU population[31,88,311,345]. The flat recovery trajectory for the 6MWT is consistent with other studies in the general ICU population[57,79]. The changes in grip strength are from very small numbers (7 patients) and warrant more study in the future. The more widely accepted, global physical measure, EQ-5D, does demonstrate a steeper patient recovery trajectory over the one-year follow-up period. This is similar to that seen in general ICU patients, specifically when compared to patients with septic shock[355].

The mental health problems experienced by caregivers were significant and striking in this study, with over half of caregivers completing the HADS survey at baseline scoring positively for anxiety. It is also notable that the median value for anxiety was higher for caregivers than patients. These high rates have been seen in other general ICU studies and these results add weight to the overall impression that PICS-F is a phenomenon experienced by caregivers of post CICU patients[356]. Given the extent of care and rehabilitation delivered by informal caregivers, more work is urgently required to understand how we can best support these groups. InS:PIRE may offer one such platform, but there is much more work needed to understand the mechanics and effectiveness behind the individual InS:PIRE components.

6.6.2 Understanding the core elements of 'cardiac' InS:PIRE

The core elements of this intervention appeared to be: social care provision; MDT follow-up; case management; and peer support.

It was the welfare advice that stood out as one of the key elements for this part of InS:PIRE. By embedding financial and social care services and other important links to the third sector, the intervention could fully integrate the biopsychosocial model of healthcare[39,357,358]. These services could be critical for all patients and caregivers, whether this involved advice on bills, housing, returning to employment, or simply accessing a falls alarm. In this way the social input was both proactive, by seeking out specific problems, yet adaptable and could respond to unexpected needs of patients and caregivers. As the programme matured over the five cohorts the team also developed more links with local organisations which enhanced the social care significantly.

A key learning point was in understanding the overall approach to recognising the social and financial issues faced by patients and caregivers, rather than the exact interventions or community links that were made at this site. If future clinics were set up in different geographical locations from other services, it is likely that links with the third sector will still be important. These links would be crucial to these InS:PIRE services even if the individual and specific needs of the patients or caregivers are different. Furthermore, the precise services on offer are likely to vary. The week-6 learning session was key to the identification of these needs as well as implementing effective change to address the unmet social and financial needs.

The concept of the MDT is discussed and utilised for many healthcare interventions[359]. In this intervention there were the core elements of the MDT that have been set out in the methods section of this thesis. The feedback received suggests that all aspects of the MDT were important and future InS:PIRE programmes should involve the core groups including: doctors; nurses; physiotherapists; pharmacists; psychologist; and community organisations.

However, the MDT also utilised the skills of professionals not directly involved in InS:PIRE. This often involved speaking to a cardiologist about the duration of

antiplatelet medication or a surgical review of a wound. These consultations could be considered referrals or advisory calls although the team did not think about these consultations in that way, instead, preferring to think of themselves as case managers. The InS:PIRE team formed the relationship with the patients and caregivers and could advise them as to the next best course of action. It was clear that the follow-up burden on many patients was very high. This could result from the disconnect between the very specialist services at the GJNH and the general services at the local hospitals the patients returned to. The team were able to advise on follow-up and guide patients as to the most important appointments and this is where the true case management occurred[360]. While all InS:PIRE programmes described in this thesis had elements of case management it was far more pronounced within the GJNH programme. This may be a further reflection of the many transitions of care that patients who are treated by a centralised regional or national service experience. Further work is required to understand this role of InS:PIRE and it would appear particularly important to target this type of case management for any ICU follow-up service involving tertiary or quaternary care.

These core elements further emphasise how and why InS:PIRE is different from CR. In fact, it was not uncommon for the InS:PIRE team to refer the patient to CR services. This was frequently due to the patient missing their CR appointment as they remained in hospital during the time period this service would normally be delivered. It is evident that CR is designed for all cardiac patients and those who have a greater severity of illness, involving treatment in CICU, are at higher risk of missing out on these more standard recovery pathways[351,361]. Furthermore, the InS:PIRE team clearly demonstrated that they perceived these services to be different, given their willingness to refer to CR. It may be that in the future, CR expands by increasing its focus on the mental health and socioeconomic wellbeing of patients, and certainly the Scottish guidelines do mention these elements of cardiac recovery[351]. However, even if every element of the Scottish guidelines were implemented and expanded on it would appear unlikely that the CR that is delivered today would meet all of the needs of CICU survivors and their families identified by this study. Instead, future developments may involve more close working between CR and InS:PIRE, perhaps inviting those delivering CR to attend InS:PIRE, thus having a direct connection to this service. This would also protect

against either service delivering overlapping care leading to inefficiencies in healthcare and redundancy for patients and caregivers.

The final aspect of the intervention that was highlighted and seen as contributing substantially to the recovery of the CICU survivors and their families was peer support. The importance of this has been emphasised through both the design of InS:PIRE and the previous chapters in this thesis. Indeed, the team delivering InS:PIRE at the GJNH equally expressed the importance of peer support as recognised throughout the ICU literature[213,333,338]. The key difference here was that lunch was delivered in the final two cohorts and the feedback from these prolonged sessions, although fewer in number, was very positive. This highlights that the perfect way to deliver peer support has not been set and that each service will have to optimise peer support to their own needs; a single peer support 'prescription' cannot be given to all CICU survivors. An important advantage of the models of peers support delivered throughout the InS:PIRE intervention, especially during the CICU programme, was that this could potentially reach participants that may not attend a traditional peer support or self-help group. This has the potential to expand access to this evolving area of critical care survivorship and recovery to a wider population[245,332]. There is also evidence from other services, particularly mental health services, that organisational flexibility can improve the effective implementation and delivery of peer support[362]. The GJNH InS:PIRE team certainly demonstrated flexibility and this is likely to have contributed to the success of the programme but particularly to the delivery of peer support. A key focus of future peer support studies should be on the adaptability of this type of service to maximise the patient and caregiver groups that this type of intervention can benefit.

6.6.3 Could InS:PIRE be embedded into Cardiac rehabilitation programmes?

A further development worth considering is whether CR could eventually deliver all aspects of InS:PIRE, or at least all the core elements perceived to be contributing to any observed treatment effect. A starting place for this would be that InS:PIRE should engage with CR and highlight (or report back) the important aspects of InS:PIRE that are missing. Given that CR is well funded at a national level and near ubiquitous, it may be that CR has better access to resources to

upskill on the missing elements that InS:PIRE offers. From this study, and an assessment of CR, it is evident that the physical rehabilitation CR offers is likely to be more comprehensive than that offered by InS:PIRE. However, the specific issues pertinent to the CICU survivor could be highlighted to CR (e.g. ICU acquired weakness), to make this more focused when the pathway to CR involves CICU. Likewise, the psychology input at CR is robust and well-funded and would need only minimal adaptation to treat the CICU patient more comprehensively. How the CICU lay summary and debrief fit into this model could be addressed with some input from the local CICU teams.

However, the most important aspects to adapt CR services for the CICU patient (and their families) would be the socioeconomic rehabilitation. This would need to incorporate all the socioeconomic aspects of InS:PIRE. The direct economic rehabilitation from citizens advice would be a clear and tangible place to start. It is less clear how peer support and the other aspects of (non-economic) social rehabilitation would fit in. Whether a mixed group of CR patients, only some of whom had been in CICU, would be able to deliver this peer support is unclear. A solution could be for a standalone CICU peer support group, but as mentioned previously, some patients may be less likely to attend a standalone group. Finally, the importance of integrating the caregiver in the patient recovery would need to be emphasised to CR and important caregiver elements should be included if CR is to take on the role of InS:PIRE.

It is evident that there is some overlap between CR and InS:PIRE but a key driver to incorporating InS:PIRE into CR is that CR has a longer history of delivery and correspondingly more robust funding. In the current economic climate, future work should focus on minimising overlap between these services and delivering targeted interventions that have the greatest impact, whether that is delivering CR with embedded elements from InS:PIRE or vice versa.

6.6.4 Strengths and limitations

The strengths of this study are numerous. This study offers a better understanding of how InS:PIRE can be modified and adapted to the needs of different services, particularly super specialised ICUs. Perhaps more importantly, the process itself of InS:PIRE modification and adaptation could be repeated for any area including

specialist or general ICUs. It is, therefore, the mechanics of how and why things were changed, rather than the exact changes made, that are critical. The description and process involved in the week-6 learning sessions could offer a template on how to introduce and adapt an InS:PIRE programme to local needs. This study is also unique because it offers insights into the long-term outcomes from a mixed medical-surgical cardiothoracic intensive care. While a number of studies have considered outcomes after OOHCA, few have considered the real-life case mix of this type of centre[341-343]. Similarly, the follow-up of caregivers of this patient population is unique when most studies have focused exclusively on the general ICU population or OOHCA patients[344]. The choice of surveys is a strength, and the use of important patient and caregiver centred outcomes improves the value of this study.

There are, however, many limitations. Firstly, this was a single centre study focusing on QI over time. As such, the ability to confidently extrapolate this to other institutions or geographical areas is limited. More studies, particularly multicentre studies, would be required to reliably understand the outcomes from different CICU centres. Similarly, the sample size is small and while this may be expected from the methodology, the numbers completing follow-up measures at one year is low. This is why further statistical testing was not carried out on any perceived trends as there could be a high chance of misinterpreting the results with a particular risk of an α-error. Similarly, the use of multiple imputation was not undertaken as the low numbers would make the process of imputation less reliable and risk adding further bias to the results. It cannot be stated confidently that the missing results were missing at random and the study has not addressed the reasons for the missing outcome measures.

Perhaps more importantly for a QI initiative, there was no formal direct feedback from patients and family collected during this evaluation. This decision was made as those participating in the intervention were already receiving a great deal of information and the priority was on programme delivery, the week-6 learning sessions, and for the participants, the completion of outcome measures. However, this is a substantial limitation. Similarly, the impression that patients and family enjoyed or appreciated the programme (Table 6-6) was an indirect measure based on informal feedback to staff, the MDTs thoughts and experiences expressed

during the week-6 learning sessions, and by the high completion rates from patients and families attending the intervention (i.e. once they attended the vast majority returned and completed the programme). This information is indirect and future developments should aim to collect more direct feedback from patients and families on their thoughts and experiences of the programme. It is very clear that this work is only a starting point for the InS:PIRE intervention and CICU and a key priority should be on the qualitative outcomes and user experiences during future cohorts. This would complement the work here and allow the decisions about programme adaptation to directly result from service user feedback.

A related limitation is that no comparator group has been used, whether from another CICU or general ICU populations. The data were collected using QI methodology and did not involve consenting the patients or caregiver, as such this data has not been directly or statistically compared to other available data. Finally, data on comorbidities was not available, most importantly, data on pre-existing mental health problems was not collected, which limits the ability to associate the mental health problems after CICU with the critical illness itself.

6.7 Conclusions

This study has demonstrated that the implementation of InS:PIRE for the survivors and caregivers of those treated in a cardiothoracic intensive care is feasible, safe, and well tolerated. Furthermore, those attending appeared to benefit from the programme. Implementation was enhanced by the use of continuous review and adaptation to meet the specific needs of this population. Finally, an evaluation of important health and QoL markers demonstrated a significant burden of problems experienced by patients and caregivers after cardiothoracic intensive care.

Chapter 7 Discussion

In this concluding chapter the findings of the thesis are briefly summarised, and the strengths and limitations of the thesis are considered. As part of this discussion the potential mechanisms behind how the InS:PIRE intervention could have lasting benefits for patients and caregivers are considered.

The implications of this work for research and practice in this field are also discussed. Future directions for research relating to this thesis are considered and a cost-effectiveness estimate for the wider implementation of the InS:PIRE intervention is offered, before the implications of this work for contemporaneous clinical practice are discussed.

7.1 Summary and thesis findings

The primary results and findings from this thesis are:

- Those recovering from critical illness experience significant problems in the domains of physical health, mental health, cognitive impairment, and socioeconomic problems. Collectively these features are known as Post-Intensive Care Syndrome (PICS) and can last long after hospital discharge, often persisting beyond one year. The family members of critical illness survivors also experience lasting emotional and socioeconomic problems after critical illness (PICS-F).

- Until now there have been no well-conducted quantitative studies of outpatient interventions that demonstrated lasting benefits for critical illness survivors. Most interventions studied involve a simple MDT (two or fewer professionals) and do not address all aspects of PICS, particularly missing family involvement and socioeconomic rehabilitation. Despite the paucity of strong evidence, there are national (UK) recommendations that intensive care survivors should receive critical care specific outpatient follow-up.

- The InS:PIRE intervention is a unique programme for outpatient critical care rehabilitation because it incorporates a complex MDT alongside psychological, social, and economic rehabilitation.

- The InS:PIRE programme is the first intervention to demonstrate lasting long-term measurable benefits for the outcomes of HRQoL and mental health (depression) for survivors of critical illness.

- Pain was a significant problem persisting at and beyond one year. InS:PIRE did not appear to have any significant effects on the experience of pain.

- Family members and caregivers attending and participating in InS:PIRE have lower rates of anxiety; strain from the caregiving role; and insomnia.

- Patients and families treated in a specialist cardiothoracic critical care unit experience features of PICS and PICS-F with these effects lasting beyond one year after a critical illness.

- The InS:PIRE intervention is an adaptable programme that tolerates changes well. The adaptations undertaken were particularly effective in addressing the needs of a group of specialist (quaternary) cardiothoracic intensive care patients and their families.

7.2 Strengths and limitations

The strengths and limitations of each study have been discussed within their respective chapters; however, it is worth considering these factors for the thesis as a whole.

7.2.1 How this work advances the literature

The three primary studies contained in this thesis described the outcomes of a total of 472 patients, caregivers, or participants up to and beyond one year after critical illness. The median size of previous studies in this field, as highlighted by the scoping review, is substantially smaller than those presented in Chapter 4 and Chapter 5 of this thesis. This thesis therefore includes two of the largest studies

comparing an outpatient intervention to usual care. This is a substantial numerical contribution to the formal literature in this field.

The outcomes studies (Chapter 4 and Chapter 5) included in this thesis have demonstrated consistent measurable correlations between improvements in QoL and attendance at the InS:PIRE intervention for ICU survivors and their families. As far as can be ascertained from the extensive scoping review, these are the first two (and the only) studies to demonstrate this broad benefit from an outpatient intervention. These results offer significant hope for patients, caregivers, and healthcare staff that there are therapies that can potentially help to ameliorate some of the problems associated with critical illness survivorship. Furthermore, this thesis offers a quantitative justification for the implementation of the InS:PIRE intervention after critical illness. Researchers can also look towards this work to better understand the type of interventions that are most likely to be beneficial. Although the methodology of these studies limited inference of causation, the signal of benefit is encouraging and offers a platform for future study and trial design.

These studies have described in detail the InS:PIRE intervention and how it was delivered. This has allowed an exploration of how the different components interact and how the traditional MDT can be integrated with social care, peer support, and community (third sector particularly) organisations. This complex structure mirrors the complexity of both PICS and PICS-F, taking into account the emerging evidence of the socioeconomic consequences of critical illness. Furthermore, Chapter 6 built on this detail to describe the process of adapting the intervention to meet the needs of different services and local requirements. This allows InS:PIRE to have a greater reach as other clinicians and researchers can look to replicate this work and to adapt it for their own healthcare setting.

7.2.2 Mechanisms behind the InS:PIRE intervention

It is worth considering where and why the InS:PIRE intervention may deliver lasting effects, at and beyond one year after critical illness. The scoping review identified that there were multiple interventions which were based on traditional and focused healthcare approaches. Overall, these interventions were simple and did not involve a complex MDT, generally being delivered by two or fewer

professionals. None of these interventions appeared to deliver lasting measurable benefits for the patients when compared to usual care. Therefore, although InS:PIRE contains many of these interventions, including medical review, onward referral, physiotherapy review, and pharmacy review, these components on their own would appear unlikely to be the primary driver for the lasting effects demonstrated in this thesis. Furthermore, extensive standalone psychological interventions have failed to demonstrate lasting benefits when delivered in isolation in the outpatient setting.

Instead, it may be that combining these elements (the hospital healthcare MDT) with the other InS:PIRE components that leads to lasting measurable effects. Some of the broad areas in which InS:PIRE diverges most from the healthcare MDT, that is the contemporaneous literature, and which could explain the lasting benefits demonstrated in this thesis include:

- Improvements in the patients' and caregivers' understanding of the critical illness and its effects: critical care debrief and education sessions.

- Treatment of the family unit as a whole: encouragement and attendance from the caregivers and family at InS:PIRE including during the one-to-one appointments with the entire MDT.

- Achieving acceptance of the individual's current health and wellbeing, planning for the future, and patient / caregiver improvements in navigating the healthcare environment: goal setting, recurring visits to the same MDT, signposting to other services, improved self-efficacy, and peer support.

- Socioeconomic rehabilitation: direct economic rehabilitation was delivered at every InS:PIRE site by a financial and social care specialist (Citizen's Advice Bureau) with a group visit (or presentation), and with individual appointments if required; social rehabilitation was delivered by peer support, goal setting, and recurring visits to the same MDT who treated barriers to engagement in pre-existing social roles.

It is the socioeconomic rehabilitation that stands out as being the most likely single component that would deliver lasting effects, over and above existing

programmes involving a hospital MDT. However, the socioeconomic rehabilitation should be considered in the broadest sense. The use of social and financial advisors in the programme are a clear and reproducible intervention that other services should consider adopting. Whether this intervention on its own is enough to explain all the benefits of InS:PIRE is unknown.

It is equally likely that InS:PIRE addressed the other elements of socioeconomic reintegration that can be more challenging to define. Peer support is an example of this, which can allow for patients and their families to engage with other people and start to identify and address issues of loneliness and social isolation. Peer support has the potential of increasing the participants' confidence of social situations beyond the programme with sustained long-term benefits of a reduction in social isolation. As such, the embedded social rehabilitation, including peer support, offers a potential mechanism behind the QoL improvements associated with InS:PIRE. Furthermore, the benefits of social reintegration could be appreciated by most (or all) participants, while the economic aspects would primarily benefit those with financial deficits that could be addressed. Another way the teams delivered social rehabilitation was by asking the participants to tell them what they wanted to achieve. This allowed the InS:PIRE teams to target advice on returning to hobbies, interests, or other activities that, although not necessarily of financial benefit, were important aspects of the participants' lives before the critical illness. Some of these changes could also be used as stepping stones towards employment with direct socioeconomic benefits and therefore link both the social and financial aspects of these crucial elements of InS:PIRE.

This thesis and programme of research were not designed to mechanistically understand the contribution of each individual component of InS:PIRE or of the socioeconomic rehabilitation. As things stand, it is not possible, or in fact desirable, to only focus on one aspect of socioeconomic rehabilitation. Instead, InS:PIRE should be considered as a package of interventions aiming to address all aspects of social and economic (or financial) wellbeing. To capture this holistic approach, Figure 7-1 outlines the socioeconomic problems faced by the ICU survivor, the effects these can have on overall health and wellbeing, and the possible solutions that InS:PIRE aims to address. It is this combined approach,

alongside the broad hospital MDT, that is most likely to lead to the lasting effects that have been demonstrated in this thesis.

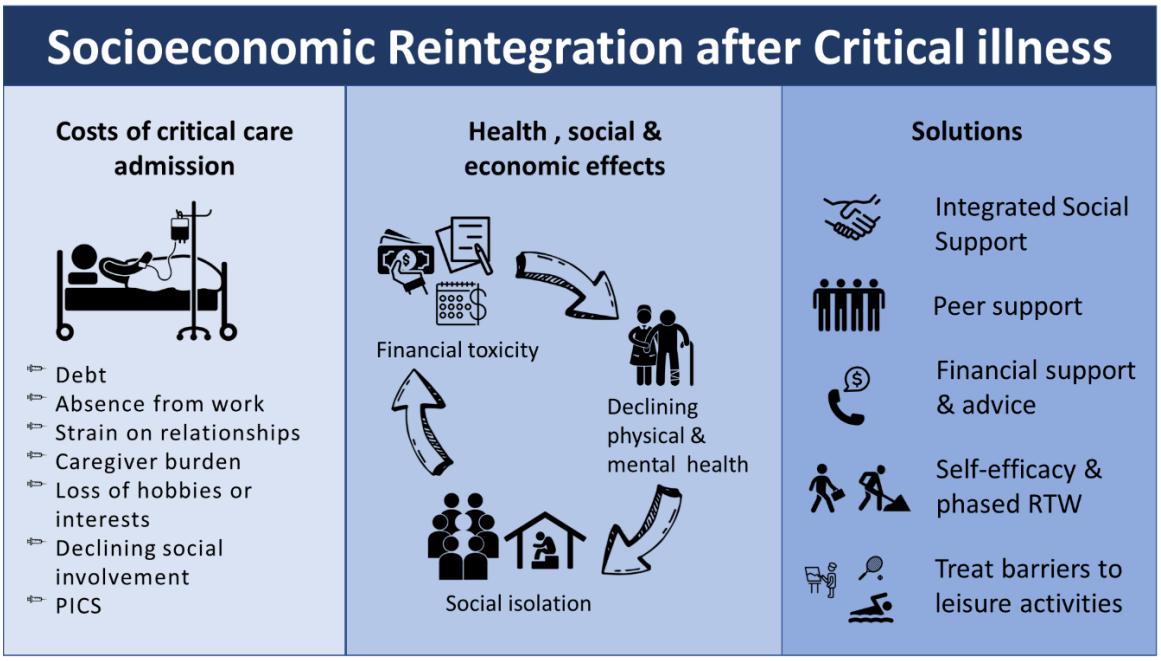


Figure 7-1: Summary of socioeconomic reintegration after critical illness[1]

PICS: Post-Intensive Care Syndrome; RTW: Return to Work. Figure designed by the thesis author and published by Springer Nature. Reproduced for this thesis with permission from Springer Nature Switzerland AG.
DOI: 10.1007/978-3-030-68680-2_18. (Licence Number: 5646401077762).
https://link.springer.com/chapter/10.1007/978-3-030-68680-2_18.

7.2.3 Thesis limitations

Despite its contribution to the field, the limitations of this thesis are significant. The studies included in this thesis are not RCTs. As such, it is more difficult to assign causation to the InS:PIRE intervention. Statistical methods have been implemented to minimise the effects of biases, but the traditional approach would be to use an RCT to reduce these effects further. The missing data, particularly in some aspects of the caregiver study, were significant. While the reasonable assumption was made that these data were missing at random, there could have been systematic causes of missing data, for which the statistical methods would not have corrected. For example, the caregiver age demographic was a particular bias resulting from the paper proformas used for this study. An RCT could improve on some of these biases, but as highlighted in the scoping review, even RCTs in

the field of long-term outcomes after critical illness can have high rates of missing data.

The outcomes studies also used different techniques to recruit and collect data; the intervention cohorts were recruited from InS:PIRE, while the usual care cohorts were recruited by postal survey. This may have affected some of the data collection and introduced some bias, particularly in the missing values.

This thesis did not include a measure of cognitive dysfunction for any of the studies. Part of the rationale for this was that this was not prioritised by patients and caregivers during the design phase. The main problem with cognitive dysfunction is that it may be underrepresented with this type of study, as those with, for example, memory impairment may be less likely to participate in this research and may not attend follow-up services. Part of the mitigation for this would be to include the use of reminders and the involvement of family but cognitive dysfunction would always be challenging to quantify. Future studies should consider inclusion of a cognitive measure to better understand whether patients with cognitive impairment are being included in follow-up services and studies.

All of this work was conducted in Scotland and therefore it may be difficult to justify the translation of these outcomes to other countries and services. While the framework for how this service may be adapted is described in Chapter 6, the outcomes could be different. Implementing and studying this intervention in different healthcare settings would improve the understanding of how transferrable this service is to these settings.

The caregiver study (Chapter 5) first relied on recruitment of the patient participants. This may have limited the caregivers involved and there may be a group of caregivers that was not represented by this data. The missing data for caregivers is a marker of this. Future studies focusing only on caregivers may offer different insights into this group and compliment this research.

The studies in this thesis also lacked details on those who did not attend InS:PIRE. Studies that recruit patients prospectively while still in ICU or the hospital may have access to more data on who fails to attend InS:PIRE. These studies could

offer more insights into this missing group and help to focus recruitment and improve participant retention.

Finally, there was no comparator group for the cardiothoracic study. The quantitative effects of InS:PIRE in this group therefore remain unknown. Future studies should aim to include a comparator group to better understand the HRQoL in this specialist population.

7.3 Future directions

7.3.1 Research

Beyond an evaluation of the effectiveness and implementation of the InS:PIRE intervention, this thesis has raised many questions and possible areas for future study. This work has highlighted what is unknown in the fields of long-term outcomes after critical illness, PICS, and PICS-F. It is also evident that the research presented herein raises more focused questions specifically about how interventions after intensive care, and InS:PIRE, should be evaluated in the future.

7.3.1.1 Data collection and future study design

The effectiveness studies in this thesis had significant limitations that have been highlighted above. If these multicentre cohort studies were to be reproduced, there are substantial areas that could be redesigned to remove some of the methodological limitations.

To address missing data, there could be substantial improvements in how the data were collected. The reliance on paper proformas had some advantages (universally available) but overall if this was repeated then an electronic data collection tool could reduce missing data. This could be sent to patients and caregivers via email or other modalities. There would also have to be multiple computers or handheld devices available at the InS:PIRE clinics to collect the information. Given the expansion of NHS telecommunications during the COVID-19 pandemic these methods would be more achievable today.

There should also be better use of phone calls and other communication strategies (e.g. digital patient visiting) to collect data. There is a careful balance to be

reached between robust data collection systems (e.g. reminders and phone calls) and the need to avoid distressing participants who no longer want to take part in follow-up. Future ethics processes including patient and caregiver advisory groups would be important to understand the best balance between these competing demands. In this study, one reminder by letter or phone call was included in ethics and subsequently used. Whether electronic systems are more acceptable to participants is unknown and should be explored. Similarly, if patients were approached in-hospital then they could engage and advise as to what modality and frequency of follow-up would be most acceptable to them. Given the high rates of cognitive dysfunction and socioeconomic problems after ICU there is unlikely to be one optimal solution, but instead a multimodal approach is likely to produce the best completion rates.

The baseline dataset could have been improved upon. Alongside the outcome data and the core datasets collected by the ICU teams, better baseline data on mental health, frailty, granular socioeconomic data (beyond SIMD), cognitive dysfunction, and baseline educational status would have enriched the studies. This would have been particularly useful during the modelling stages, both during regression analysis and propensity score matching. This would also give a better understanding of the reach of InS:PIRE, i.e. the demographics of those likely to attend and of those unlikely to attend despite having potential to benefit from the service. This data could also be further used to predict those who are at risk of PICS and PICS-F, which could lead to more focused services targeting those who are likely to benefit most.

When considering the outcomes collected, a survey of cognitive dysfunction is the most obviously missing assessment, as previously mentioned. It would be useful to understand what the cognitive outcomes were after critical care, and the impact of InS:PIRE on these. Inclusion of a cognitive measure (e.g. MoCA) would also be valuable in understanding whether cognitive dysfunction itself led to missing data or missing outcome measures. This would increase the understanding of how best to conduct these studies in the future and was perhaps a missed opportunity during this programme of research. Understanding the effects of cognitive dysfunction and its overlap with other aspects of PICS and PICS-F would also be valuable.

Future studies should collect data on the patients and caregivers who do not attend InS:PIRE and perhaps those who do not complete usual care follow-up. The ethical position of using this data should be carefully considered. However, some statistical patterns and understanding should be possible from appropriately anonymised routinely collected data, having completed appropriate data governance and ethical review processes. This would greatly improve the understanding of who misses InS:PIRE, while increasing understanding of who is not benefitting from the InS:PIRE intervention and how it can be adapted to meet their needs.

An even more granular approach may be to survey those who decline to attend InS:PIRE at the time of offering. It is unknown whether these patients have recovered well and therefore do not perceive of any benefit from InS:PIRE. Conversely, these patients may have significant unmet problems, particularly mental health, cognitive, and socioeconomic problems that make attendance at any service a difficult or unachievable task. Understanding this group with both quantitative and qualitative data collection would help researchers to adapt interventions to meet the needs of this unrepresented group.

The issue of pain after critical illness has been identified by this work. High rates of pain were clearly an issue; however, InS:PIRE did not appear to address or attenuate the effects of pain in any way. Future work should focus on understanding who experiences pain, what type this is, the effects of pain on HRQoL, and whether any intervention can reduce the incidence, severity, or interference of pain in daily life.

As highlighted by the limitations section (7.2.3), given that this was a single country study, it would be of value to repeat this research in different healthcare settings, particularly those with different funding arrangements (e.g. private healthcare settings), different cultural considerations, and variable pre-existing follow-up services.

The optimal timing of InS:PIRE has still not been assessed. It is unclear whether an earlier intervention would have a variable effect, or if the intervention could even start before hospital discharge. A qualitative study on delivering InS:PIRE early (at or within one month of discharge) vs delivering this late (e.g. after 4 to

6 months) may be of value. While it could be assumed that there are greater benefits from an early intervention, this is not known. Equally, it could be possible that some patients are not ready to benefit from InS:PIRE in this timeframe and the socioeconomic benefits can only be realised after a longer period post hospitalisation.

Furthermore, bringing more of the InS:PIRE components into the hospital setting may be of value. For example, it remains unknown whether the pharmacy intervention is best delivered as an outpatient or if an ICU pharmacist review in hospital can avoid problems of medicines management after discharge.

Finally, this thesis did not study a few established and emerging areas, specifically the impact of fatigue on outcomes and cognitive dysfunction (as mentioned above). Both aspects would warrant further work.

7.3.1.2 Traditional effectiveness studies: observational cohort studies and RCTs

As stated, InS:PIRE has never been studied as part of an RCT. While RCTs are the primary method for proving and understanding causation, other observational or novel study methods could provide equally useful data. Regardless of the precise study type chosen, there will be common methodological challenges in any InS:PIRE study that aims to recruit patients to an intervention cohort (or arm) and a usual care cohort (or arm). This section aims to outline these challenges and the key decisions that would need to be made before future effectiveness studies of an outpatient intervention were implemented.

A key consideration for any intensive care study of long-term outcomes is the challenge of patient and / or caregiver recruitment, particularly the timing of recruitment. The most pragmatic time may be in ICU. However, this has significant limitations as the loss to follow-up rate is likely to be very high from participants consented in hospital. Furthermore, given the mortality rate from critical illness, those participants who do not survive the acute illness would be included in a study that they could never benefit from. As has been demonstrated, later recruitment could suffer from high rates of missing data and little or no information on those who do not accept the offer of attending the intervention.

These two competing strategies would need to be balanced during the trial design phase.

Perhaps a more challenging question would be whether a true control group with no follow-up would be justified or ethically acceptable. As has been demonstrated, the proliferation of ICU specific follow-up in the UK has been significant, although contemporaneous usual care remains GP delivered care without specific ICU follow-up[278]. These antithetical positions are also reflected in the formal literature with examples of patient advisory groups considering that being included in a group receiving no intervention was "unacceptable" despite the absence of any specific ICU follow-up being usual care at the time[219]. As such, future interventional studies of any design, but particularly RCTs, may find the inclusion of an arm or cohort without any intervention ethically challenging. In the UK the proliferation of follow-up services has in part been driven by national guidance recommending ICU follow-up and this could further make no intervention (i.e. a control or true usual care arm) unacceptable[10].

It therefore may not be possible to repeat the research in this thesis, with the usual care group receiving no follow-up. Instead, future interventional studies may have to use some follow-up as the control or usual care group. This may make differences more difficult to detect, if it is assumed that some follow-up improves outcome compared to no follow-up. It may be that future studies will have to be larger to account for this.

7.3.1.3 Newer and novel study designs

The challenges and limitations of studying InS:PIRE through cohort observational studies or RCTs may make the practicalities and economics of implementing these traditional effectiveness methodologies undesirable for researchers, funding bodies, ethics committees, and participants themselves. Instead, alternative novel approaches may balance the need for robust assessments of intervention effectiveness alongside pragmatic study design. Novel approaches also have potential to enhance understanding of the effects of the individual components that make up complex interventions such as InS:PIRE.

Recently, adaptive platform trials with various degrees of pragmatic participant treatment arm assignment, blinding, and randomisation, have evolved. These could be used to assess complex interventions such as InS:PIRE. These trial designs have been particularly effective within critical care research with the REMAP-CAP (Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia) group at the forefront of this methodology[363]. The key features of this study type are that multiple different treatments can be randomised and implemented at the same time with significant overlap. The adaptive terminology relates to the way treatments are removed from, or added to, the randomisation process over time. Repeated statistical analysis influences which therapies remain in the study protocol. Perhaps more importantly, this trial design is most effective when there is a short time from intervention delivery to measurement of the outcome of interest. This has been highlighted by the ROSSINI 2 (Reduction Of Surgical Site Infection using several Novel Interventions) investigators, whose measurement of surgical site infection up to 30 days after intervention was seen as ideal for this type of design[364]. The long-term outcomes measured as part of InS:PIRE would make the adaptive process and feedback loop too long to be desirable. As such, before this approach was undertaken, first there would have to be observational work to better understand which outcomes measured early (e.g. between 30 and 90 days) correlated with longer-term outcomes (≥ one year). This would help to reduce the feedback time from the implementation of interventions to outcome measurement and then study adaptation. This primary observational work could also address other unknown aspects of PICS and PICS-F, particularly if it was able to accurately predict who was at greatest risk of long-term problems in HRQoL after critical illness. If the InS:PIRE adaptive trial embedded this prediction model into the methodology, then this would allow for the creation and continual evolution of PICS and PICS-F prediction models, alongside an assessment of component effectiveness.

For reasons of scale and pragmatism, treatment arm assignment (i.e. whether the patient receives certain components or not) would best be delivered at a site or cohort randomisation level rather than at a patient level. As such, centres would need to be randomised to deliver InS:PIRE with certain elements. This would have to occur after a pilot phase to allow the teams and staff to upskill in new areas of service implementation. This would be most straightforward when initially

establishing a new InS:PIRE treatment arm as the pragmatic approach in this thesis of completing two cohorts before collecting data would be reasonable. However, this pilot phase would also have to apply when the interventions were being adapted, after the initial treatment arm was established. This could be done across all recruitment centres or randomly assigned to different centres. An example might be if a pharmacist joined an InS:PIRE service (or treatment arm) that initially did not have a pharmacist. The data collected during the early cohorts (e.g. first two cohorts) with a pharmacist would need to be considered a learning or transition phase and should either not be included in the analysis, or as a minimum, addressed during statistical modelling.

There are many other quantitative study designs that could have utility for assessments of complex interventions and treatment programmes. The Decision Architecture Randomisation Trial (DART) is another design that could work with InS:PIRE[365]. This study design has been proposed to assess the impact of certain (usually electronic) prompts on clinician decision making and how these decisions result in different outcomes for patients. However, this methodology could be adapted to assess patient and caregiver responses to different InS:PIRE prompts rather than clinician responses. If this were combined with robust observational data collection, then this could produce a very informative dataset to help understand how different aspects of InS:PIRE alter the behaviours of participants and ultimately influence their long-term outcomes. This would work well alongside a broader implementation of InS:PIRE, particularly if different regions subtly adapted the intervention to their own needs. This would also allow the ongoing assessment of real-world InS:PIRE data while offering minimal or no disruption to the running of each intervention.

Perhaps the most pragmatic and useful future quantitative assessment would be to utilise a stepped-wedge cluster randomised approach[366]. Given the substantial time commitment from those delivering InS:PIRE, it may be best to combine a widescale rollout of InS:PIRE with a pre-implementation control group phase. Over time, as new ICUs are randomised to implement InS:PIRE, these sites would become treatment centres and move from usual care data collection into treatment arm data collection. This would have significant benefits of economies

of scale. It would also avoid centres being randomised to stop delivering InS:PIRE, or certain elements of it, which could occur with adaptive designs.

While there are limitations to this study design, at the time of writing it would appear to offer the best balance between methodological rigour and the practicalities of study implementation. If funded appropriately this could also allow InS:PIRE to be studied in the greatest number of participants and by the greatest number of clinicians. Furthermore, it would be advisable to collect data on ICU practices at each site before and after implementation. This would allow the capture of the inpatient (ICU) changes (the 'reverse benefits') that occur due to the implementation of InS:PIRE. Examples of this may include improvements in medicines reconciliation processes or discharge paperwork resulting from observations made at InS:PIRE. Perhaps the most robust solution would be a mixed methods study combining qualitative analysis (including participant feedback) with a stepped-wedge cluster randomised design. This would present a significant opportunity to improve the understanding of how different aspects of the healthcare system respond to the implementation of such a complex intervention, while also measuring effectiveness. While this study design could be challenging, combining these methodologies would maximise learning from such a large study offering substantial improvements in trial cost-effectiveness. These mixed methods would also help to address knowledge gaps around the mechanisms behind any benefits observed from the InS:PIRE programme.

7.3.1.4 Qualitative methods

Finally, from a research perspective, this thesis has not utilised qualitative methods to assess outcomes. The cardiac chapter did address some aspects of service evaluation and adaptation, but any patient and family feedback were indirect. As such, qualitative methods, with a particular focus and centre on patient and family outcomes and feedback could substantially add to the work of this thesis.

This thesis has offered some discussion about the possible mechanisms behind InS:PIRE based on a comparison between the contemporaneous literature and InS:PIRE itself. However, mechanistic studies are very difficult to design, and causation, even within RCTs, can be difficult to prove. This is where qualitative

methods may be particularly strong. By allowing study participants to add more granular detail to our understanding of how and why InS:PIRE changed their recovery trajectory, it may be possible to better understand which aspects or elements of InS:PIRE are most effective. Similarly, if granular qualitative data were collected on usual care groups, then these results could have powerful outputs, aiding our understanding of exactly how long-term outcomes can be modified and improved. This would also aid in understanding which elements are not as useful, leading to more pragmatic and cost-effective interventions. Ultimately, the most powerful benefits would come from combining both quantitative and qualitative methods in one study to offer a numerical effect estimate as well as a mechanistic discussion and thematic analysis.

Qualitative work for usual care and intervention analysis would also be particularly important for any local implementation of InS:PIRE. It would be worthwhile conducting patient and caregiver interviews and / or focus group sessions before implementing any new InS:PIRE service to confirm local needs. This could then be repeated after InS:PIRE implementation. This before-and-after qualitative design would help to ensure that the new InS:PIRE intervention was addressing these local needs alongside those identified by international primary research. Furthermore, this level of evidence, although challenging to collect, could be completed by local teams to help reassure funders that InS:PIRE was offering the benefits outlined by the quantitative techniques. Qualitative data would also be less onerous to assess from a statistical viewpoint and be in line with the clinical skills and experience of local areas unable to access robust statistician input.

7.3.2 Policy and implementation

While there will always be more research that can and should be done, this academic activity is only likely to benefit patients and their families in the future. However, it is evident that there is a significant burden of morbidity associated with critical illness that could be addressed today. Given the strength of associations of better outcomes with InS:PIRE demonstrated throughout this thesis, there is a reasoned argument that InS:PIRE could become the new baseline or standard of care after critical illness. As a reminder, usual care in the UK is the care delivered by GPs, without any specific critical care orientated follow-up. For the patient this means that they are not reviewed by anyone with specialist

knowledge of intensive care or its expected recovery trajectories. Similarly, with large GP patient lists, it is unlikely that a single GP will treat many post-ICU patients annually. As such, neither the patient nor the GP will have a deep understanding of what to expect after critical illness. Furthermore, NICE has advocated that patients should receive specific critical care follow-up after ICU but with limited specifics on what that care should involve. This thesis could fill this gap and offers a blueprint of how follow-up services can be delivered and organised.

7.3.2.1 Cost-effectiveness evaluation

If InS:PIRE were to be adopted more widely, a key question or limitation would be the cost, alongside the benefits of the intervention. The baseline costs were discussed earlier (Section 3.3.6) and highlighted in Appendix 6. This demonstrated that the cost of delivery of the intervention was ~£1,300 per family unit (patient and caregiver). The use of the EQ-5D in these studies allows for a basic health economic assessment.

Taking the patient outcomes and effect size into account, the cost of a single Quality Adjusted Life Year (QALY) gained would be £3,400. This assumes that the effect observed at one year would reduce by 25% year-on-year, with no effect beyond five years. Depending on the assumptions made in the cost-effectiveness assessment, the range is likely to be from £1,400 to £12,000 per QALY gained. The worst-case scenario estimate (£12,000) assumes that only five patients will attend each cohort and allows for up to £2,500 of additional costs which could include accommodation expenses, additional patient transfer costs, unexpected staff overtime, or staff sickness, and locum costs. Full details of these assumptions and calculations can be found in Appendix 15. All of the estimates, even with the most pessimistic assumptions, are significantly below the proposed cost-effectiveness threshold that has been suggested by NICE of £20,000 per QALY gained[367]. While this cannot be the only factor determining whether an intervention is implemented, it adds weight to the argument that InS:PIRE is a cost-effective intervention that could be considered for wider (national) implementation.

These estimates serve as a guide only, and it would be advisable to complete a comprehensive health economics assessment once any additional programmes are

implemented. This simplified cost-effectiveness assessment is likely an overestimate of the cost of one QALY gained through InS:PIRE. This is because there are many unmeasured benefits that have not been considered. Specifically, any benefits to the caregivers as highlighted by this thesis have not been taken into account. Similarly, the potentially greater cascading benefits of improvement in socioeconomic reintegration including return to work have not been possible to quantify for this analysis. As such, future health economic assessments should consider these wide-ranging potential benefits from InS:PIRE and include these in any cost-effectiveness analysis.

Future work on the cost-effectiveness would allow the calculation of both the duration and attrition of the effect size over time. This would allow these estimates to be refined further. However, the extent to which this is necessary or required before broader implementation of InS:PIRE is uncertain. As has been demonstrated, the estimates generated from this thesis are well within standardised acceptable thresholds for social and public healthcare (NHS) system cost-effectiveness. Furthermore, this is before any assessment of how improvements in efficiency could be undertaken. An example of this was given in the cardiac outcomes section (Chapter 6) where family units only attended for three of the five weeks. If all of this was considered, then the costs per QALY would be far lower than the estimates outlined in Appendix 15.

The conclusions from this cost-effectiveness analysis are that the InS:PIRE intervention is an effective programme, with costs well below standard thresholds for widescale implementation. It is then incumbent upon clinicians, policy makers, and healthcare leaders to create the environment to implement this intervention more widely. It would not be unreasonable to assume that, without further confounding evidence, InS:PIRE could become the usual care of the future with significant cost-effective benefits for patients and their families.

7.3.2.2 Integrating InS:PIRE into the wider healthcare environment

Any new service cannot be implemented overnight and naturally there would be lead-in time and upskilling for the staff involved in any new InS:PIRE programme. Some of this delay could be mitigated by incorporating learning from InS:PIRE into other services. This would allow patients and their families to benefit from the

most important aspects of InS:PIRE almost immediately. In the first instance, the key learning to disseminate to other services would be that critical illness survivors would benefit from an assessment of socioeconomic needs alongside a pain assessment after intensive care. This could be highlighted and fed back to GPs, cardiac rehabilitation services, and other general services that commonly treat post-ICU patients. If this learning was incorporated into these services broadly and accompanied by qualitative service evaluations, then subsequent InS:PIRE programmes could be more streamlined, further enhancing cost-effectiveness. Furthermore, this would also allow patients and families to start benefiting from the learning of this thesis without a delay while new services were being implemented. Perhaps more importantly, this education loop could have benefits beyond patients and families who are treated from ICUs without access to InS:PIRE; also benefitting those who have access to InS:PIRE but choose not to attend. As such, even where InS:PIRE services already exist, there is a need to disseminate the learning that these patients could benefit from integrated health and socioeconomic assessment. Certainly, the trajectories of patients and families who do not engage in recovery and rehabilitation services is unknown, and wider understanding of the problems faced by this post-ICU group by the medical community could have substantial benefits for this difficult to reach cohort.

Finally, other services that treat multisystem conditions could be upskilled to deliver key (or potentially all) InS:PIRE components. This approach could apply not just to cardiac patients as discussed in Chapter 6, but also to other multisystem diseases. An obvious example would be COVID-19 recovery clinics and services. Many of these patients will have experienced ICU and many of these services are already funded. Furthermore, with the reducing impacts of COVID-19, it would be reasonable for policy makers to consider whether some funding for COVID-19 recovery services could be redirected to include the recovery of patients and families experiencing acute multisystem inflammatory conditions more generally. This would include the general ICU population. Furthermore, service efficiency could be improved overall with minimal overlap, redundancy, and repetition for patients and their families. By recognising the body, mind, and socioeconomic overlap in these severe illnesses there would be an economy of scale where patients who have experienced multisystem disease are treated by a single provider incorporating learning from InS:PIRE and other services. A unified

multiservice approach may enhance sustainability, while the increased numbers of patients and families treated through such a service would allow for a more rapid quality improvement process. This could shorten the feedback loop and time from service evaluation to implementation. As such, this collaborative approach could have lasting benefits for those beyond the InS:PIRE intervention itself.

7.4 Thesis conclusion

This thesis has demonstrated that attendance at a complex health and social care rehabilitation programme (InS:PIRE) was associated with better long-term quality of life and mental health outcomes for ICU survivors and their families. Furthermore, the programme was adaptable and demonstrated utility for those treated in general ICUs as well as specialist (cardiothoracic) critical care services. It is clear that there is much more work to be done. However, this thesis should give hope to patients, families, healthcare professionals, researchers, and policymakers that follow-up services can have a measurable effect in helping to ameliorate the problems associated with critical illness survivorship.

Appendices

Appendix 1: Literature search strategies

Appendix 2: Study characteristics for scoping review

Appendix 3: Ethical approval

Appendix 4: Patient and caregiver consent forms

Appendix 5: Participant invitation letter and information sheet (patient and caregiver)

Appendix 6: Estimated staff time and costs per cohort of InS:PIRE

Appendix 7: Characteristics of responders and non-responders in the postal survey (usual care cohort)

Appendix 8: Interpretation of common plots used in this thesis

Appendix 9: Missing values for patient one-year outcomes

Appendix 10: Regression models for all patient outcomes

Appendix 11: Unadjusted and unmatched patient outcomes

Appendix 12: EQ-5D domain models and breakdown

Appendix 13: Patient characteristic of those with a consenting caregiver compared to those without.

Appendix 14: Caregiver one-year outcome models

Appendix 15: Cost-effectiveness estimates for the InS:PIRE programme

Appendix 1

Complete electronic database searches for the scoping review (Chapter 2)

Embase search 22nd May 2023

1	critical illness/	35690
2	intensive care/	147684
3	intensive care unit/	223956
4	(critical* adj (care or ill* or condition)).tw.	153815
5	(lifethreatening illness or life-threatening illness).tw.	2639
6	(Early Goal-Directed Therapy or EGDT).tw.	1006
7	(intensive care or ICU).tw.	361761
8	(health shock? or sepsis or septic).tw.	248791
9	(acute respiratory distress syndrome or ARDS or acute lung injury).tw.	61381
10	exp Acute Lung Injury/ or exp Respiratory Distress Syndrome, Adult/	70972
11	(major trauma or major physical trauma).tw.	6693
12	sepsis/	204039
13	or/1-12	872350
14	(post adj5 (intensive or critical* or ICU)).tw.	11587
15	(discharge adj5 (intensive or critical* or ICU)).tw.	10714
16	(after adj5 (intensive or critical* or ICU)).tw.	42668
17	(syndrome* adj5 (intensive or critical* or ICU)).tw.	7884
18	(survivor* adj5 (intensive or critical* or ICU)).tw.	4898
19	(caregiver* adj5 (intensive or critical* or ICU)).tw.	1416
20	(post intensive care syndrome or postintensive care syndrome or post ICU syndrome or postICU syndrome).tw.	754
21	PICS.tw.	2104
22	exp survivor/	112186
23	exp hospital discharge/	180548
24	(weakness adj5 (ICU or critical* or intensive)).tw.	1500
25	((polyneuropathy or myopathy or neuropathy) adj5 (intensive or critical* or ICU)).tw.	1602
26	((posttraumatic or postraumatic or post traumatic or PTSD) adj5 (intensive or critical* or ICU)).tw.	1027
27	(chronic* adj2 (intensive or critical* or ICU)).tw.	1844
28	or/14-27	353694
29	Muscle Weakness/	57690
30	polyneuropathy/	21178
31	(rehab* adj5 (intensive or critical* or ICU)).tw.	6298
32	(recovery adj5 (intensive or critical* or ICU)).tw.	5743
33	(follow-up adj5 (intensive or critical* or ICU)).tw.	6042
34	(followup adj5 (intensive or critical* or ICU)).tw.	160
35	(outpatient? adj5 (intensive or critical* or ICU)).tw.	2546
36	(out patient? adj5 (intensive or critical* or ICU)).tw.	140
37	(clinic? adj5 (intensive or critical* or ICU)).tw.	2510
38	(survivor* adj5 (intensive or critical* or ICU)).tw.	4898
39	((follow or following) adj5 (intensive or critical* or ICU)).tw.	18298
40	or/29-39	114890
41	13 and 28 and 40	9932
42	limit 41 to english language	9520

Medline search 22nd May 2023

1	Critical Illness/	38362
2	Critical Care/	60185
3	Intensive Care Units/	69756
4	(critical* adj (care or ill* or condition)).tw.	95970
5	(lifethreatening illness or life-threatening illness).tw.	1808
6	(Early Goal-Directed Therapy or EGDT).tw.	549
7	(intensive care or ICU).tw.	216740
8	(health shock? or sepsis or septic).tw.	156443
9	(acute respiratory distress syndrome or ARDS or acute lung injury).tw.	40049
10	exp Acute Lung Injury/ or exp Respiratory Distress Syndrome, Adult/	47346
11	(major trauma or major physical trauma).tw.	4511
12	Sepsis/	70419
13	or/1-12	511640
14	(post adj5 (intensive or critical* or ICU)).tw.	6032
15	(discharge adj5 (intensive or critical* or ICU)).tw.	5793
16	(after adj5 (intensive or critical* or ICU)).tw.	25926
17	(syndrome* adj5 (intensive or critical* or ICU)).tw.	5358
18	(survivor* adj5 (intensive or critical* or ICU)).tw.	2869
19	(caregiver* adj5 (intensive or critical* or ICU)).tw.	963
20	(post intensive care syndrome or postintensive care syndrome or post ICU syndrome or postICU syndrome).tw.	471
21	PICS.tw.	1472
22	exp Survivors/	41837
23	exp Patient Discharge/	39213
24	(weakness adj5 (ICU or critical* or intensive)).tw.	938
25	((polyneuropathy or myopathy or neuropathy) adj5 (intensive or critical* or ICU)).tw.	945
26	((posttraumatic or postraumatic or post traumatic or PTSD) adj5 (intensive or critical* or ICU)).tw.	747
27	(chronic* adj2 (intensive or critical* or ICU)).tw.	1226
28	or/14-27	123486
29	Muscle Weakness/	9587
30	Polyneuropathies/	5665
31	(rehab* adj5 (intensive or critical* or ICU)).tw.	3669
32	(recovery adj5 (intensive or critical* or ICU)).tw.	3737
33	(follow-up adj5 (intensive or critical* or ICU)).tw.	3520
34	(followup adj5 (intensive or critical* or ICU)).tw.	44
35	(outpatient? adj5 (intensive or critical* or ICU)).tw.	1487
36	(out patient? adj5 (intensive or critical* or ICU)).tw.	66
37	(clinic? adj5 (intensive or critical* or ICU)).tw.	1329
38	(survivor* adj5 (intensive or critical* or ICU)).tw.	2869
39	((follow or following) adj5 (intensive or critical* or ICU)).tw.	10968
40	or/29-39	37621
41	13 and 28 and 40	4957
42	limit 41 to english language	4700

CINHAL search 22nd May 2023

1	MH "Critical Illness"	15013
2	MH "Critical Care"	25544
3	MH "Intensive Care Units"	43899
4	(TI ((critical* W1 (care or ill* or condition)))) OR (AB ((critical* W1 (care or ill* or condition))))	53624
5	(TI(("life threatening illness" OR "lifethreatening illness"))) OR (AB(("life threatening illness" OR "lifethreatening illness")))	1019
6	(TI (("Early Goal-Directed Therapy" or EGDT))) OR (AB (("Early Goal- Directed Therapy" or EGDT)))	296
7	(TI (("intensive care" or ICU))) OR (AB (("intensive care" or ICU)))	94998
8	(TI ("health shock#" or sepsis or septic)) OR (AB ("health shock#" or sepsis or septic))	37215
9	(TI ("acute respiratory distress syndrome" or ARDS or "acute lung injury")) OR (AB ("acute respiratory distress syndrome" or ARDS or "acute lung injury"))	11797
10	(MH "Acute Lung Injury+") OR (MH "Ventilator-Induced Lung Injury+") OR (MH "Respiratory Distress Syndrome, Acute")	16265
11	(TI("major trauma" or "major physical trauma")) OR (AB("major trauma" or "major physical trauma"))	2063
12	(MH "Sepsis+")	31347
13	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	200779
14	(TI (post W5 (intensive or critical* or ICU))) OR (AB (post W5 (intensive or critical* or ICU)))	1828
15	(TI (discharge W5 (intensive OR critical* OR ICU))) OR (AB (discharge W5 (intensive OR critical* OR ICU)))	1706
16	(TI (after W5 (intensive or critical* or ICU))) OR (AB (after W5 (intensive or critical* or ICU)))	6200
17	(TI (syndrome* W5 (intensive or critical* or ICU))) OR (AB (syndrome* W5 (intensive or critical* or ICU)))	1399
18	(TI (survivor* W5 (intensive or critical* or ICU))) OR (AB (survivor* W5 (intensive or critical* or ICU)))	909
19	(TI (caregiver* W5 (intensive or critical* or ICU))) OR (AB (caregiver* W5 (intensive or critical* or ICU)))	578
20	(TI ("post intensive care syndrome" or "postintensive care syndrome" or "postintensive care syndrome" or "post ICU syndrome" or "post-ICU syndrome")) OR (AB ("post intensive care syndrome" or "postintensive care syndrome" or "postintensive care syndrome" or "post ICU syndrome" or "post-ICU syndrome"))	323
21	TI PICS OR AB PICS	851
22	MH "Survivors+"	31271
23	MH "Patient Discharge+"	35753
24	(TI (weakness W5 (ICU or critical* or intensive))) OR (AB (weakness W5 (ICU or critical* or intensive)))	294
25	(TI ((polyneuropathy or myopathy or neuropathy) W5 (intensive or critical* or ICU))) OR (AB ((polyneuropathy or myopathy or neuropathy) W5 (intensive or critical* or ICU)))	161
26	(TI ((posttraumatic or postraumatic or post traumatic or PTSD) W5 (intensive or critical* or ICU))) OR (AB ((posttraumatic or postraumatic or post traumatic or PTSD) W5 (intensive or critical* or ICU)))	314
27	(TI (chronic* W2 (intensive or critical* or ICU))) OR (AB (chronic* W2 (intensive or critical* or ICU)))	515
28	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	77756
29	MH "Muscle Weakness+"	5351
30	MH "Polyneuropathies+"	9218
31	(TI (rehab* W5 (intensive or critical* or ICU))) OR (AB (rehab* W5 (intensive or critical* or ICU)))	860
32	(TI (recovery W5 (intensive or critical* or ICU))) OR (AB (recovery W5 (intensive or critical* or ICU)))	894
33	(TI (follow-up W5 (intensive or critical* or ICU))) OR (AB (follow-up W5 (intensive or critical* or ICU)))	671
34	(TI (followup W5 (intensive or critical* or ICU))) OR (AB (followup W5 (intensive or critical* or ICU)))	11
35	(TI (outpatient# W5 (intensive or critical* or ICU))) OR (AB (outpatient# W5 (intensive or critical* or ICU)))	292
36	(TI (out patient# W5 (intensive or critical* or ICU))) OR (AB (out patient# W5 (intensive or critical* or ICU)))	219
37	(TI (clinic# W5 (intensive or critical* or ICU))) OR (AB (clinic# W5 (intensive or critical* or ICU)))	351
38	(TI (survivor* W5 (intensive or critical* or ICU))) OR (AB (survivor* W5 (intensive or critical* or ICU)))	909
39	(TI ((follow or following) W5 (intensive or critical* or ICU))) OR (AB ((follow or following) W5 (intensive or critical* or ICU)))	2599
40	S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39	19867
41	S13 and S28 and S40	1827
42	S13 and S28 and S40 (Limiters - English Language)	1768

Cochrane database search 22nd May 2023

1	MeSH descriptor: [Critical Illness] this term only	3231
2	MeSH descriptor: [Critical Care] this term only	2261
3	MeSH descriptor: [Intensive Care Units] this term only	3271
4	(critical* NEAR/1 (care or ill* or condition)):ti,ab	11076
5	("lifethreatening illness" or "life-threatening illness"):ti,ab	154
6	("Early Goal-Directed Therapy" or EGDT):ti,ab	161
7	("intensive care" or ICU):ti,ab	32614
8	("health shock?" or sepsis or septic):ti,ab	13333
9	("acute respiratory distress syndrome" or ARDS or "acute lung injury"):ti,ab	3806
10	MeSH descriptor: [Acute Lung Injury] explode all trees	700
11	MeSH descriptor: [Respiratory Distress Syndrome] explode all trees	3275
12	("major trauma" or "major physical trauma"):ti,ab	288
13	MeSH descriptor: [Sepsis] this term only	3440
14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	51831
15	(post NEAR/5 (intensive or critical* or ICU)):ti,ab	1261
16	(discharge NEAR/5 (intensive or critical* or ICU)):ti,ab	2000
17	(after NEAR/5 (intensive or critical* or ICU)):ti,ab	4636
18	(syndrome* NEAR/5 (intensive or critical* or ICU)):ti,ab	397
19	(survivor* NEAR/5 (intensive or critical* or ICU)):ti,ab	465
20	(caregiver* NEAR/5 (intensive or critical* or ICU)):ti,ab	150
21	("post intensive care syndrome" or "postintensive care syndrome" or "post ICU syndrome" or "postICU syndrome"):ti,ab	82
22	PICS:ti,ab	124
23	MeSH descriptor: [Survivors] explode all trees	2320
24	MeSH descriptor: [Patient Discharge] explode all trees	2218
25	(weakness NEAR/5 (ICU or critical* or intensive)):ti,ab	248
26	((polyneuropathy or myopathy or neuropathy) NEAR/5 (intensive or critical* or ICU)):ti,ab	82
27	((posttraumatic or postraumatic or post traumatic or PTSD) NEAR/5 (intensive or critical* or ICU)):ti,ab	1496
28	(chronic* NEAR/2 (intensive or critical* or ICU)):ti,ab	139
29	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28	12462
30	MeSH descriptor: [Muscle Weakness] this term only	847
31	MeSH descriptor: [Polyneuropathies] this term only	260
32	(rehab* NEAR/5 (intensive or critical* or ICU)):ti,ab	995
33	(recovery NEAR/5 (intensive or critical* or ICU)):ti,ab	614
34	("follow-up" NEAR/5 (intensive or critical* or ICU)):ti,ab	745
35	(followup NEAR/5 (intensive or critical* or ICU)):ti,ab	599
36	(outpatient? NEAR/5 (intensive or critical* or ICU)):ti,ab	394
37	("out patient?" NEAR/5 (intensive or critical* or ICU)):ti,ab	14
38	(clinic? NEAR/5 (intensive or critical* or ICU)):ti,ab	216
39	(survivor* NEAR/5 (intensive or critical* or ICU)):ti,ab	465
40	((follow or following) NEAR/5 (intensive or critical* or ICU)):ti,ab	1753
41	#30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40	5094
42	#14 and #29 and #41	887

Appendix 2

Study characteristics for scoping review (Chapter 2)

Study	Population	Location	N recruited	N completing	Study type	Control?	Study components
Stollings 2023[190]	All ICU patients	USA, UK	507	472	Cohort	No	pharmacist
Rousseau 2023[188]	All ICU patients non-COVID vs COVID	Belgium	495	143	Cohort	Yes	ICU nurse; ICU doctor; physiotherapist; dietician/nutritionist
Vanderhaeghen 2023[187]	surgical patients with good Quality of Life before ICU	Belgium	85	42	Cohort	Yes	ICU doctor
Balakrishnan 2023[185]	COVID-19	USA	40	36	RCT	Yes	ICU doctor
Boehm 2023[189]	Septic shock and ARDS	USA	NA	32	Qualitative / mixed methods	No	ICU doctor; pharmacist; psychologist/therapist; case manager; caregivers; peer support
Sayde 2023[184]	COVID-19 plus one of: mechanical ventilation 24 hours; sepsis; delirium	USA	44	21	Cohort	No	Physiotherapist; pharmacist; psychologist/therapist; other nurse; other doctor; case manager; critical care debrief
Kovaleva 2023[186]	ICU: sepsis or ARDS	USA	19	12	Qualitative / mixed methods	No	ICU doctor; pharmacist; psychologist/therapist; caregivers
Weidman 2022[193]	ICU COVID-19 survivors	USA	NA	280	Cohort	Yes	ICU doctor; pharmacist; dietician/nutritionist; social care specialist; digital component
Mohammad 2022[195]	ICU with sepsis and / or ARDS	USA	NA	104	Cohort	Yes	ICU doctor; physiotherapist; pharmacist; social care specialist

Study	Population	Location	N recruited	N completing	Study type	Control?	Study components
Vlake 2022[197]	COVID-19 ICU survivors	Netherlands	89	77	RCT	Yes	ICU nurse; ICU doctor; critical care debrief; digital component
Adie 2022[196]	CICU ≥48 hours	USA	106	70	Cohort	No	Pharmacist
op't Hoog 2022[191]	COVID-19 ARDS patients	Netherlands	49	46	Cohort	No	ICU nurse; ICU doctor; caregivers
Bates 2022[192]	COVID-19 ARDS ICU patients, minimum 24 hours in ICU	UK	26	23	RCT	Yes	ICU nurse; ICU doctor; physiotherapist; occupational therapist; peer support; digital component
Gilmartin 2022[194]	ICU COVID-19 survivors	Ireland	NA	22	Cohort	No	ICU nurse; ICU doctor; physiotherapist; psychologist/therapist
Glimelius-Petersson 2021[204]	ICU ≥72 hours	Sweden	656	372	Cohort	No	ICU nurse; caregivers
Nakamura 2021[203]	ICU LOS >1 day, other critical care LOS >5 days	Japan	397	133	Cohort	No	ICU nurse; ICU doctor; physiotherapist; written information
Villa 2021[202]	ICU LOS >96 hours, mechanical ventilation, and or use of vasoactive drugs	Italy	95	51	Cohort	No	ICU nurse; ICU doctor
Fernandes 2021[200]	COVID-19 ICU (>24 hours) survivors	Portugal	NA	45	Case series	No	ICU nurse; ICU doctor
Parker 2021[209]	COVID-19 ICU	UK	38	36	Cohort	No	ICU nurse; ICU doctor; physiotherapist; occupational therapist
Major 2021[198]	Mechanical Ventilation >48 hours plus indication for physical therapy	Netherlands	43	34	Cohort	Yes	Physiotherapist
Ahlberg 2021[207]	ICU ≥72 hours	Sweden	38	33	Qualitative / mixed methods	Yes	ICU nurse; caregivers; peer support
Rousseau 2021[201]	COVID-19 in ICU ≥1 week	Belgium	42	32	Cohort	No	ICU nurse; ICU doctor; physiotherapist; psychologist/therapist; dietician/nutritionist

Study	Population	Location	N recruited	N completing	Study type	Control?	Study components
Ward 2021[208]	COVID-19 ICU patients	UK	42	32	Cohort	No	ICU nurse; ICU doctor; physiotherapist; pharmacist; psychologist/therapist; dietician/nutritionist; SALT; written information
Howroyd 2021[199]	COVID-19 ICU survivors	UK	76	28	Cohort	No	ICU nurse; physiotherapist; peer support; digital component
Bottom-Tanzer 2021[206]	Acute care surgery and trauma patients in ICU ≥72 hours	USA	82	26	Cohort	No	ICU doctor; physiotherapist; pharmacist; other nurse; other doctor
Prevedello 2021[205]	ICU ≥5 days	Belgium	NA	21	Qualitative / mixed methods	No	ICU nurse; ICU doctor; physiotherapist; psychologist/therapist; social care specialist
Wang 2020[212]	All ICU patients; Mechanical ventilation or delirium ≥48 hours	USA	NA	120	QI project	No	ICU doctor; pharmacist; psychologist/therapist; social care specialist; case manager; caregivers
Boehm 2020[213]	All ICU patients and caregivers	USA	268	106	QI project	No	ICU nurse; social care specialist; caregivers; peer support; volunteers; clergy
Vranceanu 2020[210]	Neurosciences ICU	USA	122	97	RCT	Yes	ICU nurse; psychologist/therapist; caregivers
Snell 2020[214]	ICU patients with one of Mechanical ventilation ≥2 days; sepsis; or delirium ≥4 days	USA	114	48	QI project	Yes	ICU doctor; psychologist/therapist; other nurse; case manager; caregivers; critical care debrief
Abdelhamid 2020[211]	ICU patients ≥5 days with diabetes	Australia	42	26	RCT	Yes	ICU doctor; other doctor

Study	Population	Location	N recruited	N completing	Study type	Control?	Study components
Bloom 2019[216]	Medical ICU ≥48 hours	USA	302	232	RCT	Yes	ICU nurse; ICU doctor; pharmacist; psychologist/therapist; case manager; written information
Bakhru 2019[218]	Medical ICU patients; septic shock; respiratory failure; ≥24 hours mechanical ventilation	USA	196	101	Cohort	No	ICU doctor; pharmacist
Cox 2019[215]	General from medical surgical and cardiac ICUs	USA	80	66	RCT	Yes	Psychologist/therapist; written information; digital component
Cox 2018[219]	ICU Mechanical ventilation ≥48 hours	USA	261	197	RCT	Yes	Psychologist/therapist; caregivers; digital component
Jonasdottir 2018[220]	Mixed ICU ≥72 hours ICU	Iceland	140	119	Cohort	Yes	ICU nurse; caregivers; critical care debrief
Bohart 2018[221]	Relatives of ICU patient	Denmark	181	111	RCT	Yes	ICU nurse; caregivers; critical care debrief
Sevin 2018[222]	Mechanical ventilation; septic shock; delirium	USA	162	62	Cohort	No	ICU nurse; ICU doctor; pharmacist; psychologist/therapist; case manager; caregivers
Bakhru 2018[223]	ICU ≥24 hours mechanical ventilation and / or septic shock	USA	NA	36	Cohort	No	ICU doctor; pharmacist
Battle 2018[217]	General ICU patients ≥48 hours	UK	60	34	RCT	Yes	Physiotherapist
Duarte 2017[226]	ICU stay >24 hours	Brazil	1858	688	Cohort	No	ICU nurse; ICU doctor; physiotherapist; psychologist/therapist; dietician/nutritionist; SALT; social care specialist
McDowell 2017[224]	General ICU, mechanical ventilation ≥96 hours	UK	60	49	RCT	Yes	Physiotherapist

Study	Population	Location	N recruited	N completing	Study type	Control?	Study components
McPeake 2017[175]	General ICU, working age, ≥72 hours ICU, >2 weeks HDU / level 2	UK	49	40	QI project	Yes	ICU nurse; ICU doctor; physiotherapist; pharmacist; psychologist/therapist; social care specialist; caregivers; critical care debrief; peer support; volunteers; signposting
Shelly 2017[225]	Mechanical ventilation ≥24 hours	India	35	28	RCT	Yes	ICU doctor; written information
Schmidt 2016[182]	General sepsis	Germany	291	207	RCT	Yes	ICU nurse; other doctor; case manager
Jensen 2016[228]	General ICU mechanical ventilation >24 hours	Denmark	386	203	RCT	Yes	Other nurse; caregivers; written information; critical care debrief
McWilliams 2016[227]	Mechanical ventilation ≥5 days	UK	73	63	RCT	Yes	Physiotherapist
Jones 2015[230]	General ICU patients with hospital LOS >5 days	UK	93	72	RCT	Yes	Physiotherapist; dietician/nutritionist; written information
Dettling-Ihnenfeldt 2015[231]	MV ≥48 hours	Netherlands	115	69	Cohort	No	ICU nurse; physiotherapist; caregivers
Connolly 2015[229]	General ICU ≥48 hours MV and ICU-AW	UK	20	16	RCT	Yes	Physiotherapist
Haraldsson 2015[232]	ICU LOS >96 hours	Sweden	12	12	Qualitative / mixed methods	No	ICU nurse; psychologist/therapist; caregivers; critical care debrief
Batterham 2014[233]	Mechanical ventilation ≥3 days; trauma or sepsis patients only	UK	59	30	Minimised controlled trial	Yes	Physiotherapist
Berney 2012[235]	ICU ≥5 days	Australia	75	25	Cohort	No	Physiotherapist
Jackson 2012[236]	Medical and surgical ICU patients involved in the "BRAIN" study	USA	26	17	RCT	Yes	Physiotherapist; psychologist/therapist; social care specialist
Cox 2012[234]	Mechanical ventilation ≥4 days; ALI / ARDS	USA	NA	14	Cohort	Yes	Other nurse; caregivers; written information

Study	Population	Location	N recruited	N completing	Study type	Control?	Study components
Elliot 2011[237]	General ICU >48 hours; Mechanical ventilation >24 hours	Australia	195	161	RCT	Yes	Physiotherapist; written information
Petersson 2011[238]	ICU ≥72 hours	Sweden	125	81	Cohort	No	ICU nurse
Cuthbertson 2009[239]	All level 3 patients	UK	286	192	RCT	Yes	ICU nurse; psychologist/therapist; written information; critical care debrief
Samuelson 2009[240]	General ICU >48 hours and referral or self-referral	Sweden	120	79	Cohort	No	ICU nurse; caregivers; written information
Douglas 2007[183]	General ICU	USA	334	247	RCT	Yes	Other nurse; case manager; caregivers
Jones 2004[241]	Relative of those who had ICU stay >48 hours; emergency admissions; all ventilated at some point	UK	104	90	RCT	Yes	Caregivers; written information
Jones 2003[242]	General ICU ≥72 hours	UK	126	102	RCT	Yes	ICU nurse; caregivers; written information
Crocker 2003[243]	ICU ≥4 days	UK	NA	101	Case series	No	ICU nurse; ICU doctor; physiotherapist; occupational therapist

Appendix 3

Ethical approval (See: Chapter 3, Chapter 4, and Chapter 5)

NHS
Health Research Authority

North West - Liverpool Central Research Ethics Committee

3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Tel: 02071048234

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

10 June 2019

Dr Joanne McPeake
Room 2.71, New Lister Building
Glasgow Royal Infirmary
Glasgow
G31 3ER

Dear Dr McPeake

Study title:	**Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE)\nA multi centre questionnaire study**
REC reference:	**17/NW/0119**
Amendment number:	**4**
Amendment date:	**25 March 2019**
IRAS project ID:	**219910**

- Amendment Proposes changes to the Protocol. These changes include more invitations being sent out to obtain a larger sample size, reminders being sent to participants, including all ventilated patients and all HDU patients for the inclusion criteria. The CI has also returned from maternity leave and will resume their role.

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The sub-committee did not raise any ethical issues.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper [Cover Letter]		14 May 2019
Letters of invitation to participant [letter of invitation]	3	25 March 2019
Letters of invitation to participant [letter of invitation tracked]	3	25 March 2019
Non-validated questionnaire [Family Questionnaire]	2	28 March 2019
Notice of Substantial Amendment (non-CTIMP) [Amendment Form]	4	25 March 2019
Participant consent form [Family Consent Form]	4	27 March 2019
Participant consent form [Patient Consent]	3	27 March 2019
Participant consent form [Patient Consent Form Tracked]	3	27 March 2019
Participant consent form [Family Consent Form _Tracked]	4	27 March 2019
Participant information sheet (PIS) [PIS Patient]	5	25 March 2019
Participant information sheet (PIS) [PIS_Family]	4	25 March 2019
Participant information sheet (PIS) [PIS_Family_Tracked]	4	25 March 2019
Participant information sheet (PIS) [PIS (Patient)_Tracked]	5	25 March 2019
Research protocol or project proposal [Protocol]	5	25 March 2019

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

17/NW/0119:	Please quote this number on all correspondence

Yours sincerely

On Behalf Of
Mr Paul Mooney
Chair

E-mail: nrescommittee.northwest-liverpoolcentral@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

North West - Liverpool Central Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 31 May 2019

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Paul Mooney	Deputy Director of Pharmacy - Operations	Yes	
Mrs Ann Williams	Commissioning and Contract Manager	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Nafeesa Khanam	Approvals Administrator

Appendix 4

Patient and family consent forms

Patient consent form: Chapter 3 and Chapter 4.

Patient Consent Form (Version Three) 27th of March 2019

NHS Greater Glasgow and Clyde

STUDY TITLE: Intensive Care Syndrome: Promoting Independence and Return to Employment
A questionnaire Study

PATIENT CONSENT FORM

I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. ☐

Where it is relevant to the research project, I understand that sections of my ICU medical notes may be looked at. I give my permission for the research team to have access to my records. I understand that all the information extracted will be anonymised. ☐

I agree to take part in the above study. ☐

----------	----------	----------
Name of Participant	Date	Signature
----------	----------	----------
Name of Witness	Date	Signature

Caregiver (family) consent form: Chapter 3 and Chapter 5

Family Member Consent Form (Version Four) 27th of March 2019

NHS Greater Glasgow and Clyde

STUDY TITLE: Intensive Care Syndrome: Promoting Independence and Return to Employment
A questionnaire Study

FAMILY MEMBER CONSENT FORM

I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. ☐

I agree to take part in the above study ☐

----------	----------	----------
Name of Participant	Date	Signature
----------	----------	----------
Name of Witness	Date	Signature

Appendix 5

Letter of invitation & participant information sheet (PIS)

Chapter 3, Chapter 4, and Chapter 5

Letter of Invitation, Version 3, 25th of March 2019

Dr Joanne McPeake
Intensive Care Unit Glasgow Royal Infirmary
Level 2, Room 2.71
New Lister Building
Glasgow Royal Infirmary
10-16 Alexandra Parade
G31 2ER
0141 2018627
gg-uhb.inspire@nhs.net

Dear Sir/Madam

As you have previously been a patient in the Intensive Care Unit, we are writing to ask if you would be willing to participate in a research study looking at rehabilitation after intensive care. The research is being carried out by doctors and nurses from the intensive care unit at Glasgow Royal Infirmary. We are working with the doctors who cared for you in intensive care as well as other professionals from intensive care across Scotland. NHS Greater Glasgow and Clyde are leading this research.

If you are agreeable, then we would ask you to read the patient information sheet, sign the consent form and then fill in the questionnaires included. We would also ask that your nearest family member or caregiver also complete the consent form and questionnaire set which is included. We have provided a stamped addressed envelope to return the forms.

Inclusion in this study is voluntary and will not affect the future care you receive.
We will send a further invitation in one month if we do not hear back from you, to ensure that you have adequate opportunity to take part.

Should you require any clarification about the study or want to ask any questions, please contact the Doctor leading this part of the project, Dr Philip Henderson (0141 2018631) and he will endeavour to answer any queries.

Many thanks for co-operation

Yours Sincerely

[redacted]

Joanne McPeake
ICU Nurse

[redacted]

Tara Quasim
ICU Consultant

Participant Information Sheet (Version six) 26th of June 2019

STUDY TITLE: **Intensive Care Syndrome: Promoting Independence and Return to Employment**
A questionnaire Study
Patient Information Sheet

Information Sheet

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

Who is conducting the research?

The research is being carried out by doctors and nurses from the intensive care unit. They are working with other professionals from intensive care across Scotland. **The doctors who cared for you when you were unwell are involved in the study.** NHS Greater Glasgow and Clyde are leading the research.

Why have I been invited?

You have been invited to take part in this study as you have previously been a patient in an Intensive Care Unit in Scotland.

Do I have to take part?

It is up to you to decide. We will describe the study in this information sheet and if you have any further queries or would prefer a telephone, or face-to-face interview, please contact Dr Philip Henderson (the doctor leading this part of the research) on 0141 201 8631. You will be asked to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving reason. This would not affect the standard of care you receive or your future treatment.

Participant Information Sheet (Version six) 26th of June 2019

What does taking part involve?

We are aware that people, both patients and their close family members, can find it a struggle to get back to their previous quality of life after an illness that requires an admission to an Intensive Care Unit. We want to find out if there are any gaps in the service we provide from Intensive Care.

This project involves you filling out questionnaires and returning them in the stamped addressed envelope provided. It will take approximately 10-15 minutes to complete. As stated earlier, if preferred we can conduct a telephone or face to face interview. This letter contains 4 questionnaires. The first is called the EQ5D which provides us with a measure of your current quality of life. The second questionnaire, called the Generalised Self Efficacy Questionnaire which looks at how you are coping after your stay in critical care. There is also a questionnaire related to Anxiety and Depression (The Hospital Anxiety and Depression Scale) and one related to any ongoing pain issues which you may have (The Brief Chronic Pain Inventory). We will also ask your family member to complete some brief questions about themselves.

The data will be stored anonymously so it cannot be traced back to an individual. This research is important as we would ideally like to provide a rehabilitation package after a stay in the Intensive Care Unit but we need to know what you felt were the important issues.

The researchers will also look at your medical notes while you were in the ICU.

What happens to the information?

NHS Greater Glasgow and Clyde is the sponsor for this study based in the UK. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. NHS Greater Glasgow and Clyde will keep identifiable information about you for five years after the study is complete.

Your rights to access, change, or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting Dr Joanne McPeake (joanne.mcpeake@glasgow.ac.uk).

Your information will only be used for the purpose of this study. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of this research. It will not be used to make decisions about future service available to you, such as insurance. Where there is a risk that you can be identified, your data will only be used in research that has been independently reviewed by an ethics committee.

NHS Greater Glasgow and Clyde will collect information about you for this study from the ICU in which you were admitted. This information will include your name, NHS number, contact details, and health information, which is regarded as a special category of information. We will use this information for the purposes of this research only.

What are the possible benefits of taking part?

There are no direct benefits for you but it is hoped that by taking part in this research, you will provide valuable information regarding quality of life after Intensive Care, which may allow us to determine what, if any, issues we can provide more help with for future patients. If completing these questionnaires causes any feelings of upset or distress, please contact us as detailed below (Dr Tara Quasim). We can then refer you to a relevant ICU follow up service to deal with these issues directly.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called the Research Ethics Committee to protect your safety, rights, well-being and dignity. Additionally, this study has been reviewed by patients and family members who have also had experience of the ICU.

Participant Information Sheet (Version six) 26th of June 2019

If you have any further questions?

We will give you a copy of the information sheet and signed consent form to keep. If you would like more information about the study and wish to speak to someone **not** closely linked to the study, please contact Professor J Kinsella (John.kinsella@glasgow.ac.uk, 0141 2018630).

Contacts:

Dr Joanne McPeake
Level 2, Room 2.71, New Lister Building
Glasgow Royal Infirmary
10-16 Alexandra Parade
G31 2ER
0141 2018627

Dr Tara Quasim
Level 2, Room 2.71, New Lister Building
Glasgow Royal Infirmary
10-16 Alexandra Parade
G31 2ER
0141 2018629

If you have a complaint about any aspect of the study?

If you are unhappy about any aspect of the study and wish to make a complaint, please contact the researcher in the first instance but the normal NHS complaint mechanism is also available to you. Alternatively, you can contact the Patient Advice and Support Service for free confidential Information (http://www.patientadvicescotland.org.uk/).

Thank-you for your time

Appendix 6

Estimated staff time and costs per cohort of InS:PIRE

Staff member	Hours required per cohort	Example grade / pay scale used for calculation	Basic staff pay per cohort	Costs with 1.13 holiday pay multiplier	Full employer costs with 1.3 multiplier
ICU consultant (one per cohort)	24 hours direct contact; 20 hours preparation and referral time	Consultant salary: e.g. threshold / pay point 5	**£2,281**	**£2,578**	**£3,351**
ICU Nurse (two per cohort)	24 hours direct contact per nurse; 10 hours administration time per nurse (phone calls and follow-up)	One band 6 nurse; One band 5 nurse; both 34 hours per cohort	**£802 (band 6)** **£655 (band 5)**	**£906 (band 6)** **£740 (band 5)**	**£1,178 (band 6)** **£962 (band 5)**
Pharmacist	24 hours contact time; 20 hours preparation time	Band 8a	**£1,384**	**£1,564**	**£2,033**
Physiotherapist	24 hours contact time; 10 hours preparation	Band 6	**£802**	**£906**	**£1,178**
Psychologist	Single session; 4 hours	Band 8b	**£147**	**£166**	**£216**
Speech and language therapist	Single session / presentation: 4 hours	Band 5	**£77**	**£87**	**£113**
Administration staff	30 hours	Band 4	**£461**	**£521**	**£677**
Total staff costs per cohort			**£6,609**	**£7,468**	**£9,709**

Costs are calculated based on the NHS Scotland Agenda for Change pay scales for 2023/2024 and the 2004 NHS Scotland consultant contract for the year 2023/2024[368,369]. The pay scales apply to NHS Scotland; pay scales for Agenda for Change are taken as the top of the pay scale for the respective pay band; and the consultant costs are based on the mid-point of the pay scale. Basic staff pay per cohort does not include employer's national insurance contributions or other additional costs. The 1.13 multiplier is used to calculate the cost of annual leave based on six weeks of leave per year per staff member. The 1.3 pay multiplier aims to take all costs into account including employer's national insurance and pensions contributions (after annual leave) and aims to estimate the complete cost to the employer and is the suggested multiplier figure by the Department of Health and Social Care[370].

Appendix 7

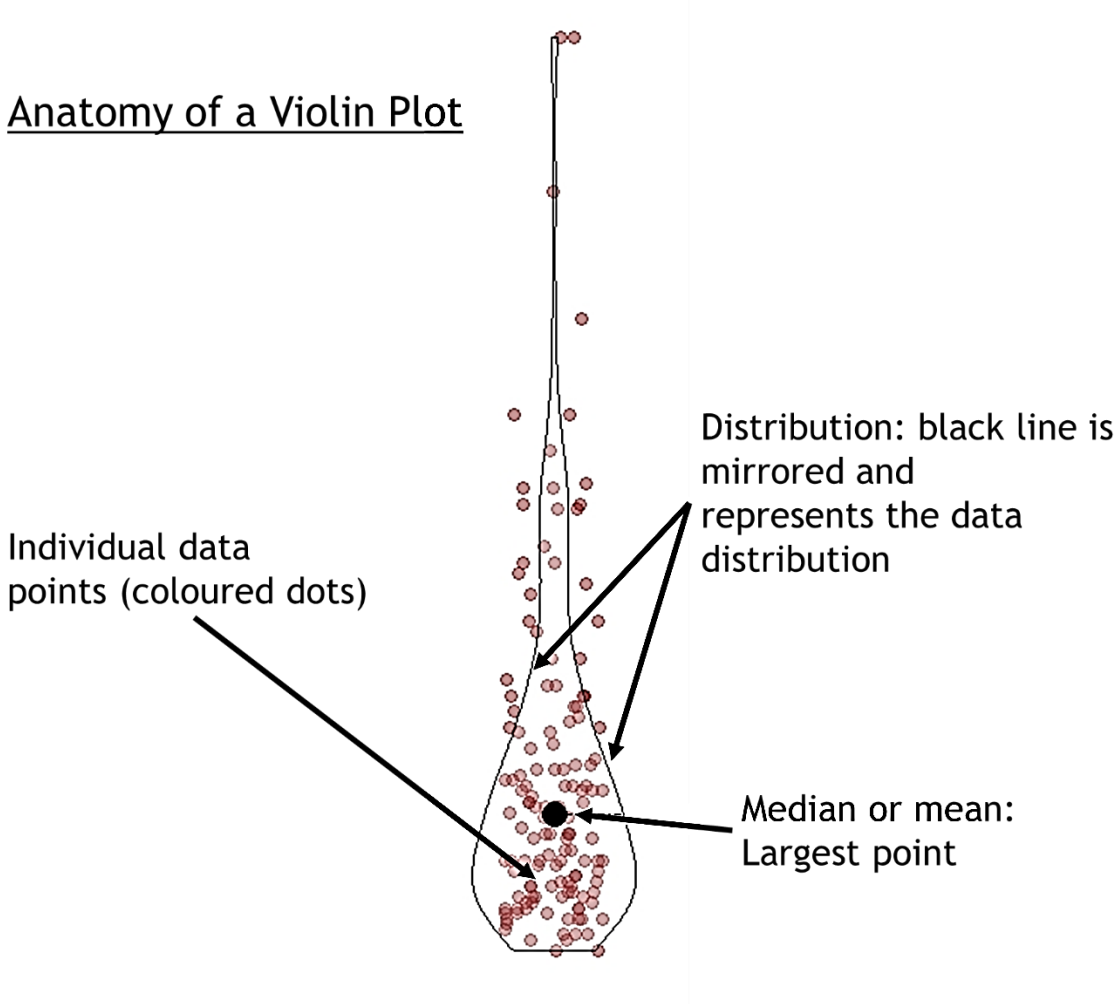
Characteristics of responders and non-responders in the postal survey (usual care cohort; Chapter 4)

Demographic	Responders (N = 115)	Non-responders (N = 337)
Age, Years, Median (IQR)	63.5 (49.5 to 71.5)	53.7 (41.5 to 64.8)
Sex, Male (%)	67 / 115 (58.3)	207 / 336 (61.6)
Admitting specialty (%):		
Medical	53 / 115 (46.1)	208 / 336 (61.9)
Surgery	62 / 115 (53.9)	126 / 336 (37.5)
Other	0 / 115 (0.0)	2 / 336 (0.6)
Surgery at admission or within seven days of ICU (%)	50 / 106 (47.2)	112 / 329 (34.0)
ICU length of stay, Median days (IQR)	4.95 (2.5 to 9.5)	4.61 (2.21 to 9.14)
Hospital Length of stay, Median days (IQR)	18.0 (11.4 to 35.0)	17.0 (8.0 to 32.3)
APACHE II score, Median (IQR)	19 (14.2 to 25.0)	18 (14 to 24)
Advanced respiratory support (%)	100 / 112 (89.3)	301 / 334 (90.1)
Complex cardiovascular support requiring multiple vasoactive drugs (%)	21 / 112 (18.8)	39 / 336 (11.6)
Renal replacement therapy (%)	19 / 112 (17.0)	64 / 334 (19.2)
Deprivation index, SIMD 2016 (%):		
Quintile 1 (most deprived)	34 / 112 (30.4)	133 / 311 (42.8)
Quintile 2	27 / 112 (24.1)	75 / 311 (24.1)
Quintile 3	12 / 112 (10.7)	48 / 311 (15.4)
Quintile 4	18 / 112 (16.1)	27 / 311 (8.7)
Quintile 5 (least deprived)	21 / 112 (18.8)	28 / 311 (9.0)
Time from hospital discharge to first recruitment letter invitation, Median months (IQR)	13.9 (12.4 to 15.2)	13.6 (12.0 to 15.1)

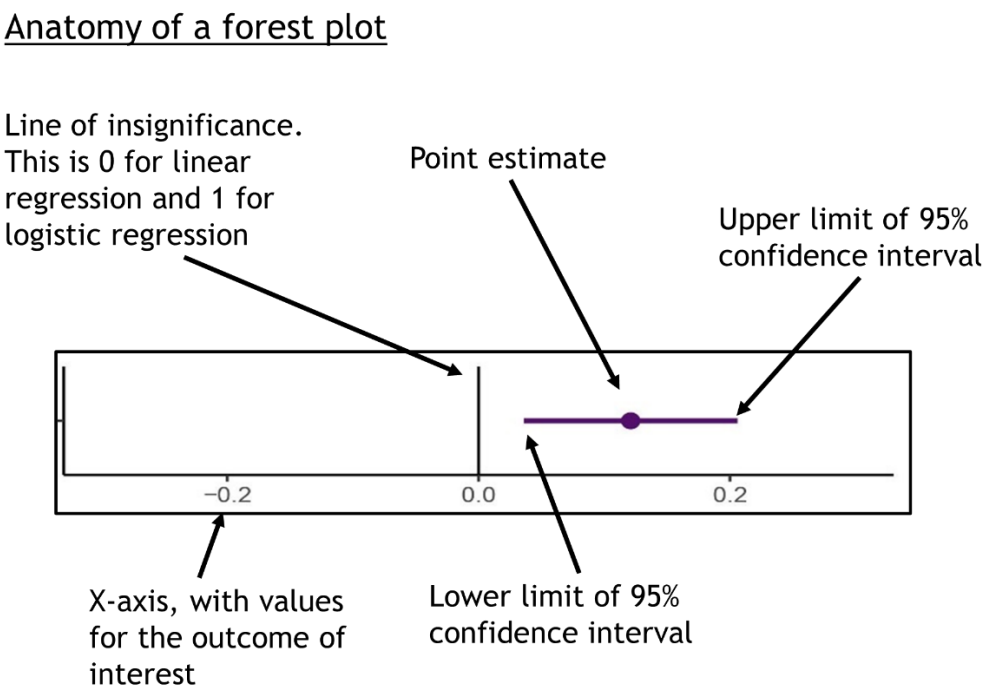
IQR: interquartile range; ICU: Intensive Care Unit; APACHE II: Acute Physiology and Chronic Health Evaluation Two; SIMD: Scottish Index of Multiple Deprivation.

Appendix 8

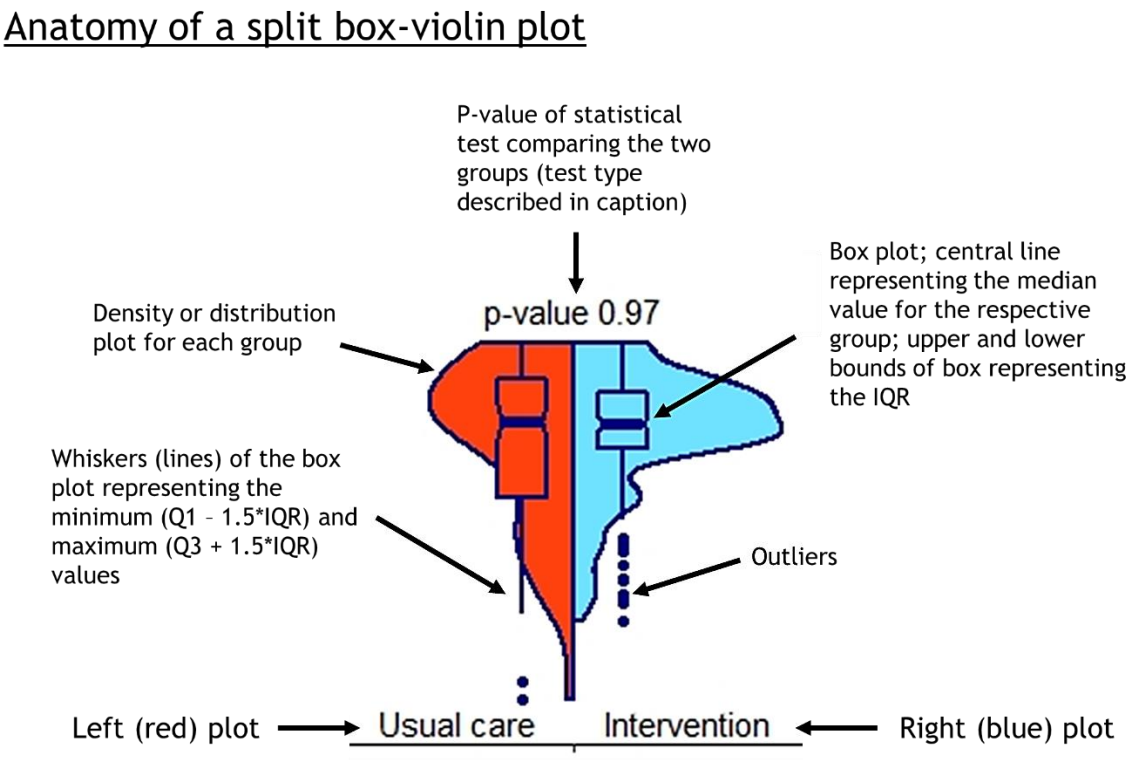
Interpretation of common plots used in this thesis (Chapter 4 and Chapter 5)



Anatomy of a violin plot demonstrating the individual data points, the distribution or density plot, and the summary value (median or mean) which will be stated on the plot. Statistical test of the differences between the groups will be stated above the plot with the corresponding p-value.



Anatomy of a forest plot



Anatomy of a split box-violin plot. IQR: Interquartile Range.

Appendix 9

Missing values for patient one-year outcomes (Chapter 4)

Missing values for the baseline patient characteristics

Covariate	Missing (%) N=252
Baseline characteristics	
Age	1.2
Sex	0
Medical or surgical admission	1.2
Surgery at admission or within seven days of ICU	4.0
ICU length of stay	1.2
Hospital Length of stay	3.2
APACHE II score	3.2
Advanced respiratory support	1.2
Complex cardiovascular support requiring multiple vasoactive drugs	1.2
Renal replacement therapy	1.2
Two or greater comorbidities	2.0
Charlson Comorbidity Index (CCI) score	1.6
Pre-existing psychiatric diagnosis	2.0
History of harmful alcohol or drug use	2.0
Pre-morbid history of chronic pain	2.0
Scottish Index of Multiple Deprivation (SIMD) quintile	1.2
Time to follow-up (months)	3.2
Days of advanced respiratory support	1.2
Days of basic cardiovascular support	1.2
Days of acute renal replacement therapy	1.2
Obesity	1.2

Covariate	Missing (%) N=252
Baseline characteristics	
Cardiovascular comorbidity count	1.2
Respiratory disease comorbidity count	2
Other comorbidity count (Non-respiratory, non-cardiovascular)	2
Complete comorbidity count	1.2
Admitting specialty short version	1.2
Days of level 3 treatment / Intensive Care	2
Days of level 2 treatment / High Dependency	2
Admitting specialty long version	1.2
Organ system failing	1.2

Missing values for patient one-year outcome measures

Covariate	Missingness, Number (%) (N = 252)
Outcome measurements	
EuroQol 5 Dimension 5 Level (EQ-5D-5L) responses	
EQ-5D-5L mobility score	2 (0.79)
EQ-5D-5L self-care score	2 (0.79)
EQ-5D-5L usual activities score	2 (0.79)
EQ-5D-5L pain and discomfort score	2 (0.79)
EQ-5D-5L anxiety and depression score	2 (0.79)
EQ-5D-5L Visual Analogue Score	10 (3.97)
Hospital Anxiety and Depression Scale (HADS): Anxiety	
I feel tense or wound up	5 (1.98)
I get a sort of frightened feeling as if something awful is about to happen	4 (1.59)

Covariate	Missingness, Number (%) (N = 252)
worrying thoughts go through my mind	4 (1.59)
I can sit at ease and feel relaxed	4 (1.59)
I get a sort of frightened feeling like butterflies in the stomach	7 (2.78)
I feel restless as if I have to be on the move	8 (3.17)
I get sudden feelings of panic	9 (3.57)
Hospital Anxiety and Depression Scale (HADS): Depression	
I still enjoy the things I used to enjoy	3 (1.19)
I can laugh and see the funny side of things	6 (2.38)
I feel cheerful	4 (1.59)
I feel as if I am slowed down	7 (2.78)
I have lost interest in my appearance	7 (2.78)
I look forward with enjoyment to things	9 (3.57)
I can enjoy a good book or radio or television programme	8 (3.17)
Generalised Self-Efficacy (GSE)	
I can always manage to solve difficult problems if I try hard enough	6 (2.38)
If someone opposes me I can find the means and ways to get what I want	9 (3.57)
It is easy for me to stick to my aims and accomplish goals	11 (4.37)
I am confident that I could deal efficiently with unexpected events	8 (3.17)
Thanks to my resourcefulness I know how to handle unforeseen situations	8 (3.17)
I can resolve most problems if I invest the necessary effort	10 (3.97)
I can remain calm when facing difficulties because I can rely on my coping abilities	9 (3.57)
When I am confronted with a problem I can usually find several solutions	8 (3.17)

Covariate	Missingness, Number (%) (N = 252)
If I am in trouble I can usually think of a solution	8 (3.17)
I can usually handle whatever comes my way	7 (2.78)
Brief Pain Inventory (short form)	
Have you had pain today?	29 (11.51)
Worst pain in past 24 hours	4 (1.59)
Least pain in past 24 hours	7 (2.78)
Average pain level	9 (3.57)
Pain right now	7 (2.78)
Pain interference with activity	14 (5.56)
Pain interference with mood	16 (6.35)
Pain interference with walking	18 (7.14)
Pain interference with normal work	17 (6.75)
Pain interference with relations with other people	15 (5.95)
Pain interference with sleep	16 (6.35)
Pain interference with enjoyment of life	16 (6.35)

Appendix 10

Regression models for patient outcomes (Chapter 4)

Adjusted, unmatched, multivariable models used for primary patient outcomes at one year. Covariates and their effects for all outcomes.

Model details

Details of variables included in the models:

- Intervention = Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE), effects compared to the usual care cohort
- Male sex effects compared to female sex
- Intensive Care Unit (ICU) length of stay, measured in days, effects per day
- Acute Physiology and Chronic Health Evaluation II (APACHE II) score, effects per point increase in score
- Time to follow-up measured in months, effects per additional month from hospital discharge to follow-up
- Scottish Index of Multiple Deprivation, five quintiles (SIMD), effects are those compared to SIMD quintile 1 (most deprived)
- Surgery at admission or within seven days of ICU, effects of having an operation around time of ICU admission compared to those not having operative management in this time frame
- Charlson Comorbidity Index (CCI) score, effects per extra index point score
- effects of specific comorbidity conditions of outcome compared to absence of the comorbidity: history of harmful alcohol or drug use, pre-morbid history of chronic pain, pre-existing psychiatric diagnosis.
- NA=not applicable.

Health utility score model: Primary patient outcomes

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.79	**<0.001**	0.57 to 1.10
Intervention (InS:PIRE)	0.12	**0.01**	0.04 to 0.20
Male sex	0.01	0.72	-0.07 to 0.10
ICU length of stay	0.00	**0.01**	-0.01 to 0.00
APACHE II score	0.00	0.53	-0.01 to 0.00
Time to follow-up (months)	-0.01	**<0.001**	-0.02 to 0.00
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	0.02	0.70	-0.08 to 0.12
SIMD quintile 3	0.07	0.28	-0.06 to 0.19
SIMD quintile 4	0.14	**0.04**	0.01 to 0.26
SIMD quintile 5 (least deprived)	0.21	**<0.001**	0.11 to 0.30
Surgery at admission or within seven days of ICU	0.02	0.69	-0.07 to 0.11
Charlson Comorbidity Index (CCI) score	0.00	0.95	-0.02 to 0.02
History of harmful alcohol or drug use	-0.09	0.11	-0.21 to 0.02
Pre-morbid history of chronic pain	-0.09	0.21	-0.24 to 0.05
Pre-existing psychiatric diagnosis	-0.17	**<0.001**	-0.27 to -0.07

Health utility score: EQ-5D-5L quality of life indicator with range of -0.594 to 1.0. Adjusted linear regression model.

EuroQol Visual Analogue Scale score: Primary patient outcomes

Covariate	Effect estimate	P value	95% confidence interval
Intercept	65.38	**<0.001**	49.57 to 81.19
Intervention (InS:PIRE)	11.88	**<0.001**	5.91 to 17.86
Male sex	-0.10	0.97	-5.76 to 5.55
ICU length of stay	-0.20	0.12	-0.46 to 0.05
APACHE II score	0.03	0.88	-0.38 to 0.44
Time to follow-up (months)	-0.52	0.14	-1.23 to 0.18
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	4.56	0.22	-2.81 to 11.93
SIMD quintile 3	5.25	0.26	-3.93 to 14.44
SIMD quintile 4	1.43	0.76	-7.83 to 10.69
SIMD quintile 5 (least deprived)	14.87	**<0.001**	6.52 to 23.22
Surgery at admission or within seven days of ICU	7.92	**0.001**	1.92 to 13.91
Charlson Comorbidity Index (CCI) score	-0.01	0.99	-1.35 to 1.32
History of harmful alcohol or drug use	-8.00	0.06	-16.33 to 0.34
Pre-morbid history of chronic pain	-4.40	0.26	-12.01 to 3.21
Pre-existing psychiatric diagnosis	-10.43	**<0.001**	-17.38 to -3.47

EuroQol Visual Analogue Scale: Range 0 to 100. Adjusted linear regression model.

Generalised Self-Efficacy: Primary patient outcomes

Covariate	Effect estimate	P value	95% confidence interval
Intercept	29.49	**<0.001**	24.94 to 34.03
Intervention (InS:PIRE)	2.32	**0.02**	0.32 to 4.31
Male sex	0.60	0.48	-1.06 to 2.26
ICU length of stay	-0.03	0.35	-0.10 to 0.04
APACHE II score	0.00	0.99	-0.13 to 0.13
Time to follow-up (months)	-0.20	0.07	-0.42 to 0.02
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	1.22	0.33	-1.25 to 3.69
SIMD quintile 3	3.04	**0.02**	0.45 to 5.63
SIMD quintile 4	2.63	0.08	-0.33 to 5.60
SIMD quintile 5 (least deprived)	3.62	**<0.001**	1.42 to 5.82
Surgery at admission or within seven days of ICU	1.73	0.05	0.03 to 3.43
Charlson Comorbidity Index (CCI) score	0.50	**0.02**	0.08 to 0.92
History of harmful alcohol or drug use	-2.44	0.10	-5.33 to 0.45
Pre-morbid history of chronic pain	-0.03	0.98	-2.90 to 2.84
Pre-existing psychiatric diagnosis	-3.16	**<0.001**	-5.24 to -1.08

Generalised Self-Efficacy: range 10 to 40. Adjusted linear regression model.

Depression odds ratios: Hospital Anxiety and Depression Scale score: Primary patient outcomes

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.82	0.83	0.13 to 5.09
Intervention (InS:PIRE)	0.38	**0.01**	0.19 to 0.76
Male sex	1.07	0.85	0.54 to 2.11
ICU length of stay	1.03	0.06	1.00 to 1.06
APACHE II score	1.00	1.00	0.95 to 1.05
Time to follow-up (months)	1.05	0.16	0.98 to 1.14
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	0.69	0.38	0.31 to 1.57
SIMD quintile 3	0.31	**0.02**	0.11to 0.85
SIMD quintile 4	0.81	0.64	0.34 to 1.96
SIMD quintile 5 (least deprived)	0.14	**0.01**	0.03 to 0.63
Surgery at admission or within seven days of ICU	0.33	**<0.001**	0.17 to 0.65
Charlson Comorbidity Index (CCI) score	0.83	0.05	0.70 to 1.00
History of harmful alcohol or drug use	2.06	0.09	0.88 to 4.81
Pre-morbid history of chronic pain	0.86	0.78	0.30 to 2.49
Pre-existing psychiatric diagnosis	3.36	**<0.001**	1.67 to 6.79

Hospital Anxiety and Depression Scale scores. Odds ratios of risk of screening positive for depression at one year. Depression = HADS-D ≥8/21

Anxiety odds ratios: Hospital Anxiety and Depression Scale score: Primary patient outcomes

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.93	0.96	0.18 to 4.82
Intervention (InS:PIRE)	0.58	0.11	0.30 to 1.13
Male sex	0.49	**0.03**	0.25 to 0.93
ICU length of stay	1.00	0.81	0.97 to 1.03
APACHE II score	1.00	0.90	0.96 to 1.5
Time to follow-up (months)	1.07	0.06	1.00 to 1.15
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	0.92	0.84	0.42 to 2.00
SIMD quintile 3	0.76	0.54	0.30 to 1.88
SIMD quintile 4	0.50	0.15	0.19 to 1.29
SIMD quintile 5 (least deprived)	0.50	0.14	0.20 to 1.27
Surgery at admission or within seven days of ICU	0.45	**0.02**	0.23 to 0.88
Charlson Comorbidity Index (CCI) score	0.87	0.12	0.73 to 1.04
History of harmful alcohol or drug use	3.37	<0.001	1.44 to 7.88
Pre-morbid history of chronic pain	1.19	0.72	0.47 to 2.98
Pre-existing psychiatric diagnosis	2.06	**0.04**	1.04 to 4.10

Hospital Anxiety and Depression Scale scores. Odds ratios of risk of screening positive for anxiety at one year. Anxiety = HADS-A ≥8/21.

Brief Pain Inventory (short form): Effects on Summary (mean) pain score: Primary patient outcomes

Covariate	Effect estimate	P value	95% confidence interval
Intercept	3.13	**<0.001**	1.38 to 4.89
Intervention (InS:PIRE)	-0.62	0.09	-1.35 to 0.11
Male sex	-0.28	0.42	-0.98 to 0.41
ICU length of stay	0.02	0.12	-0.01 to 0.05
APACHE II score	-0.06	**0.02**	-0.11 to -0.01
Time to follow-up (months)	0.11	**<0.001**	0.05 to 0.17
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.40	0.41	-1.35 to 0.56
SIMD quintile 3	-1.30	**0.04**	-2.52 to -0.08
SIMD quintile 4	-0.96	0.09	-2.09 to 0.16
SIMD quintile 5 (least deprived)	-2.24	**<0.001**	-3.10 to -1.38
Surgery at admission or within seven days of ICU	-0.69	0.08	-1.47 to 0.09
Charlson Comorbidity Index (CCI) score	0.16	0.07	-0.01 to 0.34
History of harmful alcohol or drug use	1.18	**0.02**	0.18 to 2.17
Pre-morbid history of chronic pain	1.15	**0.01**	0.24 to 2.05
Pre-existing psychiatric diagnosis	0.53	0.21	-0.31 to 1.36

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Brief Pain Inventory (short form): Effects on average pain score (single question from survey): Primary patient outcomes

Covariate	Effect estimate	P value	95% confidence interval
Intercept	3.25	**<0.001**	1.42 to 5.08
Intervention (InS:PIRE)	-0.75	0.05	-1.50 to 0.00
Male sex	-0.22	0.56	-0.94 to 0.51
ICU length of stay	0.03	0.06	0.00 to 0.06
APACHE II score	-0.05	**0.04**	-0.10 to 0.00
Time to follow-up (months)	0.10	**<0.001**	0.03 to 0.17
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.39	0.44	-1.37 to 0.60
SIMD quintile 3	-1.30	**0.04**	-2.58 to -0.03
SIMD quintile 4	-0.80	0.20	-2.01 to 0.41
SIMD quintile 5 (least deprived)	-2.12	**<0.001**	-3.06 to -1.18
Surgery at admission or within seven days of ICU	-0.71	0.08	-1.50 to 0.09
Charlson Comorbidity Index (CCI) score	0.21	**0.04**	0.01 to 0.40
History of harmful alcohol or drug use	1.38	**0.01**	0.35 to 2.42
Pre-morbid history of chronic pain	0.80	0.09	-0.14 to 1.74
Pre-existing psychiatric diagnosis	0.26	0.56	-0.61 to 1.12

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Brief Pain Inventory (short form): Effects on worst pain score (single question from survey): Primary patient outcomes

Covariate	Effect estimate	P value	95% confidence interval
Intercept	4.64	**<0.001**	2.72 to 6.55
Intervention (InS:PIRE)	-0.59	0.16	-1.41 to 0.23
Male sex	-0.57	0.16	-1.38 to 0.23
ICU length of stay	0.03	0.14	-0.01 to 0.06
APACHE II score	-0.08	**<0.001**	-0.14 to -0.03
Time to follow-up (months)	0.11	**<0.001**	0.04 to 0.17
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.59	0.26	-1.63 to 0.44
SIMD quintile 3	-1.60	**0.03**	-3.02 to -0.17
SIMD quintile 4	-0.84	0.22	-2.19 to 0.51
SIMD quintile 5 (least deprived)	-2.36	**<0.001**	-3.42 to -1.30
Surgery at admission or within seven days of ICU	-0.91	**0.04**	-1.77 to -0.14
Charlson Comorbidity Index (CCI) score	0.16	0.14	-0.05 to 0.37
History of harmful alcohol or drug use	1.47	**0.01**	0.39 to 2.55
Pre-morbid history of chronic pain	1.31	**0.01**	0.29 to 2.33
Pre-existing psychiatric diagnosis	0.75	0.12	-0.18 to 1.68

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Brief Pain Inventory (short form): Effects on enjoyment in life: pain interference (single question from survey): Primary patient outcomes

Covariate	Effect estimate	P value	95% confidence interval
Intercept	4.23	**<0.001**	2.00 to 6.46
Intervention (InS:PIRE)	-1.00	**0.03**	-1.89 to -0.11
Male sex	0.41	0.37	-0.48 to 1.31
ICU length of stay	0.03	0.16	-0.01 to 0.07
APACHE II score	-0.06	0.07	-0.12 to 0.00
Time to follow-up (months)	0.09	**0.02**	0.01 to 0.17
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.54	0.37	-1.72 to 0.65
SIMD quintile 3	-1.67	**0.02**	-3.12 to -0.22
SIMD quintile 4	-1.47	**0.04**	-2.87 to -0.07
SIMD quintile 5 (least deprived)	-3.14	**<0.001**	-4.20 to -2.07
Surgery at admission or within seven days of ICU	-0.80	0.09	-1.71 to 0.12
Charlson Comorbidity Index (CCI) score	-0.07	0.57	-0.30 to 0.17
History of harmful alcohol or drug use	1.03	0.10	-0.22 to 2.27
Pre-morbid history of chronic pain	1.32	**0.04**	0.09 to 2.54
Pre-existing psychiatric diagnosis	1.11	**0.04**	0.05 to 2.17

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Brief Pain Inventory (short form): Effects on normal work: pain interference (single question from survey): Primary patient outcomes

Covariate	Effect estimate	P value	95% confidence interval
Intercept	4.23	**<0.001**	1.90 to 6.56
Intervention (InS:PIRE)	-0.69	0.16	-1.66 to 0.28
Male sex	-0.13	0.78	-1.08 to 0.81
ICU length of stay	0.04	0.10	-0.01 to 0.08
APACHE II score	-0.06	0.09	-0.12 to 0.01
Time to follow-up (months)	0.08	0.09	-0.01 to 0.17
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.43	0.53	-1.77 to 0.91
SIMD quintile 3	-1.69	**0.03**	-3.21 to -0.17
SIMD quintile 4	-1.42	0.07	-2.94 to 0.11
SIMD quintile 5 (least deprived)	-3.24	**<0.001**	-4.47 to -2.02
Surgery at admission or within seven days of ICU	-0.44	0.40	-1.45 to 0.25
Charlson Comorbidity Index (CCI) score	0.10	0.43	-0.14 to 0.33
History of harmful alcohol or drug use	1.00	0.16	-0.40 to 2.41
Pre-morbid history of chronic pain	1.06	0.10	-0.21 to 2.33
Pre-existing psychiatric diagnosis	1.43	**0.01**	0.29 to 2.57

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Brief Pain Inventory (short form): Pain interference summary: mean pain interference (summary score): Primary patient outcomes

Covariate	Effect estimate	P value	95% confidence interval
Intercept	4.05	**<0.001**	2.09 to 60.20
Intervention (InS:PIRE)	-0.73	0.07	-1.52 to 0.06
Male sex	0.03	0.94	-0.73 to 0.78
ICU length of stay	0.03	0.07	0.00 to 0.06
APACHE II score	-0.06	**0.04**	-0.11 to 0.00
Time to follow-up (months)	0.08	**0.04**	0.00 to 0.16
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.65	0.22	-1.68 to 0.39
SIMD quintile 3	-1.80	**<0.001**	-3.03 to -0.57
SIMD quintile 4	-1.50	**0.01**	-2.71 to -0.30
SIMD quintile 5 (least deprived)	-2.91	**<0.001**	-3.79 to -2.04
Surgery at admission or within seven days of ICU	-0.60	0.15	-1.43 to 0.22
Charlson Comorbidity Index (CCI) score	0.00	0.98	-0.20 to 0.19
History of harmful alcohol or drug use	1.25	**0.02**	0.16 to 2.34
Pre-morbid history of chronic pain	1.37	**0.01**	0.36 to 2.38
Pre-existing psychiatric diagnosis	1.07	**0.02**	0.18 to 1.96

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Matched regression models: patient one-year outcomes

Health utility score model (matched regression models)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.79	**<0.001**	0.54 to 1.03
Intervention (InS:PIRE)	0.14	**0.003**	0.05 to 0.22
Male sex	0.04	0.23	-0.03 to 0.12
ICU length of stay	-0.01	**<0.001**	-0.01 to 0.00
APACHE II score	0.00	0.56	-0.01 to 0.01
Time to follow-up (months)	-0.01	0.13	-0.02 to 0.00
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	0.00	0.94	-0.08 to 0.09
SIMD quintile 3	0.01	0.86	-0.11 to 0.13
SIMD quintile 4	0.14	0.02	0.02 to 0.25
SIMD quintile 5 (least deprived)	0.16	**<0.001**	0.07 to 0.25
Surgery at admission or within seven days of ICU	-0.02	0.69	-0.10 to 0.07
Charlson Comorbidity Index (CCI) score	0.00	0.61	-0.01 to 0.02
History of harmful alcohol or drug use	-0.12	0.06	-0.24 to 0.00
Pre-morbid history of chronic pain	-0.11	0.16	-0.26 to 0.05
Pre-existing psychiatric diagnosis	-0.17	**<0.001**	-0.26 to -0.08

Health utility score: EQ-5D-5L quality of life indicator with range of -0.594 to 1.0.
Adjusted linear regression model.

EuroQol Visual Analogue Scale score (matched regression models)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	64.92	**<0.001**	42 to 87.84
Intervention (InS:PIRE)	12.30	**<0.001**	7.46 to 17.15
Male sex	-0.52	0.85	-6.16 to 5.13
ICU length of stay	-0.36	**<0.001**	-0.59 to -0.13
APACHE II score	0.13	0.57	-0.36 to 0.62
Time to follow-up (months)	-0.34	0.41	-1.21 to 0.53
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	2.86	0.44	-4.84 to 10.56
SIMD quintile 3	0.63	0.87	-6.98 to 8.24
SIMD quintile 4	-0.36	0.94	-10.05 to 9.34
SIMD quintile 5 (least deprived)	12.47	**<0.001**	5.66 to 19.24
Surgery at admission or within seven days of ICU	6.41	0.08	-0.92 to 13.75
Charlson Comorbidity Index (CCI) score	-0.62	0.47	-2.44 to 1.20
History of harmful alcohol or drug use	-7.68	**0.04**	-15.08 to -0.27
Pre-morbid history of chronic pain	-3.11	0.36	-9.93 to 3.71
Pre-existing psychiatric diagnosis	-11.18	**0.02**	-20.39 to -1.96

EuroQol Visual Analogue Scale score: Range 0 to 100. Adjusted linear regression model.

Generalised Self-Efficacy (matched regression models)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	26.71	**<0.001**	19.25 to 34.16
Intervention (InS:PIRE)	2.86	**0.001**	1.24 to 4.47
Male sex	0.37	0.63	-1.17 to 1.91
ICU length of stay	-0.02	0.60	-0.10 to 0.06
APACHE II score	-0.02	0.79	-0.15 to 0.11
Time to follow-up (months)	0.04	0.80	-0.31 to 0.39
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	0.86	0.47	-1.59 to 3.32
SIMD quintile 3	0.86	0.50	-1.73 to 3.46
SIMD quintile 4	2.33	0.25	-1.91 to 6.58
SIMD quintile 5 (least deprived)	3.10	**0.01**	0.78 to 5.42
Surgery at admission or within seven days of ICU	1.08	0.32	-1.17 to 3.33
Charlson Comorbidity Index (CCI) score	0.45	**0.04**	0.01 to 0.90
History of harmful alcohol or drug use	-2.06	0.11	-4.63 to 0.50
Pre-morbid history of chronic pain	-0.11	0.95	-4.34 to 4.12
Pre-existing psychiatric diagnosis	-3.75	**<0.001**	-5.60 to -1.90

Generalised Self-Efficacy: range 10 to 40. Adjusted linear regression model.

Depression odds ratios: Hospital Anxiety and Depression Scale score (HADS) (matched regression models)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	1.49	0.78	0.06 to 36.50
Intervention (InS:PIRE)	0.33	**0.002**	0.17 to 0.65
Male sex	0.97	0.93	0.45 to 2.09
ICU length of stay	1.02	0.16	0.99 to 1.06
APACHE II score	1.01	0.75	0.95 to 1.07
Time to follow-up (months)	1.01	0.84	0.88 to 1.17
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	0.80	0.62	0.30 to 2.09
SIMD quintile 3	0.40	**0.04**	0.17 to 0.98
SIMD quintile 4	0.72	0.53	0.24 to 2.14
SIMD quintile 5 (least deprived)	0.08	**0.01**	0.01 to 0.48
Surgery at admission or within seven days of ICU	0.33	**0.03**	0.12 to 0.89
Charlson Comorbidity Index (CCI) score	0.82	0.14	0.62 to 1.09
History of harmful alcohol or drug use	2.55	0.20	0.53 to 12.18
Pre-morbid history of chronic pain	0.64	0.49	0.15 to 2.74
Pre-existing psychiatric diagnosis	3.69	**0.02**	1.29 to 10.55

Hospital Anxiety and Depression Scale scores. Odds ratios of risk of screening positive for depression at one year. Depression = HADS-D ≥8/21

Anxiety odds ratios: Hospital Anxiety and Depression Scale score (HADS) (matched regression models)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.75	0.76	0.11 to 5.06
Intervention (InS:PIRE)	0.59	0.05	0.35 to 1.00
Male sex	0.61	0.14	0.31 to 1.20
ICU length of stay	0.99	0.57	0.96 to 1.02
APACHE II score	0.99	0.47	0.95 to 1.02
Time to follow-up (months)	1.10	0.08	0.99 to 1.23
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	1.06	0.86	0.55 to 2.05
SIMD quintile 3	0.82	0.69	0.13 to 2.18
SIMD quintile 4	0.27	0.10	0.05 to 1.42
SIMD quintile 5 (least deprived)	0.70	0.58	0.16 to 2.99
Surgery at admission or within seven days of ICU	0.42	0.14	0.12 to 1.44
Charlson Comorbidity Index (CCI) score	0.90	0.36	0.72 to 1.14
History of harmful alcohol or drug use	4.20	**<0.001**	1.63 to 10.80
Pre-morbid history of chronic pain	1.62	0.42	0.46 to 5.68
Pre-existing psychiatric diagnosis	1.95	0.08	0.91 to 4.17

Hospital Anxiety and Depression Scale scores. Odds ratios of risk of screening positive for anxiety at one year. Anxiety = HADS-A ≥8/21

Brief Pain Inventory (short form): Effects on Summary (mean) pain score (matched regression models)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	3.21	**<0.001**	1.65 to 4.77
Intervention (InS:PIRE)	-0.80	**0.02**	-1.43 to -0.17
Male sex	-0.41	0.17	-1.00 to 0.18
ICU length of stay	0.04	0.06	0.00 to 0.09
APACHE II score	-0.07	**<0.001**	-0.11 to -0.03
Time to follow-up (months)	0.10	0.11	-0.03 to 0.23
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.08	0.84	-0.89 to 0.74
SIMD quintile 3	-0.77	0.13	-1.77 to 0.23
SIMD quintile 4	-1.00	0.11	-2.27 to 0.26
SIMD quintile 5 (least deprived)	-1.72	**<0.001**	-2.50 to -0.93
Surgery at admission or within seven days of ICU	-0.40	0.30	-1.19 to 0.40
Charlson Comorbidity Index (CCI) score	0.16	**0.04**	0.01 to 0.31
History of harmful alcohol or drug use	0.94	0.08	-0.14 to 2.03
Pre-morbid history of chronic pain	0.96	0.10	-0.20 to 2.12
Pre-existing psychiatric diagnosis	0.77	0.12	-0.23 to 1.77

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Brief Pain Inventory (short form): Effects on average pain score (single question from survey) (matched regression models)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	3.14	**<0.001**	1.64 to 4.64
Intervention (InS:PIRE)	-0.90	**0.01**	-1.59 to 0.21
Male sex	-0.28	0.35	-1.87 to 0.31
ICU length of stay	0.04	0.12	-0.01 to 0.09
APACHE II score	-0.06	**0.03**	-0.12 to 0.01
Time to follow-up (months)	0.11	**0.04**	0.01 to 0.22
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.21	0.63	-1.09 to 0.68
SIMD quintile 3	-0.94	0.08	-2.00 to 0.11
SIMD quintile 4	-0.86	0.17	-2.11 to 0.40
SIMD quintile 5 (least deprived)	-1.90	**<0.001**	-2.82 to -0.98
Surgery at admission or within seven days of ICU	-0.31	0.42	-1.10 to 0.48
Charlson Comorbidity Index (CCI) score	0.22	**0.02**	0.04 to 0.40
History of harmful alcohol or drug use	1.12	0.05	0.00 to 2.25
Pre-morbid history of chronic pain	0.56	0.34	-0.68 to 1.81
Pre-existing psychiatric diagnosis	0.38	0.40	-0.55 to 1.32

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Brief Pain Inventory (short form): Effects on worst pain score (single question from survey) (matched regression models)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	4.29	<**0.001**	2.74 to 5.83
Intervention (InS:PIRE)	-0.70	**0.03**	-1.33 to -0.06
Male sex	-0.61	0.10	-1.33 to 0.12
ICU length of stay	0.04	0.08	-0.01 to 0.09
APACHE II score	-0.09	**0.01**	-0.15 to -0.03
Time to follow-up (months)	0.10	0.05	0.00 to 0.21
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.36	0.44	-1.29 to 0.58
SIMD quintile 3	-0.90	0.14	-2.10 to 0.31
SIMD quintile 4	-0.64	0.43	-2.38 to 1.09
SIMD quintile 5 (least deprived)	-1.75	**<0.001**	-2.84 to -0.65
Surgery at admission or within seven days of ICU	-0.49	0.26	-1.36 to 0.39
Charlson Comorbidity Index (CCI) score	0.18	0.05	0.00 to 0.35
History of harmful alcohol or drug use	1.16	**0.04**	0.04 to 2.28
Pre-morbid history of chronic pain	1.39	**0.03**	0.14 to 2.65
Pre-existing psychiatric diagnosis	1.11	0.05	0.00 to 2.22

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Brief Pain Inventory (short form): Effects on enjoyment in life: pain interference (single question from survey) (matched regression models)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	4.22	**<0.001**	2.15 to 6.28
Intervention (InS:PIRE)	-1.36	**0.02**	-2.44 to -0.28
Male sex	0.15	0.70	-0.62 to 0.93
ICU length of stay	0.04	0.15	-0.02 to 0.10
APACHE II score	-0.05	0.13	-0.13 to 0.02
Time to follow-up (months)	0.07	0.28	-0.07 to 0.21
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.23	0.68	-1.38 to 0.92
SIMD quintile 3	-0.71	0.27	-1.98 to 0.56
SIMD quintile 4	-1.75	0.06	-3.63 to 0.13
SIMD quintile 5 (least deprived)	-2.54	**<0.001**	-3.91 to -1.16
Surgery at admission or within seven days of ICU	-0.23	0.64	-1.28 to 0.81
Charlson Comorbidity Index (CCI) score	-0.05	0.62	-0.27 to 0.16
History of harmful alcohol or drug use	0.85	0.18	-0.41 to 2.10
Pre-morbid history of chronic pain	1.43	**0.01**	0.32 to 2.54
Pre-existing psychiatric diagnosis	1.80	**0.02**	0.35 to 3.24

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Brief Pain Inventory (short form): Effects on normal work: pain interference (single question from survey) (matched regression models)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	3.74	**<0.001**	1.79 to 5.70
Intervention (InS:PIRE)	-0.88	0.07	-1.84 to 0.07
Male sex	-0.19	0.65	-1.03 to 0.65
ICU length of stay	0.05	0.10	-0.01 to 0.12
APACHE II score	-0.06	0.08	-0.13 to 0.01
Time to follow-up (months)	0.08	0.12	-0.02 to 0.18
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.20	0.71	-1.29 to 0.89
SIMD quintile 3	-0.97	0.14	-2.28 to 0.34
SIMD quintile 4	-1.42	0.12	-3.25 to 0.41
SIMD quintile 5 (least deprived)	-2.80	**<0.001**	-3.89 to -1.71
Surgery at admission or within seven days of ICU	-0.12	0.78	-1.02 to 0.77
Charlson Comorbidity Index (CCI) score	0.18	0.16	-0.07 to 0.43
History of harmful alcohol or drug use	0.68	0.45	-1.32 to 2.68
Pre-morbid history of chronic pain	0.92	0.25	-0.76 to 2.60
Pre-existing psychiatric diagnosis	1.97	**<0.001**	0.88 to 3.07

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Brief Pain Inventory (short form): Pain interference summary: mean pain interference (summary score) (matched regression models)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	4.17	**<0.001**	2.54 to 5.79
Intervention (InS:PIRE)	-0.97	**0.02**	-1.75 to -0.18
Male sex	-0.13	0.69	-0.80 to 0.53
ICU length of stay	0.03	0.15	-0.01 to 0.08
APACHE II score	-0.06	0.05	-0.12 to 0.00
Time to follow-up (months)	0.06	0.26	-0.05 to 0.16
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.35	0.50	-1.42 to 0.72
SIMD quintile 3	-1.01	0.06	-2.08 to 0.07
SIMD quintile 4	-1.64	0.06	-3.34 to 0.07
SIMD quintile 5 (least deprived)	-2.48	**<0.001**	-3.51 to -1.45
Surgery at admission or within seven days of ICU	-0.31	0.44	-1.12 to 0.51
Charlson Comorbidity Index (CCI) score	0.06	0.57	-0.14 to 0.25
History of harmful alcohol or drug use	1.04	0.09	-0.20 to 2.28
Pre-morbid history of chronic pain	1.31	0.07	-0.12 to 2.74
Pre-existing psychiatric diagnosis	1.55	**0.01**	0.53 to 2.57

Linear regression model: Brief Pain Inventory: score range 0 to 10.

Hospital site: fixed and mixed effects models

Fixed effects model

Health utility score model with hospital site fixed effects (hospital site sensitivity analysis)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.76	**<0.001**	0.55 to 0.98
Intervention (InS:PIRE)	0.12	**<0.001**	0.04 to 0.20
Large tertiary referral hospital	0.02	0.61	-0.06 to 0.10
Male sex	0.01	0.72	-0.06 to 0.09
ICU length of stay	0.00	**0.01**	-0.01 to 0.00
APACHE II score	0.00	0.49	-0.01 to 0.00
Time to follow-up (months)	0.06	0.26	-0.05 to 0.16
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD quintile 2	-0.35	0.50	-1.42 to 0.72
SIMD quintile 3	-1.01	0.06	-2.08 to 0.07
SIMD quintile 4	-1.64	0.06	-3.34 to 0.07
SIMD quintile 5 (least deprived)	-2.48	**<0.001**	-3.51 to -1.45
Surgery at admission or within seven days of ICU	-0.31	0.44	-1.12 to 0.51
Charlson Comorbidity Index (CCI) score	0.00	0.93	-0.02 to 0.02
History of harmful alcohol or drug use	-0.09	0.08	-0.20 to 0.01
Pre-morbid history of chronic pain	-0.09	0.09	-0.20 to 0.01
Pre-existing psychiatric diagnosis	-0.17	**<0.001**	-0.26 to -0.08

Health utility score: EQ-5D-5L quality of life indicator with range of -0.594 to 1.0.
Adjusted linear regression model.

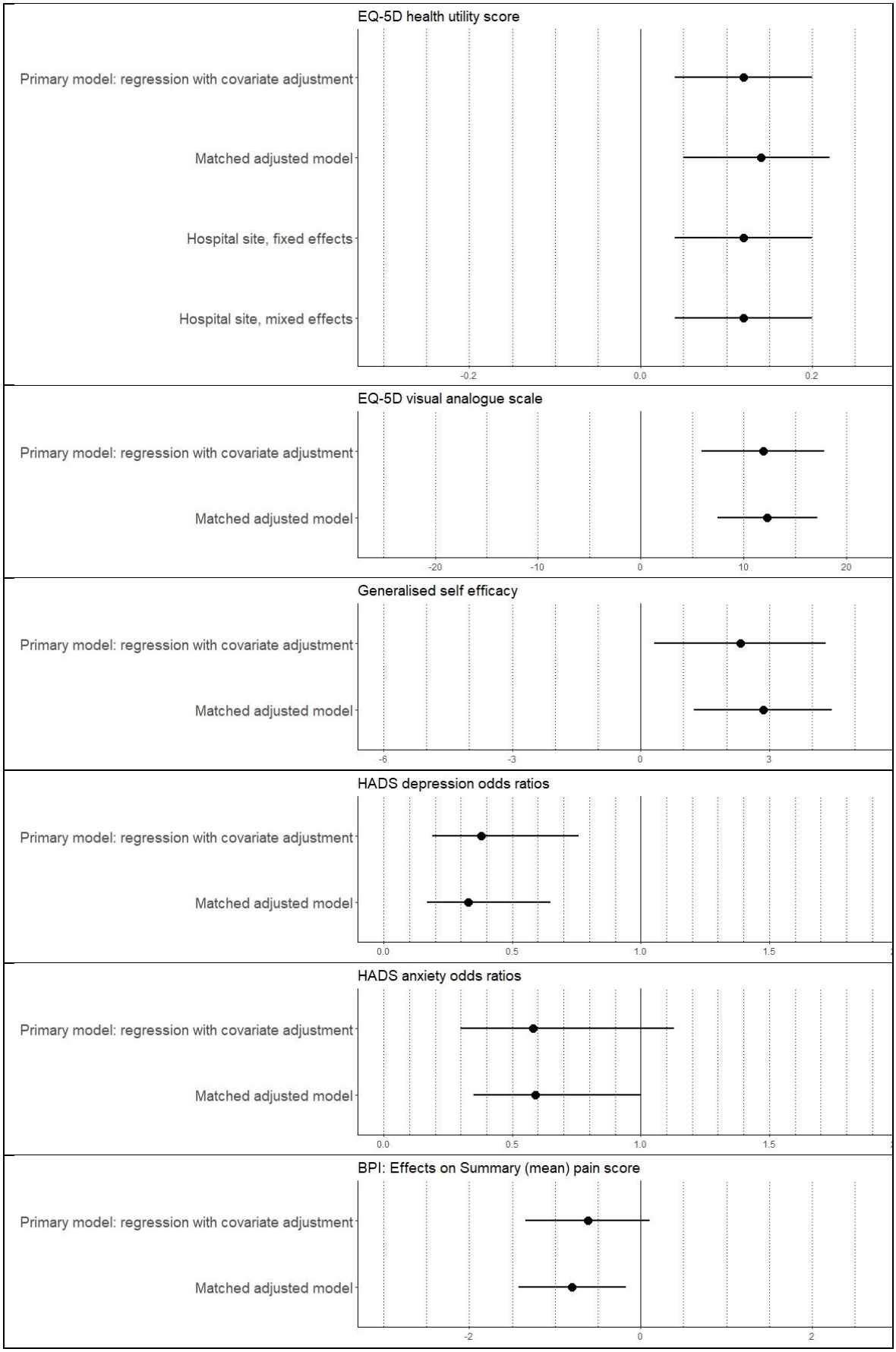
Large tertiary referral hospital fixed effects added to the previous multivariable regression model outlined in the patient outcomes section of the thesis (Chapter 3 and Chapter 4) with the reference being participants treated in an Intensive Care Unit from a medium general acute hospital.

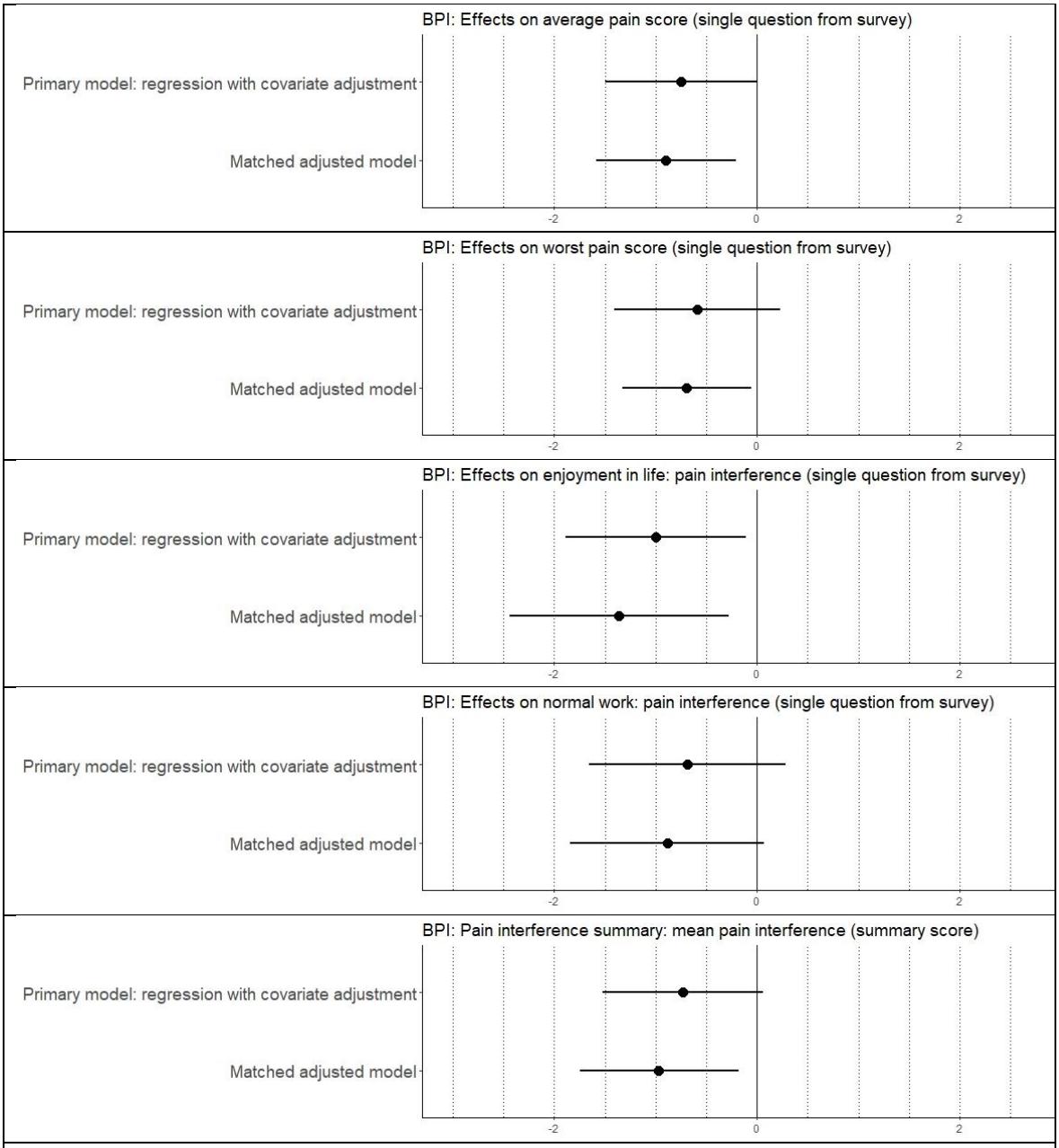
Mixed effects model analysis for hospital clustering
Health utility score model with hospital site, mixed effects: hospital type cluster analysis (hospital site sensitivity analysis)

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.76	**<0.001**	0.55 to 0.98
Intervention (InS:PIRE)	0.12	**<0.001**	0.04 to 0.20
Large tertiary referral hospital	0.02	0.61	-0.06 to 0.10
Male sex	0.01	0.72	-0.06 to 0.09
ICU length of stay	0.00	**0.01**	-0.01 to 0.00
APACHE II score	0.00	0.49	-0.01 to 0.00
Time to follow-up (months)	-0.01	**0.01**	-0.02 to 0.00
SIMD quintile 1 (most deprived)	0	NA	Reference quintile
SIMD Quintile 2	0.02	0.64	-0.07 to 0.12
SIMD Quintile 3	0.08	0.23	-0.05 to 0.20
SIMD Quintile 4	0.14	**0.03**	0.02 to 0.27
SIMD Quintile 5 (least deprived)	0.21	**<0.001**	0.10 to 0.32
Surgery at admission or within seven days of ICU	0.02	0.69	-0.06 to 0.09
Charlson Comorbidity Index (CCI) score	0.00	0.93	-0.02 to 0.02
History of harmful alcohol or drug use	-0.09	0.08	-0.20 to 0.01
Pre-morbid history of chronic pain	-0.09	0.09	-0.20 to 0.01
Pre-existing psychiatric diagnosis	-0.17	**<0.001**	-0.26 to -0.08
Random effects	**Variance: random effects on intercept**		
Large tertiary referral and medium general acute hospital	1.61×10^{-06}		

Health utility score: EQ-5D-5L quality of life indicator with range of -0.594 to 1.0.
Adjusted linear regression model.
Large tertiary referral hospital fixed effects added to the previous multivariable regression model outlined in the patient outcomes section of the thesis (Chapter 3 and Chapter 4) with the reference being participants treated in an Intensive Care Unit from a medium general acute hospital. Addition of hospital type cluster expressed as random effects on both large tertiary referral and medium general acute hospitals.

Forest plots comparing all sensitivity analyses of patient outcomes at one year after hospital discharge





Coefficient graph of effect size. Effect of intervention: absolute change in scores (linear models) and odds risk ratio of screening for the condition one year after hospital discharge compared to usual care. Estimate values (point) and 95% confidence interval. EQ-5D health utility score: EuroQol Health Utility Score, absolute change, taken from EuroQol 5-Dimension 5-level (EQ-5D-5L) 'crosswalk UK scores', range -0.594 to 1.0; EuroQol Visual Analogue Scale (EQ-VAS), absolute change, range 0 to 100; Generalised Self-Efficacy: absolute change, range 10 to 40; HADS: Hospital Anxiety and Depression Scale, individual component scores, odds risk ratios of having anxiety or depression (score ≥8/21 for each component); Brief Pain Inventory (BPI), absolute change in pain scores, all scores range from 0 to 10, average (single component score), worst pain (single component score), and summary score (composite / mean score from four pain scores: 'average', 'worst', 'least' and 'pain right now'); Pain interference scores from BPI, absolute change, scores range from 0 to 10, enjoyment in life (single component), work (single component), and summary pain interference (composite / mean score from seven interference components).

Appendix 11

Unadjusted outcomes from the unmatched cohorts (Chapter 4)

Outcome measure	Usual care cohort (n = 115)	Intervention cohort (n = 137)	P value
EQ-5D summary scores			
Health Utility Score, Median (IQR)	0.648 (0.309 to 0.837)	0.639 (0.528 to 0.790)	0.97
EQ-5D VAS, Median (IQR)	60 (40 to 80)	70 (50 to 86)	**0.04**
Generalised Self-Efficacy, Median (IQR)	31 (25 to 36)	31 (27 to 35)	0.38
Brief Pain Inventory scores			
Summary (mean) pain score (across BPI), median (IQR)	3.50 (1 to 6)	3.25 (0.5 to 6)	0.68
Average pain score (single question), median (IQR)	4 (1 to 6)	4 (0.5 to 5)	0.40
Worst pain score (single question), median (IQR)	4 (1 to 7)	4 (0 to 7)	0.97
Pain interference with enjoyment of life (single question), median (IQR)	3 (0 to 8)	3 (0 to 6)	0.50
Pain interference on normal work (single question), median (IQR)	3 (0 to 8)	4 (0 to 8)	0.98
Mean pain interference summary, median (IQR)	3 (0 to 7)	3 (0 to 6)	0.76
Hospital Anxiety and Depression Scale (HADS)			
Depression score, median (IQR)	6 (2 to 11)	6 (3 to 10)	0.69
Depression, total scoring ≥8/21, total (%)	45/107 (42.1)	49/131 (37.4)	0.47
Anxiety score, median (IQR)	7 (4 to 12)	7 (4 to 12)	0.90
Anxiety, total scoring ≥8/21, total (%)	52/110 (47.3)	59/127 (46.5)	0.90

Unadjusted (and unmatched) testing completed with the Mann-Whitney U test for continuous variables and Pearson's chi-squared test for categorical variables (using non-missing values). EQ-5D: EuroQol 5-Dimension instrument; IQR: Interquartile Range; VAS: Visual Analogue Scale; BPI: Brief Pain Inventory.

Appendix 12

Details of adjusted multivariable models used for specific EQ-5D domain analysis (Chapter 4)

The following tables describe the covariates and their effects for each EuroQol 5-Dimension 5-Level (EQ-5D-5L) domain. These are: mobility; self-care; usual activities; anxiety and depression; and pain and discomfort. Each domain has five levels from one to five. All models are multivariable logistic regression comparing the odds risk of a score of three or greater (≥3/5) within each domain. A score of three is described as moderate problems within the respective domain.

EQ-5D domain: Mobility

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.309	0.15	0.063 to 1.524
Intervention (InS:PIRE)	0.747	0.34	0.408 to 1.367
Male sex	0.875	0.66	0.486 to 1.575
ICU length of stay	1.040	**0.01**	1.008 to 1.072
APACHE II score	0.998	0.93	0.958 to 1.040
Time to follow-up (months)	1.044	0.21	0.976 to 1.116
SIMD quintile 2	0.959	0.91	0.469 to 1.959
SIMD quintile 3	0.882	0.79	0.354 to 2.200
SIMD quintile 4	0.606	0.30	0.234 to 1.570
SIMD quintile 5 (least deprived)	0.204	**0.003**	0.072 to 0.581
Surgery at admission or within seven days of ICU	0.572	0.07	0.311 to 1.054
Charlson Comorbidity Index (CCI) score	1.133	0.12	0.968 to 1.326
History of harmful alcohol or drug use	0.985	0.97	0.442 to 2.196
Pre-morbid history of chronic pain	1.803	0.18	0.766 to 4.244
Pre-existing psychiatric diagnosis	2.154	**0.03**	1.088 to 4.265

Moderate mobility problems or greater (odds ratios): Adjusted logistic regression

Intervention, Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE), effects compared to the usual care cohort; male sex effects compared to female sex; Intensive Care Unit (ICU) length of stay, measured in days, effects per day; Acute Physiology and Chronic Health Evaluation II (APACHE II) score, effects per point increase in score; time to follow-up measured in months, effects per additional month from hospital discharge to follow-up; Scottish Index of Multiple Deprivation, five quintiles, effects are those compared to SIMD quintile 1 (most deprived); surgery at admission or within seven days of ICU, effects of having an operation around time of ICU admission compared to those not having operative management in this time frame; Charlson Comorbidity Index (CCI) score, effects per extra index point score; effects of specific comorbidity conditions of outcome compared to absence of the comorbidity: history of harmful alcohol or drug use, pre-morbid history of chronic pain, pre-existing psychiatric diagnosis.

EQ-5D domain: Self-care

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.097	**0.01**	0.016 to 0.600
Intervention (InS:PIRE)	0.305	**0.002**	0.145 to 0.643
Male sex	1.749	0.15	0.813 to 3.760
ICU length of stay	1.040	**0.02**	1.007 to 1.075
APACHE II score	1.030	0.25	0.979 to 1.083
Time to follow-up (months)	1.038	0.30	0.968 to 1.112
SIMD quintile 2	1.257	0.58	0.561 to 2.814
SIMD quintile 3	0.578	0.37	0.173 to 1.934
SIMD quintile 4	0.195	**0.03**	0.046 to 0.818
SIMD quintile 5 (least deprived)	0.164	**0.03**	0.034 to 0.801
Surgery at admission or within seven days of ICU	0.727	0.41	0.338 to 1.563
Charlson Comorbidity Index (CCI) score	0.881	0.21	0.723 to 1.074
History of harmful alcohol or drug use	1.440	0.43	0.579 to 3.579
Pre-morbid history of chronic pain	2.947	**0.03**	1.139 to 7.625
Pre-existing psychiatric diagnosis	2.417	**0.03**	1.094 to 5.340

Adjusted logistic regression (odds ratios) model of moderate self-care problems or greater.

EQ-5D domain: Usual activities

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.397	0.27	0.077 to 2.048
Intervention (InS:PIRE)	0.616	0.11	0.339 to 1.118
Male sex	0.929	0.80	0.523 to 1.651
ICU length of stay	1.004	0.75	0.977 to 1.032
APACHE II score	0.991	0.67	0.951 to 1.033
Time to follow-up (months)	1.077	0.05	0.999 to 1.162
SIMD quintile 2	0.886	0.74	0.433 to 1.812
SIMD quintile 3	0.772	0.57	0.313 to 1.906
SIMD quintile 4	0.657	0.36	0.267 to 1.617
SIMD quintile 5 (least deprived)	0.289	**0.01**	0.113 to 0.741
Surgery at admission or within seven days of ICU	0.894	0.71	0.493 to 1.621
Charlson Comorbidity Index (CCI) score	1.015	0.84	0.878 to 1.173
History of harmful alcohol or drug use	0.898	0.79	0.404 to 1.996
Pre-morbid history of chronic pain	1.030	0.94	0.448 to 2.369
Pre-existing psychiatric diagnosis	2.765	**0.003**	1.415 to 5.404

Adjusted logistic regression (odds ratios) model of moderate problems with usual activities or greater.

EQ-5D domain: Pain and discomfort

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.604	0.53	0.125 to 2.924
Intervention (InS:PIRE)	0.754	0.36	0.414 to 1.375
Male sex	0.965	0.91	0.536 to 1.737
ICU length of stay	1.018	0.20	0.991 to 1.046
APACHE II score	0.992	0.71	0.953 to 1.033
Time to follow-up (months)	1.028	0.42	0.962 to 1.098
SIMD quintile 2	0.695	0.33	0.337 to 1.437
SIMD quintile 3	0.564	0.22	0.224 to 1.419
SIMD quintile 4	0.498	0.15	0.192 to 1.290
SIMD quintile 5 (least deprived)	0.213	**0.002**	0.082 to 0.553
Surgery at admission or within seven days of ICU	0.782	0.44	0.418 to 1.462
Charlson Comorbidity Index (CCI) score	1.115	0.16	0.958 to 1.298
History of harmful alcohol or drug use	1.810	0.16	0.784 to 4.182
Pre-morbid history of chronic pain	2.451	**0.049**	1.005 to 5.974
Pre-existing psychiatric diagnosis	2.046	**0.04**	1.036 to 4.039

Adjusted logistic regression (odds ratios) model of moderate problems with pain and / or discomfort or greater.

EQ-5D domain: Anxiety and depression

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.968	0.97	0.165 to 5.666
Intervention (InS:PIRE)	0.667	0.26	0.331 to 1.346
Male sex	0.936	0.86	0.460 to 1.908
ICU length of stay	1.028	0.08	0.996 to 1.060
APACHE II score	0.981	0.44	0.936 to 1.029
Time to follow-up (months)	1.027	0.47	0.956 to 1.103
SIMD quintile 2	0.455	**0.048**	0.208 to 0.993
SIMD quintile 3	0.371	0.07	0.129 to 1.073
SIMD quintile 4	0.308	0.03	0.105 to 0.90
SIMD quintile 5 (least deprived)	<0.001	1.0	0 to Inf*
Surgery at admission or within seven days of ICU	0.373	**0.009**	0.178 to 0.784
Charlson Comorbidity Index (CCI) score	0.899	0.24	0.751 to 1.076
History of harmful alcohol or drug use	2.543	**0.04**	1.043 to 6.196
Pre-morbid history of chronic pain	1.203	0.70	0.463 to 3.130
Pre-existing psychiatric diagnosis	2.873	**0.005**	1.374 to 6.008

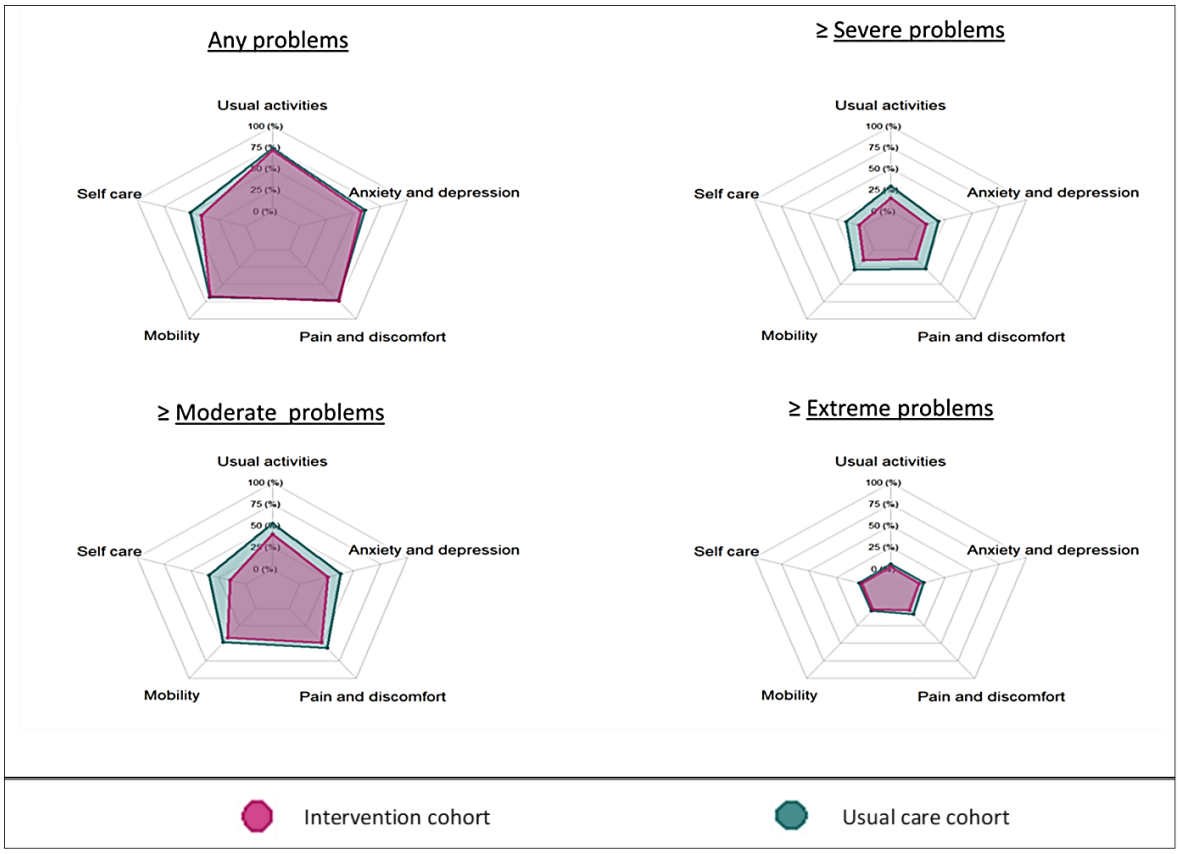
Adjusted logistic regression (odds ratios) model of moderate anxiety and / or depression or greater.*Note no patients classified as SIMD quintile 5 reported an anxiety or depression score ≥3 /5 (moderate or greater) on the EQ-5D-5L. Therefore, the model could not estimate this effect and infinity was included in the 95% confidence interval. See next page for full breakdown.

Comparison of EQ-5D emotional health vs SIMD

		Scottish Index of Multiple Deprivation (SIMD) quintile				
		1 (most deprived)	2	3	4	5, (least deprived)
EQ-5D-5L domain: Anxiety or depression problems	Nil or mild problems, score 1 or 2	40 (49%)	42 (67%)	24 (75%)	25 (78%)	38 (100%)
	Moderate problems or greater, score 3, 4, or 5	42 (51%)	21 (33%)	8 (25%)	7 (22%)	0 (0%)

N is the count of patients in each cross tabulation category. Percentages are the proportion of each SIMD class experiencing moderate anxiety or depression or greater at one year post critical illness.

EQ-5D domain breakdown by severity in the matched cohorts



Appendix 13

Comparison between the characteristics of the 136 patients who had a consenting caregiver attend with them to InS:PIRE vs the 69 patients who attended InS:PIRE without a consenting caregiver.

Demographic **Patient participant characteristics for those attending InS:PIRE**	**Participants without consenting caregivers** **(n = 69)**	**Participants with consenting caregivers** **(n = 136)**	**P value**
Age, Years, Median (IQR)	56.5 (50.2 to 65.7)	58.5 (49.3 to 65.7)	0.91
Male sex, n (%)	37 (53.6)	75 (55.1)	0.84
Admitting specialty, n (%):			0.17
Medical	46 (66.7)	77 (56.6)	
Surgery	23 (33.3)	59 (43.4))	
Surgery at ICU admission or within one week of admission, n (%)	18 (26.1)	46 (33.8)	0.23
ICU length of stay, Median (IQR)	8.9 (5.9 to 15.5)	11.7 (6.7 to 19.1)	**0.03**
Hospital Length of stay, Median (IQR)	28.5 (13.8 to 41.8)	31.0 (17.0 to 52.7)	0.22
APACHE II score, Median (IQR)	20 (15 to 24)	19.5 (15 to 25)	0.76
Advanced respiratory support, n (%)	55 (79.7)	125 (91.9)	**0.01**
Two or greater comorbidities, n (%)	37 (53.6)	57 (41.9)	0.11
Pre-existing psychiatric diagnosis, n (%)	28 (40.6)	40 (29.4)	0.11
History of harmful alcohol or drug use, n (%)	25 (36.3)	27 (19.9)	**0.01**
Pre-morbid history of chronic pain, n (%)	16 (23.2)	31 (22.8)	0.95
Deprivation index, SIMD 2016, n (%):			**0.03**
Quintile 1 (most deprived)	36 (52.2)	47 (34.6)	
Quintile 2	18 (26.1)	32 (23.5)	
Quintile 3	5 (7.2)	26 (19.1)	
Quintile 4	7 (10.1)	15 (11.0)	
Quintile 5 (least deprived)	3 (4.3)	16 (11.8)	

ICU: Intensive Care Unit; APACHE II: Acute Physiology and Chronic Health Evaluation Two; SIMD: Scottish index of multiple deprivation. Statistical tests: Pearson's chi-squared test for categorical variables; Mann-Whitney U Test for continuous variables.

Note the participant flow (Figure 5-1) describes 70 patients who attended InS:PIRE but did not have a consenting caregiver. However, one patient was lost to follow-up before reliable baseline data were collected and as such only 69 participants are included in the analysis of those who attended InS:PIRE but did not have a consenting caregiver.

Appendix 14

Caregiver one-year outcome models (Chapter 5)

All of the caregiver outcomes were modelled using logistic regression, generating odds risk ratios. The following appendix outlines the details of each model. The variables included in the models is as follows:

Details of variables included in the models:

- Intervention = Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE), effects compared to the usual care cohort.
- Relationship with the patient. Partner or spouse used as the reference and the effect size is that of another relationship compared to partner/spouse.
- Caregiver age: effect per each additional year.
- Caregiver male sex: effect compared to female sex as reference.
- Time to follow-up measured in months, effects per additional month from (patient) hospital discharge to caregiver follow-up
- Scottish Index of Multiple Deprivation, five quintiles (SIMD), effects are those compared to SIMD quintile 1 (most deprived)
- Hospital length of stay: Effects per each additional day the patient was treated in hospital.
- Patient age: effect per each additional year.
- Patient pre-existing psychiatric or mental health diagnosis: effect if present compared to this characteristic not being present.

Definition of condition present for all models

- Anxiety = HADS-A ≥8/21
- Depression = HADS-D ≥8/21
- Insomnia = ISI ≥8/28
- Caregiver strain = CSI ≥7/13

Caregiver anxiety logistic regression model: Primary (original) model odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	8.43	0.09	0.73 to 97.73
Intervention (InS:PIRE)	0.42	**0.02**	0.20 to 0.89
Relationship with the patient (other vs partner or spouse)	0.74	0.50	0.32 to 1.76
Caregiver age	0.96	**0.03**	0.92 to 0.99
Caregiver male sex	0.81	0.58	0.38 to 1.71
Time to follow-up (per month)	1.07	0.15	0.98 to 1.17
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	0.72	0.53	0.26 to 2.03
SIMD quintile 3	1.37	0.58	0.45 to 4.12
SIMD quintile 4	1.22	0.75	0.37 to 4.05
SIMD quintile 5 (least deprived)	0.77	0.64	0.25 to 2.36
Hospital length of stay (patient characteristic)	1.01	0.31	0.99 to 1.02
Patient age	0.99	0.55	0.96 to 1.02
Patient pre-existing psychiatric or mental health diagnosis	2.80	**0.04**	1.06 to 7.39

Caregiver depression logistic regression model: Primary (original) model odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.84	0.88	0.08 to 8.30
Intervention (InS:PIRE)	0.58	0.19	0.26 to 1.31
Relationship with the patient (other vs partner or spouse)	0.53	0.19	0.21 to 1.38
Caregiver age	0.97	0.07	0.93 to 1.00
Caregiver male sex	0.97	0.95	0.44 to 2.16
Time to follow-up (per month)	1.04	0.29	0.97 to 1.12
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	0.95	0.93	0.33 to 2.80
SIMD quintile 3	1.89	0.30	0.57 to 6.29
SIMD quintile 4	1.53	0.53	0.41 to 5.69
SIMD quintile 5 (least deprived)	0.68	0.62	0.14 to 3.31
Hospital length of stay (patient characteristic)	1.00	0.58	0.99 to 1.02
Patient age	1.00	0.89	0.97 to 1.04
Patient pre-existing psychiatric or mental health diagnosis	3.60	**0.008**	1.41 to 9.16

Caregiver Strain Index logistic regression model: Primary (original) model odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	2.32	0.51	0.19 to 28.59
Intervention (InS:PIRE)	0.39	**0.04**	0.16 to 0.98
Relationship with the patient (other vs partner or spouse)	1.89	0.17	0.77 to 4.67
Caregiver age	0.98	0.18	0.94 to 1.01
Caregiver sex (male vs female)	0.53	0.15	0.22 to 1.26
Time to follow-up (per month)	1.02	0.60	0.93 to 1.13
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	1.45	0.51	0.47 to 4.54
SIMD quintile 3	1.07	0.92	0.26 to 4.42
SIMD quintile 4	1.19	0.81	0.30 to 4.67
SIMD quintile 5 (least deprived)	0.78	0.73	0.18 to 3.27
Hospital length of stay (patient characteristic)	1.01	0.34	0.99 to 1.02
Patient age	0.98	0.20	0.95 to 1.01
Patient pre-existing psychiatric or mental health diagnosis	3.57	**0.007**	1.43 to 3.57

Insomnia Severity Index logistic regression model: Primary (original) model odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	6.76	0.10	0.67 to 67.94
Intervention (InS:PIRE)	0.36	**0.009**	0.17 to 0.77
Relationship with the patient (other vs partner or spouse)	0.69	0.40	0.29 to 1.65
Caregiver age	0.98	0.34	0.95 to 1.02
Caregiver sex (male vs female)	0.45	**0.047**	0.21 to 0.99
Time to follow-up (per month)	1.02	0.59	0.94 to 1.11
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	0.55	0.26	0.19 to 1.58
SIMD quintile 3	0.77	0.66	0.23 to 2.54
SIMD quintile 4	1.29	0.69	0.36 to 4.65
SIMD quintile 5 (least deprived)	0.52	0.26	0.17 to 1.62
Hospital length of stay (patient characteristic)	1.01	0.30	0.99 to 1.02
Patient age	0.99	0.48	0.96 to 1.02
Patient pre-existing psychiatric or mental health diagnosis	5.84	**<0.001**	2.11 to 16.14

Sensitivity analyses: caregiver age removed from the models

Caregiver anxiety logistic regression model: models with caregiver age removed odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	2.52	0.39	0.30 to 20.82
Intervention (InS:PIRE)	0.39	**0.01**	0.19 to 0.81
Relationship with the patient (other vs partner or spouse)	1.24	0.59	0.57 to 2.67
Caregiver male sex	0.73	0.39	0.36 to 1.50
Time to follow-up (per month)	1.07	0.11	0.98 to 1.16
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	0.80	0.65	0.30 to 2.14
SIMD quintile 3	1.26	0.67	0.44 to 3.59
SIMD quintile 4	1.01	0.98	0.31 to 3.27
SIMD quintile 5 (least deprived)	0.72	0.55	0.24 to 2.18
Hospital length of stay (patient characteristic)	1.01	0.21	1.00 to 1.02
Patient age	0.97	**0.008**	0.94 to 0.99
Patient pre-existing psychiatric or mental health diagnosis	2.34	0.06	0.96 to 5.72

Caregiver depression logistic regression model: models with caregiver age removed odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.39	0.38	0.05 to 3.25
Intervention (InS:PIRE)	0.53	0.12	0.24 to 1.18
Relationship with the patient (other vs partner or spouse)	0.74	0.49	0.31 to 1.76
Caregiver male sex	0.89	0.78	0.41 to 1.96
Time to follow-up (per month)	1.05	0.23	0.97 to 1.13
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	0.97	0.96	0.34 to 2.76
SIMD quintile 3	1.76	0.34	0.55 to 5.58
SIMD quintile 4	1.28	0.70	0.35 to 4.63
SIMD quintile 5 (least deprived)	0.61	0.52	0.13 to 2.92
Hospital length of stay (patient characteristic)	1.01	0.49	0.99 to 1.02
Patient age	0.98	0.21	0.96 to 1.01
Patient pre-existing psychiatric or mental health diagnosis	3.20	**0.01**	1.33 to 7.74

Caregiver Strain Index logistic regression model: models with caregiver age removed odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	1.13	0.91	0.12 to 10.80
Intervention (InS:PIRE)	0.37	**0.03**	0.15 to 0.91
Relationship with the patient (other vs partner or spouse)	2.39	**0.04**	1.05 to 5.41
Caregiver sex (male vs female)	0.50	0.12	0.21 to 1.19
Time to follow-up (per month)	1.03	0.55	0.93 to 1.13
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	1.49	0.49	0.48 to 4.58
SIMD quintile 3	1.03	0.97	0.26 to 4.13
SIMD quintile 4	1.02	0.97	0.27 to 3.93
SIMD quintile 5 (least deprived)	0.71	0.63	0.17 to 2.93
Hospital length of stay (patient characteristic)	1.01	0.29	0.99 to 1.02
Patient age	0.97	**0.03**	0.94 to 1.00
Patient pre-existing psychiatric or mental health diagnosis	3.22	**0.01**	1.32 to 7.86

Insomnia Severity Index logistic regression model: models with caregiver age removed odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	4.22	0.17	0.52 to 34.08
Intervention (InS:PIRE)	0.35	**0.007**	0.16 to 0.74
Relationship with the patient (other vs partner or spouse)	0.85	0.68	0.38 to 1.88
Caregiver age			
Caregiver sex (male vs female)	0.44	**0.04**	0.21 to 0.95
Time to follow-up (per month)	1.02	0.53	0.95 to 1.11
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	0.57	0.29	0.20 to 1.62
SIMD quintile 3	0.76	0.64	0.24 to 2.46
SIMD quintile 4	1.22	0.75	0.34 to 4.38
SIMD quintile 5 (least deprived)	0.51	0.24	0.17 to 1.58
Hospital length of stay (patient characteristic)	1.01	0.26	0.99 to 1.02
Patient age	0.98	0.10	0.96 to 1.00
Patient pre-existing psychiatric or mental health diagnosis	5.38	**0.001**	1.99 to 14.53

Sensitivity analyses: Original model with 30 imputations

Caregiver anxiety logistic regression model: Original model with 30 imputations odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	9.15	0.07	0.83 to 100.86
Intervention (InS:PIRE)	0.41	**0.02**	0.19 to 0.87
Relationship with the patient (other vs partner or spouse)	0.79	0.60	0.33 to 1.90
Caregiver age	0.96	**0.02**	0.92 to 0.99
Caregiver male sex	0.80	0.54	0.38 to 1.68
Time to follow-up (per month)	1.06	0.20	0.97 to 1.15
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	0.81	0.69	0.29 to 2.31
SIMD quintile 3	1.52	0.46	0.49 to 4.75
SIMD quintile 4	1.29	0.68	0.39 to 4.32
SIMD quintile 5 (least deprived)	0.72	0.56	0.24 to 2.14
Hospital length of stay (patient characteristic)	1.01	0.34	0.99 to 1.02
Patient age	0.99	0.48	0.96 to 1.02
Patient pre-existing psychiatric or mental health diagnosis	2.66	**0.04**	1.07 to 6.61

Caregiver depression logistic regression model: Original model with 30 imputations odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	0.85	0.89	0.08 to 8.75
Intervention (InS:PIRE)	0.57	0.18	0.25 to 1.30
Relationship with the patient (other vs partner or spouse)	0.56	0.24	0.21 to 1.48
Caregiver age	0.97	0.09	0.93 to 1.01
Caregiver male sex	0.96	0.92	0.43 to 2.14
Time to follow-up (per month)	1.04	0.30	0.97 to 1.12
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	1.14	0.81	0.39 to 3.37
SIMD quintile 3	2.11	0.21	0.65 to 6.92
SIMD quintile 4	1.72	0.41	0.47 to 6.25
SIMD quintile 5 (least deprived)	0.60	0.47	0.14 to 2.47
Hospital length of stay (patient characteristic)	1.00	0.62	0.99 to 1.02
Patient age	1.00	0.94	0.97 to 1.04
Patient pre-existing psychiatric or mental health diagnosis	3.58	**0.006**	1.46 to 8.78

Caregiver Strain Index logistic regression model: Original model with 30 imputations odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	2.04	0.56	0.18 to 22.69
Intervention (InS:PIRE)	0.40	**0.04**	0.16 to 0.96
Relationship with the patient (other vs partner or spouse)	1.91	0.16	0.78 to 4.70
Caregiver age	0.97	0.17	0.94 to 1.01
Caregiver sex (male vs female)	0.54	0.17	0.22 to 1.30
Time to follow-up (per month)	1.04	0.34	0.96 to 1.12
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	1.41	0.55	0.46 to 4.31
SIMD quintile 3	1.19	0.80	0.31 to 4.55
SIMD quintile 4	1.25	0.75	0.31 to 4.96
SIMD quintile 5 (least deprived)	0.72	0.64	0.18 to 2.88
Hospital length of stay (patient characteristic)	1.01	0.45	0.99 to 1.02
Patient age	0.98	0.20	0.95 to 1.01
Patient pre-existing psychiatric or mental health diagnosis	3.50	**0.007**	1.41 to 8.66

Insomnia Severity Index logistic regression model: Original model with 30 imputations odds risk ratios

Covariate	Effect estimate	P value	95% confidence interval
Intercept	7.04	0.10	0.67 to 74.18
Intervention (InS:PIRE)	0.36	**0.01**	0.17 to 0.78
Relationship with the patient (other vs partner or spouse)	0.73	0.50	0.29 to 1.82
Caregiver age	0.99	0.48	0.95 to 1.02
Caregiver sex (male vs female)	0.46	**0.046**	0.21 to 0.99
Time to follow-up (per month)	1.02	0.61	0.94 to 1.10
SIMD quintile 1 (most deprived)	1	NA	Reference quintile
SIMD quintile 2	0.52	0.22	0.19 to 1.48
SIMD quintile 3	0.84	0.75	0.28 to 2.51
SIMD quintile 4	1.25	0.73	0.35 to 4.44
SIMD quintile 5 (least deprived)	0.42	0.13	0.14 to 1.31
Hospital length of stay (patient characteristic)	1.01	0.32	0.99 to 1.02
Patient age	0.99	0.38	0.96 to 1.02
Patient pre-existing psychiatric or mental health diagnosis	5.32	**0.001**	1.94 to 14.56

Appendix 15

Cost-effectiveness estimates for the InS:PIRE programme, with assumptions and calculations for each assessment.

Assumptions	Worst-case scenario	Central estimate	Best-case scenario
Cost per cohort:	£12,500	**£10,000**	£9,000
Patients per cohort:	5	**8**	12
Cost per patient:	£2,500	**£1,300**	£750
Point estimate of effect on quality of life:	0.12	**0.12**	0.12
Maximum effect duration:	3 years	**5 years**	10 years
Effect change over time (year-on-year reduction):	50%	**25%**	20%
Cummulative effect size:	0.21	**0.37**	0.54
QALY cost	**£12,000**	**£3,400**	**£1,400**

QALY: Quality Adjusted Life Year. Note all values are rounded to two significant figures or £500.

The calculations above are based on cost estimates for running a single cohort of InS:PIRE. This was estimated to cost the employer (NHS) £10,000 per cohort, which included £9,700 to cover staff salaries, holiday pay, national insurance contributions, and pension contributions (see Appendix 6). The additional £300 was to cover associated administration and sundries. There were no costings for accommodation or outpatient clinic space as the services developed as part of this thesis were not required to pay for this. The worst-case scenario estimate allows a further £2,500 of additional costs per cohort, which could include accommodation expenses, additional patient transfer costs, unexpected staff overtime, staff sickness, or locum costs. This estimate also assumes that only five participants will attend each cohort that could be the case for InS:PIRE services being delivered from smaller ICUs. The best-case scenario reduces the costs by 10% which could be done with reduced patient contact time e.g. running the cohort over fewer weeks or only having 3 hours paid contact time per week. This also assumes 12 patients per cohort.

The calculation of "cumulative effect size" assumed a QoL effect per patient (as per Chapter 4) of 0.12 for the first year after InS:PIRE as measured by the EuroQol EQ-5D-5L health utility score UK crosswalk figures. For each subsequent year included in the analysis this figure (0.12) was reduced by the fraction outlined in the "effect change over time" row. The "cumulative effect size" was then simply an addition of the estimated effect per year up to the maximum expected duration of effect (estimated effect range: 3 to 10 years). After this the cost of delivering the intervention per patient was divided by this cumulative effect size. Thus, a single figure for the cost of one additional Quality Adjusted Life Year (QALY) associated with attendance at InS:PIRE was calculated.

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