Aus dem
CharitéCentrum 1 für Human- und Gesundheitswissenschaften
Institut für Allgemeinmedizin
Direktor: Prof. Dr. Christoph Heintze, MPH

# Habilitationsschrift:

# „Hausärztliche Versorgung nach Intensivtherapie“

zur Erlangung der Lehrbefähigung
für das Fach Allgemeinmedizin

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von

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geboren in Rehren

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## IN DIESE KUMULATIVE SCHRIFT EINGEHENDE ARBEITEN

1. Mehlhorn J, Freytag A, **Schmidt K**, Brunkhorst FM, Graf J, Troitzsch U, Schlattmann P, Wensing M, Gensichen J. Rehabilitation interventions for post intensive care syndrome. A systematic review. *Crit Care Med* 2014;42(5):1263-71. doi: 10.1097/CCM.0000000000000148.

2. **Schmidt K**, Thiel P, Mueller F et al. Sepsis survivors monitoring and coordination in outpatient health care (SMOOTH): Study protocol for a randomized controlled trial. *Trials* 2014;15(1):283 (IF: 3,22). doi: 10.1186/1745-6215-15-283.

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# INHALTSVERZEICHNIS

# ABKÜRZUNGEN

| | |
|---|---|
| AUROC | Area Under the Receiver Operating Characteristic |
| CIM | Critical Illness Myopathy |
| CI | Confidence Interval |
| CIP | Critical Illness Polyneuropathy |
| DMP | Disease Management Program |
| ERIC | Enhanced Recovery after Intensive Care |
| GCPS | Graded Chronic Pain Scale |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluation |
| HRQoL | Health-related Quality of Life |
| (I)ADL | (Instrumental) Activities of Daily Living |
| ICD | International Classification of Diseases |
| ICU | Intensive Care Unit |
| iTAU | Improved Treatment As Usual |
| ITS | Intensivstation |
| KFM | Kurzfragebogen zum Medikamentengebrauch |
| MDI | Major Depression Inventory |
| MUST | Malnutrition Universal Screening Tool |
| NET | Narrative Expositionstherapie |
| NSS | NeuropathySymptom Score |
| PDS | Posttraumatic Diagnostic Scale |
| PICS | Post Intensive Care Syndrome |
| PICTURE | PTSD after ICU Survival, Caring for Patients with Traumatic Stress Sequelae following Intensive Medical Care |

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|---|---|
| PTSD | Posttraumatic Stress Disorder |
| PTSS-10 | Posttraumatic Stress Syndrome 10-Questions Inventory |
| PZN | Pharmazentralnummer |
| RCT | Randomized Controlled Trial |
| SF-36 | Short Form 36 Health Survey |
| BP | Bodily Pain |
| PCS | Physical Component Score |
| PF | Physical Functioning |
| RP | Physical Role |
| SMOOTH | Sepsis survivors Monitoring and cOordination in OutpatienT Healthcare |
| TICS-M | Modified Telephone Interview for Cognitive Status |
| XSFMA | Extra Short Musculoskeletal Function Assessment |

# 1. EINLEITUNG*

## 1.1 Klinische Residuen nach Intensivtherapie

Dank fortgeschrittener Intensivmedizin überleben zunehmend mehr Patienten# kritische Erkrankungen wie die schwere Sepsis und kehren – meist nach einer Phase der Rehabilitation – in die ambulante Versorgung zurück [1]. Viele dieser Überlebenden leiden noch über Monate oder Jahre unter multiplen organischen wie mentalen Residuen. Mit dem Terminus „PostIntensive Care Syndrome“ (PICS) wurde hierfür auf einer Konsensuskonferenz 2012 erstmals eine Entität geschaffen [3].

Bei allein in Deutschland jährlich zwei Millionen intensivmedizinischen Behandlungsfällen [4] ist das Krankheitsbild kein Randphänomen. Durch die zu erwartende Zunahme des Anteils multimorbider Patienten – bedingt durch den demographischen Wandel und weitere technische Innovationen in der Intensivmedizin – ist von einer zukünftig noch steigenden Inzidenz auszugehen. Zusätzlich verstärkt wird diese Entwicklung durch die gegenwärtige SARS-CoV-2-Pandemie: Die britische Gesellschaft für Physiotherapie sagt gar einen „Tsunami“ an Rehabilitationsanforderungen voraus [5]. Längst hat die Thematik damit auch hausärztliche Relevanz erreicht, wird doch ein Großteil der Patienten nach Intensivtherapie im Langzeitverlauf hausärztlich versorgt, wie es bei den meisten chronisch Erkrankten der Fall ist [6]. Durch die langjährige Arzt-Patient-Beziehung besteht in der Hausarztmedizin oft ein ausgeprägtes Vertrauensverhältnis mit tiefem Verständnis der klinischen Verläufe und der psychosozialen Biographie der Patienten. Somit kommt dem Hausarzt eine Schlüsselrolle in der Behandlung von post-ITS-Komplikationen zu.

* Stark modifiziert aus den eigenen Arbeiten [1] und [2] entnommen, mit freundlicher Genehmigung des Medicom Verlags GmbH sowie des Ith-Verlages.

# Stets sind Personen männlichen und weiblichen Geschlechts gleichermaßen gemeint. Aus Gründen der einfacheren Lesbarkeit wird im Folgenden nur das generische Maskulinum verwendet.

## 1.2 Krankheitsbilder und therapeutische Konsequenzen

Exemplarisch sollen hier einige typische Krankheitsbilder nach Intensivtherapie genannt werden, die in der Literatur häufig beschrieben sind, einschließlich zentraler Implikationen für die hausärztliche Praxis (entnommen aus der eigenen Arbeit [2]):

- „Entzündungsbedingte Läsionen von Muskeln und peripheren Nerven sind unter den Begriffen Critical Illness Polyneuropathie (CIP) und Critical Illness Myopathie (CIM) seit mehr als zwei Jahrzehnten bekannt [7]. Viele Patienten leiden an Langzeitfolgen wie Muskelschwäche oder Sensibilitätsstörungen. Der Verlauf ist nur schwer zu beeinflussen, regelmäßige neurologische Untersuchungen und die ausreichende Verordnung von Physiotherapie sind die wichtigsten Maßnahmen durch den Hausarzt.

- Vor allem durch die neuropathische Komponente (s.o.) ist die Inzidenz von chronischen Schmerzen nach schwerer Sepsis signifikant erhöht [8]. Durch die Einbeziehung von Antikonvulsiva und/ oder Antidepressiva kann der Hausarzt die analgetische Pharmakotherapie unter engmaschiger Symptomkontrolle entsprechend anpassen.

- Durch Steigerung des Energieumsatzes und Immobilisierung auf der Intensivstation sowie dem Muskelabbau im Rahmen einer Myopathie (s.o.) kann bei vielen Patienten eine auch über Monate persistierende Kachexie beobachtet werden. Die regelmäßige Abfrage des Körpergewichtes und ggf. eine Ernährungsberatung sollten so zum Standard der Intensivnachsorge gehören.

- Inflammatorische Mediatoren, ein inadäquater zerebraler Perfusionsdruck, Veränderungen der Blut-Hirn-Schranke und weitere Faktoren führen zum Vollbild einer septischen Enzephalopathie, die sich klinisch ähnlich einer Alzheimer-Demenz äußern kann [9]. Bei auch hier fehlenden kausalen Therapieansätzen stehen in der hausärztlichen Versorgung die Komplettierung der Demenzdiagnostik und die Mithilfe bei der Organisation des Lebensumfeldes im Vordergrund, sowie der Ausschluss therapierbarer Differentialdiagnosen wie einer Hypothyreose oder eines Normaldruckhydrozephalus.

- Durch ein intensivtherapeutisch bedingtes Delirium und die perihospitalen funktionellen Einschränkungen werden die Patienten extremem Stress exponiert. So scheint der Aufenthalt auf einer Intensivstation auf viele Patienten eine ähnlich traumatisierende Wirkung zu haben wie die Erfahrung von Gewalt oder Krieg [10]. Da die Erstmanifestation [posttraumatischer Symptome] bis zu sechs Monate nach dem traumatisierenden Ereignis auftreten kann, kommt der hausärztlichen Behandlung gerade hier eine Schlüsselrolle zu. Aktives Nachfragen und ein rechtzeitiger Therapiebeginn können die Prognose einer posttraumatischen Belastungsstörung (PTBS) entscheidend verbessern.

- Durch die häufig folgenden funktionellen wie sozialen Einschränkungen ist auch das Auftreten von depressiven Symptomen nach Entlassung von der Intensivstation gut belegt [11]. Je nach Schweregrad sind die Initiierung von Psychotherapie und die Gabe von Antidepressiva durch den Hausarzt indiziert."

- Schließlich hat etwa ein Drittel der Patienten mit langfristiger mechanischer Beatmung anhaltende Schluckbeschwerden [12], was das Risiko für Aspiration und Pneumonie erhöht. Die aufmerksame Beobachtung des Schluckaktes in der Sprechstunde sowie eine ggf. umgehende Überweisung in die Logopädie sind die wichtigsten Konsequenzen für die hausärztliche Praxis [13].

## 1.3 Herausforderungen im Versorgungsprozess

Identifikation und Zuordnung der oben beschriebenen Krankheitsbilder sind nicht trivial, da sich die Symptome häufig mit denen weiterer chronischer Erkrankungen multimorbider Patienten überschneiden: So können die polyneuropathische Symptome einer CIP auch der diabetischen Polyneuropathie eines Diabetikers zugeordnet werden, der Kognitionsverlust durch die septische Enzephalopathie einer beginnenden Alzheimer-Demenz. Die Behandlung der intensivmedizinischen Spätfolgen wurde so in der Vergangenheit oft gegenüber den Grunderkrankungen vernachlässigt. Erschwerend hinzu kommt die häufig fragmentierte Versorgung dieser Patienten zwischen Intensiv-, Rehabilitations- und Primärmedizin. Viele Informationen gehen bei der Über- und Einweisung zwischen den Versorgungssektoren verloren. Nur wenige Hausärzte verfügen über eigene intensivmedizinische

Arbeitserfahrungen, um die Symptomatik ihrer Patienten mit der Phase der intensivmedizinischen Akutbehandlung in Verbindung zu bringen. Dazu ist die Behandlung des PICS bislang kein allgemeinmedizinischer Ausbildungsinhalt, nur wenige Hausärzte fühlen sich adäquat auf diese Aufgabe vorbereitet [14].

## 1.4 Post-ICU Ambulanzen

International wurden bereits verschiedene Ansätze zur Versorgung von ITS-Überlebenden entwickelt, zu erwähnen sind vor allem wie die sogenannten *ICU follow-up*-Ambulanzen:

„Vorreiter ist Großbritannien – bereits 1993 wurde in Reading eine solche Einrichtung ins Leben gerufen. 48 (27 %) von 182 befragten britischen Krankenhäusern gaben an, Nachsorgetermine anzubieten, 10 verfügen über eigene Rehabilitationsprogramme [15]. Die Organisation liegt meistens im pflegerischen Bereich, Zielgruppe sind Patienten nach mehr als dreitägigem Intensivaufenthalt. Etwa ein Drittel der Zentren vermittelt auch physiotherapeutische und psychologische Therapien [16]. Die erste *ICU follow-up*-Ambulanz in den Vereinigten Staaten wurde 2011 als *Critical Care Recovery Center* an der *Indiana University*, Indianapolis, gegründet [17], fokussiert auf geriatrische Patienten mit depressiven und posttraumatischen Symptomen. 2012 folgte das *ICU Recovery Center* an der *Vanderbilt University* in Nashville/Tennessee [18]: In einem breiten, multidisziplinären Ansatz werden hier sowohl pulmonale, kognitive, (neuro-)psychologische, pharmakologische als auch soziale und alltagspraktische Aspekte in einer ein- bis zweistündigen Konsultation evaluiert, mit abschließendem Behandlungsplan für die weitere ambulante Versorgung. Einbezogen werden alle Patienten nach Sepsis, ARDS, Delirium oder mechanischer Beatmung.“ (Schmidt et al., Intensiv-News 2016, S. 26f [1]).

Auch an der Charité wurde 2018 – hervorgegangen aus dem ERIC-Projekt des Innovationsfonds [19] – durch die Klinik für Anästhesiologie mit Schwerpunkt operative Intensivmedizin eine „Hochschulambulanz für *Post Intensive Care Syndrome*“ initiiert [20]. Hier wird der Rehabilitationsbedarf durch ein interdisziplinäres Team aus Intensivmedizinern, Neurologen, Psychologen und Physiotherapeuten drei und sechs Monate nach Entlassung von der Intensivstation überprüft.

Eine flächendeckende Versorgung mit solchen Ambulanzen ist für Deutschland allerdings noch lange nicht in Sicht. Dazu scheint die Verstetigung all jener Ambulanzen problematisch: Als Barrieren für eine weitere Ausweitung werden fehlende Finanzierungsmodelle, ungenügend ausgebildetes Personal und die logistisch schwierige Zuweisung der auf Normalstation oder in eine Rehaklinik verlegten Patienten angegeben [15]. Schließlich ergab sich für *ICU follow-up*-Ambulanzen in randomisiert-kontrollierten Studien bislang keine eindeutige Evidenz zu Wirksamkeit, Kosteneffizienz, Frequenz der Konsultationen, Definition der genauen Zielgruppe sowie Intensität und Auswahl geeigneter Interventionen [21].

## 1.5 Zielsetzung und Aufbau der Habilitationsschrift

So wird die Nachsorge für einen Großteil der betroffenen Patienten absehbar weiterhin durch den Hausarzt erfolgen. Angesichts des oben beschriebenen Versorgungsdefizites und der zu erwartenden steigenden Inzidenz liegt der Bedarf an hausärztlichen Nachsorgekonzepten auf der Hand, wie sie bereits zur Versorgung chronischer Einzelerkrankungen wie Depression [22] oder auch chronischer Mehrfacherkrankungen [23, 24] entwickelt wurden. Schon 2011 forderten McGovern et al. im *British Journal of General Practice* eine aktive Einbeziehung der Hausärzte in Versorgungsprogramme von Patienten nach Intensivtherapie [25], was 2019 von Taylor et al. nochmals bekräftigt wurde [26]. Im 2014 erschienenen *Textbook of Post-ICU Medicine* [27] wird gar ein phasenspezifischer, transsektoraler Bezugsrahmen für Patienten nach Intensivtherapie gefordert, wie er für Patienten nach Schlaganfall bereits existiert [28].

Hieraus wurde die übergreifende Forschungsfrage der vorliegenden Habilitationsschrift entwickelt:

***„Wie kann die hausärztliche Versorgung***
***von Patienten nach Intensivtherapie verbessert werden?“***

Zur Adressierung dieser Fragestellung startete 2009 am Institut für Allgemeinmedizin des Universitätsklinikums Jena das im Folgenden beschriebene Forschungsprogramm, eingebettet in das integrierte Forschungs- und Behandlungszentrum (IFB) „Sepsis und Sepsisfolgen“ (*Center for Sepsis Control and Care*, kurz: CSCC), gefördert durch das Bundesministerium für Bildung und Forschung (BMBF).

Zunächst erfolgte die systematische Erfassung der Literatur zu rehabilitativen Interventionen nach Intensivtherapie (siehe 2.1). Darauf aufbauend wurde am Beispiel der Indikatorerkrankung „schwere Sepsis/septischer Schock“ ein spezifisch hausärztliches Nachsorgeprogramm entwickelt (siehe 2.2). Im Rahmen der randomisiert-kontrollierten “SMOOTH”-Studie *(Sepsis survivors Monitoring and cOordination in OutpatienT Healthcare)* wurde diese Intervention auf ihre Wirksamkeit überprüft, siehe 2.3 und 2.4. In einem *mixed-methods*-Ansatz ergänzen qualitative Interviews und sekundäre Verlaufsanalysen die Hauptstudie methodisch, siehe 2.4 und 2.5. Die Ergebnisse aus SMOOTH und Begleitprojekten sowie aus einem weiteren Literaturreview (siehe 2.6) flossen in die Konzeption des Nachfolgeprojektes „PICTURE“ ein, einer hausärztlichen Intervention zur Behandlung von posttraumatischen Beschwerden nach Intensivtherapie, siehe 2.7.

# 2. EIGENE ARBEITEN

## 2.1 Interventionen nach kritischer Erkrankung: ein systematischer Literaturreview

***Originalarbeit:***

*Mehlhorn J, Freytag A, **Schmidt K**, Brunkhorst FM, Graf J, Troitzsch U, Schlattmann P, Wensing M, Gensichen J. Rehabilitation interventions for post intensive care syndrome. A systematic review. Crit Care Med 2014;42(5):1263-71. doi: 10.1097/CCM.0000000000000148.*

Ziel dieses Teilprojektes war die systematische Exploration der Effektivität bestehender Nachsorgeprogramme für Patienten nach kritischer Erkrankung. Dies war Voraussetzung zur Konzeption der unter 2.2 beschriebenen Intervention.

***2.1.1 Hintergrund:*** Eine systematische Effektivitätserfassung und -bewertung von spezifischen Nachsorge- und Rehabilitationsmaßnahmen für Erwachsene nach Entlassung von der Intensivstation (ITS) ist bisher nicht verfügbar.

***2.1.2 Fragestellung:*** Gibt es effektive Nachsorge- und Rehabilitations-Interventionen? Haben spezifische Nachsorge- und/oder Rehabilitationsverfahren nach Entlassung von der Intensivstation positive Effekte auf den Verlauf typischer Spätfolgen nach kritischer Erkrankung (PICS) bei erwachsenen Patienten?

***2.1.3 Methodik:*** Ein systematischer Literaturreview wurde nach PRISMA-Vorgaben erstellt [29, 30], mit extensiver Suche in den Datenbanken PubMed, MEDLINE, EMBASE, Cochrane Central, PsycInfo und CINAHL, Handsuche und Screening von Quellenverzeichnissen relevanter Literatur. Eligibel waren alle zwischen September 1991 und Juni 2012 veröffentlichten Studien mit mindestens einer der folgenden Zielgrößen: gesundheitsbezogene Lebensqualität, Folgeerscheinungen kritischer Erkrankungen, funktioneller Verlauf, Hilfsbedürftigkeit/ Autonomie, Mortalität oder stationäre Wiedereinweisung.

***2.1.4 Ergebnisse:*** 18 Studien mit insgesamt 2.510 eingeschlossenen Patienten erfüllten die Einschlusskriterien. Darunter waren vier stationäre, neun ambulante und fünf sektorübergreifende Interventionen.

20 verschiedene Zielgrößen mit mehr als 45 Messinstrumenten wurden erhoben. Acht Studien wurden aufgrund guter bis moderater Studienqualität in die Effektivitätsbewertung einbezogen. Sie umfassen stationäre geriatrische wie auch ambulante Rehabilitationen, Sprechstunden zur ITS-Nachsorge, *Disease Management* Programme sowie ITS-Tagebücher. Fünf dieser Studien untersuchten den Einfluss auf Posttraumatische Belastungsstörungen (PTBS), wobei vier davon einen positiven Effekt zeigten: Durch das Pflegepersonal geführte ITS-Tagebücher (n=2), welche den ITS-Aufenthalt der Patienten dokumentieren, reduzierten das Neuauftreten einer PTBS nach drei Monaten und bestehende Symptome nach einem Jahr. In einer ITS-Nachsorge-Sprechstunde behandelte Frauen zeigten geringere Symptome und ein Selbsthilfemanual [31] reduzierte Symptome nach acht Wochen, jedoch nicht nach sechs Monaten. Keine der anderen Zielgrößen konnte in mehreren Studien effektiv beeinflusst werden.

***2.1.5 Diskussion:*** Die untersuchten Interventionen zeigten insgesamt kaum klinische Effekte. Allenfalls einzelne Zielgrößen konnten positiv beeinflusst werden, bezogen insbesondere auf die PTBS. Ursächlich hierfür könnte die Heterogenität der Studienpopulation kritisch Kranker sein sowie ein möglicher Selektions- oder *Attrition Bias*. Die Durchführung einer Metaanalyse war aufgrund der begrenzten Datenlage nicht möglich. Die Suchstrategie war extensiv, jedoch wurden wegen den noch stark variierenden Begrifflichkeiten des Forschungsfeldes möglicherweise nicht alle relevanten Studien gefunden. Die Klassifizierung der Interventionen bleibt aufgrund ihrer Vielfältigkeit rein deskriptiv. Die verwendeten Parameter wurden eigenständig aus der Zusammenschau der Interventionen abgeleitet, da kein gültiger Klassifikationsstandard verfügbar und somit anwendbar war.

***2.1.6 Schlussfolgerungen:*** Bisher sind kaum effektive Nachsorgeinterventionen für kritisch kranke Patienten verfügbar. ITS-Tagebücher haben das Potential zur Prävention und Behandlung der PTBS.

# Rehabilitation Interventions for Postintensive Care Syndrome: A Systematic Review*

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## 2.2 Entwicklung einer strukturierten hausärztlichen Sepsis-Nachsorge

***Originalarbeit:***

***Schmidt K****, Thiel P, Mueller F et al. Sepsis survivors monitoring and coordination in outpatient health care (SMOOTH): study protocol for a randomized controlled trial. Trials. 2014;15(1):283 (IF: 3,22). doi: 10.1186/1745-6215-15-283.*

***2.2.1 Hintergrund und Fragestellung:*** *siehe 1.3 sowie 1.5.*

***2.2.2 Methodik:*** Als theoretisch-konzeptioneller Hintergrund für eine strukturierte hausärztliche Sepsis-Nachsorge wurden das *„Chronic-Care"* Modell nach Wagner [32] bzw. das *„teamlet"*-Modell nach Bodenheimer [33] gewählt, in denen die traditionelle, arztzentrierte Organisation der Primärversorgung erweitert wird durch Patientenzentrierung, strukturierte Einbeziehung weiterer Professionen, Entscheidungsunterstützung für Hausärzte sowie Stärkung des Selbstmanagements der Patienten. Hieran anknüpfend umfasste die insgesamt zwölf-monatige Intervention drei zentrale Bereiche: strukturiertes Entlass-Management, intensiviertes Monitoring der Patienten und Schulung von Hausärzten und Patienten.

Eine regelmäßige Kontaktaufnahme im Rahmen des Monitorings sowie die Schulung der Patienten wurde durch ***Case-Manager*** ermöglicht, deren Rolle meist durch in der Praxis angestellte medizinische Fachangestellte (MFA) übernommen wurde. In bestehenden *Disease Management* Programmen konnten sich *Case Manager* bereits als kosteneffektive Entlastung der Hausärzte bewähren [34]. Ärztliches Pendant war der so genannte **Liaisonarzt**, ein innovativer, beratender Partner des Hausarztes: Er schulte den Hausarzt in evidenzbasierter Sepsis-Nachsorge und wurde durch den *Case Manager* über die Ergebnisse des Monitorings informiert. Bei Auffälligkeiten und Handlungsbedarf beriet er darauf den Hausarzt zur Einleitung einer gezielten Diagnostik und Therapie. Im Verlauf der 24-monatigen Beobachtung jedes Patienten wurden insgesamt 32 Zielgrößen erhoben - vor allem durch Patienteninterviews, aber auch durch Abfrage der stationären und hausärztlichen Dokumentation.

Eine ausführliche Beschreibung von Intervention und erhobenen Zielgrößen findet sich im Anhang, siehe 6.2.

***2.2.3 Diskussion und Schlussfolgerung:*** Die beschriebene Intervention stellt den nach Wissen des Autors international ersten Ansatz dar, Spätfolgen nach Sepsis hausärztlich in einem strukturierten Nachsorgeprogramm zu adressieren. Die Einbindung mehrerer Akteure, die Abdeckung vieler klinischer Komponenten sowie die hohe Anzahl sekundärer Zielgrößen trägt den komplexen Verläufen nach Sepsis Rechnung. Der lange Beobachtungszeitraum von 24 Monaten ermöglicht Aussagen zur Nachhaltigkeit der Intervention und berücksichtigt dazu die oft langwierigen Verläufe nach Sepsis. Die Einführung neuer, innovativer Akteure wie des Liaisonarztes oder des *Case Managers* könnten darüber hinaus einen Beitrag zur strukturellen Entwicklung der deutschen Primärversorgung leisten.

TRIALS


# Sepsis survivors monitoring and coordination in outpatient health care (SMOOTH): study protocol for a randomized controlled trial

Schmidt *et al.*

BioMed Central

Schmidt *et al. Trials* 2014, **15**:283
http://www.trialsjournal.com/content/15/1/283

Schmidt et al. Trials 2014, 15:283
http://www.trialsjournal.com/content/15/1/283

TRIALS

STUDY PROTOCOL Open Access

# Sepsis survivors monitoring and coordination in outpatient health care (SMOOTH): study protocol for a randomized controlled trial

Konrad Schmidt[1,5*], Paul Thiel[1,5], Friederike Mueller[1,5], Katja Schmuecker[1,5], Susanne Worrack[1,5], Juliane Mehlhorn[1,5], Christoph Engel[2], Katja Brenk-Franz[1], Stephan Kausche[1], Ursula Jakobi[1,5], Anne Bindara-Klippel[1,5], Nico Schneider[1], Antje Freytag[1], Dimitry Davydow[6], Michel Wensing[4,1], Frank Martin Brunkhorst[3,5], Jochen Gensichen[1,5] and Smooth Study Group

## Abstract

**Background:** Sepsis sequelae include critical illness polyneuropathy, myopathy, wasting, neurocognitive deficits, post-traumatic stress disorder, depression and chronic pain. Little is known howlong-term sequelae following hospital discharge are treated. The aim of our study is to determine the effect of a primary care-based, long-term program on health-related quality of life in sepsis survivors.

**Methods/Design:** In a two-armed randomized multicenter interventional study, patients after sepsis (n = 290) will be assessed at 6, 12 and 24 months. Patients are eligible if severe sepsis or septic shock (ICD-10), at least two criteria of systemic inflammatory response syndrome (SIRS), at least one organ dysfunction and sufficient cognitive capacity are present. The intervention comprises 1) discharge management, 2) training of general practitioners and patients in evidence-based care for sepsis sequelae and 3) telephone monitoring of patients. At six months, we expect an improved primary outcome (health-related quality of life/SF-36) and improved secondary outcomes such as costs, mortality, clinical-, psycho-social- and process-of-care measures in the intervention group compared to the control group.

**Discussion:** This study evaluates a primary care-based, long-term program for patients after severe sepsis. Study results may add evidence for improved sepsis care management. General practitioners may contribute efficiently to sepsis aftercare.

**Trial registration:** U1111-1119-6345. DRKS00000741, CCT-NAPN-20875 (25 February 2011).

**Keywords:** Severe sepsis, Sequelae, Critical illness, Primary health care, Aftercare

## Background

Sepsis is a worldwide major health concern with increasing incidence [1]. About 85,000 patients a year survive severe sepsis or septic shock [2,3] in Germany. Main sepsis sequelae include critical illness polyneuropathy/myopathy, cognitive deficits and chronic pain, all symptoms of neuronal degeneration [4-7]. In addition, post-traumatic stress disorder (PTSD) and depression are prevalent after stress exposure in the intensive care unit (ICU) [8,9].

Thus, the majority of sepsis survivors suffer from a considerable deficit in physical and psycho-social functions [10], showing a reduced health-related quality of life [11-13]. In addition to the individual burden, sepsis causes significant health economic costs, about four to seven billion Euro/year for Germany alone, including indirect costs due to loss-of-work [3].

At least, sepsis sequelae are considered to be generic for symptoms after critical illness in general [13], which is of even more clinical and socioeconomic relevance.

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To improve care for long-term conditions, coordination of the fragmented process by structured interventions is effective [14]. The British National Institute for Health and Clinical Excellence's guideline *Rehabilitation after critical illness* states that 'evidence is often missing and only incorporates aftercare for up to three months' [15]. Based on a current systematic review, few follow-up interventions have been published [16]. Of these, Hacking *et al*. observed functional improvement of amputations associated with sepsis by an intensive rehabilitation program [17]. Jones *et al*. presented an increase of physical function in 126 critical illness patients who were provided a self-help manual for six months [18]. A British pilot study of Jackson *et al*., with 21 critical care patients, showed a non-significant reduction of post-traumatic symptoms using an in-house, multifaceted telemedicine program [19]. In contrast, a home-based rehabilitation program for eight weeks did not lead to better health-related quality of life or to better physical function in Australian critical illness patients [20]. A nurse-based translational pilot program that incorporated case management for patients with chronic critical illness was not effective for clinical or psycho-social outcomes [21,22].

After ICU care and hospital-based rehabilitation, most sepsis survivors receive aftercare from their primary care physician, as with most chronically ill patients. This setting is characterized by a long-lasting doctor-patient relationship, with all health services being coordinated [23]. Primary care-based interventions to improve sepsis sequelae are still rare [16].

This study will evaluate the effects of a primary care-based intervention to improve aftercare for sepsis survivors.

## Methods/Design

### Aim of the study

This study will evaluate whether health-related quality of life (SF-36) and further clinical, psycho-social, process-of-care outcomes and costs of sepsis survivors will be improved by a primary care-based, sepsis-specific aftercare program.

### Scientific hypothesis

After six months, the intervention group will show an improved primary outcome (SF-36) compared to patients with usual care in the control group.

### Study design

The study is a multicenter, prospective, two-armed randomized controlled trial. Since the intervention could compromise educational elements for primary care physicians and patients, we are not able to perform a blinded intervention. GPs are allocated only to one patient - either to the control or intervention group.

### Sample size

A wide range of effect sizes is found in comparable studies. Jackson *et al*. [19] reported that for executive functioning ability a Cohen's d =1.1 Elliott *et al*. [20] reported that for the SF-36 physical and mental summary scores, Cohen's d = 0.14/0.13, respectively. For our study, we assume a medium Cohen's d = 0.5 for our primary outcome, which is between these 'extreme values'.

With a statistical power of 90% and a significance level of 0.05, we need n = 172 patients at T2 for two-sided tests. Assuming a 40% drop-out rate [24] and 30% mortality [25], 290 patients are needed at T1.

### Data collection

Patients will be recruited from 20 ICUs in nine study centers across Germany (see Additional file 1). Eligible survivors of severe sepsis or septic shock are screened on a daily basis by ICU consultants and reported to the study team. Within one month after discharge from ICU, patients are contacted by a study physician and asked to participate in the study. For eligibility, a cognition test is performed [26]. All patients are informed about the study course.

Within one month after discharge from ICU, the first data set (T1) is collected by the study nurse, including clinical and socio-demographic characteristics. At the same time, the liaison physician contacts the responsible general practitioner (GP) by telephone to ask for study participation.

### Randomization

Given the GP's written consent, patients are randomized in the intervention versus control group with n = 145 patients per group. Randomization sequence is computer-generated and provided in a sealed opaque envelope.

### Inclusion criteria

Patients are eligible on the presence of severe sepsis or septic shock, as defined by the definitions of the German Sepsis Society [27]. Two systemic inflammatory response syndrome (SIRS) criteria have to be completed and at least one organ dysfunction (see Additional file 2). Inclusion criteria are checked by the participating ICU doctors.

Furthermore, patients must be 18 years or older and capable of sufficient German language skills.

### Exclusion criteria

Patients are excluded from study participation due to insufficient German language skills, deafness, blindness or speech impairment. Furthermore, patients suffering from severe cognitive impairment are not eligible for study participation (determined by a telephone interview of cognitive status (TICS-M) ≤27 points) [26].

**Intervention treatment**

The intervention contains three main components:

1. Discharge management with structured information between inpatient and outpatient care in accordance with the transitional care model [28], which was shown to reduce costs and rehospitalization rates [29].
2. Training of GPs and patients in sepsis sequelae and evidence-based treatment options [30]. A special focus lies on an effective self-management of patients, which improves health-related quality of life in post-intensive care patients [31].
3. Monthly telephone monitoring of patients through specifically designed telephone interviews is provided for 12 months regarding sepsis sequelae symptoms. Systematic monitoring improves the physician-patient interaction and supplies relevant information on patient clinical status to the GP, according to the chronic care model [32,33].

The intervention is delivered by a study center-based case manager and a liaison physician (see Figure 1). The case manager is a nurse by qualification, trained in sepsis aftercare. She acts as an attendant for the patient, asking about the patient's health constitution and actual problems, and provides training and monitoring. The liaison physician as the GP's contact person is responsible for the education and reporting of the monitoring results and offers feedback if required. The liaison physician also determines further patient educational elements to the case manager.

After discharge from the ICU, intervention patients receive specific discharge forms from the case manager. All treating physicians (ICU, general wards and rehabilitation clinic) are requested to record sepsis-related clinical and social information about the patients and his or her needs. This supports the GP to manage ambulant treatment and special therapeutic needs of the patient like home care, physiotherapy, specific adjuvants *etcetera.*

Both, patients and GPs are trained in evidence-based diagnostics and therapy of the most prevalent sepsis sequelae. The liaison physician trains the GP face-to-face using audiovisual education material to impart knowledge about etiology, symptoms, diagnostic instruments and therapy options of sepsis sequelae.

Patients in the intervention group are educated as well in a face-to-face situation by the case manager to get better information about:

1. the study course,
2. the monitoring program,
3. origin and therapy of sepsis,
4. possible sepsis sequelae,
5. physical and psychological impacts of intensive therapy and
6. coping strategies and self-efficacy.

Patients and GPs receive a written manual, including both training content and monitoring instruments. Manuals are used to support training sessions. The patient manual is based on the Discern-criteria [34]. Patients are contacted every month during the first six months after discharge from ICU and every three months during months 7 to 12 for the monitoring. This telephone interview includes established short form instruments for the most common sepsis sequelae, differing from outcome instruments (see Additional file 3). Based on the monitoring results, patients are encouraged to work toward target agreements in daily life. Patient compliance is requested and monitored in the course.

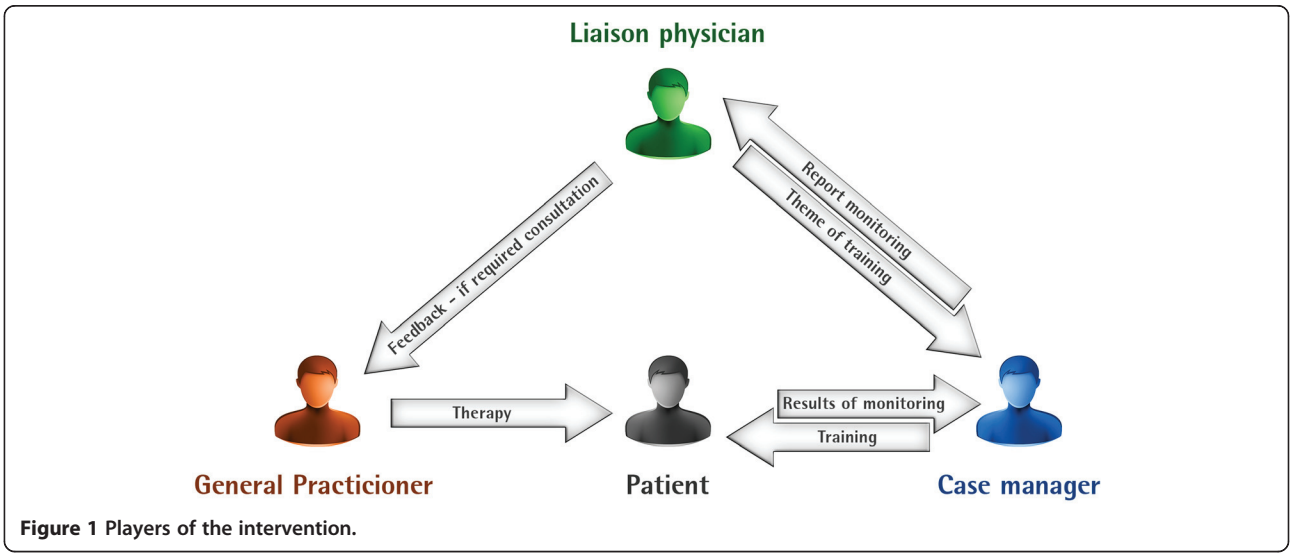


**Figure 1** Players of the intervention.

The liaison physician provides this information to the GP with the help of a stratification of urgency (traffic light scheme). The GP is contacted immediately by phone if a new clinical condition arises and gets information about diagnostic and therapeutic possibilities, whereas the liaison physician is available for supervision and requests. In addition, the patient is asked to visit his/her GP if health problems occur.

#### Control treatment

Patients in the control group are treated as usual by their GPs or ambulant specialists without any additional information or monitoring. There aren't any outpatient sepsis follow-up clinics in Germany.

Due to the lack of sepsis aftercare guidelines in Germany, there is no treatment standard available. Usual care is assessed in control group patients. Qualitative interviews of GPs and patients provide additional information.

#### Data collection

Data are collected from patients in questionnaires by trained study staff, initially face to face, and from T2 onwards, by phone call. In addition, GPs and ICU staff are asked to provide clinical information after patients have given their informed and written consent. Data are documented as written case report forms and stored in a protected cabinet.

#### Outcome measures

Measurements take place from 3 months before hospitalization (**T-1**, retrospectively) until 1, 6, 12 and 24 months after discharge from the ICU (**T1-4**).

Primary outcome is the health-related quality of life assessed by the Short Form 36 Health Questionnaire (SF-36), a multidimensional construction of physical, mental, social and behavior-related components of well-being and operational capability, validated also for German primary care [35].

Secondary outcomes focus on the most relevant sepsis sequelae, including the assessment of physical activity, level of pain, and cognitive deficits or neuropathic symptoms by established questionnaires, all of which are patient-reported outcomes.

Furthermore, for GP compliance review, treatment and cost-effectiveness analysis, patient rehospitalizations, medication, care needs, mortality, physical therapy and instrumental diagnostic procedures are documented by the primary care provider. GPs are asked to provide details of their practice characteristics.

For clinical analysis, diagnoses and ICU procedures are extracted from the ICU documentation system.

For detailed variable/outcome parameter descriptions see Table 1 and Additional file 4.

To gain insight into processes, barriers and mechanisms of the intervention, qualitative interviews with patients and GPs are performed on a subsample. In this context, the roles of patients' relatives are also to be evaluated.

#### Data analysis

Randomization process will be proofed using binary logistic regression. The dependent variable logarithmic odds ratio of patient is in the intervention versus control group. As predictors, we use potential confounders (for example, socio-demographic or clinical variables). Primary outcome will be analyzed based on a two-sided t-test. Secondary endpoints will be analyzed depending on scale level, using descriptive or hypothesis generating test procedures. For evaluation of average treatment effects, we will analyze the outcome variables with a generalized analysis of covariance (g-ANCOVA) and control for potential confounders. Based on these results, we are able to adjust means, which are comparable with outcome means of a perfect randomized and balanced design [49,50].

Furthermore, mortality is taken into account. Using survival analysis models, we are able to examine the relationship between mortality and treatment. In this way, we also try to identify mortality risk factors.

Finally, we plan cost-effectiveness analyses. Therefore, we sum up the costs of micro interventions and compare the averages of treatment and control group using g-ANCOVA (see above).

#### Description of risks

Showing 6- month mortality of more than 30% [25], severe sepsis ranks among critical long-term conditions. Serious risks or undesired effects of completing questionnaires have not been reported by clinical expertise of the scientific experts in the advisory board of the study (see Additional file 1). There are no specific risks related to the intervention. Thus, there are no rules for stopping the intervention.

#### Ethical principles

The study is planned and conducted in accordance with medical professional codex and the Helsinki Declaration of 1996 as well as the Federal Data Protection Act (BDSG).

Patients participate in the study voluntarily and give written informed consent. Patients are informed that they can cancel their participation at any time without disclosing reasons for their cancellation and without negative consequences for their future medical care. The study protocol was approved by the institutional review board of the University of Jena, 26 January 2011 (No.3001/111).

#### Data security

The patient names and other confidential information are secured by the medical confidentiality rules and are treated according to Federal Data Protection Act (BDSG).

**Table 1 List of variables/outcome parameters**

| Variables | Time of measurement | Instrument used (number of items) |
|---|---|---|
| Intensive care unit (ICU) | | |
| Documentation | | |
| ICU stay | $T_1$ | Days |
| Mechanical ventilation | $T_1$ | Days |
| Kidney replacement therapy | $T_1$ | Days |
| Diagnoses at ICU discharge | $T_1$ | ICD-10 |
| Focus of infection | $T_1$ | schematized (13) |
| Microbiological analysis | $T_1$ | pathogen cluster (8) |
| Use of sedatives, steroids | $T_1$ | schematized (4) |
| Patient reported | | |
| Educational status | $T_1$ | schematized (2) |
| Socio-economic status | $T_{-1 \text{ to } 4}$ | schematized (8) |
| Outcome measure (patient ratings) | | |
| Health-related quality of life | $T_{-1 \text{ to } 4}$ | Short Form 36 Health Survey (SF-36) (36) [35] |
| Depressive symptoms | $T_{1 \text{ to } 4}$ | Major Depression Inventory (MDI) (12) [36] |
| Post-traumatic symptoms | $T_{1 \text{ to } 4}$ | Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10) (10) [37] |
| Motoric function | $T_{2 \text{ to } 4}$ | Short Musculoskeletal Function (XSMFA-D) (16) [38] |
| Impairment of swallowing, hearing, smelling | $T_{-1 \text{ to } 4}$ | 4-stepped Likert scale (4) |
| Chronic pain | $T_{1 \text{ to } 4}$ | Graded Chronic Pain scale (GCPS) (7) [39] |
| Neuropathic symptoms | $T_{1 \text{ to } 4}$ | Neuropathic Symptom Score (NSS) (6) [40] |
| Nutritional status | $T_{-1 \text{ to } 4}$ | Malnutrition Universal Screening Tool (MUST) (4) [41] |
| Cognitive status | $T_{1 \text{ to } 4}$ | Telephone Interview of Cognitive Status (TICS-M) (21) [42,43] |
| Sleep | $T_{2 \text{ to } 4}$ | Regensburg Insomnia Scale (RIS) (15) [44] |
| Medication addiction | $T_{2 \text{ to } 4}$ | Short form for medication use (KFM) (12) [45] |
| Patient assessment of care | $T_{-1, 2 \text{ to } 4}$ | Patient Assessment of Care for Chronic Conditions (PACIC) (20) [46,47] |
| Compliance/adherence | $T_{-1,2 \text{ to } 4}$ | Modified Morisky questionnaire (4) [48] |
| Activities of daily life | $T_{2 \text{ to } 4}$ | (Instrumental) Activities of daily life (ADL/IADL) (11) |
| General practitioner (GP) documentation | | |
| Mortality | $T_{2 \text{ to } 4}$ | |
| Current diagnoses | $T_{-1,2 \text{ to } 4}$ | ICD-10 |
| GP consultation | $T_{2 \text{ to } 4}$ | Number |
| Stay in hospital | $T_{2 \text{ to } 4}$ | Days |
| Inability to work | $T_{2 \text{ to } 3}$ | Days |
| Medication | $T_{-1, 2 \text{ to } 4}$ | agent, dosage |
| Stay in rehabilitation clinic | $T_{1 \text{ to } 4}$ | Days |
| Remedies and therapeutic aids | $T_{2 \text{ to } 4}$ | schematized (1) |
| Nursing level | $T_{2 \text{ to } 4}$ | schematized (2) |
| Contacts to specialists, diagnostic procedures | $T_{1 \text{ to } 4}$ | schematized (7) |

All study-related data and documents are stored on a protected central server at Jena University Hospital. Only members of the study team have access to the study files.

Intermediate and final reports are stored in the office of the Institute of General Practice and Family Medicine at the Jena University Hospital.

## Discussion

### Limitations

Contacting control patients via phone calls for data collection may create a small intervention (Hawthorne) effect in the control group. Therefore, the intervention effect is likely to be underestimated. This might be

acceptable because we would not overuse any effect of the trial.

In addition, contamination by information flow between the intervention and control group cannot be excluded. However, this risk seems to be minimized by the allocation of one GP to one patient of either intervention or control group. Most GPs in Germany practice alone.

### Strengths/conclusion

To our knowledge, SMOOTH is the first study evaluating the effects of a primary care-based intervention for patients after a critical illness, that is sepsis [16]. Using established primary care structures, SMOOTH may provide a cost-effective addition to sepsis aftercare. Furthermore, considering the long-term impact of sepsis sequelae, 24-month follow-up data will be provided, which are rarely published and allow analysis of intervention sustainability. As a further innovative element, an external medical consultant in primary care (the liaison physician) might help to support quality of care in primary care settings - strengthening the GP as a reliable clinical partner for patients after critical illness.

## Trial status

The first patient was included on 28 February 2011. Patient recruitment is ongoing but not completed.

## Additional files

**Additional file 1: Scientific advisory council and SMOOTH study centres.**

**Additional file 2: SIRS/Sepsis Criteria.**

**Additional file 3: Monitoring instruments.**

**Additional file 4: Outcome instruments.**

#### Abbreviations

CSCC: Center of Sepsis Control and Care; g-ANCOVA: generalized analysis of covariance; GCPS: graded chronic pain scale; GP: general practitioner; GSS: German Sepsis Society; I/ADL: instrumental activities of daily life; ICD-10: international statistical classification of diseases and related health problems; ICU: intensive care unit); KFM: short form for medication use; MDI: major depression inventory; MUST: malnutrition universal screening tool; NSS: neuropathic symptom score; ODSS: modified overall disability sum score; PACIC: patient assessment of care for chronic conditions; PHQ-9: patient health questionnaire; PTSD: post-traumatic stress disorder; PTSS-10: post-traumatic stress syndrome 10-questions inventory; RIS: Regensburg insomnia scale; SF-36: short form 36 health survey; SIRS: systemic inflammatory response syndrome; SMOOTH: Sepsis Survivors Monitoring and Coordination in Outpatient Health care; STIFT: Thuringian Foundation for Technology, Innovation and Research; TICS-M: modified telephone interview for cognitive status; XSMFA-D: short musculoskeletal function.

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

FM, JG, KS, JM and PT participated in the study design, study conduct/data collection and in writing the final manuscript; KBF, KSc, NS and SW participated in the study design and study conduct/data collection. AF, ChE, DD, FMB and MW participated in study design and the critical revision of the manuscript. ABK, StK and UJ participated in the study conduct and data collection. All authors approved the final version of the manuscript.

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**Members of the SMOOTH-study group**

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## 2.3 Effekte einer hausärztlichen Intervention für Sepsis-Überlebende

***Originalarbeiten:***

***Schmidt K**, Worrack S, Von Korff M et al., for the SMOOTH Study Group. Effect of a primary care management intervention on mental health-related quality of life among survivors of sepsis: a randomized clinical trial. JAMA. 2016;315(24):2703-11. doi: 10.1001/jama.2016.7207.*

***Schmidt K,** Schwarzkopf D, Baldwin LM, Brunkhorst FM, Freytag A, Heintze C, et al. Long-Term Courses of Sepsis Survivors: Effects of a Primary Care Management Intervention. The American Journal of Medicine 133.3 (2020): 381-385. doi: 10.1016/j.amjmed.2019.08.033.*

***2.3.1 Hintergrund:*** Siehe Einleitung sowie 2.2

***2.3.2 Fragestellung:*** Kann die (mentale) gesundheitsbezogene Lebensqualität von Sepsispatienten sechs Monate nach Entlassung von der Intensivstation durch ein hausärztliches, strukturiertes Nachsorge-Programm im Vergleich zur Routineversorgung signifikant mit einer Effektstärke von > 0,4 verbessert werden?

***2.3.3 Methodik:*** Zwischen Februar 2011 und Dezember 2014 wurden Patienten von neun Intensivstationen an Standorten in Thüringen, Sachsen und Berlin in einen *randomized controlled trial* eingeschlossen. Zur Überprüfung der Hypothese wurde ein *Welch T-Test* für unabhängige Gruppen als *intention-to-treat* Analyse durchgeführt. Eine ausführliche Beschreibung von Intervention und Zielgrößen findet sich unter 2.2.

***2.3.4 Ergebnisse:*** Die Intervention konnte erfolgreich in 148 Hausarztpraxen implementiert werden, die Ausfallrate der eingeschlossenen Patienten (22,7 % zu sechs Monaten und zusätzlich 6,2 % bzw. 5,5% zu zwölf und 24 Monaten nach Entlassung von der Intensivstation) war meist durch die erwartet hohe Mortalität bedingt. Nur 9,4% Patienten zu sechs Monaten und 1,7% zu zwölf Monaten beendeten die Studienteilnahme auf eigenen Wunsch. 98 (66%) der Teilnehmer der Interventionsgruppe sowie 88 (62%) der Kontrollgruppe nahmen an der Datenerhebung zu 24 Monaten teil. Von den 307 angefragten Hausärzten willigten 294 (95,8%) ein, an der Studie teilzunehmen. Über die Hälfte der teilnehmenden Patienten (62,6%) litten an mehr als drei chronischen Erkrankungen, gemessen am *Charlson* Komorbiditäts-Index [35]. Das Durchschnittsalter betrug 61,6 Jahre, 66,2% der Studienpopulation war männlich.

Nach sechs Monaten zeigten sich keinerlei signifikante Veränderungen zwischen Interventions- und Kontrollgruppe in der primären Zielgröße, der mentalen gesundheitsbezogenen Lebensqualität. In der motorischen Funktion und bei Ausübung von Tätigkeiten des alltäglichen Lebens war in der Interventionsgruppe sowohl zu sechs als auch zu zwölf Monaten nach Entlassung von der Intensivstation eine signifikante Verbesserung zu beobachten. Nach 24 Monaten, d.h. zwölf Monate nach Beendigung der Intervention waren weder Unterschiede in der gesundheitsbezogenen Lebensqualität noch in der motorische Funktion zwischen beiden Gruppen nachweisbar. Beobachtet werden konnten zu diesem Zeitpunkt jedoch signifikant stärkere posttraumatische Symptome in der Kontrollgruppe.

***2.3.5 Diskussion:*** Die mentale gesundheitsbezogene Lebensqualität als primäre Zielgröße konnte durch die Intervention nicht beeinflusst werden: Möglicherweise war der *Short Form 36 Health Survey* (SF-36) [36] als globaler, kaum veränderungssensitiver Parameter wenig geeignet, eventuelle spezifische Veränderungen zu erfassen. Dazu könnten die Einschränkungen der Patienten zu heterogen gewesen sein, um in der Summe von einer zwar umfassenden, aber nur wenig individualisierten Intervention signifikant verbessert zu werden. Die Verbesserungen in motorischer Funktion und Tätigkeiten des alltäglichen Lebens sind möglicherweise auf eine erhöhte hausärztliche Aufmerksamkeit sowie die mobilisierende Aktivierung durch die *Case Manager* zurückzuführen.

Das verminderte Auftreten von posttraumatischen Symptomen in der Interventionsgruppe könnte auf einen langfristig protektiven Effekt des intensivierten Kontaktes betroffener Patienten zu Hausärzten und *Case Managern* hinweisen: Soziale Unterstützung trägt zur Resilienz nach traumatischen Erlebnissen bei [37]. Die geringe Rate an Ablehnung bei angefragten Praxen kann als Indikator für eine hohe hausärztliche Bereitschaft gewertet werden, Intensivnachsorge zukünftig in die Primärversorgung zu integrieren.

***2.3.6 Schlussfolgerung:*** Ein hausärztliches Nachsorgeprogramm für Sepsis-Überlebende erscheint durchführbar. Für dessen Effektivität ergaben sich Hinweise, jedoch kein signifikanter Nachweis. Die heterogenen Einschränkungen von Patienten nach Sepsis sind möglicherweise nicht durch eine einzelne, globale Intervention effektiv adressierbar. Spezifische Interventionen und Zielgrößen sollten sich zukünftig auf abgrenzbare Aspekte der Spätfolgen nach Sepsis fokussieren.

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Effect of a Primary Care Management Intervention on Mental Health–Related Quality of Life Among Survivors of Sepsis
## A Randomized Clinical Trial

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**IMPORTANCE** Survivors of sepsis face long-term sequelae that diminish health-related quality of life and result in increased care needs in the primary care setting, such as medication, physiotherapy, or mental health care.

**OBJECTIVE** To examine if a primary care–based intervention improves mental health–related quality of life.

**DESIGN, SETTING, AND PARTICIPANTS** Randomized clinical trial conducted between February 2011 and December 2014, enrolling 291 patients 18 years or older who survived sepsis (including septic shock), recruited from 9 intensive care units (ICUs) across Germany.

**INTERVENTIONS** Participants were randomized to usual care (n = 143) or to a 12-month intervention (n = 148). Usual care was provided by their primary care physician (PCP) and included periodic contacts, referrals to specialists, and prescription of medication, other treatment, or both. The intervention additionally included PCP and patient training, case management provided by trained nurses, and clinical decision support for PCPs by consulting physicians.

**MAIN OUTCOMES AND MEASURES** The primary outcome was change in mental health–related quality of life between ICU discharge and 6 months after ICU discharge using the Mental Component Summary (MCS) of the 36-Item Short-Form Health Survey (SF-36 [range, 0-100; higher ratings indicate lower impairment; minimal clinically important difference, 5 score points]).

**RESULTS** The mean age of the 291 patients was 61.6 years (SD, 14.4); 66.2% (n = 192) were men, and 84.4% (n = 244) required mechanical ventilation during their ICU stay (median duration of ventilation, 12 days [range, 0-134]). At 6 and 12 months after ICU discharge, 75.3% (n = 219 [112 intervention, 107 control]) and 69.4% (n = 202 [107 intervention, 95 control]), respectively, completed follow-up. Overall mortality was 13.7% at 6 months (40 deaths [21 intervention, 19 control]) and 18.2% at 12 months (53 deaths [27 intervention, 26 control]). Among patients in the intervention group, 104 (70.3%) received the intervention at high levels of integrity. There was no significant difference in change of mean MCS scores (intervention group mean at baseline, 49.1; at 6 months, 52.9; change, 3.79 score points [95% CI, 1.05 to 6.54] vs control group mean at baseline, 49.3; at 6 months, 51.0; change, 1.64 score points [95% CI, −1.22 to 4.51]; mean treatment effect, 2.15 [95% CI, −1.79 to 6.09]; $P$ = .28).

**CONCLUSIONS AND RELEVANCE** Among survivors of sepsis and septic shock, the use of a primary care–focused team-based intervention, compared with usual care, did not improve mental health–related quality of life 6 months after ICU discharge. Further research is needed to determine if modified approaches to primary care management may be more effective.

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Sepsis is a major health problem worldwide.[1] It has been estimated that sepsis occurred in 2% of hospitalized patients in the United States in 2008, and incidence is expected to increase further in the future, with an even higher incidence in developing countries.[2] The risk of dying from sepsis has decreased in recent decades, owing to earlier detection and more effective treatment.[3] Although more patients survive sepsis and are increasingly discharged from the hospital,[4] they often experience functional disability, cognitive impairment, and psychiatric morbidity,[5,6] resulting in diminished health-related quality of life,[7] increased health care costs,[8,9] and burden on patients and their families.[7,10]

Many survivors of sepsis have multiple medical comorbidities that are typically managed in primary care. Yet interventions for managing sepsis sequelae in primary care have not been developed.[5,11] A systematic review of outpatient interventions for patients surviving critical illnesses showed heterogeneous and small effects on clinical outcomes such as depression and symptoms of posttraumatic stress disorder (PTSD).[12] Studies with post-intensive care unit (ICU) follow-ups of 6 months or more are rare.[7]

The purpose of this randomized clinical trial was to assess whether a primary care–based intervention[13] would improve mental health–related quality of life among survivors of sepsis compared with usual care.

## Methods

### Study Design and Population

A multicenter, unblinded, 2-group randomized clinical trial was performed. The institutional review board of the Jena University Hospital approved the study protocol (protocol available in Supplement 1). All patients and primary care physicians (PCPs) in the study provided written informed consent. Serious adverse events were reported to a data and safety monitoring board. Patients were recruited in 9 ICU study centers across Germany between February 2011 and December 2013. Follow-up assessments were completed in December 2014. Patients were eligible for inclusion if they were adult (≥18 years) survivors of severe sepsis, (now defined as "sepsis"[14]) or septic shock and fluent in the German language.

Clinical diagnoses of sepsis were made by intensivists according to *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes (R65.1/R57.2) and American College of Chest Physicians/Society of Critical Care Medicine consensus criteria.[15] Baseline interviews of patients were conducted by the study team within 1 month of ICU discharge. The key exclusion criterion was cognitive impairment, as determined by the Telephone Interview of Cognitive Status (score ≤27).[16] After determining patient eligibility, the study team invited each patient's PCP to participate in the trial.

Randomization was stratified by ICU study centers and performed using computer-generated random permutated blocks (block size range, 2-6) provided by an independent center for clinical trials at the University of Leipzig.

### Intervention

The intervention was based on the chronic care model.[17] Its core components included case management focusing on proactive patient symptom monitoring, clinical decision support for the PCP, and training for both patients and their PCPs in evidence-based care. Three nurses with ICU experience were trained as outpatient case managers for survivors of sepsis in an 8-hour workshop. The training included information on sepsis sequelae, communication skills, telephone monitoring, and behavioral activation of patients that included goal setting (Sepsis Case Manager Manual in Supplement 2). Each case manager worked with 38 to 65 patients, starting with a 60-minute face-to-face training on sepsis sequelae (Sepsis Help Book in Supplement 2) that took place a median of 8 days after ICU discharge (interquartile range [IQR], 2-20). This was followed by monthly telephone contact for 6 months, then once every 3 months for the final 6 months. Case managers monitored patients' symptoms using validated screening tools (Sepsis Monitoring Checklist in Supplement 2) to assess critical illness polyneuropathy/myopathy, wasting, neurocognitive deficits, PTSD, depressive and pain symptoms, as well as patient self-management behaviors focusing on physical activity and individual self-management goals. Each case manager reported results to 1 of 3 assigned consulting physicians (medical doctors with background in primary and critical care), who supervised the case managers and provided clinical decision support to the PCPs using a structured written report that included the Sepsis Monitoring Checklist (Supplement 2; eFigure 3 in Supplement 3). The reports were stratified by urgency using a traffic-light scheme: red signified "immediate intervention recommended"; yellow, "intervention should be considered"; and green, "acceptable clinical status." Evidence-based sepsis aftercare training for the patients' PCPs was provided in person on an individual basis by the consulting physicians (Sepsis PCP Manual in Supplement 2). Intervention delivery was considered to have high integrity if the training was delivered both to patients and to PCPs and the patient was monitored 5 or more times.

Patients in the control group received care as usual from their PCPs without additional information or monitoring. Usual sepsis aftercare included periodic contacts, referrals to specialists, and prescription of medication and therapeutic aids at quantities comparable with those for other populations with multiple chronic conditions.[18] In Germany, most primary care practices are privately operated by 1 or 2 PCPs, with limited access to specialist care.[19] There are no outpatient postsepsis/ICU follow-up clinics or national treatment guidelines for sepsis aftercare in Germany.

### Baseline Data and Outcomes

Baseline data were collected at in-person interviews with patients while they were still hospitalized. Further clinical data were obtained from their ICU records. Since the majority of patients remained hospitalized and incapacitated, baseline data collection of activities of daily living (ADL), physical function, and insomnia was not feasible.

The primary outcome was change in mental health–related quality of life between ICU discharge and 6 months after

ICU discharge, as assessed by the Mental Component Summary (MCS) score of the 36-Item Short Form Health Survey (SF-36 [range, 0-100; higher scores indicate lower levels of impairment[20]]). The SF-36 consists of 8 subscores and is valid and reliable in both post-ICU discharge[21] and German primary care populations.[22]

Secondary outcomes at 6 months were derived from (1) the other SF-36 scales (range, 0-100; higher scores indicate lower levels of impairment); (2) overall survival; (3) mental health outcomes, including the Major Depression Inventory (range, 0-50; higher scores indicate greater impairment[23]), the Posttraumatic Symptom Scale (range, 10-70; higher scores indicate greater impairment[24]), and the Telephone Interview of Cognitive Status (range, 0-50; higher scores indicate greater impairment[16]); (4) functional outcomes including ADL (range, 0-11; higher scores indicate lower levels of impairment[25]), the Extra Short Musculoskeletal Function Assessment regarding physical function (XSFMA-F) and disability (XSMFA-B [range for both, 0-100; higher scores indicate greater impairment[26]), the Graded Chronic Pain Scale including a Disability Score and Pain Intensity (range, 0-100; higher scores indicate greater impairment[27]), the Neuropathy Symptom Score (range, 0-10; higher scores indicate greater impairment[28]), the Malnutrition Universal Screening Tool (range, 0-2; higher scores indicate greater impairment[29]) including body mass index,[30] and the Regensburg Insomnia Scale (range 0-40; higher scores indicate greater impairment[31]).

Process-related outcomes included the Patient Assessment of Care for Chronic Conditions (range, 0-10; higher scores indicate lower levels of impairment)[32,33] and measures of medication adherence, the modified Morisky questionnaire (range 1-5; higher scores indicate greater impairment,[34] and the Short Form for Medication Use (range, 0-12; higher scores indicate greater impairment.[35] In addition, process-related data from PCP documentation were derived, including PCP contacts (No.), referrals to specialists (No.), level of nursing, inability to work (days), remedies and therapeutic aids (No.), and length of stay in the hospital and rehabilitation clinic (days). All 31 secondary outcomes prespecified in the statistical analysis plan (Supplement 4) are reported in eTables 2-8 in Supplement 3.

In addition, we also included as secondary outcomes all of the above measured at 12 months after ICU discharge. Outcome assessment was conducted by nonblinded assessors by telephone.

Initially, the MCS as well as the Physical Component Summary score of the SF-36 were chosen for primary outcome to provide a multicomponent score reflecting health-related quality of life (as noted in the study protocol[13] and the ISRCTN registration). However, based on review of the literature[12] highlighting the importance of mental health outcomes in post-ICU care, the primary outcome was specified to the MCS.

### Statistical Analysis

The aim of the study was to detect a difference at 6 months of 5 points or more in mean MCS scores, since this amount of change is thought to be clinically meaningful.[22] A common standard deviation of 10 was assumed on the basis of a typical German population with acute and chronic diseases.[36] At a 2-sided significance level of $\alpha = .05$, a total of $2 \times 86 = 172$ patients were required to detect the above-mentioned effect with a power of 90%. Allowing for an additional approximately 40% for dropouts and mortality, an initial sample size of 287 was required.

The confirmatory test for the primary outcome was the Welch *t* test for independent groups, which was run in the intention-to-treat population. The confirmatory analyses did not consider intrapractice clustering because 155 (96.9%) of intervention practices and 141 (95.1%) of control practices included only 1 patient. The effect clustering and missing values were explored using, for example, linear mixed models and imputations by regression models. Details on methods and results of exploratory sensitivity analyses are provided in the eMethods in Supplement 3.

All secondary outcome analyses were exploratory and not adjusted for multiple tests. These analyses were performed using the *t* test, Fisher exact test, and the Wilcoxon-Mann-Whitney test, as appropriate. Overall survival was estimated using the Kaplan-Meier method, with study groups compared using the log-rank test. A confirmatory and exploratory 2-sided significance level of $\alpha = .05$ was applied, and effect size estimates with 95% confidence intervals were reported.

All statistical analyses were performed using R version 3.2.3 (R Project for Statistical Computing).[37]

## Results

### Baseline Characteristics

A total of 361 patients were eligible, of which 291 (80.6%) agreed to participate, with 148 patients randomized to the intervention and 143 patients to the control group (**Figure**). Overall, baseline characteristics were well balanced (**Table**). The mean age of the cohort was 61.6 years (SD, 14.4); 244 patients (84.4%) received mechanical ventilation, and the median ICU length of stay was 26 days (IQR, 13-46). Mental health–related quality of life was close to that of the normal population (mean MCS score, 49.0 [SD, 12.5]), physical health–related quality of life was low (mean SF-36 [Physical Component Summary] score, 25.3 [SD, 8.8]); 68 of 281 (24.2%) had substantial depressive symptoms, 41 of 281 (14.6%) reported substantial PTSD symptoms, and 54 of 276 (19.6%) indicated severe pain (Table). Among the entire cohort, 164 of 277 (59.2%) reported neuropathic symptoms.

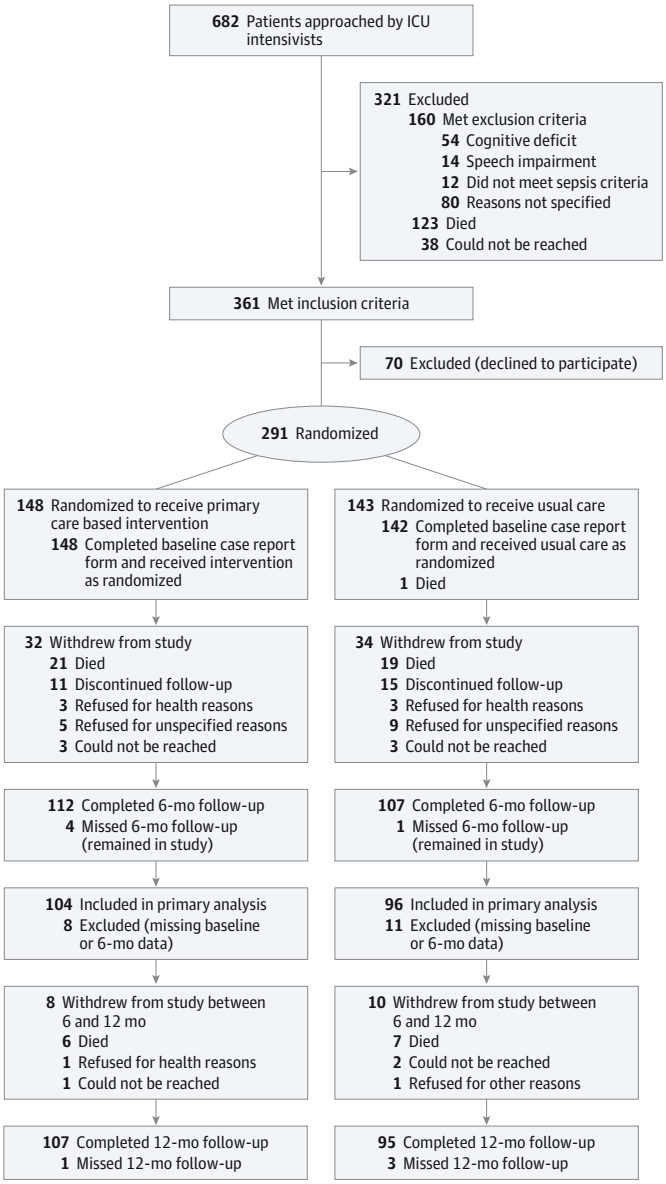
### Follow-up

All included 291 patients were cared for by 159 intervention PCPs and 148 control PCPs. Because of some patient-initiated PCP changes, the number of PCPs was slightly larger than the number of patients (eMethods in Supplement 3). Among the 307 assigned PCPs, 294 (95.8%) were willing to participate. Loss to follow-up due to withdrawal or nonresponse totaled 66 patients (22.7%) at 6 months and an additional 18 patients (6.2%) at 12 months after ICU discharge and was evenly distributed across study groups (Figure).

### Intervention Delivery

Of the 148 patients assigned to the intervention, 130 (87.8%) received patient training from case managers; 125 (84.5%) of

Figure. CONSORT Flow Diagram of Patient Recruitment and Retention During the Study




ICU indicates intensive care unit.

their PCPs received training from a consulting physician. There was a mean gap of 62.38 days (IQR, 36-99) between ICU discharge and PCP training, caused by the wide range of patient clinical courses. One hundred-four patients (70.3%) in the intervention group received the planned intervention at high levels of intervention integrity (eFigure 2 in Supplement 3). Incomplete intervention was usually attributable to death of the patient (24 [54%] of those with fewer than 5 monitoring calls). Reduction of motor function (204 [27.1%]) and pain intensity (201 [27.2%]) were the postsepsis symptoms most rated "red" (ie, "immediate intervention recommended") in all 756 structured monitoring reports (eTable 10 in Supplement 3).

No adverse events related to the intervention were reported.

## Primary Outcome

There was no significant difference between groups in the primary outcome: The mean change MCS score was 3.79 score points (95% CI, 1.05 to 6.54) for the intervention group and 1.64 score points (95% CI, 1.22 to 4.51) for the control group, leading to a mean treatment effect of 2.15 (95% CI, −1.79 to 6.09); $P$ = .28; baseline mean, 49.1 for intervention vs 49.3 for control; 6-month mean, 52.9 for intervention vs 51.0 for control (all data related to n = 200 patients [n = 104 intervention, n = 96 control]), with both MCS scores available at baseline and 6 months; due to rounding, change scores presented may not add up precisely). These results were unchanged in several sensitivity analyses (eTable 1 in Supplement 3).

Table. Baseline Characteristics

| Characteristic | All (N = 290) | Intervention (n = 148) | Control (n = 142) | Not Available | |
|---|---|---|---|---|---|
| | | | | Intervention | Control |
| **Sociodemographics** | | | | | |
| Age, mean (SD), y | 61.6 (14.4) | 62.1 (14.1) | 61.2 (14.9) | 0 | 0 |
| Men, No. (%) | 192 (66.2) | 105 (70.9) | 87 (61.3) | 0 | 0 |
| Married, No. (%) | 148 (52.1) | 84 (57.9) | 64 (46.0) | 3 | 3 |
| Educational status <high school, No. (%) | 98 (34.0) | 54 (36.7) | 44 (31.1) | 1 | 1 |
| **Care Measures** | | | | | |
| Recent surgical history, No. (%) | | | | 2 | 1 |
| Emergency | 106 (36.8) | 49 (33.6) | 57 (40.1) | | |
| Elective | 62 (21.5) | 34 (23.3) | 28 (19.7) | | |
| No history | 73 (25.3) | 39 (26.7) | 34 (23.9) | | |
| Source of infection, No. (%) | | | | | 5 |
| Community acquired | 102 (36.0) | 54 (37.2) | 48 (34.8) | | |
| Nosocomial | | | | | |
| ICU or intermediate care | 139 (49.1) | 70 (48.3) | 69 (50.0) | | |
| General ward or nursing home | 42 (14.8) | 21 (14.5) | 21 (15.2) | | |
| ICU length of stay, d | | | | 16 | 11 |
| Mean (SD) | 34.4 (27.2) | 31.5 (27.7) | 35.2 (26.7) | | |
| Median (IQR) | 26 (4-27) | 23 (4-26) | 29 (5-28) | | |
| Mechanical ventilation, No. (%) | 244 (84.4) | 121 (82.3) | 123 (86.6) | 1 | 1 |
| If applicable, d | | | | 5 | 4 |
| Mean (SD) | 18.5 (19.2) | 17.0 (17.5) | 19.9 (20.7) | | |
| Median (IQR) | 12 (4-27) | 10 (4-26) | 14 (5-28) | | |
| Renal replacement therapy, No. (%) | 82 (28.5) | 43 (29.3) | 39 (27.7) | 1 | 2 |
| If applicable, d | | | | 5 | 5 |
| Mean (SD) | 12.3 (13.2) | 11.9 (13.7) | 12.8 (12.8) | | |
| Median (IQR) | 8 (4-15) | 7 (4-14) | 8 (5-16) | | |
| **Clinical Measures** | | | | | |
| Charlson Comorbidity Index, mean (SD)[a] | 4.0 (2.9) | 4.0 (3.0) | 4.0 (2.9) | 1 | 1 |
| *ICD-10* diagnoses, No. | | | | 6 | 7 |
| Median | 9 | 9 | 10 | | |
| Mean (SD) | 10.1 (4.7) | 9.6 (4.4) | 10.6 (5.1) | | |
| BMI, mean (SD) | 27.3 (6.0) | 27.3 (6.0) | 27.3 (5.9) | 3 | 9 |
| Depression | | | | 3 | 6 |
| MDI, mean (SD)[b] | 18.1 (10.0) | 18.4 (9.8) | 17.8 (10.1) | | |
| Depressive symptoms, No. (%) | 68 (24.2) | 36 (24.8) | 32 (23.5) | | |
| PTSD | | | | 3 | 6 |
| PTSS-10, mean (SD)[c] | 23.6 (10.4) | 24.0 (11.0) | 23.2 (9.7) | | |
| Score >35, No. (%) | 41 (14.6) | 22 (15.2) | 19 (14.0) | | |
| TICS-M, mean (SD)[d] | 33.4 (3.6) | 33.7 (3.4) | 33.1 (3.9) | 1 | 0 |
| Neuropathic symptoms | | | | 4 | 9 |
| NSS, mean (SD)[e] | 3.6 (3.2) | 3.6 (3.3) | 3.7 (3.1) | | |
| Score 3-10, No. (%) | 164 (59.2) | 83 (57.6) | 81 (60.9) | | |
| Pain | | | | | |
| Intensity: GCPS PI, mean (SD)[f] | 43.8 (24.4) | 43.7 (25.6) | 43.9 (23.1) | 5 | 9 |
| Disability: GCPS DS, mean (SD)[f] | 36.2 (34.6) | 36.0 (34.5) | 36.4 (34.8) | 7 | 12 |
| Severe pain: GCPS category >1, No. (%) | 54 (19.6) | 26 (18.2) | 28 (21.0) | 5 | 9 |
| **Health-Related Quality of Life, Mean (SD)[g]** | | | | | |
| SF-36 | | | | 12 | 15 |
| MCS | 49.0 (12.5) | 48.8 (12.5) | 49.2 (12.6) | | |
| PCS | 25.3 (8.8) | 25.9 (9.4) | 24.7 (8.0) | | |

Abbreviations: BMI, body mass index; GCPS DS, Graded Chronic Pain Scale Disability Score; GCPS PI, Graded Chronic Pain Scale Pain Intensity; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; ICU, intensive care unit; MDI, Major Depression Inventory; NSS, Neuropathic Symptom Score; PTSD, Posttraumatic Stress Disorder; PTSS, Posttraumatic Symptom Scale; SF-36 MCS, Short Form 36 Health Survey Mental Component Score; SF-36 PCS, Short Form 36 Health Survey Physical Component Score; TICS-M, modified Telephone Interview for Cognitive Status.

[a] Range of possible scores, 0-37. High score indicates high impairment.

[b] Range of possible scores, 0-50. High score indicates high impairment.

[c] Range of possible scores, 10-70. High score indicates high impairment.

[d] Range of possible scores, 0-50; includes only values greater than 27 (inclusion criterion). High score indicates low impairment.

[e] Range of possible scores, 0-10. High score indicates high impairment.

[f] The range of possible scores is 0-100. High score indicates high impairment.

[g] Range of possible scores, 0-100. High score indicates low impairment.

### Secondary Outcomes

A total of 63 secondary outcomes were analyzed at both 6 and 12 months (including the 12-month MCS score).

A respective 28 (6 months) and 30 (12 months) outcomes did not show significant differences (at an uncorrected α = .05) between both groups, including physical health-related quality of life and mental health outcomes (eTable 2 and eTable 3 in Supplement 3). Overall mortality was 13.7% (n = 40) at 6 months after ICU discharge and 18.2% (n = 53) at 12 months after ICU discharge (eFigure 1 in Supplement 3). If any, potential intervention effects were observed in measures of functional outcomes only: at 6 months, sepsis survivors receiving the intervention had better physical functioning (mean XSFMA-F score, 38.0 [95% CI, 32.5 to 43.5] vs 46.9 [95% CI, 40.9 to 52.9]; *P* = .04; difference, −8.9 [95% CI, −17.02 to −0.78]), less physical disability (mean XSFMA-B score, 42.5 [95% CI, 36.6 to 48.4] vs 52.4 [95% CI, 46.2 to 58.7]; *P* = .03; difference, −9.9 [95% CI, −18.49 to −1.31]), and fewer ADL impairments (mean, 8.6 [95% CI, 8.0 to 9.1] vs 7.6 [95% CI, 7.0 to 8.2]; *P* = .03; difference, 1.0 [95% CI, 0.16 to 1.84]) than usual care. After adjusting for prespecified baseline covariates, these potential effects were persistent. In addition, survivors of sepsis receiving the intervention had potentially fewer sleep impairments at 12 months after ICU discharge than controls (mean Regensburg Insomnia Scale score, 10.3 [95% CI, 9.2 to 11.4] vs 12.1 [95% CI, 10.8 to 13.4]; difference, −1.8 [95% CI, −3.5 to −0.10]).

In addition, the PCP documentation data at 6 and 12 months provided no evidence for group differences in PCP care (eTable 8 in Supplement 3).

## Discussion

Among survivors of sepsis, a primary care-based intervention, compared with usual care, did not improve mental health-related quality of life.

To our knowledge, this is the first large-scale, randomized controlled clinical trial of an intervention to improve outcomes in survivors of sepsis in primary care.

This sample of survivors of sepsis had similar mean ages and rates of existing comorbidities as compared with other cohorts.[38,39] The prevalence of depressive and PTSD symptoms was slightly less than that among other populations of survivors of critical illness,[40,41] whereas neuropathic symptoms and severe pain were more frequent.[42,43] Physical function, as measured by the SF-36 Physical Function subscore, was substantially lower than in the German population (mean, 85.71 [SD, 22.1]; n = 2886)[36] and also lower than in some comparable cohorts[44,45] and intervention studies.[46,47] Thus, patients may have been more sensitive to the intervention's focus on increasing motivation to be physically active.

Study patients were exposed to longer durations of mechanical ventilation and ICU length of stay than reported in other studies.[4] ICU length of stay and duration of mechanical ventilation were shown to generally be longer in Europe than in the United States, especially in survivors of sepsis.[48,49] In addition, extensive ICU length of stay may have facilitated patient identification by the intensivists.

There was no evidence for a differential treatment effect on the study's primary outcome, postsepsis MCS scores. This finding is similar to those from previous trials of care management interventions following critical illness.[12,46,47,50] The absence of an intervention effect on the primary and most secondary outcomes can be considered using the PICO (Population, Intervention, Controls, Outcome) frameworks.[51]

### Population

The studied cohort experienced heterogeneous clinical multiple conditions. This primary care-based intervention may not have been sufficiently focused to address all their diverse medical and psychological needs.[52] Future trials may evaluate interventions in different patient subgroups targeting specific postsepsis sequelae. Larger samples should be included to address smaller but potentially still clinically relevant effects of primary care interventions.

### Intervention

The exploratory analyses indicated no intervention effects on mental health symptoms. These results may reflect lack of intervention intensity and specificity or absence of clinically effective interventions. However, there is growing evidence that after critical illness, mental health outcomes can be improved through effective psychological interventions targeting specific syndromes.[52,53]

### Controls

According to process data derived from control PCPs (eTable 8 in the Supplement), usual sepsis aftercare in Germany seems to be highly intensive. PCP training and consultation may have been insufficient to yield a meaningful improvement in the level of care. Observational research may provide more insights into existing usual sepsis aftercare in diverse health care systems.

### Outcome

The wide range of postsepsis sequelae may not be adequately reflected in a rather global outcome measure, such as change in SF-36 MCS score. Furthermore, the cohort's baseline mental health-related quality of life was similar to healthy population norms in Germany, reflecting a limited potential for improvement in the MCS score. Last, the exclusion of patients with more severe cognitive dysfunction may have led to a ceiling effect compared with other trials. For future trials, more specific primary outcomes should be considered.

Up to years after the ICU discharge, many patients seem to share their needs with a reliable medical professional.[54] Yet the PCP is not involved systematically in post-ICU care.[55,56] This study may shed light on PCP relevance, addressing major concerns recently identified as "barriers to practice."[57] These include checks on transition from ICU through to community reintegration, linkage, and clinical decision support to primary care, inclusion of a case manager, and educational information for patients and PCPs. Compared with the large-scale PRACTICAL trial on follow-up care in ICU clinics,[47] this study defines a clear

function for the PCP in sepsis aftercare. Follow-up care combining specialized ICU clinics and integrated PCPs may improve outcomes.

This study's exploratory findings suggest possible improvements of physical function and ADL impairments. Additional research is needed to confirm these results. Possible mechanisms of action for these findings may include increased patient motivation (despite the presence of pain) to partake in physical activity owing to regular case manager telephone calls with goal-setting and basic behavioral activation. Increased PCP supportiveness in the intervention group may also have motivated patients to be more proactive, possibly reflected by the increased rating in number of Patient Assessment of Care for Chronic Conditions items (eTable 9 in Supplement 3).

This study has strengths and limitations. It was possible to enroll a large number of patients in spite of the challenges of recruiting critically ill patients for research.[58] Intervention integrity went as planned[59] (eFigure 2 in Supplement 3), including the acceptance of an external medical consultant by the patient's PCP. These findings are encouraging for further interventions in the primary care setting.

Loss to follow-up was balanced between the groups and low, in contrast to sample size calculations that allowed for 40% dropout. Baseline values were missing for some secondary outcomes owing to patients' severely impaired clinical condition. A carryover effect (from treatment to control) may have occurred for 1 PCP, inducing a bias toward a null effect. Calling control patients to collect follow-up data may have led to an intervention effect, possibly leading to underestimation of the intervention effects.[60] In addition, nonblinded outcome assessments also may have biased the results.[61] The intervention is not generalizable to all survivors of sepsis in various outpatient settings.

## Conclusions

Among survivors of sepsis or septic shock, the use of a primary care–focused team-based intervention, compared with usual care, did not improve mental health–related quality of life 6 months after ICU discharge. Further research is needed to determine if modified approaches to primary care management may be more effective.

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BRIEF OBSERVATION

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# Long-Term Courses of Sepsis Survivors: Effects of a Primary Care Management Intervention

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## 2.4 Qualitative Experteninterviews mit Patienten und Hausärzten zur Wahrnehmung einer hausärztlichen Sepsis-Nachsorge

***Originalarbeiten:***

*Gehrke-Beck S, Bänfer M, Schilling N, **Schmidt K**, Gensichen J, Heintze Ch. The specific needs of patients following sepsis: a nested qualitative interview study. BJGP Open 1.1 (2017). doi: 10.3399/bjgpopen17X100725.*

*Gehrke-Beck S, Turner K, Gensichen J, Heintze Ch, **Schmidt K** (shared last authors). GPs' perspective and experiences in caring for patients with post-intensive care syndrome. A qualitative study. BMJ open 11.2 (2021): e040533. doi: 10.1136/bmjopen-2020-040533.*

***2.4.1 Hintergrund und Zielsetzung:*** Das Erleben der postakuten Phase nach Sepsis sowie einer strukturierten hausärztlichen Nachsorge durch Patienten und Hausärzte werden durch eine quantitative Datenerfassung nur unzureichend abgebildet. Eine qualitative Exploration dieser Themen kann dazu beitragen, diese Lücken zu schließen.

***2.4.2 Methodik:*** Gegliedert nach den Interventionselementen Schulung und *Monitoring* wurden qualitative, leitfadengestützte und semistrukturierte Interviews mit 19 Patienten [38, 39] und 13 bzw. 14 Hausärzten [40] durchgeführt, digital aufgezeichnet, transkribiert und mittels qualitativer Inhaltsanalyse nach Mayring ausgewertet.

***2.4.3 Ergebnisse:*** Die im *British Journal of General Practice* publizierte Arbeit fokussiert die Wahrnehmung der patientenbezogenen Interventionselemente: Von den Patienten selbst wurde die Begleitung durch die *Case Manager* überwiegend positiv bewertet. Schulung sowie *Monitoring* vermittelten einigen Betroffenen ein Gefühl von Sicherheit und ermöglichten ihnen eine hilfreiche Reflexion des eigenen Gesundheitszustandes. Einige Patienten lehnten jedoch tiefergehende Befragungen zu ihrer Erkrankung ab, andere vermissten handlungsrelevantere Unterstützung. Ein Großteil der Hausärzte schätzte die regelmäßigen klinischen Informationen sowie die zusätzliche Betreuung der Patienten durch das *Monitoring.* Einige Kollegen äußerten sich kritisch zu Zeitaufwand, klinischer Relevanz der Informationen sowie zur Delegation von Versorgungsaufgaben an die *Case Manager*.

Die Publikation im *British Medical Journal open* vertieft die hausärztliche Perspektive um generelle Aspekte der Sepsis-Nachsorge sowie auf die empfangene Hausarztschulung. Die

stabile, langfristige Beziehung zu ihren Patienten mit guter Kenntnis des medizinischen Hintergrundes wurde als hilfreich für die Sepsis-Nachsorge gewertet. Allerdings fehlt oft spezifisches Wissen. Die Hausarztschulung und der damit verbundene Wissenszuwachs wurden von den meisten Kollegen geschätzt.

***2.4.4 Diskussion und Schlussfolgerung:*** Ein Großteil der befragten Sepsispatienten scheint von der Intervention profitiert zu haben. Dennoch kann eine sepsisspezifische Schulung durch mögliche Aktivierung von schweren Erinnerungen die Betroffenen auch psychisch belasten. Hier sollte zukünftig vor Thematisierung der Zeit auf der Intensivstation die Bereitschaft dazu und ggf. Hinweise auf eine bereits bestehende Symptomatik psychischer Belastung eruiert werden.

Hausärzte sind durch ihre langfristige Arzt-Patientenbeziehung und das ganzheitliche Verständnis ihrer Patienten wichtige Akteure in der Sepsis-Nachsorge. Eine spezifische Schulung sowie ein *Case Management* durch medizinische Fachangestellte könnten Wissenstransfer und Organisation der Sepsis-Nachsorge unterstützen, wenn sie auf die Arbeitsabläufe in der Hausarztpraxis abgestimmt sind. Wünschenswert wären dazu ein verbesserter intersektoraler Informationsfluss sowie die Implementierung von Inhalten post-intensivmedizinischer Nachsorge in die hausärztliche Fort- und Weiterbildung.

*(Durch die Einbeziehung der hausärztlichen Perspektive in beide Arbeiten wurden teilweise identische Zitate verwendet.)*

BJGP Open

RESEARCH

# The specific needs of patients following sepsis: a nested qualitative interview study

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## Abstract

**Background:** Survivors of sepsis suffer from multiple critical disease sequelae when discharged to primary care. There is a lack of structured aftercare programmes and case managers may be helpful in caring for patients with chronic critical disease.

**Aim:** To gain insight into the functioning of a structured aftercare programme for post-sepsis patients in general practice.

**Design & setting:** A qualitative study using semi-structured interviews with patients and GPs across Germany who participated in an randomised controlled trial of a structured aftercare programme for post-sepsis patients, which included patient education and case manager monitoring.

**Method:** Qualitative interviews with 19 patients and 13 GPs were audiorecorded, transcribed verbatim, and analysed using qualitative content analysis.

**Results:** Patients appreciated the information given in the patient education session, but some disliked it because it reminded them of their serious illness. GPs appreciated patient education because well-informed patients are more likely to participate in follow-up. Patients appreciated the case monitoring because it made them feel safer and more cared for and helped them reflect on their health issues. However, some patients felt uncomfortable with the regular questioning. GPs appreciated the case management programme because they received regular clinical information. However some GPs were wary of the clinical relevance of the information, the delegation of the patient to the nurse, and efficiency of time. Both patients and GPs requested more clinical support, such as easier access to psychotherapists.

**Conclusion:** In general, both patients and their GPs appreciated patient education and monitoring following sepsis. Patients' retrospections and worries about their serious illness need to be considered.

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## How this fits in

After discharge from hospital with sepsis, patients experience long-term physical and psychological sequelae of their illness. No aftercare schemes are established so far and follow-up interventions in

randomised controlled trials (RCTs) showed heterogeneous results. This interview study nested in an aftercare RCT, elicited the effectiveness of a case manager follow-up. Possible barriers that emerged were concerns about education for patients and delegation of tasks and care for GPs.

## Introduction

In an intensive care unit, sepsis is a common diagnosis with 4% of all ICU stays accounting for sepsis and 11% for severe sepsis.[1] In primary care, the follow-up of a post-sepsis patient is not an everyday routine event and a GP can expect to see a patient for follow-up after sepsis two to three times per year.[1]

Post-sepsis patients can experience multiple sequelae. Nearly all patients discharged after critical care have impaired activity of daily life;[2] up to 50% suffer from critical illness-like neuropathy and myopathy.[2] Post-traumatic stress disorder (PTSD) and depression affect one-third of patients[2–5] and long-term mortality after discharge is significantly increased.[6] GPs need to initiate, monitor, and coordinate care for the complex needs of these patients after discharge. A structured aftercare programme could be helpful and support GPs but currently one does not exist. General hospital-based aftercare programmes have been evaluated with heterogeneous effects.[7]

The SMOOTH (Sepsis Survivors Monitoring and Coordination in Outpatient Healthcare) study evaluated a structured aftercare programme in primary care. The study included adult survivors of severe sepsis or septic shock according to International Classification of Diseases-10 (ICD-10) codes in 19 intensive care units in Germany. The structured aftercare included patient and GP education and patient monitoring by a case manager. Intensive care nurses were trained as case managers. The educational session for patients took place at their homes. The case manager provided information on sepsis sequelae and treatment options, and encouraged adherence to medication, physiotherapy, and a recommended diet. Monitoring consisted of one initial home visit and consecutive calls every 4 weeks for half a year. The results of the monitoring were sent to the liaison GP, who provided clinical decision support to the patient's GP. Details of the RCT are published elsewhere.[8] The study did not find improvement in mental health-related quality of life.[8]

The aim of this interview study was to elicit the views of patients and their GPs on the functioning of the case manager intervention.

## Method

### Design and participants

This was a qualitative, observational study using semi-structured interviews with patients and GPs from the SMOOTH study in Germany. Patients and GPs that had experienced the intervention for at least 8 months between April 2013 and March 2014 were interviewed. Maximum variation sampling using the criteria age, sex, and pre-existing chronic disease was conducted and saturation was reached after 19 patient interviews and 13 interviews with GPs.

### Data collection and analysis

Interview guides for patients and doctors were developed from a theoretical framework derived from literature research covering sepsis sequelae, sepsis aftercare, and case-manager intervention in other chronic conditions.[7,9–12] This study reports the perspectives of patients and GPs on the case manager functioning in the intervention; that is, on the delivery of patient education and on the monitoring.

After written consent, two trained researchers from medical and nursing backgrounds conducted the interviews. Most patients chose to be interviewed at home (with one in a dialysis practice, and one in the workplace) and all doctors chose to be interviewed in their practice.

Interviews were audiorecorded, transcribed verbatim, and checked against the audiorecording by an independent researcher. Interviews were analysed using qualitative content analysis using Mayring.[13] Patients and GPs interviews were analysed separately but preliminary results were discussed among the coders and new questions to the material evolved. The researchers started coding with a deductive codes framework derived from literature research. By analysing the text step-by-step, they inductively added and changed categories deriving from the material. The final coding

Box 1. Coding framework

| | | | |
|---|---|---|---|
| **Patient perspective** | | | |
| Patient education | Information | Written information as reference for arising questions | |
| | | Lack of interest | |
| | | Refusal of information | Recall of burdensome memories |
| | Education session | No recall of education | |
| | | Effect on health behaviour | |
| Monitoring | Questioning | Safety | |
| | | Personal attention | |
| | | Encourages personal reflection on health | |
| | | Inconvenient | |
| | | Recall of burdensome memories | |
| | Care | Helpful talking | |
| | | Practical help | |
| | | Lack of practical support and direct help | |
| | Feedback of results | Feedback not noticed | |
| | | Feedback noticed, not discussed with GP | |
| | | Results discussed with GP | |
| | | GP considered monitoring results irrelevant | |
| **GPs' perspective** | | | |
| Patient education | Not noticed | | |
| | Considered unnecessary | | |
| | Patient autonomy improves GP care | | |
| Monitoring | Effects on care | Enhances patient wellbeing | |
| | | Additional medical information | |
| | | Unnecessary for uncomplicated patient | |
| | | Not time saving | |
| | Delegation | Personal patient contact necessary | |
| | | Time and money expenses | |
| | | Burden for patients | |
| | | Benefits of delegation | Additional perspective |
| | | | Additional home visit |
| | | | Active questioning |
| | Implementation of therapy | No problems | Problems expectes in similar patients in different circumstances (location, insurance status) |
| | | Financial strains | |
| | | Problems of avaibility | |
| | | Problems of transport | |

framework (***Box 1***) was applied to all interviews. Intercoder reliability was assessed in two interviews in each group. Quotations were translated to from German to English for this article.

# Results

## Study population

Nineteen patients and 13 GPs were interviewed (see ***Table 1*** for participant characteristics). Patient interviews lasted 18–67 minutes (mean 39 minutes), interviews with GPs lasted 12–28 minutes (mean 20 minutes).

## Patient education: the patient perspective

Some of the patients interviewed did not remember the education session or any information given to them at all, even when they were reminded of the circumstances. Of those who could recall the education session or the manual being handed over, some stated a lack of interest, as they felt quite well again:

> 'That wasn't necessary. Don't know what they wanted with it. Don't have a clue. Well, as I didn't feel bad.' (P11)

Some even refused the information that was given to them. They felt burdened as the issue of their illness was picked up again and made them remember their time at the intensive care unit:

> 'Yes, I got a manual ... it was somehow just too much for me then.' (P14)

Some patients appreciated the information given in the education session and used the written manual provided later on as a source of information when needed:

> 'The manual is very important to me. It's in the living room. In case I want to look something up. And if I am unsure — I often get it out.' (P10)

Some reported changing their health behaviour after they got more information and as a consequence, got more involved in the treatment of their illnes:

> '... with regard to that I may say that some things got to me, so I started again to rebuild me, especially regarding food, when it wasn't tasty what should I say? You just eat five meals. Yes, you just eat five meals then. Ok.' (P16)

## Patient education: the GP perspective

Some of the GPs interviewed did not know about or notice the patient education:

> 'Well, I don't know if he got some education ... did I get any reports?' (GP2)

Some considered patient education in this context as unnecessary, as patients were feeling well again or were well informed beforehand. A few GPs noticed theirs patient were well informed because of the education given to them by the case manager and acknowledged that it made the treatment easier:

> 'I found that unusual, that he was so well-informed. I appreciated that. Well, that really helps.' (GP9)

**Table 1.** Participants characteristics

| | Patients | GPs |
|---|---|---|
| Total | 19 | 13 |
| Male | 12 | |
| Female | 7 | |
| Mean age (range), years | 61 (42–84) | 54 (41–64) |
| Mean time working in practice (range), years | – (–) | 19 (9–33) |

## Case manager monitoring: the patient perspective

Patients' views of case manager monitoring concerned the monitoring visits and phone calls and the consequences they experienced in their care.

### Experiences of questioning

Some patients reported that the repeated questioning by the case manager made them feel safe:

> 'That was reassuring to me. That was reassuring — I felt in good hands.' (P2)

And that they received personal attention:

> 'Somehow, that was pleasant, as I was still at home, I still was on sick leave, when she phoned and asked whether I had half an hour. That was, well, somehow nice. I would say.' (P13)

Some patients explained that the repeated questions made them think more about their health issues:

> 'I could reflect on my own then, how I really felt. For that, it wasn't bad actually ... well, I considered it helpful. For me as a patient.' (P18)

A few stated irritation with the monitoring process as it was inconvenient to them:

> 'There was a short time, it simply was annoying to me. Yes. Let's be honest. It was annoying to me.' (P1)

Some found the monitoring wearing as they did not want to talk about their illness and did not want to be reminded of their time spent in the intensive care unit:

> 'As I wanted to get done with it — well, that was always refreshed again, I had that feeling. As I said, I was sometimes so irritated, not with the woman, but as I didn't want to talk about it anymore.' (P13)

### Experiences of care

Some patients felt cared for with the case manager monitoring as talking about their health issues and the counselling taking place was helpful:

> 'It was pleasant, that one could talk to someone else, too. As sometimes I, as before Christmas, when sometimes I start again a depressive phase ... that there is another someone. That helped me.' (P15)

Some got practical support from the case manager in sorting out organisational matters:

> 'When I approached her ... when I had problems ... with [*prolonging my*] sick leave. Yes, and then she at once was willing [*to help me*] to get a letter and a report written from.' (P2)

A number of patients felt that the questioning only occurred to get study data and did not see the benefit of monitoring for them. They felt a lack of care and missed practical support:

> 'The woman, from the study, you could tell her: look, I have a problem since then, yes. And she passed it on and I told her: my hip is aching. She passed that on. But there was nothing that was done.' (P14)

### Feedback to GPs

Many patients did not notice that the results of the case manager monitoring went back to their GP so that they could adapt treatment:

> 'The feedback and the advice you were asking about I have noticed nothing, nothing negative, nothing positive. I would have liked to notice it, one way or another.' (P7)

Some knew, that their GP got information from the study but that was not discussed with them:

'Yes, he has these SMOOTH study papers lying around. I went last week to see him. Then I saw that paper lying around.' (P3)

A few patients said that results were discussed with them:

'She always said when I was there: yes, it arrived and actually everything was ok. There were no aspects that suggested that something should be done.' (P18)

Some reported that the GP felt the monitoring was unnecessary:

'Yes, he told me the lady [*case manager*] was there. And then he died laughing at the many questions.' (P10)

## Case manager monitoring: the GP perspective

GPs reported that three main aspects of case manager monitoring evolved: effects, delegation, and problems of implementation of advised therapy.

### Effects of regular case manager monitoring

A number of GPs assumed their patients felt cared for and safe when being monitored by a case manager and that that may help them getting better:

'I do think so, I do think so, because it gave her some safety and kept her grounded, that simply there is somebody who pays attention and she knew, she comes again and that was enhancing her quality of life I think.' (GP5)

Few GPs reported gaining additional information from the monitoring that was helpful for guiding or initiating therapy and that may have been missed otherwise:

'At one point, it happened, I believe, the patient had more severe pain and that came as feedback from the study, the red flag came and what should I do ... I must say, that I am not very keen on home visits and the patient, as I said, wasn't mobile really. There was the contact with his wife and I went there when it got worse. But she didn't report about that and he did not phone up here either and say, you have to come.' (GP11)

Some GPs considered the monitoring unnecessary, as their patient had an uncomplicated course of disease:

'No, nothing at all. Everything was calm and uncomplicated. Basically, after the rehabilitation therapy everything was uncomplicated and after that it remained uncomplicated ... yes, well, he was really like he was before.' (GP10)

Some considered the monitoring by a case manager as generally ineffective, as they felt that this task could not be delegated and they could rely only on what they see themselves:

'... well, I think it doesn't release me from my duties, well, for the patient it is certainly pleasant ... I'd say for me as a GP ... what the colleague did there, the talking, is detailed and specific for that condition, but well, I think, basically one doesn't absolutely need it.' (GP5)

### Concepts of delegation

Some GPs expressed that any history taking and examination could only be done by doctors as the personal contact with the patient is most important:

'I take all histories myself, the patients then can relate to me ... and I know how the patient is. One also gets to know the character during the history taking and now when I only get a paper from somebody else, which is very thorough ... I am not interested in that.' (GP6)

Some noted the financial and time costs of the case manager monitoring:

'We just don't have the time to read through such folders for each patient .'(GP6)

One GP mentioned a possible burden for patients when an additional person is involved in their care:

> 'Mostly, that [*involvement of another person*] is an excessive demand for elderly people and they feel it is a burden and don't want that.' (GP12)

Some GPs saw the benefits of involving a case manager in the follow-up of patients. Advantages they mentioned were a different point of view, additional home visits, and active questioning:

> 'Yes, well, its probably not wrong to ... that patients are monitored long-term and also questioned even independently or just independently from the doctor, because the doctor has a certain point of view, especially when he has known the patient a long time, well ... this external business ... can bring a new aspect to the matter. Well for the patient, it is, I believe, not wrong, such long-term-monitoring.' (GP11)

### Implementation of therapy

A number of GPs reported no problems in implementing the therapy necessary for patients following sepsis. Some added that this was the case if the patient was uncomplicated, privately insured, or because the practice was situated in a big city, but they assumed that there may have been problems otherwise:

> 'Here in Berlin we are lucky, we have psychological care available and rehabilitation care, we have everything readily available here in Berlin. We are better off than a rural GP in [*small town*], where I come from.' (GP10)

Some GPs reported financial limitations. German GPs have a limited budget for medication and physiotherapy and some found it difficult to care for those patients within these boundaries:

> 'When it comes to physiotherapy, speech therapy, occupational therapy even when she has a severe critical illness, we are left alone, well that is for me the biggest problem ... that we really want to treat the severely ill patients well and according to guidelines and that we don't have the possibility to do it.' (GP1)

Some mentioned problems finding a psychotherapist or rehabilitation clinic for their patient:

> 'Well, he still has a post traumatic distress syndrome and he still is looking for a psychologist. I believe, he has now found one, but it isn't definite, it is only a trial appointment. Here ... it is very difficult to find something. (GP4)

Some experienced problems with transport for patients who were not able to walk:

> 'As I said, [*the patient*] needs a rollator and a daily walk to physiotherapy is not reasonable for him, this they don't understand, well, normally he should, there is an outpatient rehabilitation programme in ... street, he would need to get transport there daily forth and back ...' (GP2)

## Discussion

### Summary

This qualitative study gained insights from patients and GPs into the case manager function in a programme for post-sepsis aftercare. Some patients reported a benefit from the patient education. Some changed their health behaviour and GPs noticed well-informed and motivated patients. Other patients had no recall of the education session. Reasons for that were not clarified completely, but problems brought up by patients were subjective and therefore some showed a lack of interest and a refusal of more information as it would bring back memories of their illness. Psychological burdens (such as PTSD or depression) may have hindered some patients from benefitting from patient education.

Patients and GPs appreciated the feeling of safety and personal attention provided by the monitoring of a case manager. As with patient education, some patients felt burdened with the repeated questioning as it recalled the difficult times of their illness. Some patients expressed the wish for more practical support with organisational issues Also, some GPs experienced organisational difficulties with the implementation of therapy.

GPs' views on the delegation of monitoring tasks to a case manager were heterogeneous. Feedback of the monitoring results back to the GP and benefit for their treatment was not clear for a number of patients. While some GPs acknowledged the potential benefits and few received additional information about their patient in the study, some felt that the personal contact with patients could not be delegated and therefore considered the case manager monitoring unnecessary.

## Strengths and limitations

This study combined data from patients and GPs and therefore explored the phenomena from two perspectives. Socially desired answers may introduce bias, however it was observed throughout the interviews that patients and GPs felt free to criticise the interventions.

In the RCT, GPs were recruited when their patient was included in the study and few GPs refused. Some GPs declined an interview due to lack of time or interest, which may have caused selection bias of motivated GPs. Most patients did not give reasons for not taking part in an interview; they may have declined because they were still psychologically distressed, or because of time constraints and financial restrictions, so therefore a selection bias of healthier patients is also possible.

## Comparison with existing literature

An appreciation of case manager follow-up by patients and GPs has been found in other studies investigating case manager programmes in other chronic diseases and frail older people.[9,14–16] Feelings of safety and control are expressed by patients in those programmes. Practical support by the case manager giving advice or solving practical problems, is experienced by patients in other studies[14] and some of the patients in the SMOOTH trial. However, some patients in the current interview study wished for more practical support and felt left burdened with organisational issues; for example, organising specialist care. Similar experiences are expressed by patients in another sepsis aftercare study: patients in that trial considered that monitoring was a mere data collection with no benefit for their therapy.[17] Problems with access to specialist care and follow-up treatment are also described in other studies.[15,18] It is possible that a lack of therapeutic consequences resulting from the case manager monitoring contributed to the SMOOTH RCT[8] showing no improvement for patients. This may be due to either ineffective communication of results back to the GPs or difficulties in initiating appropriate therapy, such as problems with access to specialist care.

Some of the interviewed patients felt uncomfortable with the patient education and the monitoring questioning as it reminded them of their time at the intensive care unit. They preferred not to stir up their memories of the severe illness. PTSD is common in sepsis survivors[19] and therefore, psychological burdens might be prevalent in a fair number of sepsis survivors. In another intervention study, the nurses conducting a monitoring intervention reported that they felt like they were intruding, when asking their questions.[17] Still, patient education should be available for all patients, as lack of knowledge and understanding of sepsis and the sequelae was shown to be common in patients and their care givers and is considered to be a barrier to adequate help seeking.[18] Patients who did not feel ready to receive information about their illness and thereby enhance autonomy and involvement in their treatment may have impaired effectiveness of patient education in the SMOOTH trial.

## Implications for research and practice

The findings of this study provide information for GPs caring for post-sepsis patients and may support the planning of new interventions for sepsis aftercare.

This study shows that aftercare for patients following sepsis needs special consideration as psychological and physical sequelae are both common and need to be addressed. PTSD and depression are often not apparent and readily reported by the patient. In this study psychological distress was a barrier for some patients to get necessary information about their illness and to accept regular

monitoring. Therefore, it is essential for GPs to understand and recognise psychological and psychiatric critical illness sequelae and address them. The availability of psychotherapy could also be a problem, as reported by some GPs in this study.

Researchers that plan aftercare schemes for post-sepsis patients should develop interventions to deal with existing psychological burdens such as PTSD. Tackling that condition could improve quality of life and enable patients to become more actively involved in their treatment and follow-up.

The effects of the monitoring by a case manager were assessed heterogeneously by the GPs. The patients' experiences of the monitoring visits were mainly positive, but did they not notice effects on the GP care. Future interventions could involve making the results and the feedback more transparent. The monitoring results and feedback from the case manager could be sent additionally to the patient to increase transparency.

Some GPs in this study were reluctant to delegate, however in Germany delegation of patient contacts to a nurse or nurse practitioner is unusual and rarely done. A few GPs saw this as an advantage as they got additional and helpful patient information from the case manager; those GPs valued the monitoring highly. The quantitative data of the trial suggest that GP therapy was rarely altered by monitoring results. In the UK and US, as delegation of follow-up to qualified nurses or nurse practitioners and their involvement in patient care in chronic illness is more common and accepted, case manager monitoring would probably be better accepted and valued by GPs. Communication of results and treatment consequences would possibly be less affected by concerns and reservations of GPs. A better applicability of the intervention in UK and US is therefore likely and could lead to effectiveness by better acknowledging of the monitoring results and more frequent therapy adaptions.

### Ethical approval

The study was approved by the Ethics Committee of the Universitätsmedicin Charité Berlin (EA4/023/13).

### Provenance

Freely submitted; externally peer reviewed.

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# General practitioners' views and experiences in caring for patients after sepsis: a qualitative interview study

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## ABSTRACT

**Background** Patients surviving critical illnesses, such as sepsis, often suffer from long-term complications. After discharge from hospital, most patients are treated in primary care. Little is known how general practitioners (GPs) perform critical illness aftercare and how it can be improved. Within a randomised controlled trial, an outreach training programme has been developed and applied.

**Objectives** The aim of this study is to describe GPs' views and experiences of caring for postsepsis patients and of participating a specific outreach training.

**Design** Semistructured qualitative interviews.

**Setting** 14 primary care practices in the metropolitan area of Berlin, Germany.

**Participants** 14 GPs who had participated in a structured sepsis aftercare programme in primary care.

**Results** Themes identified in sepsis aftercare were: continuity of care and good relationship with patients, GP's experiences during their patient's critical illness and impact of persisting symptoms. An outreach education as part of the intervention was considered by the GPs to be acceptable, helpful to improve knowledge of the management of postintensive care complications and useful for sepsis aftercare in daily practice.

**Conclusions** GPs provide continuity of care to patients surviving sepsis. Better communication at the intensive care unit–GP interface and training in management of long-term complications of sepsis may be helpful to improve sepsis aftercare.

**Trial registration number** ISRCTN61744782.

## Strengths and limitations of this study

- ► This is the first study to explore in detail general practitioners' (GPs) views of managing sepsis survivors.
- ► Using qualitative interviews meant GPs could raise issues that were salient to them.
- ► Some of the interviews were short due to GPs having limited time to take part.
- ► Only GPs in one metropolitan area were interviewed.

## INTRODUCTION

An increasing number of patients are treated in intensive care units (ICUs) and survive a critical illness such as sepsis.[1] After discharge, patients may suffer from long-term consequences,[2] such as critical illness polyneuropathy, critical illness myopathy, cognitive decline, chronic pain,[3–6] depression or posttraumatic stress disorder.[3 7 8] These sequelae are referred to as the 'postintensive care syndrome' (PICS).[1] They result in lower health-related quality of life and elevated mortality rates, as well as increased healthcare use.[9–11]

International guidelines state that patients with PICS should have ongoing, long-term monitoring and therapy.[12 13] Some patients discharged from ICUs are referred to ICU follow-up clinics. The purpose and structure of these clinics vary between countries, but change of clinical outcomes are rarely shown.[14–17] In addition, continuity of care at an ICU follow-up clinic may be difficult when the patient lives far from the ICU and needs frequent follow-up.[18–20] Even if intensive care doctors and nurses are familiar with complications after critical illness, their role in coordinating ICU follow-up is discussed controversially[17 21]: They seem not to be trained in outpatient care coordination and the clinical variety of possible post-ICU complications.[17] Additionally, they do not know their patients for long and therefore may lack insight into the patient's psychosocial background.[22] On the contrary, general practitioners (GPs) have a long-lasting relationship with their patients and provide care coordination as a core task,[23] which is highly appreciated by the patients.[24] This makes GPs ideal advocates of patients in their rehabilitation pathways. Thus, a Dutch retrospective cohort study found an increased consultation rate in primary care following ICU discharge.[25] Considering that there were more than two million intensive care treatment cases just in Germany in 2017[26] and an assumed increase driven by the COVID-19 pandemic,[27] GPs need to know how to provide best postintensive care to these patients, as it

has been already called for by others.[28] The concept of the PICS is quite recent, but GPs' intensive care experiences may date back to medical studies or early hospital rotations. In a qualitative study, GPs reported lack of background knowledge and confidence in diagnosing and treating postsepsis complications.[29] Kahn and Angus[22] states that GPs need to be educated in how to care for patients after critical illness but do not provide suggestions about how this should be done.[22]

Outreach education delivered by academics to the GPs appeared to change their clinical behaviour and improve patient care.[30] However, current evidence mainly focuses on changing prescribing patterns rather than on complex treatment strategies. Educational outreach visits providing knowledge to primary care for relatively rare medical problems are shown to enhance confidence[31] and are acceptable to GPs.[32] Such an intervention may be effective in educating GPs in how to effectively care for patients with PICS. However, whether it is needs to be assessed.

The SMOOTH trial evaluated a structured aftercare programme in general practice for sepsis survivors including an outreach education for GPs.[33 34] Sepsis is one of the leading causes of long-term-ICU stays and can be viewed as a model illness for critical disease.[35] The intervention evaluated in the trial was designed with reference to the Chronic Care Model[36] at the level of a GP practice. It is focused on patient empowerment, a proactive care team and case management to ensure continuity of care. The trial did not find an improvement in mental health-related quality of life at 6 months after ICU discharge compared with usual care.[33 34] As part of this trial, in-depth interviews were held with GPs to explore their experiences with patients discharged from ICU and the intervention. Qualitative research has been conducted with post-ICU patients in detail[37–43] but, to date, no one had explored in depth the views and experiences of GPs caring for these patients. The aim of this study is to describe GPs' views and experiences of caring for postsepsis patients and of participating a specific outreach training, in order to inform and contribute to applicable future aftercare structures in primary care.

## METHODS

### The SMOOTH trial

The SMOOTH trial is a multicentre randomised controlled trial (RCT) evaluating a primary care based aftercare intervention for sepsis survivors. The intervention included monitoring of the patient by a case manager (a specialised nurse), a patient education session delivered by the case manager and an educational outreach visit by a liaison physician to the GP; details are reported elsewhere.[33] Patients were recruited in the ICU, and when they agreed to participate, their GPs were contacted and asked to join also the trial. Two hundred and ninety-one patients agreed to participate, with 148 patients were randomised to the intervention and 143 patients to the control group receiving usual care. As some patients changed their GPs during the trial, the number of GPs was slightly larger than the number of patients. Three hundred seven GPs were approached to participate. Two hundred and ninety-four (95.8%) agreed and were included in the trial. Of the total 159 GPs in the intervention group, 55 were recruited at the Berlin trial site.

The intervention directed at the GP consisted of one outreach educational visit by a liaison physician—a GP trained in sepsis aftercare. The visit was scheduled after the patient's discharge and according to time preferences of the GPs. It took place in the GP practice and lasted about one hour. The education session included a brief overview of sepsis epidemiology and diagnosis, including red flags in primary care, but focused specifically on the six most common sequelae of sepsis ('Sepsis Six'). The epidemiology of long-term sequelae, practical tools for diagnoses and monitoring, as well as evidence-based therapeutic options in routine outpatient care were presented. A detailed manual covering all the information given and a brief sepsis pocket card summarising main points for everyday practice were handed over to the GP, published elsewhere.[34] The GP was asked to contact the liaison physician later at any moment in the study if questions arose during follow-up of the patient.

### Study design and data collection

As part of implementation evaluation, semistructured interviews were held with the GPs in the intervention group of the RCTs to gain insight into their experiences caring for patients surviving sepsis and the GP education that had been delivered as part of the intervention.

Qualitative methods are applied within the research paradigm of critical realism to complete the results of the quantitative evaluation using a qualitative exploration.[44] Critical realism can be used to understand the complexities in primary care and events and phenomena in this setting.[45] The aim was to illuminate and understand the functioning of the intervention in the social background of a GP practice and to extract suggestions for future and optimised aftercare in general practice.

The research team consisted of a fourth year medical student (NS), who conducted the interviews as part of a research project and four academic GPs (SGB, CH, KS and JG) who were involved in analyses of the data. NS had received training in qualitative research interviews and was regularly supervised throughout the study by SGB and CH, who are experienced qualitative researchers. NS had not been involved in the SMOOTH trial, and interviewees were informed of this, to ensure they felt comfortable making any negative comments about the trial. SGB, CH, KS and JG were involved in the trial. At the time of the interviews, they were not aware that the outreach education did not change patient's mental health-related quality of life (primary outcome).

A topic guide was developed and based on the aims of the study and an understanding of relevant literature. The questions included focused on the GPs' experiences of caring for patients who had survived sepsis and their experiences of the trial intervention.

We purposefully sampled GPs for interview to ensure interviews were held with GPs of varying gender and duration of work experience. All those approached for interview had worked at the Berlin trial site. If GPs were willing to be interviewed, they were mailed information about the interviews and a consent form. GPs willing to be interviewed could stipulate the time and location of their interview. The first interview was used as a pilot, but as no changes were made to the topic guide, this interview was included in the analysis. With participant consent, the interviews were audiotaped and transcribed verbatim by NS. GPs were interviewed until data saturation was reached; that is, when no new themes were identified in the later interviews.

### Patient and public involvement

Patient's perspectives and needs were included into topic guide development by the study team. Beside literature research, it was based on the results of qualitative interviews with sepsis survivors, using the same methodical approach and being published elsewhere.[42]

### Data analysis

The interviews were analysed thematically.[46] Inductive thematic coding was used to gain an overall insight into the perspectives of the GPs. Transcripts of four interviews were read and reread by different members of the research team (SGB, CH, KS and JG) who identified themes and developed initial coding frames. These researchers repeatedly discussed their codes and interpretation of the data. Once the coding frames had been agreed, they were applied to all interviews (see table 1A and B). Coding was done manually by SGB. Results were presented to the research team and discussed until consensus was reached (SGB, CH, JG and KS).

## RESULTS

### Participants

We contacted 18 GPs for interview. Four GPs declined to participate due to lack of time. The 14 GPs who agreed to be interviewed (table 2) chose to be interviewed at work, on practice premises, in a private room. Details of the patients the GPs cared for are shown in table 3. After 14 interviews, theoretical saturation was reached with no new aspects emerging in the last two interviews. The interviews were conducted from January to August 2013 and lasted 12–28 min (mean 20 min). Themes considered relevant to this paper with corresponding quotes are shown in tables 4 and 5.

### Caring for patients after critical illness

When analysing the GPs' accounts, three main themes related to their experience of caring for patients after intensive care were identified as continuity of care and good relationship with patients, GP's experiences during their patient's critical illness and impact of persisting symptoms after discharge.

**Table 1** (A) Coding framework: caring for patients after critical illness. (B) Coding framework: impact of the outreach education

| Themes | *Subthemes* |
|---|---|
| **(A) Coding framework: caring for patients after critical illness** | |
| **Continuity of care and good relationship with patients** | *Previous health status* |
| | *Personality and illness behaviour* |
| | *Social background* |
| | *Continuity of care* |
| **GP's experiences during their patient' s critical illness** | *Lack of information* |
| | *Emotional impact* |
| **Impact of persisting symptoms** | General weakness and limited functioning |
| | Alteration to presepsis condition |
| | Specific diagnosis of common complications after intensive care |
| | Individual complication |
| **(B) Coding framework: impact of the outreach education** | |
| **Acceptability** | *Convenience by outreach visit* |
| | *Time strains and competing tasks* |
| **Improvement of knowledge** | *Persisting elevated mortality after discharge* |
| | *Specific long-term complications (polyneuropathy and post-traumatic distress)* |
| | *Diagnosis of sepsis* |
| | *Relevant summary for practice* |
| **Transfer into practice** | *Identifying complications* |
| | *Initiation of specific therapy* |
| | *Diagnosis of sepsis* |
| | *Low relevance as small patient numbers in practice* |

This study refers to the standards for reporting qualitative research.[56]
GPs, general practitioners.

### Continuity of care and good relationship with patients

At the start of the interview, the GPs were asked to talk freely about their patient. The accounts given suggested that specific medical diagnoses and the acute sepsis diagnosis played a limited role in the GPs' narration. GPs often commented on the patient's condition before they were diagnosed with sepsis, discussing their pre-existing disease and previous general health status. It was evident that many of them were familiar with the patients' medical history.

Many GPs also talked about the patient's personality. They often focused on the patient's coping and illness behaviour as one GP explained:

> … she is actually a very modest… and shy person and for her medical problems she only claimed what she

Table 2 Self-declared details of interviewed general practitioners (GPs).(N=14)

| | |
|---|---|
| **Age* (years)** | 41–68 (mean: 55) |
| Sex | **N (%)** |
| Male | 8 (42.9) |
| Female | 6 (57.2) |
| **Practice organisation** | |
| Joint practices (2–6 GPs) | 6 (57.2) |
| Single practices | 8 (42.9) |
| **Licence to practice since*** | |
| 10–20 years | 1 (7.1) |
| 20–30 years | 3 (21.4) |
| 30–40 years | 6 (57.2) |
| >40 years | 2 (14.3) |
| No data | 2 (14.3) |
| **Practice opening*** | |
| <10 years | 1 (7.1) |
| 10–20 years | 5 (35.7) |
| 20–30 years | 4 (28.6) |
| 30–40 years | 4 (28.6) |
| **Specialisation** | |
| GPs | 7 (50) |
| General internists† | 6 (57.2) |
| Practitioner without specialisation | 1 (7.1) |
| **Practice characteristics, subspecialisations‡)** | |
| Complementary medicine | 7 (50) |
| Psychosomatics | 3 (21.4) |
| Pain management | 2 (14.3) |
| Gastroenterology | 1 (7.1) |
| Infectiology | 1 (7.1) |
| Oncology | 1 (7.1) |
| Diabetology | 1 (7.1) |
| **Home visits per week** | |
| <5 | 3 (21.4) |
| 5–10 | 4 (28.6) |
| >10 | 2 (14.3) |
| None | 2 (14.3) |
| No data | 3 (21.4) |
| **Patients >60 years** (estimate) | |
| <30% | 5 (35.7) |
| 30%–50% | 6 (57.2) |
| >50% | 2 (14.3) |
| **Academic teaching practice** | |
| Yes | 7 (50) |
| No | 7 (50) |

*At the time of the interview.
†A considerable proportion of primary care in Germany is provided by general internists.
‡Multiple mention possible.

Table 3 Characteristics of postsepsis patients cared for by the general practitioners (N=14)

| | |
|---|---|
| Age (years) | 45–82 (mean 66) |
| **Sex** | **N (%)** |
| Male | 11 (78.6) |
| Female | 3 (21.4) |
| **Sepsis focus** | **N (%)** |
| Pulmonal | 3 (21.4) |
| Gastrointestinal | 2 (14.3) |
| Renal | 3 (21.4) |
| Tissue infection | 3 (21.4) |
| Unknown | 3 (21.4) |

really needed urgently at that moment. A very kind and pleasant patient. GP 12

Some GPs also reported on the personal and employment situation of their patients, especially if they felt that this had been important to the recovery of the patient:

> Despite being my age, she had a young daughter and I think that's why she needed to be functioning and go back to work and she needed the money, yes. GP 6

Even if most GPs seemed to know their patients very well, two GPs stated that they started caring for their patients only after the sepsis hospital stay:

> Well, I basically got to know Mr. (…) only as an acute patient after the hospital admission. He looked for a new GP after this adverse fate happened to him.

These two GPs gave little information about their patients.

### GP's experiences during their patient's critical illness

Most GPs commented that they lacked information about the acute sepsis event. They had not been informed about their patient's condition or involved in any of the treatment decisions made while their patient was in hospital. Several GPs could not specify the exact diagnosis and focus of the sepsis.

> The event of sepsis itself, as I said, wasn't diagnosed by me, in the practice, but happened in hospital after the operation and that's why I sort of got him back here as everything was finished. I just had to sort of accept that (…) in the end, I didn't have much to do with it and that's why I don't know much about it. GP 8

Some GPs perceived the acute sepsis event as a tragic lifetime event for their patients and discussed the emotional impact of the serious impact on the patient and his or her family.

> This was a very unlucky course of events (…) surely, everybody asks, why is it just me? GP 3

**Table 4** Quotations: caring for patients after critical illness

| Themes *and subthemes* | Quotation |
|---|---|
| **Continuity of care and good relationship with patients** | |
| **Previous health status** | 'Well, he was a spry patient, he bore his age well and he had no relevant preexisting disease (…) and he came mainly for check-ups'. GP 9 |
| | 'Yes, she needed home visits before. She had an insulin-dependent diabetes, COPD, an heavy nicotine abuse she gave up after a hospital admission, we had home oxygen therapy before, there was a problem with alcohol meanwhile, she had skin problems, heart failure, high blood pressure, all that existed before'. GP 5 |
| | 'A young man, I know him since his school times, over time he developed arterial hypertension. It is obviously in the family, as both his parents suffered from it and a chronic gastritis, apart from this no abnormalities'. GP 3 |
| | 'I didn't have much contact to (him) before, because he was comparatively fit for his age. He predominantly had orthopedic problems. He is still active, playing golf and so on and (…) but internal diseases, that were serious, he didn't have that'. GP 8 |
| *Personality and illness behaviour* | 'She was actually- or she is actually a very modest…. and shy person and for her medical problems she only claimed what she really needed urgently at that moment. A very kind and pleasant patient'. GP 12 |
| | '… (she is a) tall and robust woman, with a croaky voice…a heavy smoker, always unhappy. Niggling, unsatisfied and complaining, but also a fighter'. GP 6 |
| | 'but she always was…she was a though woman and she never liked taking pills and she eventually said, it is too much, she can't take it and she got used to the symptoms and she would like to take smaller doses (…), she preferred to be without pills'. GP 5 |
| | '… well, a rather moaning patient, that came with all kinds of ailments and I considered him generally to be healthier than he himself did'. GP 7 |
| *Social background* | 'She had a quite young daughter. Despite being my age, she had a young daughter and I think that's why she needed to be functioning and go back to work and she needed the money, yes'. GP 6 |
| | '… he himself less, but his wife is quite depressive and that means eventually one has problems in everyday life'. GP 8 |
| | 'I know the whole family (…) I know him only since about ten years but the rest of the family more than 30 years (…). They are all very scientific, that's what I would say. His wife is in a high position in the administration of veterinary surgeons (…), the son is biologist and works in science and the other daughter is a psychologist'. GP 10 |
| | '… she had a comparatively young daughter, despite being my age, she has a young daughter and I think that's why she was in need to come back to normal and go working and she needed the money'. GP 6 |
| *Continuity of care* | 'Well, I basically got to know Mr. (…) only as an acute patient after the hospital admission. He looked for a new GP after this adverse fate happened to him'. GP 2 |
| **GP's experiences during their patient's critical illness** | |
| *Lack of information* | 'The event of sepsis itself, as I said, wasn't diagnosed by me, in the practice, but happened in hospital after the operation and that's why I sort of got him back here as everything was finished. I just had to sort of accept that (…) in the end, I didn't have much to do with it and that's why I don't know much about it'. GP 8 |
| | 'I only saw him again after rehabilitation, I didn't get a discharge letter either. I only got notice of these things as he stood here in front of me'. GP 4 |
| *Emotional impact* | 'This was a very unlucky course of events (….) surely, everybody asks, "why is it just me?"' GP 3 |
| | 'I once visited him in hospital and was shocked (…) well, this was a dramatic story'. GP 10 |
| **Impact of persisting symptoms** | |
| *General weakness and low functioning* | 'Well, she was a shadow of her former self'. GP 6 |
| | '… he is not up and about again. Well, he can't leave the flat, he walks short distances like to the toilet, from bed to toilet, from bed to living room'. GP 11 |
| | 'I have visited him once in the hospital and was shocked. He could only talk slowly, maybe in an orderly way, but he was heavily impaired after this intensive care therapy. And afterwards, it got better, he became clearer from the cerebral point of view and the slowing, that was extreme, went away'. GP 10 |
| | '… in the beginning, she needed house visits, well, I can only see that her health condition only improved very slowly over a long period of time. That's all I can say about it'. GP 12 |
| *Alteration to presepsis condition* | '… but, I must say, (he) had some problems with his peripheral nerves before due to his lifestyle, (due to) alcohol (…) There was some damage before and then, with the sepsis, that only came to the point it became clinically apparent and now that is the situation'. GP 2 |
| | '… just like before, she has from time to time exacerbations of her COPD'. GP 12 |
| | '… he had depression before and had depression afterwards and I believe his depression was even less, (…) He had a longstanding depression so you can't put these things (sepsis) forward'. GP 10 |
| | '… basically, he kept all the diseases he had before and everything grew gradually worse'. GP 11 |

Continued

Table 4 Continued

| Themes *and subthemes* | Quotation |
|---|---|
| *Specific diagnosis of common complications after intensive care* | '… he had this critical illness neuropathy with pains and muscle weakness and at the beginning also psychological problems with insomnia'. GP 1 |
| | '… now (she suffers from) increasing polyneuropathic pain, that needs to be treated with strong pain killers, with opioids'. GP 2 |
| | '… well, he still has a post traumatic distress syndrome, he is still looking for a psychologist'. GP 4 |
| | '… he is impaired a bit by the polyneuropathy'. GP 9 |
| *Individual complication* | '… because she had, she lost her leg with the sepsis and she, she had an amputation and before she could move about and could leave the apartment. But, afterwards, not anymore because she couldn't manage the stairs with one leg'. GP 5 |
| | '… and then she was depressive because she had the colostomy'. GP 6 |

GP, general practitioner.

### Impact of persisting symptoms

GPs mentioned a number of different aspects when they described the condition of their patients after discharge and the impact of sepsis sequelae in their quality of life: general weakness and low functioning, the impact of preexisting diseases, individual specific health impairments and—less frequently—specific diagnosis of long-term complications contributing to PICS.

Many interviewees described a general weakness and low functioning of their patients. They attributed this to the severe illness and the long hospital stay, without specifying the factors and causes contributing to the weakness like underlying illnesses, specific complications or treatment side effects. The focus of their reports was on the consequences for independence and autonomy of their patients rather than underlying pathomechanisms.

> Well, she was a shadow of her former self. GP 6

Many GPs compared their patients' health status to their condition before critical illness. In some cases, they saw their patients' impairment after discharge as, at least in part, attributable to pre-existing and chronic illness. In their perception, the acute sepsis event did not alter status of these patients much.

> Essentially, he kept the diseases he had before and everything got gradually a bit worse. He tended to be depressive before and now it isn't much worse. GP 11

The report about their patient condition and complications after sepsis was in many cases given in common, everyday language without listing specific medical diagnoses or specific sepsis complication. They rather concentrated on reporting on everyday functioning and overall well-being. Only some GPs classified specific sepsis sequelae and precisely stated these diagnoses. Some added being only aware of the diagnosis after the education session, they received as part of the study intervention.

> And mainly… he was quite distressed by the gait disturbance; by the painful paresthesia he had (…) the polyneuropathy was what was left from the sepsis syndrome. GP 8

Some GPs reported individual complications of sepsis or sepsis therapy had the main impact on the patient's quality of life afterwards, for example, the loss of a limb or a persisting colostomy.

> As she had, because of this sepsis, she basically lost the leg, well, she had an amputation and … hmm… she was still quite mobile before and could leave the flat. Hmm, afterwards no longer, because with one leg she couldn't manage the stairs. GP 5

One GP could not contribute to that aspect, as his patient died shortly after discharge.

### Impact of the outreach education

Three main themes that described the impact of the education session were identified: acceptability, improvement of knowledge and the transfer to professional practice.

#### Acceptability

Most participants stated that they appreciated the time and the effort on the side of the liaison physician to come to their premises and adapt to their schedule. They commented that this was an advantage for their own time schedule and comfort.

> I was approached at a time that was convenient for me (…), I didn't need to move anywhere, that could happen here, well, the colleague bothered to come (…) and as I said that was ideal, I would say. GP 2

However, some GPs said they had many patients to care for and tasks to cope with and could not spare any time for the training. A few also mentioned that post sepsis patients are rare in a GP practice and that they would rather save time in continuing education for more common diseases.

> Well, it was very interesting, the education, but this is just another additional point, that takes time and

Table 5 Themes, subthemes and quotations: impact of outreach education

| Themes *and subthemes* | Quotation |
|---|---|
| **Acceptability** | |
| *Convenience by outreach visit* | 'I was approached at a time, I had time and as we arranged it, that was ideal (…) it was announced early enough and I got a mail-reminder an I didn't have to move anywhere, that could happen here, well, the colleague was really committed (…) I would say that was ideal'. GP 2 |
| | '… well, that (the outreach education) happened here in the practice …nice and friendly… adapted to the needs of the doctor… very good, that was comfortable. Didn't burden me much either'. GP 6 |
| *Time strains, competing tasks* | '… well, it was really very interesting, the training, but this is – like today (the interview) – just one more thing, that delays and I would rather for example, go for lunch or something else'. GP 11 |
| | 'We have two thousand patients, work has grown so intense, that one has to leave out everything that is not absolutely necessary'. GP 12 |
| **Impact on knowledge** | |
| *Persisting elevated mortality after discharge* | 'The mortality after discharge, (…) that was very impressive, well, because I thought: sepsis overcome, well, everything is fine and the bird flies on'. GP 2 |
| | '… that statistic, that said, ok, patients that survived this have a much higher mortality (…) these numbers were quite alarming'. GP 5 |
| *Specific long-term complications (polyneuropathy and post-traumatic distress)* | '…well, that was mainly new, that one looks at sepsis as a complex illness with long-term complications. I did look at is more as a complication, that, when cured, is presumably good and done with'. GP 11 |
| | '… the most helpful was, as I said, the connection. Generally with sepsis, that sepsis can cause other diseases (…) it seems, sepsis can cause serious alterations in the peripheral nerves'. GP 2 |
| | '… the fact, that polyneuropathy had a connection to sepsis was not known to me at all'. GP 12 |
| *Diagnosis of sepsis* | '… what kind of symptoms, how sepsis manifests itself, because, one doesn't consider it so much, isn't it?' GP 6 |
| *Relevant summary for practice* | '… we all have learnt that during medical studies, but it is not…one doesn't meet a sepsis survivor every day. It is not everyday business. And that's why I found it interesting, that you had it explained again'. GP 5 |
| | '… in continuing education, we don't get the things that are relevant for practice enough, in that way, it was a nice, short update and training, but nothing really new'. GP 8 |
| **Transfer to practice** | |
| *Identifying complications* | '… and since then, I turn my attention more to those symptoms, (…) I really pay attention to things now, that I didn't consider before. It really helped me'. GP 6 |
| | 'One is sensitized for it. Yes, I now pay more attention, especially regarding polyneuropathy and so on, I watch more closely, I say, ok, be careful, here you must consider that, that is a case you must watch out and ask, if she doesn't tell herself, whether she has symptoms'. GP 5 |
| *Initiation of specific therapy* | '… now, I would always look first, that I talk with him about what he went through and how it felt in the hospital, what impressions, what experiences, what feelings and that one really goes on to arrange for psychological care more quickly'. GP 4 |
| | '… and I also did some of that in practice, I mentioned the referral to a psychologist and that became very clear'. GP 4 |
| | '… from that training I learnt, that it makes sense, to send the patient to physiotherapy. That it is not only about medication, his usual medication and putting it - may be a bit trivial- I would prescribe antidepressants as well'. GP 7 |
| *Diagnosis of sepsis* | '… (reporting a case of postoperative sepsis) and I really was more careful and said, this lady has a sepsis. (…) I now have an eye on these symptoms and I refer more quickly'. GP 6 |
| Low relevance as small patient numbers in practice | 'I don't have any patients after sepsis, that's why I can't change what I am doing'. GP 3 |

> I would prefer for example, to have lunch or something similar. GP 11

### Improvement of knowledge

The majority of practitioners stated that they had gained new knowledge from the education. Many interviewees reported it was new to them that sepsis can cause specific disease sequelae into after hospital discharge.

> Yes, that was largely new to me, that sepsis is seen as a complex illness with long lasting complications. Till now, I saw it more as a complication, that, when cured, is resolved. GP 11

GPs often also stated that they were not aware that mortality is still elevated long-term after discharge until they heard about that in the education session.

> Most helpful was (…) that sepsis for example, has a high mortality, the numbers were alarming! I mean, the mortality after discharge, (…) basically, I thought: Sepsis survived, ok, the bird flies on. GP 2

Some of the GPs reported that they did not know before that polyneuropathy and psychological problems were common consequences after sepsis and intensive care.

I think, I would not have seen the connection before. Because she had so many other reasons for a polyneuropathy, I would have probably linked it to the diabetes. GP 5

One GP acquired more information about diagnosis of a sepsis in a patient, even though that was not in the focus of the education session.

Some GPs stated that they already knew the information given to them, but even when this was the case, they still appreciated the repetition and summary preparing them for the care of the patient.

Well, I didn't find anything really new to me. But it was brought back and I did concentrate on it and looked closer to it. That was new to me and helps me for, well, aftercare. GP 9

One doctor saw no benefit from the education; he had done research in this field before his GP work and had the relevant knowledge before.

### Transfer to practice

Most of the GPs interviewed said that the new information helped them care for the patient included in the trial and that it would help them in their future work with similar patients. Most of them saw a benefit in identifying sepsis sequelae.

… mainly the polyneuropathy and so on, I look out for it more closely. I say to myself: Look out! You must keep that in mind and ask for it, when they don't tell on their own, if they have problems. GP 5

Some reported consequences for the therapy of the patient they cared for within the study and some stated that they would probably change their therapeutic approach to similar patients in the future.

I believe I changed some things afterwards. I mentioned the psychotherapist afterwards, that became quite clear, and (patient's name) did agree to that. GP 4

One GP had quickly diagnosed a patient with acute sepsis since the training, even though diagnosis of sepsis was not its main focus.

Some GPs doubted the relevance of the information for their work. They stated that caring for similar patients was a very rare event in their practice, and therefore, they did not think they would apply the knowledge they had learnt.

I don't have any sepsis patients - that's why I can't change anything about what I do. GP 3

## DISCUSSION

Findings from this study suggest that GPs provide continuity of care and a good relationship with patients and consider pre-existing and chronic disease, personality and coping patterns, as well as social background, when providing post-ICU care to patients. Many interviewees described the long-term impact of sepsis on their patients as a general weakness and malfunctioning and considered it in relation to the patient's presepsis constitution. Some GPs expressed empathy with the serious life event their patient experienced. GPs reported a lack of information about the course of the disease and their patient's condition while they were in the hospital. Diagnosing and listing specific sepsis sequelae played a minor role.

The outreach education session was acceptable to most GPs. Most GPs acquired new information about long-term complications of sepsis. They considered this information as helpful to identify and start treatment for specific postsepsis symptoms. This finding is consistent with findings from a recent qualitative study critical care nurses delivering a recovery programme to ICU survivors.[47] However, some GPs did not value it and pointed to the small numbers of postsepsis patients being in competition with other patients and tasks.

While most of the GPs' accounts suggested a longstanding knowledge of the patient and an individual appraisal of their health impairments after discharge, they lacked detailed medical knowledge about sepsis complications. The outreach education was mainly well accepted and seemed to provide a valid setting to improve knowledge about specific diagnostic and therapeutic concepts GPs can apply in their professional practice.

### Comparison with existing literature

Patients' perceptions of their quality of life after an ICU stay have been examined in several qualitative studies.[43] A wide range of ongoing health impairments was identified, and loss of autonomy was a main aspect.[37–39] The views of the GPs identified here is very close to patients' perspectives. The GPs also reported general weakness and low functioning as a main aspect and a very individual apprehension of complaints and impairment. This congruence may facilitate a patient-centred aftercare especially in a primary care setting.

Difficulties in information flow between ICUs and GPs had been identified before: lack of information about admission or discharge and ongoing needs of patients after an ICU stay and no involvement in treatment decisions were reported by GPs in other studies.[48–50] As valid data on the course of disease and current diagnoses and treatment is essential for follow-up, information during hospital stay and more detailed discharge information for GPs may be essential to enhance quality in aftercare.

It has been shown that GPs lack information on sepsis and identification of post-ICU complications.[29 50] The acquisition of clinical knowledge has been described and explained by forming of 'scripts' with repeated exposure to clinical patterns.[51] With no ongoing experience in handling ICU patients and limited encounters of post-ICU patients, scripts related to the PICS cannot be expected to evolve in GPs in everyday practice. In our study, the educational intervention led to additional knowledge about specific post-ICU complications. This may meet patient's ongoing need for feedback of their ICU history, as well as the resulting impairments.[43]

GPs appreciate personal discussion with experts as a valuable method of continuing education,[52] and outreach visits as a method to reach GPs have been used before and shown to be accepted well.[30] Knowledge gain has been demonstrated, but transfer to practice seemed to be difficult.[30 53] Patient-related intervention may be especially helpful[30] to facilitate knowledge transfer. In our study, GPs reported transfer to practice of the knowledge they acquired, which may be achieved by the patient-related education and the individual discussion of diagnosis and treatment in the practice.

Lack of continuum of care is a major patient concern after ICU discharge.[37 38] The Chronic Care Model can be used to inform the ongoing care at the level of an individual practice and also to organise patient-centred trans-sectoral and interdisciplinary care.[36] Local organisation of a follow-up multiprofessional network and a stepped-care approach could help to ensure continuity of care. This study demonstrates that GPs are familiar with their patients, know about their medical and psychosocial background and consider these aspects when caring for their patients. Therefore, GPs seem to be appropriate ICU aftercare providers. In addition, increased intersectoral information flow could contribute to ensure continuity of care; for example, quality of discharge letters may be improved by training, checklists, software solutions or positive peer pressure.[54 55]

### Limitations

Since 307 GPs were asked to take part in the trial, and 294 agreed, it is likely those who took part in the trial are representative of other GPs in Germany.[34] Being involved in a sepsis aftercare trial informed GPs about the functioning of the RCTs intervention but may have changed their perception of the postsepsis patients they care for. They may have been more preoccupied with and focused on that patient than otherwise. It might be those who agreed to be interviewed were more interested than their peers in sepsis as 4 of the 18 GPs approached for interview declined. As only GPs in the urban area of Berlin were interviewed, specific aspects of GPs in rural settings may have been missed.

The interviews were fairly short, which may limit depth of insights. Time constraints are typical of GPs work and were mentioned repeatedly throughout the interview. As GPs are used to work under pressure, they were able to answer questions quickly and to summarise their experiences. Due to the time pressures they were under, those interviewed were not contacted again to explore whether they agreed with the researchers' analysis of the data. However, themes and subthemes were discussed repeatedly in the research group.

## CONCLUSION

GPs are in a good position to offer continuity of care to sepsis survivors. However, they need training and information flow from secondary care for optimal aftercare provision.

GPs provide a profound and holistic knowledge of these complex patients and to address individually their impairments and residual symptoms. However, lack of specific knowledge about critical illness complications and lack of information and communication with ICU care providers are barriers to optimal follow-up in primary care settings.

GPs should get the necessary background knowledge and individual information of their patients to provide high-quality aftercare. Taking into account time constraints and preferred education formats, outreach visits in the context of discharge of a post-ICU patient may be a valuable source of information and support.

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**Contributors** SGB, KS and CH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: SGB, CH, JG and KS. Outreach training conduction: KS. Acquisition and analysis of data: SGB. Interpretation of data: all authors. Drafting of the manuscript: SGB, KS and KMT. Critical revision of the manuscript for important intellectual content: all authors.

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## 2.2 Implikationen für zukünftige Studiendesigns anhand von Verlaufsformen motorischer Funktion nach Sepsis

***Originalarbeit:***

*Puthucheary ZA, Gensichen JS, Cakiroglu AS, Cashmore R, Edbrooke L, Heintze Ch, Neumann K, Wollersheim T, Denehy L,* ***Schmidt KFR****. Implications for post critical illness trial design: sub-phenotyping trajectories of functional recovery among sepsis survivors. Crit Care. 2020;24(1):577.(IF: 6,7). doi: 10.1186/s13054-020-03275-w.*

***2.5.1 Hintergrund:*** Nach einer kritischen Erkrankung leiden viele Patienten unter teils erheblichen motorischen Einschränkungen. Der Einfluss von Rehabilitationsstrategien konnte bislang nicht eindeutig geklärt werden. Dies liegt unter anderem an der Heterogenität dieser spezifischen Patientenpopulation. Bislang existieren keine Standards zur Auswahl valider Messinstrumente, um motorische Verläufe nach kritischer Erkrankung zu erfassen.

***2.5.2 Fragestellung:*** Ziel dieser Sekundäranalyse war es,

1) Unterschiede zwischen den Verlaufstypen motorischer Verläufe nach überlebter Sepsis hinsichtlich klinischer Parameter sowie
2) klinometrische Eigenschaften der verwendeten Instrumente zur Beurteilung der motorischen Funktion zu evaluieren.

***2.5.3 Methodik:*** 291 erwachsene Sepsis-Überlebende wurden 24 Monate nach Entlassung von der Intensivstation regelmäßig telefonisch befragt. Zur Erfassung der körperlichen Funktion wurden der *Physical Component Score* (PCS) des *Short Form-36 Health Survey* (SF-36) [36] sowie das *Extra Short Musculoskeletal Function Assessment* (XSFMA-F/B) [41] verwendet. Zusätzlich wurden Aktivitäten des täglichen Lebens erfragt. Die Verlaufsformen wurden durch eine Faktorenanalyse verschiedenen Verlaufstypen *(Clustern)* zugeordnet. Der Zusammenhang von Patientencharakteristika und *Cluster-Z*uordnung wurde in logistischen Regressionsanalysen untersucht. Validität, Boden- und Deckeneffekte der verwendeten Instrumente wurden innerhalb der Verlaufstypen bewertet.

***2.5.4 Ergebnisse:*** 159 Patienten konnten über 24 Monate beobachtet werden. Die physische gesundheitsbezogene Lebensqualität war insgesamt gering. Zwei Verlaufstypen konnten identifiziert werden: Eine Gruppe von 61 Patienten (38,4%) zeigte eine fast vollständige Wiederherstellung der motorischen Funktion. Eine weitere Gruppe von 76 (47,8%) Patienten war anhaltend beeinträchtigt. 22 (13,8%) Patienten konnten keinem der beiden Verläufe zugeordnet werden. Alter, Bildungsgrad und Anzahl der Komorbiditäten erwiesen sich als unabhängige Determinanten für eine bleibende Beeinträchtigung (AUROC 0,743 (95%CI 0,659-0,826), $p < 0,001$). In der Gruppe mit anhaltenden Beeinträchtigungen fiel ein hohes Maß an Bodeneffekten in drei der erfragten Domänen des SF-36 auf – körperliche Funktionsfähigkeit (PF) (21 %), körperliche Rollenfunktion (RP) (71 %) und körperlicher Schmerz (BP) (12 %). In der genesenen Gruppe hingegen zeigten sich in denselben Domänen Deckeneffekte: PF (15%), RP (45%), BP (57%). Die Domäne der körperlichen Funktionsfähigkeit (PF) zeigte eine hohe Responsivität zwischen der Entlassung aus der Intensivstation und dem Zeitpunkt sechs Monate danach und war prädiktiv für eine anhaltende Beeinträchtigung (AUROC 0,859 (95%CI 0,804-0,914/ $p < 0.001$).

***2.5.5 Diskussion und Schlussfolgerung:*** Innerhalb einer Population von Sepsis-Überlebenden konnten zwei unterschiedliche Verlaufstypen physischer Funktion identifiziert werden. Ältere Patienten mit hoher Komorbidität und niedrigem Bildungsgrad waren besonders gefährdet für eine anhaltende motorische Beeinträchtigung. Die Domäne der körperlichen Funktionsfähigkeit (PF) des SF-36 zeigte sich als aussagekräftig für den weiteren Verlauf und könnte in zukünftigen Studien vermehrt als primärer Endpunkt eingesetzt werden. Auch sollte zunehmend die Anwendung adaptiver Studiendesigns in Betracht gezogen werden, die einen Umgang mit *Non-Respondern* und spezifische Zielgrößen für Subgruppen beinhalten.

*(Abstrakt entspricht inhaltlich der Originalpublikation, Übersetzung durch den Autor.)*

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RESEARCH Open Access

# Implications for post critical illness trial design: sub-phenotyping trajectories of functional recovery among sepsis survivors

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## Abstract

**Background:** Patients who survive critical illness suffer from a significant physical disability. The impact of rehabilitation strategies on health-related quality of life is inconsistent, with population heterogeneity cited as one potential confounder. This secondary analysis aimed to (1) examine trajectories of functional recovery in critically ill patients to delineate sub-phenotypes and (2) to assess differences between these cohorts in both clinical characteristics and clinimetric properties of physical function assessment tools.

**Methods:** Two hundred ninety-one adult sepsis survivors were followed-up for 24 months by telephone interviews. Physical function was assessed using the Physical Component Score (PCS) of the Short Form-36 Questionnaire (SF-36) and Activities of Daily Living and the Extra Short Musculoskeletal Function Assessment (XSFMA-F/B). Longitudinal trajectories were clustered by factor analysis. Logistical regression analyses were applied to patient characteristics potentially determining cluster allocation. Responsiveness, floor and ceiling effects and concurrent validity were assessed within clusters.

**Results:** One hundred fifty-nine patients completed 24 months of follow-up, presenting overall low PCS scores. Two distinct sub-cohorts were identified, exhibiting complete recovery or persistent impairment. A third sub-cohort could not be classified into either trajectory. Age, education level and number of co-morbidities were independent determinants of poor recovery (AUROC 0.743 ((95%CI 0.659–0.826), $p < 0.001$). Those with complete recovery trajectories demonstrated high levels of ceiling effects in physical function (PF) (15%), role physical (RP) (45%) and body pain (BP) (57%) domains of the SF-36. Those with persistent impairment demonstrated high levels of floor effects in the same domains: PF (21%), RP (71%) and BP (12%). The PF domain demonstrated high responsiveness between ICU discharge and at 6 months and was predictive of a persistent impairment trajectory (AUROC 0.859 (95%CI 0.804–0.914), $p < 0.001$).

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**Conclusions:** Within sepsis survivors, two distinct recovery trajectories of physical recovery were demonstrated. Older patients with more co-morbidities and lower educational achievements were more likely to have a persistent physical impairment trajectory.
In regard to trajectory prediction, the PF score of the SF-36 was more responsive than the PCS and could be considered for primary outcomes. Future trials should consider adaptive trial designs that can deal with non-responders or sub-cohort specific outcome measures more effectively.

**Keywords:** Sepsis, Post intensive care syndrome (PICS), Physical function, Health-related quality of life (HRQoL), Patient-reported outcome measures (PROMS), Co-morbidity

## Background

Increasing numbers of patients are successfully surviving critical illness. Unfortunately, residual functional and/or mental disabilities affect many critical care survivors after hospital discharge [1, 2]. Despite extensive research into rehabilitation strategies, few studies have been able to demonstrate a positive effect on this ensuing dysfunction or improve health-related quality of life (HRQoL) [3–6]. Given that rehabilitation strategies have a strong evidence base in other patient populations [7], trial-related methodological issues have been proposed as a source of influence in this area and examined [8, 9].

Population heterogeneity within the critically ill cohort is one area that may hinder current outcome analysis. Certain specific patient characteristics have already been identified as influential in regard to an individuals' subsequent HRQoL outcome. To date, these include age [10], pre-critical illness comorbidity [11] and socioeconomic status [12]. Severity of critical illness, intensive care unit (ICU) length of stay and the effect of within-ICU physiology remain unclear influences, as does sex [10, 11, 13–16]. If these factors are not accounted for in a trial design, patient stratification, or analysis, outcome data may be unintentionally skewed. Many of the current outcome assessments for trials in critical care fail to account for these confounders [15, 17]. Patient-reported outcome measures are increasingly prioritised as endpoints [18–20]. The Physical Component Score (PCS) of the Short Form-36 Questionnaire (SF-36) is used to demonstrate the physical disability of critical care survivors [21] and is widely reported in rehabilitation trials.

Several re-analyses have demonstrated sub-phenotypes based on recovery trajectories [9, 15, 22]. How these sub-phenotypes respond to the variety of assessments that measure HRQoL currently in use is not yet defined. It may be that these assessments, often applied as outcome measures, have different clinimetric properties within patient sub-populations. Understanding this aspect of measurement in addition to recovery trajectories will be important to future trial design and outcome interpretation.

We performed a secondary analysis of a critical care trial of sepsis survivors using 2-year follow-up data [23]. The aim of this was to (i) examine the trajectories of functional recovery in critically ill patients using an agnostic approach to delineate patient sub-phenotypes; (ii) examine the distinguishing clinical characteristics between these cohorts and (iii) assess the differences in clinimetric properties of assessment tools of physical function between cohorts.

## Methods

The patient cohort comprised of those recruited to a randomised control trial conducted between February 2011 and December 2015 evaluating a primary care-based sepsis aftercare intervention [23, 24]. Two hundred ninety-one adult survivors of sepsis were recruited from nine centres across Germany. Trial design, methodology and outcomes are described in detail in the original manuscript [23, 25]. Briefly, trained study nurses collected baseline data at in-person interviews while participants were still hospitalised. Follow-up data pertaining to HRQoL and physical function were collected at 6 months, 12 months and 24 months by telephone interviews. Those instruments specific to this analysis were the Physical Component Score (PCS) of the SF-36 [26], three of its four subdomains (physical function, role physical and body pain), activities of daily living (ADL) and the Extra Short Musculoskeletal Function Assessment regarding physical function and disability (XSFMA-F/B) [27]. This extra short questionnaire is derived from the 101-item Musculoskeletal Function Assessment (MFA) by Engelberg et al. to assess functional status from the patient's perspective [28]. It has been mainly used in Germany for patients following orthopaedic surgery [27]. Functional outcome data were also analysed for sub-phenotype concurrent validity and clinimetric properties. Both randomisation groups were included into analyses, as no effects of the intervention were shown regarding functional or HRQoL outcomes [23]. Only those with complete data sets (all four time points) were used in this analysis.

Education and family status classifications are shown in Additional Table 1 and addressed domains of instruments used in Additional Table 1.1.

### Trajectory projection cluster analysis

Groups of longitudinal trajectories of Physical Component Scores of the SF-36 (the most commonly reported 6-month HRQoL outcome measure [3, 6, 29–34]) were clustered using the R-package TRAJ [35–37] and applied. Briefly, this package implements a 3-step procedure [36]. Firstly, 24 summary measures (available in Additional Table 2) are calculated that measure the features of trajectories. These measures were then analysed using factor analysis to select those that best describe the main features of trajectories. Lastly, using these factors the trajectories were clustered.

### General statistical analysis

Continuous data were assessed for normality using D'Agostino and Pearson omnibus normality tests and analysed using paired two-tailed Student's $t$ test or Mann-Whitney $U$ test as appropriate. Normally distributed data were described using the mean (95% confidence interval) and non-normally distributed data as median (interquartile range). Categorical variables were analysed by $\chi^2$ testing. Multivariable and univariable logistic regression analyses were applied to variables potentially determining cluster allocation (dependent variable). Unclustered participants were not used in the logistical analysis, and a multinomial regression performed as a sensitivity analysis. Independent variables were determined as characteristics (Table 1), with a univariable screening threshold set at $p < 0.10$. Significance for all other tests was set at $p < 0.05$. The area under the receiver-operator-curve was used to test the predictive capacity of early ICU discharge and 6 months of assessments for persistent functional impairment.

### Floor and ceiling effects

Scores at their lowest point are defined as 'floor effects' and a 'ceiling effect' occurs where patients 'may show no improvement in function if a functional scale is not able to assess high-level instrumental ADLs (a ceiling effect) [38, 39]. Floor and ceiling effects render a measure unable to discriminate between participants at either extreme of the scale. This negatively affects measurement properties, including sample size requirements. Reducing these effects by choice of the right measure can therefore improve study efficiency [40]. Floor effects were calculated as the percentage of participants scoring the worst possible score for the measure. Ceiling effects were calculated as the percentage of participants scoring the best possible score for the measure. Components of the SF-36 were examined at the differing time points for floor and ceiling effects, for the cohort as a whole and for the individual clusters. Floor and ceiling effects were considered relevant if > 15% of the participants had the highest or lowest score respectively [41].

**Table 1** Baseline characteristics of different cohorts

| | Persistent impairment | NA | Complete recovery | NA | Unclustered | NA | |
|---|---|---|---|---|---|---|---|
| *n* | 76 | | 61 | | 22 | | |
| Age (years) | 65 (54.3–72) | | 56 (43–70) | | 63 (52–69.3) | | **$p = 0.002$*** |
| Male sex (*n*)[#] | 47 (61.8%) | | 44 (72.1%) | | 16 (72.7%) | | $p = 0.205$ |
| ICULOS | 23.0 (12.8–39.5) | 2 | 19 (10.0–31.0) | 6 | 40.5 (15.3–48.3) | 2 | $p = 0.207$ |
| MV(day) | 9 (2–20) | 1 | 6 (2–22) | 2 | 10 (4–29) | 3 | $p = 0.746$ |
| CCI | 3 (1–5.8) | | 3 (1–5) | 1 | 2.5 (1.8–6) | | $p = 0.246$ |
| RRT (day) | 0 (0–0.75) | | 0 (0–2.5) | 3 | 0 (0–2.5) | | $p = 0.650$ |
| Tracheostomy (*n*)[#] | 20 (26.3%) | 21 | 18 (29.5%) | 13 | 11 (50%) | 3 | $p = 0.678$ |
| Intervention group (*n*)[#] | 38 (50%) | | 38 (62.2%) | | 11(50%) | | $p = 0.150$ |
| Education[‡$] | 5 (1–9) | | 5 (2–9) | | 5 (2–9) | | **$p = 0.039$*** |
| BMI | 27.8 (24.4–32.5) | | 25.8 (22.6–29.1) | 1 | 26.7 (23–30) | 2 | **$p = 0.006$*** |
| Family status[‡$] | 2 (1–6) | 1 | 2(1–6) | | 2(1–4) | 1 | **$p = 0.021$*** |
| No. of ICD diagnoses at discharge | 9 (6–15) | | 9 (5–11) | | 8 (6–15.8) | | $p = 0.077$ |

Data are shown as medians (interquartile ranges), except for percentages and mode (range). *p* values represent Mann-Whitney *U* tests between persistent impairment and complete recovery, except for [#]chi-squared test

*ICULOS* intensive care length of stay (days), *MV*(d) period of mechanical ventilation (days), *CCI* Charlston Co-morbidity Index, *RRT*(d) renal replacement therapy (days) and *NA* not available

[$]Indicated mode (range) with the significance taken to be $p < 0.05$

*$p < 0.05$

[‡]Categories shown in Additional Table 1

### Concurrent validity

Concurrent validity is a measure of how well a test compares to a gold standard (such as the PCS) [38] and its substitutability. Therefore, it is a component of criterion validity, an estimate of accuracy based on an external criterion [42]. Coefficient of determination from regression between parameters was used to measure concurrent validity (the degree to which a test can be used as a substitute measure for the gold standard) between the PCS and PF of the SF-36, ADLs and XSFMA-F/B. All coefficients were interpreted as little (0.00–0.25), fair (0.25–0.50), moderate (0.50–0.75) and excellent association (0.75–1.0) [43].

### Responsiveness

Responsiveness is a measure of sensitivity to change and discriminatory properties (the ability to detect a clinically relevant change in health status over time), and part of the COSMIN checklist (COnsensus-based Standards for the selection of health Measurement INstruments) [42, 44, 45]. Change in scores from hospital discharge to 24 months was assessed using paired $t$ tests and data represented as mean difference and 95% CI [43]. Responsiveness of each test to time/recovery post critical illness was calculated using the effect size index, calculated as the mean change score divided by the baseline pooled standard deviation [38, 46]. Changes were interpreted according to Cohen's d effect size as small (0.2 to 0.49), moderate (0.5 to 0.79) and large (> 0.80) [47, 48].

## Results

Of the original 291 participants recruited, 24-month follow-up data was collected on 186 participants (41 lost to follow-up, 64 died < 24 months). Complete data was available on 159 participants who were included in the final analyses. Those with incomplete follow-up were not included. When compared, those who died were older, had a longer length of stay and more comorbidities, all of which is not unexpected (see Additional Table 3).

PCS of the SF-36 for critically ill participants were reduced relative to population norms at ICU discharge and remained low at 24 months (Fig. 1a).

### Trajectory clustering

Trajectory projection analysis identified two distinct sub-cohorts: one cohort exhibited a faster and more complete recovery trajectory defined as within one standard deviation of population norms ($n$ = 61). A second cohort exhibited more persistent functional impairment ($n$ = 76) (Fig. 1b). The remaining 22 participants were not classified into either cohort, as no clear trajectory was seen (Additional Fig. 2). The differing characteristics of the cohorts are shown in Table 1.

The complete recovery cohort was on average younger (56 years (IQR 43–70) vs. 65 years (IQR 54–72), $p$ = 0.002, Fig. 2a), with higher education levels (5(4–8) vs. 5(3–5), $p$ = 0.039, Fig. 2b), more likely to be unmarried (Fig. 2d) and had a lower BMI (25.8(22–29) vs. 27.8(24–32), $p$ = 0.006.

A multivariable logistic regression analysis demonstrated age, education level and number of comorbidities as independent determinants of poor recovery (Additional Table 4). A model with these factors had a predictive capacity with an AUROC of 0.743 ((95%CI 0.659–0.826); $p$ < 0.001; Additional Fig. 1) for cohort membership and was not over-fitted (Hosmer-Lemeshow statistic 8.456, $p$ = 0.390). Neither body mass index

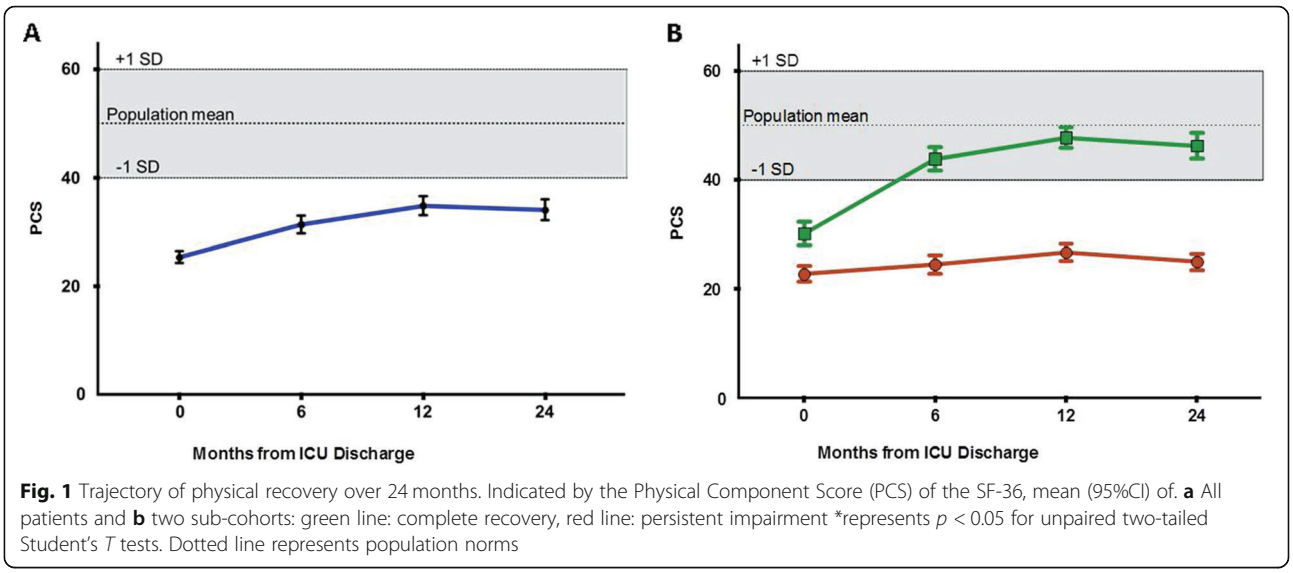


**Fig. 1** Trajectory of physical recovery over 24 months. Indicated by the Physical Component Score (PCS) of the SF-36, mean (95%CI) of. **a** All patients and **b** two sub-cohorts: green line: complete recovery, red line: persistent impairment *represents $p$ < 0.05 for unpaired two-tailed Student's $T$ tests. Dotted line represents population norms

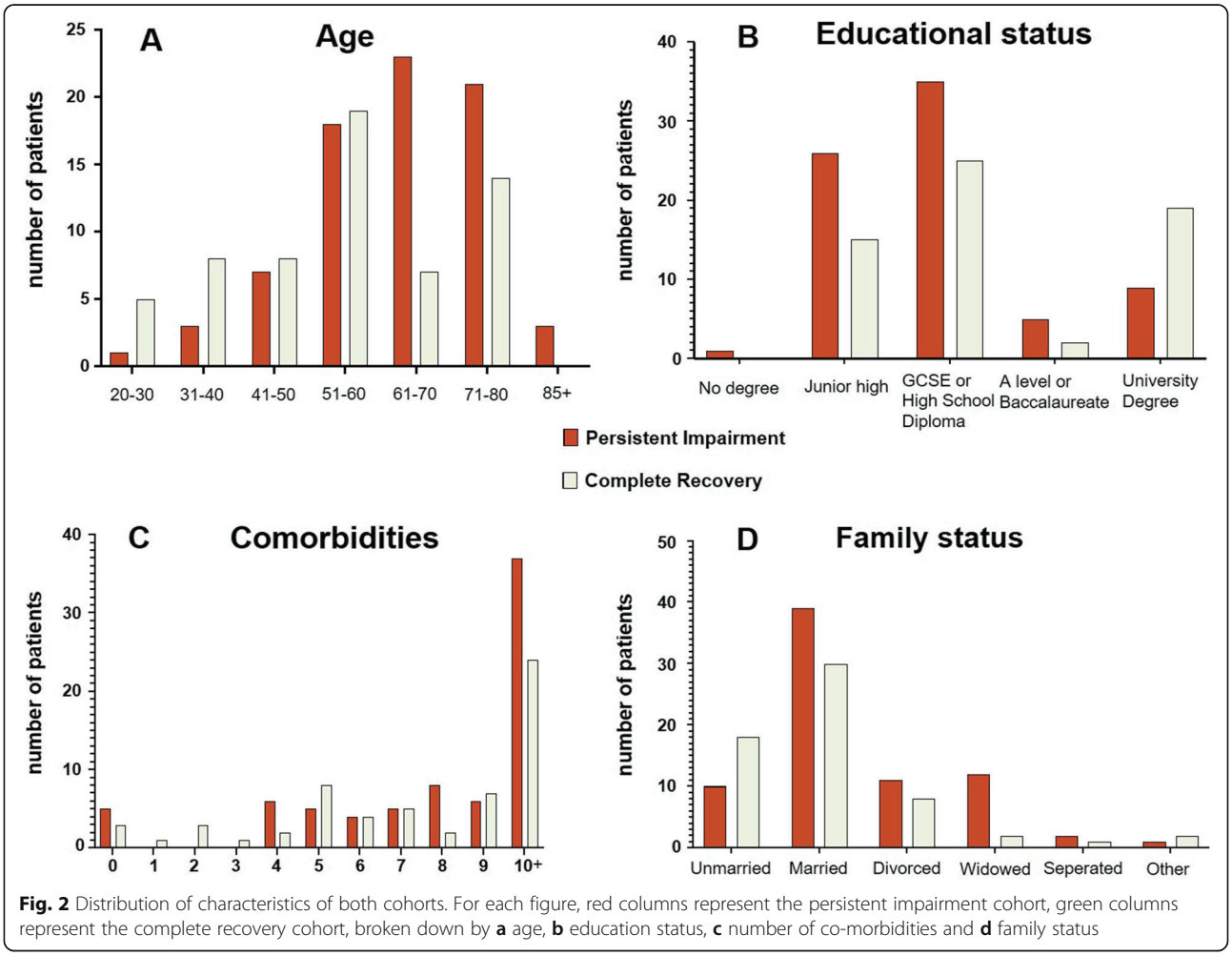


**Fig. 2** Distribution of characteristics of both cohorts. For each figure, red columns represent the persistent impairment cohort, green columns represent the complete recovery cohort, broken down by **a** age, **b** education status, **c** number of co-morbidities and **d** family status

nor family status at discharge were significant within this analysis. In a multinomial analysis, age and education remained independent determinants of recovery with the addition of body mass index (Additional Table 4.1) but not the number of co-morbidities ($p = 0.051$). No determinants were independently associated with the unclustered trajectory (see Additional Table 4.2).

### Floor and ceiling effects

At a 24-month follow-up, participants in the completed recovery cohort demonstrated relevant ceiling effects within the physical function (15%), role physical (45%) and body pain (57%) domains of the SF-36. In contrast, those participants with persistent functional disability demonstrated the reverse, with relevant floor effects

**Table 2** SF-36 components floor and ceiling effects at 24 months after ICU discharge

| Follow-Up | Whole cohort *N* = 159 | | Completed recovery *N* = 61 | | Persistent impairment *N* = 76 | |
|---|---|---|---|---|---|---|
| | Floor (0) | Ceiling (100) | Floor (0) | Ceiling (100) | Floor (0) | Ceiling (100) |
| **PF** | 16 (10) | 9 (6) | 0 (0) | 9 (15)* | 16 (21)* | 0 (0) |
| **RP** | 71 (45)* | 35(22)* | 9 (15)* | 27 (45)* | 54 (71)* | 3 (4.0) |
| **BP** | 11 (7) | 52(33)* | 1 (2) | 35 (57)* | 9 (12) | 7 (9.2) |
| **GH** | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) |
| **XSFMA-F** | 29(18)* | 0(0) | 29 (46) | 0(0) | 0(0) | 0(0) |

Data are shown as numbers of patients with percentages. Data of unclustered group ($n = 22$) not shown (raw data shown in Additional Fig. 2)
*PF* physical function, *RP* role physical, *BP* bodily pain and *GH* general health, *XSFMA-F* Extra Short Form Musculoskeletal Function Assessment regarding physical function (F)
*A value of > 15% denoting relevant effects [41]

within physical function (21%) and role physical (71%) but not bodily pain (12%), see Table 2 and Fig. 3. These results were relatively consistent over the preceding 24 months (Additional Tables 5A and B). Floor scores at ICU discharge were only moderately associated with a persistent functional impairment trajectory (PF (AUROC 0.609 (95%CI 0.537–0.681); $p = 0.002$) and RP (AUROC 0.653 (95%CI 0.584–0.721); $p < 0.001$)). However, floor scores at 6 months were good predictors of a trajectory of persistent functional impairment (RP (AUROC 0.586 (95%CI 0.513–0.658); $p = 0.014$)), and PF (AUROC 0.938 (95%CI 0.901–0.974); $p < 0.001$)).

### Concurrent validity

Those participants with complete recovery demonstrated moderate to excellent concurrent validity between SF-36 PCS and both XSFMA-B AND XSFMA-F, and fair validity with ADL scores. Those participants with persistent disability demonstrated moderate concurrent validity between SF-36 PCS and both XSFMA-B AND XSFMA-F, and fair validity with ADL scores (Table 3).

### Responsiveness

High responsiveness was seen in the complete recovery group at all time points in the Physical Component Score (> 1.0) and most notably in the physical function domain (> 1.6), with a similar pattern seen in role physical. However, this was not seen in the persistent impairment cohort, where physical function and role physical achieved only moderate responsiveness at 6 months (> 0.7). All other scores and time points demonstrated at best-limited responsiveness (Table 4). PF responsiveness between ICU discharge and 6 months was predictive of a trajectory of persistent impairment (AUROC 0.859 (95%CI 0.804–0.914); $p < 0.001$).

## Discussion

This post hoc study examines the trajectories of functional impairment in cohorts of sepsis survivors regarding sub-phenotypes and specific clinical characteristics.

Two distinct sub-cohorts were identified: one of faster and more complete recovery and the other of slower recovery with more persistent functional impairment. A third sub-cohort could not be classified into either trajectory. This study also demonstrates that the older patient with more co-morbidities and with lower educational achievements is more likely to have a trajectory associated with persistent functional impairment. Importantly, the measures used exhibit very different clinimetric properties when HRQoL is measured longitudinally in different sub-cohorts. Those with good recovery have significant ceiling effects with the physical components of the SF-36 questionnaire and demonstrate high responsiveness over time. The reverse is seen in those with persistent impaired HRQoL, where significant floor effects are seen and limited responsiveness. Moderate to excellent concurrent validity was obtained across tests of HRQoL and physical function. The physical function (PF) score had the highest degrees of responsiveness across sub-cohorts and time and was predictive of a trajectory of persistent impairment when measured up to 6 months. Scoring the lowest value of PF at 6

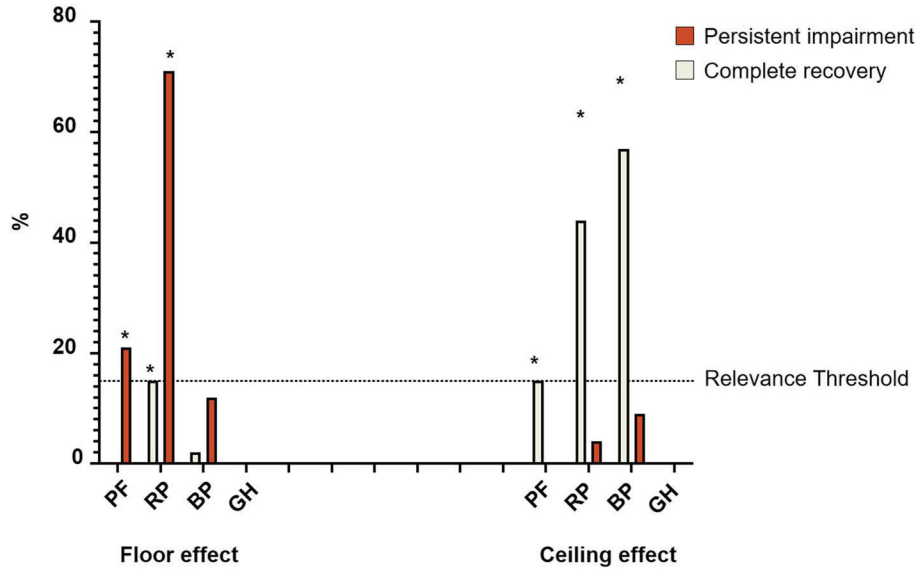


**Fig. 3** SF-36 components floor and ceiling effects. Red columns represent the persistent impairment cohort, and green the completed recovery cohort, both at 24 months. PF physical function, RP role physical, BP bodily pain and GH general health. *A value of > 15% denoting relevant effect

**Table 3** Concurrent validity of physical function assessment tools

| | |
|---|---|
| 0.00-0.25 | Little |
| 0.25-0.50 | Fair |
| 0.50-0.75 | Moderate |
| 0.75-1.0 | Excellent |

| | All | | | | | Complete recovery | | | | | Persistent impairment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PCS | PF | XSFMA-F | XSFMA-B | ADL | PCS | PF | XSFMA-F | XSFMA-B | ADL | PCS | PF | XSFMA-F | XSFMA-B | ADL |
| **PCS** | | 0.87 | -0.80 | -0.75 | -0.61 | | 0.82 | -0.71 | -0.60 | -0.42 | | 0.60 | -0.62 | -0.55 | -0.44 |
| **PF** | 0.87 | | -0.89 | -0.82 | -0.73 | 0.82 | | -0.81 | -0.65 | -0.61 | 0.60 | | -0.81 | -0.71 | -0.62 |
| **XSFMA- F** | -0.80 | -0.89 | | 0.91 | 0.84 | -0.71 | -0.81 | | 0.81 | 0.58 | -0.62 | -0.81 | | 0.84 | 0.78 |
| **XSFMA- B** | -0.75 | -0.82 | 0.91 | | 0.79 | -0.60 | -0.65 | 0.81 | | 0.41 | -0.55 | -0.71 | 0.84 | | 0.71 |
| **ADL** | -0.61 | -0.73 | 0.84 | 0.79 | | -0.42 | -0.61 | 0.58 | 0.41 | | -0.44 | -0.62 | 0.78 | 0.71 | |

Data shown as coefficients of determination at 24 months after ICU discharge
*PCS* Physical Component Score of the SF-36, *PF* physical function subscore, *XSFMA-F/B* Extra Short Form Musculoskeletal Function Assessment regarding physical function (F) and disability (B) and *ADL* activities of daily living

months also was predictive of poorer outcomes at 24 months, which might be an indicator for the necessity to develop individualised rehabilitation programs for every patient.

### Individual patient characteristics

These data reiterate the role that age and multiple chronic diseases have on recovery of physical HRQoL post critical illness. Interestingly, the individual odds ratios for these factors are lower than that of educational status. This may be because educational status is reflective of poorly quantified and measured socioeconomic factors as well as individual coping abilities that are essential for the rehabilitation process [12]. However, chronological age is increasingly recognised as less accurate in terms of function relative to physiological age in the elderly [49], and the Charlston Co-morbidity Index was not designed or validated for the critical care survivor population. Ultimately, these data demonstrate that stratification (or population enrichment strategies) on one or two of these variables are unlikely to be sufficient. We have begun to understand how frailty, cognitive deficits [50], comorbidities [9], age and ICU length of stay [22, 51] interact to result in post critical illness disability, and our data confirm these findings but also suggest that these factors need to be integrated with

**Table 4** Responsiveness of physical function scores at 6, 12 and 24 months post ICU discharge

| | All | | | Complete Recovery | | | Persistent impairment | | |
|---|---|---|---|---|---|---|---|---|---|
| **Month** | 6 | 12 | 24 | 6 | 12 | 24 | 6 | 12 | 24 |
| **PCS** | 0.36 | 0.70 | 0.47 | 1.00 | 1.44 | 1.14 | 0.01 | 0.25 | 0.15 |
| **PF** | 1.02 | 0.88 | 0.50 | 1.75 | 2.05 | 1.63 | 0.71 | 0.42 | 0.37 |
| **RP** | 0.68 | 0.34 | 0.31 | 0.73 | 1.07 | 1.16 | 0.70 | 0.07 | 0.03 |
| **BP** | 0.15 | 0.34 | 0.03 | 0.19 | 0.46 | 0.38 | 0.11 | 0.30 | 0.31 |
| **XSFMA-F** | | 0.39 | 0.28 | | 0.42 | 0.33 | | 0.40 | 0.27 |
| **XSFMA-B** | | 0.43 | 0.34 | | 0.39 | 0.51 | | 0.46 | 0.27 |
| **ADL** | | 0.28 | 0.18 | | 0.19 | 0.05 | | 0.35 | 0.24 |

Responsiveness was measured using Cohens' d, with changes interpreted as minimal (0.0 to 0.2, dark grey) small (0.2 to 0.49, grey), moderate (0.5 to 0.79, yellow) and large (> 0.80, green). Six-month XSFMA-F/B data were used as the baseline for responsiveness

socioeconomic data for improved identification of sub-phenotypes. The impact of social isolation is reported in other chronic diseases and needs more attention in critical illness populations [12].

### Physical function and health-related quality of life outcome measures

The use of HRQoL and patient-reported outcome measures is important and increasingly mandated, and the data reported here may help to focus the field on the appropriateness of the specific domains of the SF-36 to measure HRQoL in different subpopulations with different illness trajectories. The PCS has been used as a primary outcome measure in rehabilitation trials [6, 29], in nutrition intervention trials [52] and is in general the most commonly reported 6-month HRQoL outcome measure [3, 6, 29–34]. The PF subscore has also been used as a primary outcome measure in critical illness [53]. Fundamentally, selection of an outcome measure assumes that the intervention is suitably designed with the primary outcome in mind. When evaluating rehabilitation trials if the primary outcome of a trial is health-related quality of life, then using the summative score (PCS, incorporating all subdomains to reflect overall health-related quality of life) would be appropriate. In contrast, if the primary outcome is physical function, then it may be more appropriate to select the physical function subdomain as the measure used to evaluate the trial. It should be noted that HRQoL outcome measures have often been shown to not be sensitive enough to be affected by the biological efficacy of current post ICU interventions [54].

To date, little exploration of the most sensitive component of the SF-36 to use in trials of rehabilitation interventions has been conducted [55]. Physical and mental health factors account for 80–85% of the reliable variance in the 8 scales of the SF-36 [56]. A scoring assumption central to the summative scores (i.e., PCS and MCS) is that score aggregation could occur without score standardisation or item weighing [57]. Our data challenge this assumption: in the presence of significant heterogeneity of physical HRQoL and disability post critical illness, individual domains are more appropriate outcome measures than summative scores for physical rehabilitation trials, given the responsiveness and predictive outcomes seen across patient sub-phenotypes. Of note, the PF score has long been known to be the most valid scale for physical activity [58] and our data demonstrate that aggregating PF with the other components of the PCS decreases the clinimetric strength. The PF domain includes questions related to activities needed for daily living rather than also including return to work and questions about pain as found in the PCS. The PF domain includes several advanced mobility measures, independent activities of daily living, some activities of daily living as well as several items of the XSFMA, which may explain the concurrent validity findings, as this may be better viewed as construct validity. It may be that in the post critical illness population, there is a more specific objective perception of physical function (the PF score, comprising of 10 questions), resulting in higher responsiveness than broader subjective limitations in daily life (the RP score, comprising of 4 questions, or General Health comprising of 5 questions) or perception of pain (the BP score, comprising of 2 questions). However, the PF score also has significant ceiling effects (in those that recover) and floor effects (in those with persistent disability), suggesting the need for concurrent measurement of other more specific outcome measures such as the XSFMA-F which showed excellent validity with the SF-36 PF to address this. Notably, using the PF domain score at 6 months can predict poorer physical HRQoL outcomes and may help to guide further community or out-patient based individualised rehabilitation treatment.

### Strengths and limitations

A major strength of these analyses are the data themselves—few long-term cohort studies exist with serial contemporaneous HRQoL and physical function data to allow detailed clinimetric testing of outcome measures. The cohort size was large relative to other long-term cohort studies with serial contemporaneous HRQoL and physical function data. It is widely accepted, and accords with common sense, that the imputation of missing data on HRQoL for a deceased participant is inappropriate [59]. This is in keeping with approaches applied to randomised controlled trials [60] and is an approach used by others (with specific expertise in imputation) within the field of rehabilitation [59, 61]. This would also be consistent with analyses applied to this cohort which we have recently published [24].

Those patients who died were older, had a longer length of stay and more co-morbidities. A 2-year follow-up period may not be appropriate for this sub-cohort.

A fundamental issue with clinimetric property assessment of summed scores like the PCS is the content overlap [57], as the used subscores are in part textual identical with the summed score, and there also was a high contentual intersection with the XSFMA-F/B and ADL scores. This is difficult to overcome, as the PCS is near ubiquitous in its use for measurement of physical HRQoL. The use of trajectory clustering techniques decreased the risk of bias relative to a researcher-driven approach. The retrospective nature of this analysis mandates that the conclusions are tested prospectively. Trajectory cluster validity is limited by 22 (13.8%) of patients being not classifiable and understanding why

these patients have unclear trajectories requires prospective analysis, using a mixed-methods approach. The XSFMA F/B scores have only been validated in German, limiting its use, though it was derived from the English SFMA [62]. Other tools such as the Functional Status Score for the intensive care unit (FSS_ICU) or the physical function in intensive care test scored (PFIT-s) may be of use, having been validated in several countries and languages [35]. While the focus of this manuscript has been on self-reported outcome measures, the subjective nature of these does constitute a limitation and comparative assessment with objective measures in subcohorts may be warranted.

### Implications for outcome selection and trial design

As HRQoL outcome measures have often shown a lack of sensitivity in post ICU interventions [54], our data offers two potential methodological solutions: Firstly, the described sub-population characteristics, especially those relating to education could be used as population refinement tools for trials, either as inclusion/exclusion criteria or for differential outcome measures set a priori. This may or may not be feasible where large samples are required, though a differential effect between subpopulations has been used in phase II trials (NCT02358512). Secondly, an adaptive trial design could use (a) the presence of a floor effect as a predictor of a poor trajectory (i.e., a non-responder) in a multi-arm, multi-stage fashion that explores treatments, doses with an option to exclude non-responders [63]; (b) the characteristics (e.g., education or socioeconomic status) for population enrichment that narrow down recruitment to those who are likely to benefit most [64] or (c) the PF score in conjunction with other markers, e.g., CRP (as a marker of persistent inflammation) in a biomarker adaptive design [65] to stratify patients. Lack of data to inform adaptive trial design remains one of the barriers to their use, and this study offers suggestions to overcome this [66].

Both subscore and summary score responsiveness varied over time in both cohorts, with a plateau seen after 6 months. These data imply that physical HRQoL endpoints may be more suited to earlier time points (e.g., 3 and 6 months), and other, more responsive endpoints are needed at 1–2 years such as measures of disability.

## Conclusion

Within sepsis survivors, two distinct recovery trajectories of physical recovery could be demonstrated. Older patient with more co-morbidities and lower educational achievements are more likely to have a trajectory associated with persistent physical impairment. In regard to trajectory prediction, the physical function score of the SF-36 was more responsive than the Physical Component Score of the SF-36 and could be considered for primary outcomes. Future trials should consider adaptive trial designs that can deal with non-responders or sub-cohort specific outcome measures more effectively.

## Supplementary information

**Supplementary information** accompanies this paper at https://doi.org/10.1186/s13054-020-03275-w.

**Additional file 1: Additional Table 1.** Categories of Educational Level and Family Status. VT=Vocational Training. GSCE=General Certificate of Secondary Education. **Additional Table 1.1.** Addressed domains of used questionnaires.

**Additional file 2: Additional Table 2.** Summary measures for Trajectory Projection. eMethods of use of trajectory projection.

**Additional file 3: Additional Table 3.** Baseline characteristics of the whole cohort and the 24 months follow-up cohort. Values shown as medians and interquartile range [IQR] except for $representing mode (range). *P*-values represent two-tailed Mann-Whitney U-tests, except for #=Chi-Squared test. ICULOS= Intensive Care length of stay. MV (d)=period of mechanical ventilation (days), CCI=Charlston Co-morbidity Index, RRT (d)= Renal Replacement Therapy (days), PCS=Physical Component Score of the SF-36, MCS=Mental Component Score recall 3 months prior to critical illness. XSFMA F/B= Extra Short Musculoskeletal Function Assessment regarding Physical Function and Disability, 3m recall=recall 3 months prior to critical illness. NA=Not available, *Categories shown in Additional Table 1. [1]47 patients without MV, 11 patients without available data, [2]209 patients without RRT, 5 patients without available data. **Additional Table 3.1.** Baseline characteristics of the whole cohort split by loss to follow-up and death. Values shown as medians and interquartile range [IQR] except for $representing mode (range). ICULOS= Intensive Care length of stay. MV (d)=period of mechanical ventilation (days), CCI=Charlston Co-morbidity Index, RRT (d)=Renal Replacement Therapy (days), PCS=Physical Component Score of the SF-36, MCS =Mental Component Score recall 3 months prior to critical illness. XSFMA F/B= Extra Short Musculoskeletal Function Assessment regarding Physical Function and Disability, 3m recall=recall 3 months prior to critical illness. NA=Not available, *Categories shown in Table S1.

**Additional file 4: Additional Table 4.** Bivariable and multivariate logistic regression analysis of cohort membership characteristics. Dependent variable: Allocation to persistent impairment cohort vs. complete recovery cohort. ICD=International Classification of Disease; ICULOS= Intensive Care Unit Length of Stay. * represents $p<0.05$. **Additional Table 4.1.** Multinomial regression for the persistent impairment group, using the full recovery as the reference group. ICD= International Classification of Disease; ICULOS= Intensive Care Unit Length of Stay; * represents p<0.05. **Additional Table 4.2.** Multinomial regression for the unclustered group, using the full recovery as the reference group. ICD=International Classification of Disease; ICULOS= Intensive Care Unit Length of Stay; * represents p<0.05.

**Additional file 5: Additional Table 5.** A and B: Ceiling and floor effects**.** Data are shown as n(%) over time for SF-36 components in patients with a persistent impairment trajectory ($n$=76) and in patients with a completed recovery trajectory ($n$=61) (Table 5A: only patients with completed recovery). PF= Physical Function; RP= Role Physical, BP=Bodily Pain, GH= General Health, XSFMA-F= Extra Short Form Musculoskeletal Function Assessment regarding physical function (F)**.** *represents a value of >15% denoting relevant effect. % may not=100 due to rounding effects.

**Additional file 6: Additional Figure 1.** Area under receiver operating characteristic curve (AUROC). Logistic regression of predictors of cluster allocation.

**Additional file 7: Additional Figure 2.** Trajectories of unclustered patients ($n$=22). Data points are means of the SF-36 Physical Component Score (PCS) over 24 months after discharge from ICU.

**Abbreviations**
ADL: Activities of daily living; BP: Body pain; GH: General health; HRQoL: Health-related quality of life; ICU: Intensive care unit; PCS: Physical component score; PF: Physical function; PROMS: Patient-reported outcome measures; RP: Role physical; SF-36: Short Form-36 Questionnaire; XSFMA-F/B: Extra Short Form Musculoskeletal Function Assessment regarding physical function (F) and disability (B)

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**Authors' contributions**
Study concept and design: ZP and KS. Data acquisition: KS, JG and ChH. Analysis of data: ZP, AC and KN. Interpretation of data and drafting of the manuscript: ZP, AC, RC, LE, ChH, KN, TW, LD and KS. Critical revision and approval of the manuscript: ZP, AC, RC, LE, ChH, KN, TW, LD and KS. The authors read and approved the final manuscript.

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**Availability of data and materials**
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**
The study protocol of the SMOOTH-Study was approved by the institutional review board of the University of Jena, January 26, 2011 (No.3001/111).

**Consent for publication**
Not applicable

**Competing interests**
Zudin Puthucheary reports honoraria for consultancy from Fresenius Kabi, Nestle and Faraday Pharmaceuticals, and Speakers fees from Nestle, Fresenius Kabi, Baxter and Nutricia. Jochen S. Gensichen, Aylin S. Cakiroglu, Richard Cashmore, Lara Edbrooke, Christoph Heintze, Konrad Neumann, Tobias Wollersheim, Linda Denehy and Konrad F.R. Schmidt declare that they have no conflict of interest.

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## Publisher's Note

## 2.6 Psychologische Interventionen mit hausärztlicher Beteiligung bei posttraumatischem Stress – systematischer Literaturreview und Metaanalyse

***Originalarbeit:***

*Gehringer R*, Freytag A*, Krause M, Schlattmann P, **Schmidt K**, Schulz S, Zezulka SJ, Wolf F, Grininger J, Berger M, Vollmar HC*, Gensichen J*. Psychological interventions for posttraumatic stress disorder involving primary care physicians: systematic review and Meta-analysis of randomized controlled trials. BMC Fam Pract. 2020;21(176).*
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***2.6.1 Hintergrund:*** Die wichtigste Konsequenz für Folgeprojekte von SMOOTH scheint die Spezifizierung künftiger Interventionen für Patienten nach kritischer Erkrankung zu sein, siehe 2.3. Die überzeugendste Evidenz scheint nach dem systematischen Literaturreview (siehe 2.1) für die Behandlung von posttraumatischem Stress zu bestehen. Dazu zeigte die Langzeitevaluation der SMOOTH-Studie eine mögliche Reduktion posttraumatischer Symptome in der Interventionsgruppe, siehe 2.3. Um die Studienlage für Interventionen zur Behandlung von posttraumatischem Stress mit hausärztlicher Beteiligung zu evaluieren, wurde ein weiterer systematischer Literaturreview initiiert. Dies geschah auch vor dem Hintergrund, dass die meisten Patienten mit posttraumatischem Stress jedweder Genese initial häufig ihren Hausarzt kontaktieren, welcher die weitere therapeutische Versorgung koordiniert [42]. Mit einer internationalen Lebenszeitprävalenz von 3,9 % gehört die posttraumatische Belastungsstörung (PTBS) zu den häufigen psychischen Erkrankungen [43].

***2.6.2 Fragestellung:*** Ziel dieser Übersichtsarbeit war die Evaluation und Charakterisierung von psychologischen Interventionen bei posttraumatischem Stress mit hausärztlicher Beteiligung.

***2.6.3 Methodik:*** Nach Registrierung des Studienprotokolls in PROSPERO [44] und Konsentierung der Suchbegriffe im Autorenteam wurden in den Datenbanken PubMed, Medline, Embase, PsycINFO, dem *Cochrane Central Register of Controlled trials* und CINAHL randomisiert-kontrollierte Studien ab November 2016 gesucht, die posttraumatischen Stress adressieren und die Primärversorgung beteiligen. Die Eligibilität der Studien wurde unabhängig von zwei Autoren geprüft, die Qualität der Evidenz wurde basierend auf GRADE [45] eingeschätzt, kontroverse Fälle wurden im Autorenteam diskutiert.

***2.6.4 Ergebnisse:*** 5.996 Einträge konnten insgesamt identifiziert werden, wovon 245 Volltexte überprüft wurden. Vier RCTs mit insgesamt 774 Patienten erfüllten die Mindestanforderungen an das Evidenzniveau nach GRADE. Alle vier eingeschlossenen Interventionen basieren auf der kognitiven Verhaltenstherapie. Drei dieser Studien adressierten Militärangehörige in den USA. In keiner Studie nahmen Hausärzte eine zentrale Rolle ein, ihr Anteil beschränkte sich u.a. auf die Verantwortung der Pharmakotherapie. In drei Studien wurde eine psychotherapeutische Intervention durch *Case Manager* durchgeführt. Diese drei Studien konnten auch für eine Metanalyse „gepoolt" werden: Es ergaben sich keine kurzfristigen Effekte, nur zwei dieser Studien zeigten im Zeitfenster von 12-18 Monaten kleine Effekte.

***2.6.5 Diskussion und Schlussfolgerung:*** Bislang existieren kaum Studien zur Behandlung von posttraumatischem Stress in der Primärversorgung. Die wenige vorhandene Literatur bezieht sich größtenteils auf die spezifische Population von US-Militärangehörigen. Hausärzte waren in allen vier untersuchten Studien nur peripher beteiligt.

Aussagen zur Wirksamkeit können aufgrund des begrenzten Evidenzniveaus der untersuchten Studien nur sehr zurückhaltend getroffen werden. Die allenfalls langfristig möglichen Effekte der Interventionen betonen die Bedeutung einer dauerhaften Arzt-Patienten-Beziehung für die Behandlung von posttraumatischem Stress, wie sie vor allem in der hausärztlichen Praxis gegeben ist. Die Notwendigkeit weiterer Forschung in diesem Bereich wird so offensichtlich.

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# Psychological interventions for posttraumatic stress disorder involving primary care physicians: systematic review and Meta-analysis of randomized controlled trials

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## Abstract

**Background:** Evidence-based psychological interventions for posttraumatic stress disorder (PTSD) are available in specialized settings, but adequate care in primary care is often lacking.
The aim of this systematic review was to determine the effectiveness of psychological interventions for PTSD involving primary care physicians (PCPs) and to characterize these interventions as well as their providers.

**Method:** A systematic review and meta-analyses of randomized controlled trials (RCTs). Primary outcome were symptoms of PTSD.

**Results:** Four RCTs with a total of 774 patients suffering from PTSD symptoms were included, all applying cognitive behavioural based interventions. Three studies with psychological interventions being conducted by case managers were pooled in a meta-analysis. Interventions were not effective in the short term (0–6 months; SMD, − 0.1; 95% CI, − 0.24-0.04; $I^2 = 0\%$). Only two studies contributed to the meta-analysis for long term (12–18 months) outcomes yielding a small effect (SMD, − 0.23; 95% CI, − 0.38- -0.08; $I^2 = 0\%$).

**Conclusions:** Psychological interventions for PTSD in primary care settings may be effective in the long term but number and quality of included studies was limited so the results should be interpreted with caution.

**Keywords:** PTSD, Primary care, Systematic review

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## Background

Traumatic experiences can have long lasting effects on an individual's mental and physical well-being including the developments of PTSD. There is an ongoing discussion about the characteristics of this disease [1], being reflected by the changes of its diagnostic criteria in the new diagnostic systems DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5th edition) and ICD-11 (International Statistical Classification of Diseases and Related Health Problems) [2, 3]. While ICD-11 requires three key symptom clusters of re-experiencing, avoidance and hyperarousal, DSM-5 added a fourth symptom cluster of persistent negative alterations in cognitions and mood.

PTSD lifetime prevalence is estimated between 1.3–8.8% in the World Mental Health Surveys [4]. The three most common causes of PTSD in the World Mental Health Surveys were rape, other sexual assault and unexpected death of a loved one [5].

Several evidence-based therapies for the treatment of PTSD are available to patients: cognitive- behavioural-based therapies (i.e. exposure therapies), eye movement desensitization and reprocessing (EMDR), and narrative exposure therapy (NET) [6]. Evidence suggests that trauma-focused therapies (i.e. exposure therapies, cognitive processing therapy, EMDR) may be more effective than non-trauma-focussed therapies [6, 7]. Pharmacological treatment using selective serotonin reuptake inhibitors may be helpful when trauma focused psychotherapies are not available or are refused by the patient [8]. Irrespective of the cause of trauma, most patients initially turn to general practitioners/primary care physicians (PCP – for reasons of consistency we refer to PCP in the further text) [9], with a median point prevalence of PTSD in primary care patients of 12.5% [10].

Despite the existence of effective interventions, there is a relevant time lag until patients receive specialist care. In the United States the median period of delay is 12 years between the onset of PTSD and first treatment contact (defined as talking about the disorder to any professional) [11]. Reasons for the delay in accessing treatment include the stigma associated with mental health care as well as cultural and institutional attitudes [12]. Additionally, there are structural impediments such as shortages of psychotherapists and inefficient allocation of patients to providers. To improve recognition and treatment of PTSD, several new approaches have been developed (e.g. internet based therapies, self-help, collaborative care) [13, 14].

National guidelines highlight that patients suffering from PTSD initially contact PCPs, who are in charge of diagnosing PTSD and organising care [15, 16]. There are several advantages in primary care settings which may facilitate the initiation and reduce barriers to psychological therapies: Treatment can be provided low-threshold and early starting compared to secondary care settings. Many patients have established a trustful relationship with their PCPs, thus an important first step within psychotherapeutic work has already been achieved [17]. PCP's knowledge of their patients' personal environment and resources can be an important resource during therapy [18, 19]. In addition, PCPs may help to close the large gap between supply and demand for the support of traumatized people [20].

Several other mental health disorders have effectively been treated in primary care, including depression and anxiety [21]. Important components for successful treatment include case management delivered by case managers (CM) with mental health training, scheduled supervision of CMs by mental health specialists, and the coordinated involvement of PCPs, CMs, and mental health specialists [22–24].

Two narrative reviews described the rationale for the management of PTSD in a primary care setting involving brief cognitive behavioural therapies (CBT); utilizing self-help and internet based approaches; as well as collaborative care [13, 14]. Based on a narrative review, Hoeft et al. suggest that collaborative care that offers psychotherapy is a promising approach [25]. The three reviews give an overview on diverse interventions investigated in a wide range of settings and with multiple designs. Given the heterogeneity of interventions, a quantitative analysis was not performed. A meta-analysis is needed to increase evidence on psychological treatment for PTSD in a primary care setting and to investigate specific intervention effects.

### Objectives

The aim of this review was to determine the effectiveness of psychological interventions for PTSD involving PCPs. The second aim was to characterize these interventions and their providers, and to describe the providers' specific tasks, as well as their interaction.

## Methods

Objectives, inclusion criteria, and methods were prespecified in a study protocol registered with Prospero (Registration number CRD42017060123).

### Eligibility criteria

Both cluster and individually RCTs were included applying psychological interventions to reduce PTSD symptoms. Participants aged 18 and older with a PTSD diagnosis (according to a valid diagnostic system, e.g. DSM-4 or 5, ICD-10) or with clinically relevant PTSD symptoms, determined by validated instruments, were considered.

Eligible interventions were: CBTs (cognitive therapy, cognitive processing therapy, cognitive restructuring therapy, coping skills training, exposure therapy including prolonged exposure and dialectical behavioural therapy), EMDR, NET and others such as writing therapy, hypnotherapy, interpersonal therapy, present centred therapy, eclectic psychotherapy and psychodynamic therapies [6, 26–30]. Application of case management only or other service delivery models such as collaborative care without the implementation of one of the above listed psychological interventions was excluded. To be eligible for inclusion, psychological therapies had to be delivered by PCPs, or by non-physician primary care providers, on condition that PCPs remained actively engaged in the intervention. Active engagement could mean treatment was linked to the monitoring, the clinical instructions, the supervision, or the advice of the PCP, or the therapist and the physician used a shared patient chart, or the PCP regularly received feedback on the therapy's progress and made recommendations for further management. Control groups may have also received active interventions such as case management, training of PCPs and collaborative care approaches without the implementation of the above listed psychological interventions.

To be eligible the primary outcome had to measure PTSD symptoms using validated instruments.

We did not apply any restrictions concerning language, publication status, or year of publication.

### Search methods

The full electronic search strategy for Medline is published in additional file 1. To identify studies we searched electronic databases (Medline, Embase, PsycINFO, the Cochrane Central Register of Controlled trials and CINAHL) from their inception until November 2016. An update search was performed for the period from December 2016 to February 2019. Additionally, we screened several conference proceedings where content was available online (see additional file 1). We also searched the International Clinical Trials Registry Platform and reference lists from included studies and relevant reviews.

### Study selection and data extraction

Eligibility assessment was performed independently from RG and MK/SJZ. After screening abstract and title, 245 full texts were reviewed.

The data extraction form was developed on the basis of the EPOC data collection form and checklist, and the EQUATOR template for intervention description and replication (TIDieR) checklist [31, 32]. Due to the limited number of included studies the extraction form was piloted with one study. We received data from the main study and, if available, study design and protocols, as well as further publications reporting relevant outcomes. Two reviewers conducted outcome extraction independently (RG/JG). The primary outcome assessed was PTSD symptoms. Secondary outcomes recorded were comorbidities, quality of life, psychopharmacologic medication use, mental health care use, adverse events, patients` satisfaction, additional costs for intervention, treatment and medication adherence, and suicidality. The remaining data (i.e. quality criteria, components of the Chronic Care Model [33]) were extracted by RG and checked by MK. Additionally, we focused on the involvement of PCPs and extracted their profession, PTSD specific training, tasks performed, and their interaction with other providers. All disagreements occurring during study selection and data extraction were resolved through discussion. If no agreement could be reached, a team of authors made the decision (AF, RG, JG1, MK, SvS, KS, HCV). When any information was missing the corresponding authors were contacted. 12 of the 22 contacted authors responded, but could not provide additional quantitative outcome data.

#### *Risk of bias assessment*

Risk of bias of included studies was assessed by two independent reviewers (RG/MK) using the Cochrane Risk of Bias Tool [34]. Resulting disagreements were resolved through discussion and with a third reviewer (AF).

The quality of evidence was assessed using GRADE [35].

### Statistical analysis

We estimated standardized mean differences with *Cohen's d* due to different scales for PTSD symptoms among studies. Heterogeneity was quantified using $I^2$-statistics and linear mixed models. Quantitative analyses were performed using R and SAS 9.4. Due to the absence of statistical heterogeneity, we used the fixed effects model for performing the meta-analysis. Because standard deviations for means of the primary outcome were neither reported nor could be calculated from the presented data in one study [36], and could not be provided by the authors, we used the reported standard deviations for baseline means also for the follow-up data. To additionally assess the effects of time, intervention, and time-intervention interaction on the primary outcome we applied a linear mixed model using a restricted maximum likelihood method on a Gaussian distribution. The model selection was based on the Bayesian information criterion (BIC). We chose the model with the lowest BIC. All calculations for regression analyses were performed using SAS (proc GLIMMIX) procedure.

Other than announced in the protocol, no further analyses (meta-regression, sensitivity analyses) were

conducted because of the limited number of included studies. Publication bias was estimated considering the inclusion of small and negative effect studies. A funnel plot could not be developed because of the small number of studies included.

## Results

### Study selection and study characteristics

We identified 5996 records in electronic databases during our search (flowchart additional file 2). An additional 48 records were found through searches in reference lists, conference proceedings, and the International Clinical Trials Registry Platform. After removing duplicates we screened 4418 records. Two hundred fourty-five full-texts were assessed for eligibility. Finally, 4 RCTs (STEP S-UP: Stepped Enhancement of PTSD Services Using Primary Care [36], DESTRESS-PC: Delivery of Self Training and Education for Stressful Situations-Primary Care version [37], CALM: coordinated anxiety learning and management [38, 39], PE-PC: Prolonged Exposure for Primary Care [40]) were included in this review with 774 participants suffering from PTSD. All studies were multicentre trials.

We extracted data from 16 reports (including research protocols, study designs and analysis of secondary data).

Study characteristics (Table 1): STEPS-UP [36] was performed on active-duty military members with 80.9% male participants in US-military primary care clinics. Relevant PTSD symptoms were measured with the PCL-C (PTSD Checklist-Civilian version) for inclusion. Details of further inclusion and exclusion criteria of single studies are summarised in additional file 3. This was the only study reporting adverse effects and no case of adverse effects was noted [36]. The intervention was a stepped-care model based on CBT, using nurse-assisted, online or telephone self-management in Step 2, and the possibility of mental health specialists delivered psychotherapy in the last step (Table 2). Psychological therapy lasted 6–9 weeks. Applied strategies to improve treatment adherence were motivational interviewing (MI) and behavioural activation (BA). The control group received collaborative care as usual care, which had been implemented within the military health care system previously and consisted of prepared primary care practices, care management and enhanced mental health specialty. PCPs prescribed psychoactive medications in both groups.

DESTRESS-PC [37] participants were recently deployed military service members and veterans. Most participants were male (81.3%). The study was set in

**Table 1** Study characteristics

| Study | STEPS-UP | DESTRESS-PC | CALM | PE-PC |
|---|---|---|---|---|
| **Country** | US | US | US | US |
| **Setting** | 18 Army primary care clinics | Dep. Defense and Veterans Affairs primary care clinics | 17 primary care clinics | two military treatment facilities |
| **Population** | active duty US military members with PTSD and/or depression | recently deployed military service members/ veterans with PTSD | primary care patients with PD, GAD, SAD, PTSD or all 4 | active duty military service members with (subthreshold) PTSD |
| **Male gender No. (%)** | 539 (80.9%) male [a] | 65 (81.3%) male | 290 (28.9%) male [b] | 50 (75%) male |
| **Age in years** | 31.2[a] | 36.5 | 43.5 [b] | 40 |
| **Sample size IG/CG No.** | 285/281[c] | 43/37 | 33/28 [d] | 34/33 |
| **Psychological intervention** | Online/ telephone delivered CBT-based therapies; other evidence based psychotherapies | CBT based nurse-assisted, online self-management tool | computerized CBT program tailored to the 4 specific anxiety disorders | brief Prolonged Exposure for Primary Care |
| **Involved providers** | CM, PCP, MHS | CM, PCP, MHS | CM, PCP, MHS | PCP, MHS |
| **PTSD diagnosis instrument** | PTSD Checklist- Civilian version (PCL-C) | Clinician administered PTSD scale (CAPS) | Mini International Neuropsychiatric Interview | PTSD Checklist-Stressor Specific version (PCL-S) |
| **PCL-C at baseline, IG/CG, mean (SD)** | 58.5 (11.1)/57.7 (10.8) [a] | 55.16 (10.89)/ 58.56 (10.01) | 57.15 (12.56) [d]/ 56.90 (12.57)[d] | 49,8 (12,8)/52,2 (14,1)e |
| **Psychiatric comorbidity outcome measures** | SCL-20 (depression), AUDIT (alcohol consumption), PHQ-15 (somatic disorder), BPI (pain) | PHQ-8 (depression), PHQ-15 (somatic disorder) | GADSS (GAD), PDSS-SR (PD), SPIN (SAD), PHQ-8 (depression), BSI (somatization and anxiety) | PHQ-9, BHM |

*CM* care manager, *PCP* primary care physician, *MHS* mental health specialist, *CBT* cognitive behavioural therapy, *PD* panic disorder, *GAD* generalized anxiety disorder, *SAD* social anxiety disorder;
[a] patients with PTSD and/or depression;
[b] all anxiety disorders (PD, GAD, SAD, PTSD);
[c] patients with PTSD;
[d] patients who selected PTSD as their principal disorder
[e] PTSD Checklist-Stressor Specific version (PCL-S)

**Table 2 Characteristics of the intervention**

| Study | | STEPS-UP | | | | DESTRESS-PC | |
|---|---|---|---|---|---|---|---|
| IC/CG | | IG | | | CG | IG | CG |
| Psychological intervention | Description of the intervention | *STEP 3:* psychotherapy | *STEP 2:* CBT based self-management | *STEP 1:* care management (education, BA, MI) | collaborative care without implementation of psychological therapies | CBT-based & stress inoculation training in a nurse-guided online patient self-management paradigm | low intensity CM and training of PCPs |
| | who received the intervention | patients' request, high risk patients, unresponsive to STEP 1 + 2, PCPs decision | patients who remain clinically symptomatic after 3–6 weeks | all patients | all patients | all patients | all patients |
| | who delivered the intervention | local MHS | CM | CM, PCP | CM, PCP, MHS | CM/computer program | CM/PCP |
| | method of delivery | in-person or via telephone | online or via telephone | via telephone, electronic messaging, in-person | via telephone, | online, via telephone, E-Mail, in-person | via telephone, E-Mail, in-person |
| | duration of the intervention | not reported | 6–9 weeks | 12 months | 12 months | 6-max. 10 weeks | not reported |
| | number of contacts | not reported | 3–9 | min. 12 | min. 12 | log in 3 times /week, number of CM-contacts not reported | 3 telephone check-ins, risk assessment at weeks 2/4/6 |
| | strategies applied to sustain/ improve treatment adherence | CM were trained in BA, problem solving and MI | | | Adherence was monitored | not reported | not reported |
| Pharmacological intervention | interventions for improved pharmacological treatment | see STEP 2 | Expert training in pharmacologic treatment for PCPs | not reported | Stepped pharmacological treatment | no intervention | no intervention |
| | who prescribed medication | PCP | | | PCP | not reported | not reported |

| Study | | CALM | | PE-PC | |
|---|---|---|---|---|---|
| IC/CG | | IG | CG | IG | CG |
| Psychological intervention | Description of the intervention | computer-assisted CBT program | usual care by PCP, referral to MHS possible | brief Prolonged Exposure for Primary Care | minimal contact group |
| | who received the intervention | patients could choose computer-assisted CBT medication, or both | all patients | all patients | all patients |
| | who delivered the intervention | CM (ACS) | PCP, MHS | PCP, MHS | PCP, MHS |
| | method of delivery | in-person (CBT), via telephone (follow-up) | in-person, via telephone | in-person | via telephone |
| | duration of the intervention | 10 to 12 weeks, symptomatic participants could | not reported | 30 min appointments delivered over 4–6 weeks | 6 weeks |

**Table 2 Characteristics of the intervention** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | | receive up to 3 more steps (i.e., another 10–12 weeks) of treatment | | | |
| | number of contacts | CBT: 6 to 8 weekly sessions | not reported | 4 | 6 |
| | strategies applied to sustain or improve treatment adherence | ACS received didactics of MI | not reported | review by an independent clinician using adherence rating forms | not reported |
| Pharmacological intervention | interventions for improved pharmacological treatment | single-session medication management training for PCPs using a simple algorithm, adherence monitoring by ACS for medication management | not reported | psychotropic medication should remain unchanged throughout the intervention | psychotropic medication should remain unchanged throughout the intervention |
| | who prescribed medication | PCP | PCP | not reported | not reported |

*IG* intervention group, *CG* control group, *CM* care manager, *PCP* primary care physician, *MHS* mental health specialist, *ACS* anxiety clinical specialist, *CBT* cognitive behavioural therapy, *BA* behavioural activation, *MI* motivational interviewing

Department of Defense and Veterans Affairs primary care clinics. The clinician administered PTSD scale (CAPS) was used for diagnosis. Similar to STEPS-UP, a CBT based, nurse-guided, online self-management paradigm constituted the intervention, which lasted 6–10 weeks. The control group received usual care which was optimized by training of PCPs in PTSD identification and treatment and basic care management including phone check-ins to monitor symptoms and feedback to providers.

The CALM trial [38, 39] was set in US-primary care clinics and included 28.9% male participants. Diagnosis instrument was the Mini International Neuropsychiatric Interview. The intervention consisted of a computer-assisted, face-to-face treatment for 10–12 weeks and could be extended up to 3 times. MI was used to increase treatment adherence. The control group received the usual PCP care with the option of mental health specialist referral.

PE-PC [40] was performed on active-duty military members with 75% male participants in two US military treatment facilities. Relevant PTSD symptoms were measured with the PCL-S (PTSD Checklist- Stressor Specific version) for inclusion. The intervention was based on a brief protocol for prolonged exposure developed for a primary care setting. Behavioural health consultants (BHCs) working in the primary care team were specially trained to deliver the intervention. Psychological therapy lasted 4–6 weeks. The control group was contacted weekly by the BHCs to monitor their status and was offered to receive PE-PC also after 6 weeks. The BHCs worked as a consultant to the PCP.

Involved providers (Table 3): PCPs always received feedback on the ongoing therapy and special training, except for PE-PC (no PCP training). They were responsible for the pharmacological treatment and were supervised by mental health specialists in two studies [36, 38, 39]. CMs (registered nurses, nurses with a bachelor or a master of science in nursing, psychiatric mental health nurse practitioners, social workers, counsellors and psychologists) had a central role in three studies [36–39]. They delivered or assisted the psychological therapies, coordinated care and communication between PCPs and mental health specialists, educated patients, delivered MI, BA and counselling, and monitored symptoms. Mental health specialists supervised CMs in three studies and pharmacological treatment in two studies [36, 38, 39]. In STEPS-UP they developed recommendations together with the CM and delivered psychotherapies for patients in STEP 3. Only in PE-PC the intervention was delivered by specially trained BHCs and no case management was applied. Due to the very different therapy concepts, this study was not included in the meta-analysis.

### *Results of individual studies*

The individual results of three RCTs included in the meta-analysis in the short (0–6 months) and long term (≥ 12 months) are presented with the forest plot in Fig. 1.

### *Synthesis of results*

In a meta-analysis we pooled the PTSD-symptom short-term (0–6 months) outcomes from three studies.

**Table 3 Involvement of treatment providers in the intervention**

| Study | Treatment providers | Profession | Special training for intervention | Tasks and interaction with other providers | Supervision received |
|---|---|---|---|---|---|
| **STEPS-UP** | PCP | not reported | Expert training in the pharmacologic treatment of depression and PTSD | - provision of information related to treatment options<br>- providing evidence based pharmacotherapy<br>- selection of the next step for a patient's treatment plan (with CM assistance)- implementation of central teams' recommendations- receives feedback from CMs and the central team | % |
| | CM | RN;<br>social workers<br>counsellors | trained and coached weekly by telephone in BA, problem solving, and MI, training in the web-based intervention | - coordinating care between involved providers<br>- improving patients activation and engagement in their care (education, MI, BA)<br>- assistance of patients and PCPs in choosing treatment options<br>- assistance with web-based or delivery of telephone CBT self-management | by MHS |
| | MHS | psychiatrists;<br>psychologists;<br>clinical social workers | trained in empirically validated psychotherapies for PTSD and depression | - delivery of empirically validated psychotherapy<br>- review of patients' medication<br>- providing CM caseload reviews<br>- training and supervision of CMs. | by psychotherapist |
| | central team | CM; psychiatrist;<br>psychologist;<br>administrative support | not reported | - coordination and supervision of the intervention<br>- development of recommendations for PCPs<br>- reformulation of CM engagement strategies<br>- ensure appropriate medication | % |
| **DESTRESS-PC** | PCP | not reported | pre-study didactic training regarding management of and clinical tools for PTSD and associated conditions | - treatment of patients with feedback from CM | % |
| | CM/ DEST RESS nurse | RN; MSN; BSN;<br>PMHNP-BC | not reported | - assistance with the web-based DESTRESS-PC interface<br>- monitoring of compliance and symptom levels<br>- reengagement of participants with ≥2 missed logons<br>- providing updates of patients' status to PCP and MHS | % |
| | MHS | not reported | not reported | - receives weekly updates from DESTRESS nurses | % |
| **CALM** | PCP | internists;<br>family physicians | single-session medication management training using a simple algorithm | - remains the clinician of record<br>- prescribed all medications | by psychiatrist |
| | ACS (CM) | social workers;<br>RN;<br>psychologists | - formal training applying the MINI- didactics for CBT program, MI, medication algorithm for anxiety | - providing eligibility assessment<br>- delivery of computerized CBT program<br>- monitoring of symptoms and adherence | by psychiatrist and psychologist |
| | MHS | psychiatrists;<br>psychologists | not reported | - providing weekly supervision of ACS for diagnostic, CBT and medication management issues<br>- providing medication consultation to PCPs. | % |
| **PE-PC** | PCP | not reported | not reported | member of the primary care team | % |
| | MHS | doctoral-level behavioral health providers (three civilian, one military psychologist) | full training workshop for PE; one to two training cases in the PE-PC intervention under close supervision | - follows up any missed appointments and attempts to reschedule<br>- delivering PE-PC | by PI and independet clinician |

*CM* care manager, *PCP* primary care physician, *MHS* mental health specialist, *ACS* anxiety clinical specialist, *RN* registered nurses, *MSN* Master of Science Nursing, *BSN* Bachelor of science in nursing, *PMHNP-BC* board certified Psychiatric Mental Health Nurse Practitioner, *BA* behavioural activation, *MI* motivational interviewing, *CBT* cognitive behavioural therapy, *PE* Prolonges Exposure, *PE-PC* Prolonged Exposure for Primary Care, *PI* primary investigator

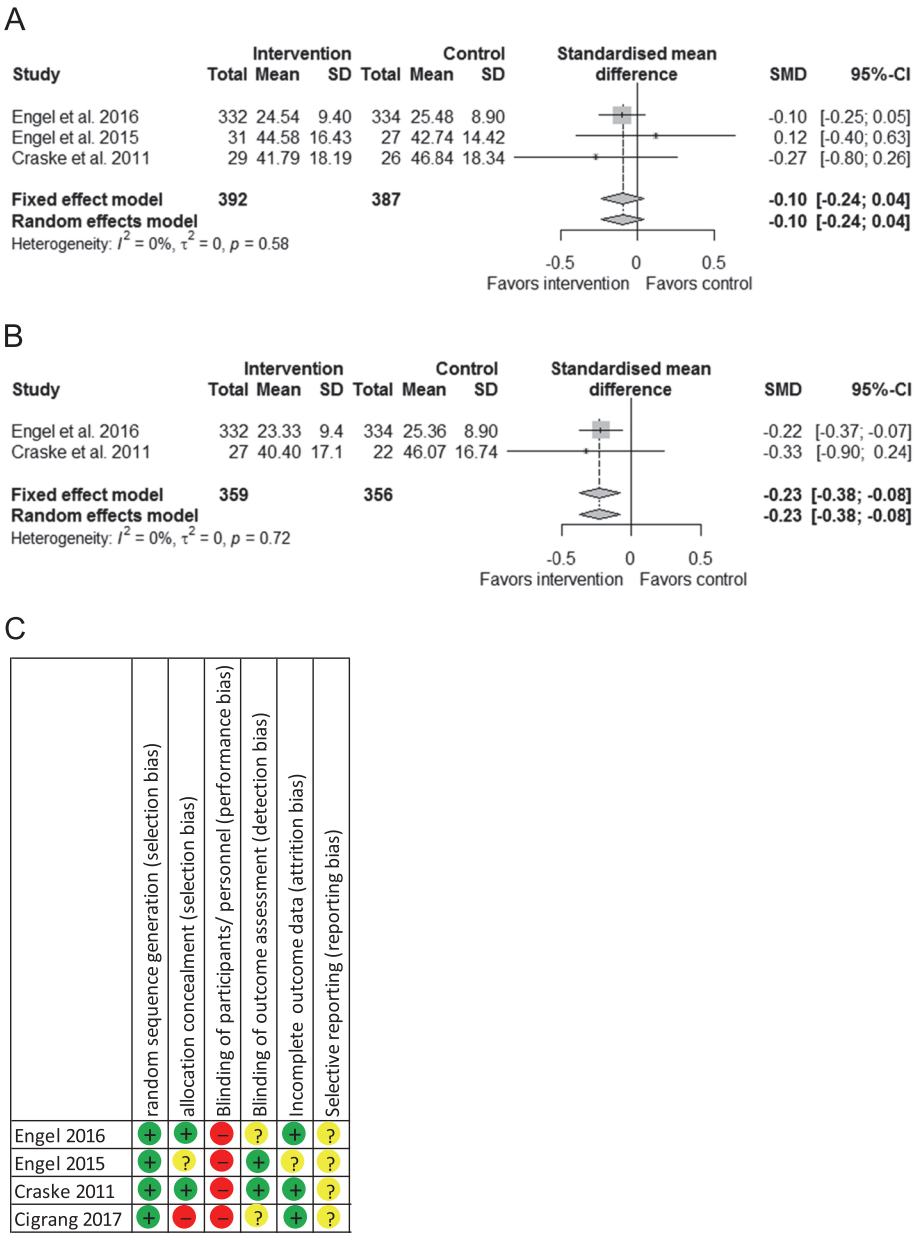


**Fig. 1** Meta-analysis of interventions for PTSD including psychological therapies in primary care vs. control; risk of bias summary. Small grey squares represent SMDs for PTSD symptom improvement of individual RCTs, large grey squares represent weights, horizontal lines show 95% CI, grey diamonds represent total SMDs of interventions and 95% CI. **a**: short-term effects (0–6 months); **b** long-term effects (12 months and longer); **c** risk of bias summary according to the Cochrane Collaboration Risk of Bias Tool

According to the pooled analysis of the three studies, multifaceted interventions including psychological therapies and involving PCPs may make little or no difference to PTSD symptoms (SMD, − 0.1; 95% confidence interval, − 0.24-0.04; Fig. 1a). No statistical heterogeneity was detected ($I^2$ = 0%; 95% CI, 0.0–80.8%). Only two studies reported on long-term outcomes (12–18 months). According to the meta-analysis of these two studies, psychological interventions in primary care may improve PTSD symptoms over time (SMD, − 0.23; 95% CI, − 0.38- -0.08; $I^2$ = 0%; Fig. 1b). Because only two studies contributed to the pooled analyses for long-term effects, we also investigated time, intervention and time-intervention interaction effects with a generalized linear mixed model. Time (regression coefficient, −.28; SE, 0.05; $P < .0001$) and time-intervention interaction (regression coefficient, −.28; SE, 0.08; $P = .0020$) were significantly associated with means of PTSD symptom measures, with the treatment effect yielding a regression coefficient equal to .94; SE 0.52; $P = .09$.

We did not perform a meta-analysis for the treatment effects on comorbidities and quality of life due to the limited number of included studies. Further secondary outcomes were mostly not reported separately for the PTSD subgroup or not reported at all.

#### *Risk of bias within studies*

A summary of risk of bias judgments can be found in Fig. 1c. For a more detailed description, with support of judgments, see additional file 4. All studies had low risk of bias for random sequence generation. Allocation concealment was judged with low risk in two studies, with unclear risk and with high risk each in one study. Blinding of participants and personnel was not possible due to intervention study design. A lack of blinding may influence outcome, thus all studies scored high risk of bias. Blinding of outcome assessment was adequately reported in two studies, but risk was unclear in two studies. Two studies showed low risk of bias for incomplete outcome data. All studies did not report on all pre-specified secondary outcomes or no pre-specified outcomes were available at all and were judged with unclear risk for reporting bias.

#### *Risk of bias across studies*

Publication bias is difficult to judge with only four included studies. We performed a comprehensive search to reduce the risk of small studies not being detected. Two included studies are small in size and report on temporary effects only [37, 40].

#### *Certainty assessment of evidence*

Using GRADE we classified the quality of evidence as low because of a limited number of studies, the heterogeneous population of general primary care settings being not represented from the included study population and comparisons between heterogeneous intervention and control groups.

## Discussion

### Summary of evidence

We identified only four studies investigating psychological interventions for posttraumatic stress disorder (PTSD) involving primary care physicians (PCPs). According to our meta- and regression-analysis, multifaceted interventions including psychological therapies in primary care may make little or no difference in the short term, but may improve PTSD symptoms in the long term. These results should be interpreted with caution due to an overall low quality of evidence. All studies were conducted in the United States and three were in military settings. Case managers (CMs) had a central role in three interventions, which were pooled in a meta-analysis. They supported or conducted psychological therapies, coordinated communication between all treatment providers and provided patient activation through patient education, behavioural activation (BA), motivational interviewing (MI), and counselling. PCPs remained responsible for pharmacological treatment, received special training, and got regular feedback on ongoing therapy within the CM-based studies. One study did not involve CMs. The therapy (Prolonged Exposure) was delivered by specially trained behavioural health consultants (BHCs) who were part of the primary care team and worked as a consultant to the PCP.

There are two explanations for the small treatment effect on PTSD symptoms which was detected in the long term (after 12–18 months) but not directly after the intervention. One reason could be the lack of long term outcomes from DESTRESS-PC, the only study with a negative effect in the short term. Another explanation may be, that the long term effect after 12 months is a "learning effect": While well-established psychological interventions are often short and intensive resulting in an immediate and strong effect, in primary care less intensive interventions are common with a lasting "learning effect", which was also shown for collaborative care for depression [23, 41].

Though our aim was to determine the effectiveness of psychological therapies for PTSD in primary care, we only found studies investigating interventions which embedded psychological therapies into multifaceted service delivery models. Besides the applied CBT (cognitive behavioural therapy)-based psychological therapies also CM initialised patient activation (BA, MI, problem solving) and evidence based pharmacotherapy with adherence monitoring may have contributed to the detected positive treatment effect. Control groups were heterogeneous, too. The control group in STEPS-UP received collaborative care, which was previously implemented to improve PTSD primary care treatment within the military health care system. In DESTRESS-PC PCP training was also part of the optimized usual care. Interestingly, control groups of all three trials show a slight improvement of PTSD symptoms which may be caused by PCP training (DESTRESS-PC), CM alone (STEPS-UP) and mental health specialist referral (CALM). PCP training might be an important component because the ViStA trial (not included in our synthesis, comparing collaborative care for PTSD with minimally enhanced usual care) found that the intervention group (with CM and PCP training) and the control group (with PCP training) improved equally [42]. In depression care, training of PCPs resulted in no or only minimal improvement [24, 43], while feedback to PCPs about the ongoing therapy was associated with positive outcome measures [24].

The low effect size may partly be explained by the above discussed improvement of PTSD symptoms in the

active control groups. In addition, the study population of the two largest trials (STEPS-UP and DESTRESS) consisted of military personnel, mainly men in their 20s, who are difficult to engage in mental health care [36, 37]. Finally the STEPS-UP population suffered from a variety of medical and psychiatric comorbidities reducing potential for improvement.

Our meta-analysis supports the explorative conclusion of a narrative systematic review suggesting collaborative care offering psychotherapy as a promising approach [25]. Looking at related diseases, short CBT interventions were effective for anxiety treatment in primary care settings, but results are heterogeneous for the effectiveness of psychotherapies in treating depression in primary care [21, 23, 24, 44]. Successful treatment of PTSD in primary care might be even more difficult than depression care: PTSD-symptom improvement was delayed compared to depressive symptoms [36] similar to previous studies showing that depressive patients with comorbid PTSD have a delayed positive response to collaborative care [45, 46]. An explanation for these findings could be that PTSD is often complicated by comorbidities, which need to be considered when designing new trials and interventions [47].

Another system of service delivery was investigated by the fourth included study [40]: the Primary Care Behavioral Health Model, with behavioural health providers integrated in primary care. In contrast to the other studies no CM and strategies to improve patient activation were applied; so it was not included within the meta-analysis. Despite the small size of the studied population ($n = 67$) the moderate to large effect sizes obtained up to six months in the follow up assessments encourage the idea that evidence based therapies for PTSD can effectively be transferred from secondary to primary care, especially for patients with mild to moderate symptom severity and enable an early starting therapy.

Because most mental health disorders are treated in general medical settings, primary care remains the first contact to establish effective therapies [48, 49]. In contrast to the central role of PCPs in many countries, in all four studies psychological therapies were provided with the assistance of a CM or by behavioural health providers, but were never delivered by the PCP in person. Only one pilot trial investigated the delivery of brief primary-care CBT delivered by a PCP, unfortunately without follow-up [50].

### Limitations

Our study has several limitations. The quality of evidence is low. There are only three studies contributing to the meta-analysis, with two studies including only a small number of patients with PTSD and one study with a short follow-up (4.5 months) limiting the generalizability of our findings. Performance bias was high in all studies. Due to study design it is difficult to blind participants and personnel for the intervention, thus introducing possible bias in subjective self-report measures. Assessing the certainty of evidence using GRADE [35] we detected serious indirectness because of applicability and indirect comparisons. The four included trials do not represent the heterogeneous population of general primary care settings. Three of four studies were conducted in military settings with mostly male patients who had experienced war-related trauma, which can be long-lasting, repetitive and may lead to complex PTSD. For this condition a sequenced or phase based multimodal therapy is recommended which can hardly be realised in primary care [51]. In non-specialised primary care settings the majority of PTSD patients may consist of female survivors of sexual assault [52].

Further indirectness arose from the multifaceted interventions and the heterogeneity in control groups as discussed above.

Reporting of results was often incomplete. In STEPS-UP a separate analysis of primary and secondary outcomes for patients with PTSD only (without depression) was missing. Study selection was difficult because descriptions of PCP involvement was insufficient and required us to contact several authors to request more detailed descriptions. Answers were not always available, so the risk remains that possibly eligible studies were not included.

Although statistical heterogeneity was not detected, all studies included in the meta-analysis show clinical diversity due to different settings (military vs. "general" primary care), different control groups (usual care vs. collaborative care vs. care management) and complex interventions including different components. Nevertheless, all studies applied CBT-based interventions with the help of a CM within a primary care setting and, therefore, it seemed appropriate to combine these studies.

The effectiveness of single intervention components could not be investigated with meta-regression due the lack of studies investigating only single components of the different service delivery models. The role of PCP involvement, especially, could not be assessed. The influence of interventions on comorbidities and quality of life could also not be calculated due to the limited number of included studies.

Our findings cannot be generalized to primary care settings in other countries because all studies were conducted in the United States and three studies were conducted in military contexts. In addition, the majority applied CM which is not always well established in other countries.

## Conclusion

To our knowledge this is the first systematic review and meta-analysis of primary care based psychological interventions for PTSD.

Four randomized controlled trails (RCTs) could be included which applied multifaceted interventions based on psychological therapies for PTSD involving PCPs. Psychological interventions for PTSD in primary care settings may be effective in the long term. Evidence supports the feasibility of primary care interventions for PTSD in general and the need for more studies examining psychological interventions for PTSD in primary care. The limited amount of research, an overall low quality of evidence and the rising number of different service delivery models in primary care require a differentiated analysis and hinder a universally valid recommendation for future treatment implications.

Some trials have only been published to date as study designs or pilot trials [53, 54], but may soon add relevant findings.

Future studies should investigate the contribution to effectiveness made by both intervention components and involved providers.

## Supplementary information

**Supplementary information** accompanies this paper at https://doi.org/10.1186/s12875-020-01244-4.

**Additional file 1.** Search strategy for Medline and conference proceedings searched.

**Additional file 2.** PRISMA Flow-Chart.

**Additional file 3.** Characteristics of included studies.

**Additional file 4.** Risk of bias in included studies.

### Abbreviations

BA: Behavioural activation; BHC: Behavioural health consultant; BIC: Bayesian information criterion; CAPS: Clinician administered PTSD scale; CBT: Cognitive behavioural therapies; CCM: Chronic care model; CM: Case manager; DSM-5: Diagnostic and Statistical Manual of Mental Disorders 5th edition; EMDR: Eye movement desensitization and reprocessing; ICD: International Statistical Classification of Diseases and Related Health Problems; MI: Motivational interviewing; NET: Narrative exposure therapy; PCL-C: PTSD Checklist-Civilian version; PCL-S: PTSD Checklist-Stressor Specific version; PCP: Primary care physician; PTSD: Posttraumatic stress disorder; RCT: Randomized controlled trial

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### Authors' contributions

RG and AF had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: MB, AF, RG, JG1, PS, KS, SS, HCV. Acquisition, analysis, or interpretation of data: All authors (RG, AF, MK, PS, KS, SS, SJZ, FW, JG, MB, HCV, JG1). Drafting of the manuscript: AF, RG, JG1, MK, KS, SS, HCV. Critical revision of the manuscript for important intellectual content: All authors (RG, AF, MK, PS, KS, SS, SJZ, FW, JG, MB, HCV, JG1). Study supervision: JG1, HCV. All authors read and approved the final manuscript.

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### Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

This contribution is a pure literature review that does not involve tests/studies on humans or animals.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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## Publisher's Note

## 2.7 Entwicklung einer hausärztlichen Kurztherapie bei posttraumatischen Beschwerden nach kritischer Erkrankung

***Originalarbeit:***

*Gensichen J, Schultz S, Adrion C,* ***Schmidt K,*** *Schauer M, Lindemann D, Unruh N, Kosilek RP, Schneider A, Scherer M, Bergmann A, Heintze C, Joos S, Briegel J, Scherag A, König HH, Brettschneider C, Schulze TG, Mansmann U, Linde K, Lühmann D, Voigt K, Gehrke-Beck S, Koch R, Zwissler B, Schneider G, Gerlach H, Kluge S, Koch T, Walther A, Atmann O, Oltrogge J, Sauer M, Schnurr J, Elbert T, Picture Study Group. Effect of a combined brief narrative exposure therapy with case management versus treatment as usual in primary care for patients with traumatic stress sequelae following intensive care medicine: study protocol for a multicenter randomized controlled trial (PICTURE). Trials. 2018;19(1):480.*
*doi: 10.1186/s13063-018-2853-7.*

***2.7.1 Hintergrund:*** Traumatische Erfahrungen von Schmerz und Hilflosigkeit können im klinischen Verlauf zu einer Störung des Gedächtnisses führen und als posttraumatische Belastungsstörung (PTBS) immer wieder neu als real erlebt werden. Dies kann nicht nur nach Naturkatastrophen oder Gewalterfahrungen der Fall sein, sondern auch nach medizinischen Maßnahmen wie einer intensivmedizinischen Behandlung [46]. Da ein Vermeidungsverhalten zu den Kardinalsymptomen der PTBS zählt, wird die Erkrankung oft nicht erkannt. Dazu sind die Kapazitäten für eine Traumatherapie durch Fachspezialisten stark begrenzt. So bleibt der Hausarzt für viele Patienten mit posttraumatischen Beschwerden nach Intensivtherapie der erste Ansprechpartner. Hausärztliche Interventionen in diesem Bereich wurden bislang jedoch kaum beschrieben, siehe 2.6.

Die Narrative Expositionstherapie (NET) ist eine psychotherapeutische Intervention für posttraumatische Beschwerden, die auf Prinzipien der kognitiven Verhaltenstherapie und der Erzähltherapie (*Testimony Therapy*) beruht [47]. Sie zeigt auch positive Effekte, wenn sie von medizinischen oder psychologischen Laien durchgeführt wird. Dies ermöglichte den Einsatz des Verfahrens in Entwicklungsländern, in denen nach Naturkatastrohen oder Bürgerkriegen für eine große Anzahl von traumatisierten Menschen praktisch keine professionelle Hilfe zur Verfügung steht. Dazu hat die Methode als Standardverfahren zur Behandlung der PTBS auch Einzug in die aktuelle S3-Leitlinie „Posttraumatische Belastungsstörung“ der Deutschsprachigen Gesellschaft für Psychotraumatologie (DeGPT) gefunden [48].

***2.7.2 Fragestellung:*** Kann eine Kurzversion der NET, welche speziell für die Hausarztpraxis adaptiert wurde, posttraumatische Symptome nach Intensivtherapie im Vergleich zu einer verbesserten Standardtherapie signifikant reduzieren?

***2.7.3 Methodik:*** Seit 2018 wird an Studienzentren München, Berlin und Hamburg die PICTURE-Studie durchgeführt (*PTSD after ICU Survival, Caring for Patients with Traumatic Stress Sequelae following Intensive Medical Care*), ein multizentrischer und zweiarmiger RCT, gefördert durch die Deutsche Forschungsgemeinschaft (DFG). Insgesamt 172 (nach aktueller Korrektur des Analyseplans) erwachsene Patienten mit leichten bis mittelschweren posttraumatischen Beschwerden sollen ab drei Monaten nach der Entlassung aus der intensivmedizinischen Behandlung eingeschlossen werden. Die Hausärzte der Patienten beider Studienarme werden leitliniengerecht in der Versorgung von Patienten mit PTBS geschult. Die Hausärzte der Kontrollgruppe behandeln die Patienten so in den ersten sechs Monaten nach Studieneinschluss an drei Terminen in einer verbesserten Standardtherapie (iTAU). Hausärzte in der Interventionsgruppe werden zusätzlich in der Durchführung einer angepassten Version der NET geschult. Diese umfasst drei Anwendungen der NET durch den Hausarzt sowie ein begleitendes, telefonisches Monitoring der Patienten durch die medizinische Fachangestellten der Praxis. Die Intervention erstreckt sich insgesamt über sechs Monate, die Nachbeobachtungsdauer beträgt zwölf Monate nach Randomisierung. Zur Beurteilung der Wirksamkeit der Intervention werden strukturierte, verblindete Telefoninterviews sechs und zwölf Monate nach Abschluss der Intervention durchgeführt. Primärer Endpunkt ist die absolute Veränderung der posttraumatischen Symptome, gemessen an der *Posttraumatic Diagnostic Scale* (PDS-5) [49] nach sechs Monaten. Als sekundäre Endpunkte werden unter anderem Skalen zu Depression, Angst, gesundheitsbezogener Lebensqualität sowie gesundheitsökonomische Parameter erfragt.

***2.7.4 Diskussion und Zusammenfassung:*** Die primärmedizinische Behandlung von posttraumatischen Beschwerden erfordert praktikable und effektive Konzepte. Im Falle eines Wirksamkeitsnachweises durch PICTURE könnte NET perspektivisch in die Primärversorgung integriert werden. Die ersten Ergebnisse werden Ende 2022 erwartet.

Gensichen et al. Trials (2018) 19:480
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Trials

STUDY PROTOCOL Open Access

# Effect of a combined brief narrative exposure therapy with case management versus treatment as usual in primary care for patients with traumatic stress sequelae following intensive care medicine: study protocol for a multicenter randomized controlled trial (PICTURE)

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## Abstract

**Background:** Traumatic events like critical illness and intensive care are threats to life and bodily integrity and pose a risk factor for posttraumatic stress disorder (PTSD). PTSD affects the quality of life and morbidity and may increase health-care costs. Limited access to specialist care results in PTSD patients being treated in primary care settings. Narrative exposure therapy (NET) is based on the principles of cognitive behavioral therapy and has shown positive effects when delivered by health-care professionals other than psychologists.
The primary aims of the PICTURE trial (from "PTSD after ICU survival") are to investigate the effectiveness and applicability of NET adapted for primary care with case management in adults diagnosed with PTSD after intensive care.

(Continued on next page)

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(Continued from previous page)
**Methods/design:** This is an investigator-initiated, multi-center, primary care-based, randomized controlled two-arm parallel group, observer-blinded superiority trial conducted throughout Germany. In total, 340 adult patients with a total score of at least 20 points on the posttraumatic diagnostic scale (PDS-5) 3 months after receiving intensive care treatment will be equally randomized to two groups: NET combined with case management and improved treatment as usual (iTAU). All primary care physicians (PCPs) involved will be instructed in the diagnosis and treatment of PTSD according to current German guidelines. PCPs in the iTAU group will deliver usual care during three consultations. In the experimental group, PCPs will additionally be trained to deliver an adapted version of NET (three sessions) supported by phone-based case management by a medical assistant. At 6 and 12 months after randomization, structured blinded telephone interviews will assess patient-reported outcomes.
The primary composite endpoint is the absolute change from baseline at month 6 in PTSD symptom severity measured by the PDS-5 total score, which also incorporates the death of any study patients. Secondary outcomes cover the domains depression, anxiety, disability, health-related quality-of-life, and cost-effectiveness. The principal analysis is by intention to treat.

**Discussion:** If the superiority of the experimental intervention over usual care can be demonstrated, the combination of brief NET and case management could be a treatment option to relieve PTSD-related symptoms and to improve primary care after intensive care.

**Trial registration:** ClinicalTrials.gov, NCT03315390. Registered on 10 October 2017.
German Clinical Trials Register, DRKS00012589. Registered on 17 October 2017.

**Keywords:** Stress disorders (MeSH), Intensive care (MeSH), Non-pharmacological (NON-Mesh), Primary health care (MeSH), Randomized controlled trial (MeSH)

## Background

In Germany, more than two million people are treated in intensive care units (ICUs) every year, more than 350,000 of whom undergo mechanical ventilation. These patients may suffer long-term functional, psychological, or medical sequelae [1–3], but there are only a limited number of treatment options [4]. Posttraumatic stress disorder (PTSD) is a common sequela (25–44%) of critical illness and ICU treatment and has a substantial impact on health-related quality of life and health-care-related costs [5, 6]. Systematic screening and early interventions in primary care may improve outcomes [7, 8]. In Germany, a guideline for treating patients with PTSD in primary care recommends supportive symptomatic pharmacologic therapy on a primary care level and referral to a specialist for psychotherapy and other non-pharmacological interventions [9]. However, access to psychiatric and psychotherapeutic specialty services, e.g. trauma therapists, is limited and waiting times are usually 5 months or longer [10, 11]. During this time, a primary care physician (PCP) is the main health-care professional attending to the patient. An effective psychological therapy for ICU-related PTSD applicable to primary care is needed [12].

### Trial rationale

Currently, the underlying mechanism of PTSD is assumed to be a disturbance in the organization and processing of memories of traumatic events, resulting in a separation of sensory, cognitive, and affective representations from the contextual and episodic memory system [13]. Patients who suffer from traumatic stressful experiences cannot clearly structure these events in chronological order and are, thus, unable to place the anxiety and helplessness associated with these events appropriately in time and space. Consequently, alarm responses can become activated by even small, subtle prompts. The resulting change affects the homeostasis of all physiological systems. The goal of psychotherapeutic interventions for PTSD is to teach survivors which cues relate to traumatic experiences in the past so that they no longer trigger an alarm response in the present.

Narrative exposure therapy (NET) is a specific form of psychotherapy for PTSD based on cognitive behavioral therapy [13]. During this treatment, the patient develops a narrative of traumatic events, which is meant to consolidate fragmented memories by setting these events into their respective context of time, place, and situation. NET typically consists of a session of psychoeducation, followed by a session in which the patient creates a graphical representation of their biography using a lifeline. Then, there are several sessions in which the patient recounts the stressful situations to recover contextual details of the traumatic event. NET is effective even when limited to only three to four sessions and also when delivered by health-care professionals other than psychotherapists [14–16].

In this study, a psychological intervention combines a brief version of NET adapted to primary care [13] with

the principles of the chronic care model for special case management (telephone monitoring by the medical assistant or MA) [17]. The latter is one of the core components of this model. It includes case management focused on proactive patient symptom monitoring, clinical decision support for the PCP, and training for PCPs in evidence-based care.

A randomized controlled two-arm study of sepsis survivors (SMOOTH trial) enrolled 291 adult patients between February 2011 and December 2014 [18]. Patients were recruited from nine ICUs across Germany after having survived sepsis and randomized to usual primary care or to a 12-month intervention, consisting of usual primary care plus additional PCP and patient training, case management provided by study nurses, and clinical decision support for PCPs by consulting physicians. Based on the SMOOTH trial, which examined whether a primary care–based intervention improved health-related quality of life in adult sepsis survivors, we designed the PICTURE trial, which aims to improve traumatic stress sequela for post ICU-patients in a primary care setting [18].

## Methods/design

### Aims and objectives

The primary aims of the PICTURE trial (from "PTSD after ICU survival") are to investigate the effectiveness, safety, and applicability of a brief NET-oriented primary care intervention combined with systematic trauma monitoring in ICU survivors compared to improved treatment as usual (iTAU), and to assess the maintenance of a possible treatment effect (defined as an improvement in PTSD-related symptoms) and applicability assessed at 6 and 12 months after baseline.

### Trial design and setting

PICTURE is a multi-center, two-arm parallel-group, observer-blinded, randomized, active-controlled superiority trial. The trial will be conducted in primary care practices across Germany. Trial management will be delivered by academic primary care institutes at university hospitals around Munich, Berlin, Hamburg, Dresden, Tübingen, and other areas. The primary care setting is associated with long-lasting doctor–patient relationships and coordination of health services, in accordance with the definition of Starfield et al. [19].

Figure 1 is a flow chart for the study. This protocol follows the "Guidance of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement" [20], and it includes the schedule of enrolment and relevant assessments (Fig. 2) based on the SPIRIT figure template. A completed SPIRIT checklist is provided in Additional file 1.

### Pre-selection of eligible patients for trial recruitment and informed consent procedures

Patients will be screened by ICU staff at the time of discharge from the ICU if they meet the following criteria:

- male or female adults aged 18 to 85 years
- duration of mechanical ventilation ≥3 days
- Sequential Organ Failure Assessment (SOFA) score ≥ 5 (i.e., the maximum SOFA score during the ICU stay)
- life expectancy ≥9 months (as assessed by the intensive care physician)

Screening at ICU discharge will use a short validated paper-based questionnaire for cognition (Six-item Screener, SIS) [21] and a short validated five-item version of the Primary Care PTSD Screen (Primary Care PTSD Screen for DSM-5, PC-PTSD-5) [22].

Screened patients with a PC-PTSD-5 total score ≥3 points and no signs of significant cognitive impairment, i.e., with a SIS score ≥4 points, at ICU discharge will be re-screened 10 weeks later by the study nurse (affiliated at the corresponding trial site) via phone using the PC-PTSD-5 questionnaire only.

If a PC-PTSD-5 score of ≥3 is measured during the re-screening 10 weeks after ICU discharge, the patient will asked to attend for a baseline assessment, including confirmation of the PTSD diagnosis, at their PCP's office. As a prerequisite for the baseline visit, the patient's PCP will be assessed for eligibility by the study nurses of the corresponding trial site and asked for written informed consent to participate in the trial, if all inclusion criteria are met.

### Target population and eligibility criteria

#### *Inclusion and exclusion criteria for patients*

For final inclusion, screened patients must meet all the following inclusion criteria to be eligible for enrollment into the trial at baseline:

- PTSD symptom level: 20-item Posttraumatic Stress Diagnostic Scale for DSM-5, PDS-5 score ≥ 20 points [23]
- able to follow study instructions and likely to attend and complete all required visits and telephone surveys
- provide written informed consent

Patients are excluded from enrolment into the study if any of the following exclusion criteria apply:

- insufficient understanding of the German language
- presence of a physical or psychiatric condition that at their physician's discretion may put the subject at

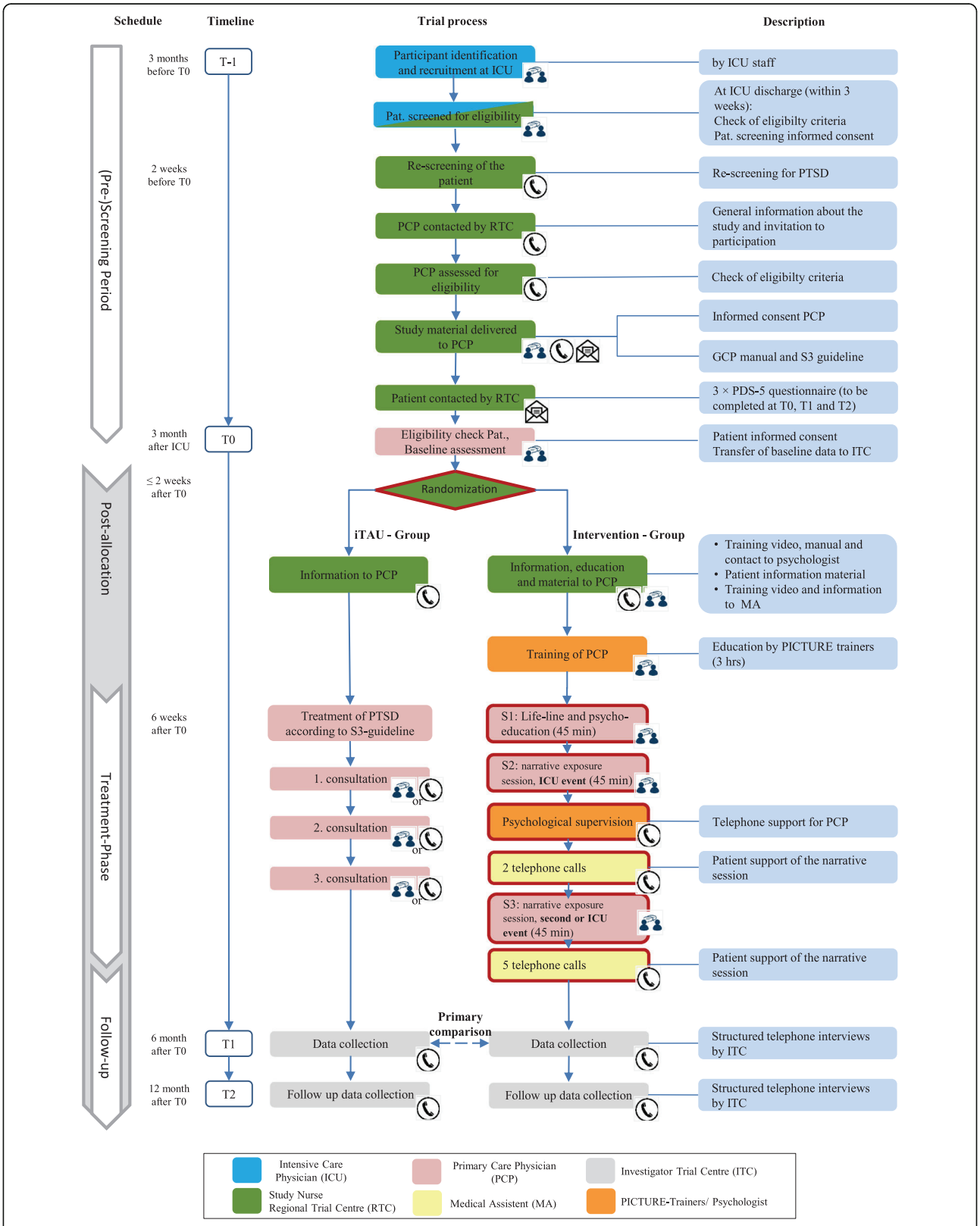


**Fig. 1** Study flow chart of the PICTURE trial: graphical depiction of study activities and components of intervention for both arms. BL baseline, GCP good clinical practice, GP general practitioner, ICU intensive care unit, ITC investigator trial center, MA medical assistant, Pat. participant, PDS Posttraumatic Stress Diagnostic Scale, PTSD posttraumatic stress disorder

| | STUDY PERIOD | | | | | | |
|---|---|---|---|---|---|---|---|
| | Enrolment | | Allocation | | Post-allocation | | |
| **TIMELINE** | **T -1** Screening | **2 weeks prior to T0** Re-Screening | **T 0** | **Randomi-zation** (≤ 2 weeks after T0) | ***Intervention period*** *(3 visits)* | **T 1 (6 months after T0)** | **T2 (12 months after T0)** |
| Patient's Informed Consent | X* | | X | | | | |
| Eligibility Screen | X | X | | | | | |
| Patient level: In-/Exclusion Criteria | | | X | | | | |
| PC-PTSD-5 | X | X | | | | | |
| SIS | X | | | | | | |
| PCP level: In-/Exclusion Criteria; PCP characteristics | | X | | | | | |
| PCP's Informed Consent | | X | | | | | |
| ICU Data (incl. SOFA score) | X | | | | | | |
| Patient medical history, demographics/ characteristics | X | | X | | | | |
| *Experimental intervention (**NET**)* | | | | ← – – | – – – → | | |
| *Control intervention (**iTAU**)* | | | | ← – – | – – – → | | |
| Documentation of SAE** | | | | ← – – | – – – – – – – – – – – → | | |
| PDS-5 | | | X | | | X | X |
| PHQ-9 | | | X | | | X | X |
| OASIS | | | X | | | X | X |
| EQ-5D-5L | | | X | | | X | X |
| PAM | | | X | | | X | X |
| WHODAS 2.0 | | | X | | | X | X |
| Modified CSSRI (incl. concomitant (drug) therapy, sociodemographic data) | | | X | | | X | X |
| Check of compliance, protocol adherence (patient and PCP level) | | | X | | X | X | |

*Patient Informed Consent for Screening

** Safety documentation: to be performed by the treating PCP starting at S1 (NET-group)/1. Consultation (iTAU-group) until T2 (assuming that information about specific safety issues experienced by the patient will be reported to his/her PCP. A deviation from the schedule of +/-3 weeks is acceptable for T1 and T2.

**Fig. 2** Standard protocol items (SPIRIT) for the PICTURE trial: schedule of enrolment, intervention, and assessments with their pre-planned time points T1 to T2. CSSRI Client Sociographic and Service Inventory, EQ-5D-5L Five-dimension Five-level EuroQol, ICU intensive care unit, iTAU improved treatment as usual, NET Narrative exposure therapy, OASIS Overall Anxiety Severity and Impairment Scale, PAM Patient Activation Measure, PC-PTSD Primary Care Posttraumatic Stress Disorder Screen, PCP primary care physician, PDS Posttraumatic Stress Diagnostic Scale, PHQ Patient health questionnaire, SAE serious adverse event, SIS Six-item Screener, SOFA Sequential Organ Failure Assessment, WHODAS World Health Organization Assessment Schedule

risk, may confound the trial results, or may interfere with the patient's participation in this clinical trial
- known or persistent abuse of medication, drugs, or alcohol
- major depression (PHQ-9 ≥ 23)
- acute suicidality
- life expectancy < 9 months (as assessed by the PCP)
- concomitant therapy: trauma-specific psychotherapy at baseline
- intake of any neuroleptic, anticholinergic, or anti-epileptic drugs up to 2 weeks prior to baseline
- severe PTSD symptoms (PDS-5 > 50)

#### *Inclusion and exclusion criteria for PCPs*

Inclusion criteria for participating PCPs are:

(1) The physician must have been registered for at least 2 years in the German statutory health-care system as a primary care physician.

(2a) The physician must have a qualification in basic psychosomatic care (Psychosomatische Grundversorgung, Bundesärztekammer, 2001) [24] to ensure that they can provide a basic level of mental health care and to ensure patient safety.

(2b) Alternatively, the PCP must have been a family doctor within the German statutory health-care system for at least 5 years with evidence of adequate psychiatric education, e.g., additional training (this is to ensure that all participating PCPs have a minimum level of psychiatric knowledge).

(3) They have provided written informed consent.

PCPs with a specialization such that more than 80% of the patients registered with their practice have a specific mental condition are excluded from the trial to ensure that enrolled practices are representative of German primary care.

### Randomization and blinding

All fully screened patients who give written informed consent for participation and who fulfill the eligibility criteria will be randomized together with the attending PCP. A full screening also includes confirmation of the PTSD diagnosis by the treating PCP of the trial participant, together with the baseline assessment at T0.

Randomization is requested by the personnel of the corresponding study site no later than 2 weeks after the baseline visit at T0. Concealed randomization to NET or iTAU will be performed with a 1:1 allocation ratio. The computer-generated randomization allocation sequence considers stratification by study site defined by the corresponding ICU. The sequence will be generated, and randomization will be performed by an independent person affiliated to the Institute for Medical Informatics, Biometry and Epidemiology of the Ludwig Maximilian University of Munich (LMU Munich) using the web-based randomization tool Randoulette [25]. The randomization list will not be accessible during the study.

After randomization, the relevant study site will have immediate access to the allocation group via online access to Randoulette and will inform the patient and the PCP practice about the respective allocation status (NET versus iTAU) via an official letter and ask the PCP practice to arrange the following appointments with the participating patient. PCPs in the intervention group will receive further information about the NET intervention and individual training.

PCPs and patients know the treatment they deliver or receive. However, this trial is designed to be *observer--blinded*. The trained interview staff affiliated to the site of the principal investigator (PI) at the Institute of General Practice and Family Medicine at LMU Munich will collect the patient-reported primary and secondary efficacy outcomes blind to group assignment. Follow-up data will be collected through structured telephone interviews at T1 and T2 without any access to additional patient data, case report forms (CRFs), or the study database. The trial statistician and the health economist will remain blinded to randomization codes throughout the trial until the study database has been finalized and locked.

### Intervention period

#### *Experimental condition*

After randomization, PCPs in the intervention group will receive training material (therapy manuals for PCPs and MAs, intervention videos, and a paper booklet), as well as face-to-face training by NET-qualified psychologists. In most cases, the training for PCPs will be on a one-to-one basis, though group training may also be arranged. Additionally, patients in the intervention group will receive written information about PTSD and trial procedures. Treatment in the intervention group consists of three NET sessions delivered by the PCP and case management delivered by the practice-based MA.

Furthermore, PCPs will receive training through written materials with information regarding study procedures as well as diagnostic examinations for and treatment of PTSD according to the German S3 Guideline on PTSD [10].

Three NET sessions of approximately 45 min each will be delivered by the PCP. The first session includes psychoeducation on PTSD and an overview of the patient's biography. In this session, the patient learns about the symptoms and the theoretical background of PTSD as well as the treatment procedure. In addition, they will identify traumatic events in their biography by constructing a lifeline. In this procedure, the patient places stickers of flowers and stones, symbols of important positive and stressful events, in chronological order on a line that they construct and draw together with the PCP on a piece of paper. The line serves as a timeline,

providing an overview of the patient's biographical burden and resources. At the end of the session, the recent ICU event will be implemented in the lifeline.

In the second session, the patient will be exposed to the traumatic events in a safe environment by giving a detailed narration of their stressful experience during their ICU stay. After the second session, a qualified psychologist will provide telephone support to the PCP to review the treatment so far, prepare the third session, and give guidance and advice on the content and mode of delivery of the therapy, if necessary. Narration on another stressful key life event identified on the lifeline is recommended as the topic for the third session. Alternatively, an additional narration of the ICU event might be chosen, if no other stressful key event can be identified, or if the ICU event is still the major key event in the patient's life.

The MAs receive written training material and personal training on case management, which is carried out by study nurses from the relevant regional trial centers. Case management consists of seven short telephone calls (approximately 15 min each), in which the MA asks about the patient's well-being, completes a PTSD-monitoring checklist, and provides social acknowledgement of the experiences the patient had during their critical illness. MAs follow written instructions for structuring the dialog and gathering information. Included in the instructions is a color-coded rating system for the PTSD screening questionnaire results. Critical responses should prompt the MA to inform the attending PCP immediately. Questionnaire responses are noted in the booklet. Two telephone calls are made between the second and third NET sessions, followed by an additional five telephone calls between the last NET session and T1 (Fig. 1).

#### *Control condition*

Patients allocated to the control group will receive iTAU during at least three consultations with their PCP. Treatment will be based on current German recommendations for the diagnosis and treatment of PTSD [10] without further specifications from the study protocol. PCPs will receive written training material and detailed medical information about PTSD, based on the current national guideline for PTSD and on the application of good clinical practice in the conduct of clinical trials [26]. Because of this explicit training, we consider this treatment approach improved in comparison to treatment as usual without any additional training.

### Informed consent procedures

Prior to enrolment, straight after the eligibility of a patient has been checked and confirmed during re-screening 2 weeks before the baseline assessment at T0, the eligibility of the relevant PCP will be assessed during a telephone interview by the investigator at the regional trial center. Once the PCP's eligibility is confirmed and they show interest in participation in the trial, both the patient and attending PCP will be provided with a full explanation of the trial in word and in writing (patient information sheet and PCP information sheet). These include detailed information about the rationale, design, conduct, potential benefits and risks, and personal implications of the trial. After the information has been provided to the patients and PCPs, they will be given sufficient time (at least 24 h) to consider participation in the trial before they are asked to do so. It is imperative that written consent is obtained before any trial-specific procedures commence. This ensures that participants have a full understanding of the trial and that the decision to participate is made voluntarily. PCPs will have the opportunity to discuss questions and concerns with the regional investigator on the phone. They will then give their patients further information about the trial and discuss open questions and concerns with them, before asking for their patient's informed consent. All participants may withdraw their informed consent from the trial at any time and without any negative consequences for further treatment.

### Study procedures and timing schedule

The baseline assessment (T0) takes place in a PCP practice 3 months after the patient's discharge from ICU by self-reported paper-based and interviewer questionnaires during a consultation with the PCP. In the intervention group, NET sessions start 4 weeks thereafter over a period of 6 weeks. In the control group, patients receive iTAU during three study-related consultations with their PCP within 6 months up to T1. the primary efficacy outcome will be assessed by self-reported paper-based questionnaires 6 months (T1) after the baseline visit (T0) while secondary efficacy outcomes will be assessed 6 months (T1) and 12 months (T2) after the baseline visit (T0) by observer-blinded telephone interviews. For a detailed description of study activities and the components of the intervention, see Fig. 1. The end of the clinical trial is defined by the last individual trial-specific examination during the last visit of the last patient who is participating in the trial.

### Participation discontinuation

If a patient withdraws their written informed consent or there is serious adverse event (SAE), the assigned study intervention will be discontinued for them. SAEs are defined as a patient's death, life-threatening event, clinically relevant severe deterioration of depression or PTSD symptoms, acute suicidality, or adverse events that would constitute an unacceptable risk for the patient. The PCP will decide which incidents have to be followed up as SAEs and will report them accordingly to the PI.

All SAEs will be evaluated by the PI. Additionally, a second evaluation of seriousness, causality, and expectedness will be performed by the Data and Safety Monitoring Board (DSMB) at the PI's discretion to ensure safety evaluations follow the four-eye principle.

Whenever a patient is withdrawn from the trial, the reasons for the withdrawal or treatment discontinuation together with the corresponding dates should be recorded in detail in the patient's medical records and the CRF. If a patient completely drops out from the study, a final examination should be conducted (e.g., by phone). In particular, every effort should be taken to assess the primary outcome. If a patient does not return for a scheduled (telephone) visit, every effort should be made to contact them to regain them for further visits according to the protocol.

For a drop-out or withdrawal of a PCP or for a SAE, immediate support will be available through the Departments of Psychiatry affiliated to the relevant regional trial center to ensure there is adequate care for patients with PTSD. The emergency back-up centers (Prof. Falkai, Department of Psychiatry and Psychotherapy, LMU Munich; Prof. Förstl, Department of Psychiatry and Psychotherapy, Technical University of Munich; Prof. Heinz, Department of Psychiatry and Psychotherapy, Universitätsmedizin Berlin, Campus Charité Mitte; Prof. Gallinat, Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf; Prof. Bauer, Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden; Prof. Elbert, Clinical Psychology, University of Konstanz) will be instructed accordingly. Affected trial participants will be part of the full analysis set according to the intention-to-treat (ITT) principle.

## Patient-reported outcomes

### *Primary efficacy outcome and endpoint*

To evaluate the PTSD symptom severity of trial participants, the German version of the self-administered PDS-5 questionnaire will be applied. Each of the 20 items refers to PTSD-related symptoms experienced in the past month and is answered on a five-point Likert scale (from 0 not at all to 4 more than five times per week/severe) [23, 27].

The primary efficacy outcome is the PDS-5 total severity score ranging from 0 to 80 points. The pre-specified primary efficacy endpoint is the absolute change from baseline to the 6-month follow-up telephone assessment.

### *Secondary efficacy outcomes*

Patient questionnaires to derive secondary efficacy outcomes were chosen based on the conceptual framework of core outcome sets [28, 29].

As depression and anxiety are known common comorbidities in patients with PTSD, trial participants are instructed to complete the primary care validated Patient Health Questionnaire 9 (PHQ-9), where each of the nine items is scored from 0 (not at all) to 3 (nearly every day), resulting in a total score of from 0 to 27 points (large scores indicate severe impairment) [30]. Anxiety will be measured by the brief Overall Anxiety Severity and Impairment Scale (OASIS) questionnaire, which contains five response options for each of the five items, coded from 0 to 4. The total score ranges from 0 (no anxiety) to 20 points, with a high score indicating severe impairment [31]. Disability will be assessed by the 12-item version of the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0), with a total score ranging from 0 to 100 and higher scores indicating higher levels of disability [32]. Patient activation will be measured by the 13-item Patient Activation Measure (PAM) [33], where each item scores from 1 to 4 (1 strongly disagree, 2 disagree, 3 agree, and 4 strongly agree; for the fifth item only, 5 is for not applicable). The evaluation for the latter is made by adding the raw values, which have a range of 13–52, and normalizing them to a scale of 0–100. We will use the version of the EuroQol questionnaire with five dimensions and five levels (EQ-5D-5L), which consists of the EQ descriptive system and the visual analogue scale (EQ-VAS) to measure health-related quality of life. The EQ-VAS is a thermometer-like rating scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state today) [34, 35]. Concomitant drug and non-drug therapies, and health service use will be assessed by means of a modified (shortened) German version of the Client Sociographic and Service receipt Inventory (CSSRI) [36].

For all these scores derived from the questionnaires mentioned above, the treatment effect will be assessed by means of the absolute change from baseline at months 6 and 12 for secondary efficacy outcomes. The detailed schedule of enrolment, interventions, and assessments with their pre-planned time points is shown in Fig. 2.

## Accompanying studies

### *Health economic evaluation*

The objective of the health economic evaluation alongside the main trial is to assess the cost-effectiveness of the NET-oriented intervention in comparison to iTAU from a societal perspective [37]. We will consider health-care costs as well as productivity losses to describe the monetary consequences of the intervention and calculate quality-adjusted life years (QALYs) as a measure of the effects. These results will inform decision makers in the health-care sector of the economic aspects of the NET intervention and support them in deciding whether the intervention should be implemented in the German health-care system.

#### Genetic evaluation

As the first side project of the trial, we also plan to investigate the genetic distinctiveness of patients after intensive care medicine. We will consider differences in the genetic characteristics of ICU patients with PTSD compared to those of ICU patients without PTSD (not participants of the PICTURE trial). The genetic evaluation will be carried out in collaboration with the Institute of Psychiatric Phenomics and Genomics, University Hospital Munich. This project has a separate trial protocol, which has the approval of the ethics committee, and it requires separate written informed consent.

#### Process evaluation

A second side project will explore the experience of the major actors (PCPs and MAs) and patients recruited at ICUs in Berlin, Hamburg, and Dresden with the experimental intervention in the NET group. This project aims to analyze the applicability of the experimental intervention. That is, it will investigate the beneficial and obstructive factors in the effectiveness, acceptance, and feasibility of the intervention, based on the theoretical framework of acceptability [38]. Qualitative interviews will be carried out with PCPs, MAs, and patients after assessing the primary endpoint at T1 for the last patient randomized.

### Statistical planning and analyses

#### Power considerations and sample size calculation

The current literature does not provide a minimal clinically important difference for the primary outcome (PDS-5 total score for DSM-5), on which we could base the sample size calculation [39]. Therefore, we will use a calibration argument to provide a rather pragmatic minimal clinically important difference for this trial. Previous NET studies defined a decline of about 25% in the baseline score as a clinically relevant change [16]. Based on the range of the PDS-5 score from 0 to 80 points, we define 40 as the mean baseline score. Thus, a 25% change from baseline gives 10 points as the mean absolute decrease. To be more conservative (also assuming a slight effect of 4 points within the control group), we consider a difference in absolute change of 6 points between both groups as clinically relevant for these post-ICU patients. Using a standard deviation of 17, this translates into a Cohen's $d$ (standardized effect size) of 0.36. This effect is assumed to be conservative compared to the reported effects for NET [13, 40]. It can be translated into a probability of 0.6 that the observed decrease in the experimental group is larger than that in the control group (assuming a standard normal distribution). The probability of 0.6 is the target parameter needed to perform a sample size calculation with the Wilcoxon–Mann–Whitney rank-sum test. A sample size of 131 patients in each group, i.e. 262 patients in total, will have 80% power to detect a decrease of PDS-5 in the intervention group as described above compared to the control group using a Wilcoxon–Mann–Whitney rank-sum test with a 0.05 two-sided significance level (software used: nQuery Advisor 7.0). To incorporate the death of patients (resulting in the efficacy outcome being truncated due to death), we apply a non-parametric worst rank score analysis ([41, 42], for details see below) and decided to randomize an additional 78 (= $2 \times 39$) patients [an increase of about 30% (= 39 / 131) derived from a simulation study]. Thus, the sample size to be allocated to the trial is $2 \times (131 + 39) = 340$ patients in total.

It is anticipated that 3000 patients can be pre-screened, of which 1000 (33%) are expected to show posttraumatic stress [5]. The rate of non-participation is expected to be about 35%, which is a conservative assumption compared to our previous study (20% non-participants in [18]). Therefore, 650 (65%) are expected to be willing to participate (patients and their PCPs). Of these, 550 patients (about 85%) could be screened by their treating PCP 3 months post-ICU discharge (assuming a mortality rate after 6 months of about 15% as in [18]), 400 (about 70%) could meet the inclusion criteria, and 340 (85%) patients (and their PCPs) could consent to participate in the study at the baseline visit. We assume a 30% drop-out rate from baseline over the 6 months before the primary endpoint is assessed. There is no pre-planned interim efficacy analysis and no sample size recalculation.

#### Statistical analyses for primary and secondary endpoints

The primary efficacy endpoint is the absolute change in the PDS total severity score from baseline at month 6: $\Delta\text{PDS} = \text{PDS(T1)} - \text{PDS(T0)}$.

By default, the mode of administration is a self-administered paper-based version. For patients who do not complete and send back the paper-based patient questionnaire (non-responding survivors), the PDS-5 total score will be assessed during the telephone surveys scheduled 6 months (T1) and 12 months (T2) after randomization.

It is assumed that death is the most likely cause of missingness. Therefore, a composite endpoint approach will be applied, combining information about the change in PDS total score and mortality into a single variable [41].

The null hypothesis, $G_{\text{NET}}(x) = G_{\text{iTAU}}(x)$ and $K_{\text{NET}}(t) = K_{\text{iTAU}}(t)$ $(0 < t \leq T$, date of death), implies that treatment groups NET and iTAU will not differ with respect to the distributions of the observed outcome measure ΔPDS. Here, $G(x)$ is the cumulative probability distribution of the observed change in PDS severity scores at T1 in groups NET or iTAU, and the distribution $K(t)$ of the date of death is the cumulative distribution of informative event times for the compared groups.

The null hypothesis will be tested by a non-parametric approach using a modified version of the Wilcoxon–Mann–Whitney $U$ test, which basically allocates the tied

worst ranks to all missing values (the worst rank score analysis was proposed by Lachin [42]). The null hypothesis can be rejected if the two-sided $p$ value related to the test statistic for the treatment effect is equal to or smaller than the significance level $\alpha = 0.05$. This test strategy is tailored to a particular alternative hypothesis, i.e., (i) NET will either be superior to iTAU in terms of ΔPDS, but with no impact on survival, (ii) NET will be superior to iTAU in terms of survival, but with no impact on ΔPDS, or (iii) NET will be superior to iTAU for both ΔPDS and survival.

If the PDS total severity scores are not informative for future death events, the worst rank replacement will simply lead to a power loss and no inflation in the type I error rate. Should the PDS total severity scores be informative for future death events, the worst rank replacement will result in an unbiased test of a particular alternative [42].

The principal analysis will be performed according to the ITT principle, and not adjusted for screening or baseline covariates or site. The significance level is set to alpha = 5% (two-sided).

Missing data prior to the follow-up measurement will occur because of an informative disease-related event (e.g., death or morbidity) or for other reasons (e.g., non-responders at follow-up measurements at T1 and T2, loss to follow-up, or consent withdrawn). To address the impact of several missingness mechanisms (missing at random or missing not at random), sensitivity analyses will be performed: mixed effect models assuming missing at random using the whole observed longitudinal PDS profile of the surviving patient; multiple imputations techniques; or even complete case analyses using the analysis of covariance (absolute change score as the response variable and treatment group as the covariate, adjusting for the baseline score value) for responding survivors until T1.

Moreover, sensitivity analyses will be performed in the per-protocol population using linear mixed effects models to explore the role of covariates (e.g., patient age and gender).

The full statistical analysis plan will be finalized and revised in a blinded manner ahead of the database lock after the last patient's last 12-month telephone call.

#### *Definition of analysis data sets*

Each trial participant's allocation to the different analysis populations (full analysis data set according to the ITT principle, per-protocol analysis data set, and safety analysis data set) will be defined and explained in the statistical analysis plan, which will be finalized before the analysis. During the data review, deviations from the protocol will be assessed as minor or major. Major deviations from the protocol will lead to the exclusion of a participant from the per-protocol analysis data set. The full analysis data set according to the ITT principle will consider all randomized patients with at least one study-related visit at a physician's office during the intervention period (for the NET group, at least one NET session and for the iTAU group, at least one face-to-face consultation). Furthermore, patients who die before the evaluation of efficacy outcomes (truncation due to death) are part of the principal analysis incorporating the timing of death of the trial participant.

### Safety assessment and reporting of adverse events

Overall, a low frequency of SAEs can be expected due to the narrative exposure itself. SAEs are events that (1) result in death, (2) are life-threatening, (3) require hospitalization or cause prolongation of existing hospitalization, (4) result in persistent or significant disability or incapability, (5) are a congenital anomaly or birth defect, or (6) require intervention to prevent permanent impairment or damage. SAEs will be regularly monitored and investigated from the start of the intervention at Session 1 in the NET group and from the first of the three PCP consultations in the iTAU-group until the end of the trial at T2. The PCP will decide which events have to be followed up as SAEs and will report them accordingly to the PI.

The PCP is the first point of contact during the intervention period, since the telephone interviews are at T1 and T2. If a patient cannot be reached via telephone at T1 and T2, the RTC will contact the respective PCP for further information on the patient's possible SAE status. For the whole trial duration from T0 up to T2, the PCP is instructed to report all SAEs, or the relocation or death of the patient proactively. Since in Germany the PCP is the first point of contact to receive updates from hospitals, specialists, or other medical services involved in the patient's care, this should enable us to monitor patient safety continuously. In addition, psychiatric back-up clinics are available at each site for emergency cases. All SAEs will be reported to the PI and the DSMB.

Since there is a great heterogeneity in adverse events in primary care, it is sometimes not possible to differentiate between adverse events and pure signs of discomfort in patients [43]. Therefore, we decided not to assess any adverse events. All documented SAEs will be listed by study site and patient and displayed in summary tables. The incidence of SAEs and their relationship to the assigned intervention will be descriptively analyzed [44, 45].

### Data management

The Institute of General Practice and Family Medicine, University Hospital, LMU Munich, as the coordinating study center, is responsible for data management, which encompasses all tasks concerning processing and utilization of study data, with the aim of guaranteeing

high-quality data and providing a valid study database for statistical analyses. All data management activities will be done according to the current standard operating procedures of the investigational trial center (ITC).

#### *Data collection and transmission*

All data collected during the trial will be documented using electronic case report forms (eCRFs). The source data will be stored regionally in the patients' files. Clinical and patient-reported outcome data will be collected by the ITC in Munich at the site of the PI via self-administered questionnaires and via phone interviews at T1 and T2. ITC staff are blinded to the assigned treatment given to the interviewed patient.

### Data handling

Data collection will be managed using a secure, web-based system (OpenClinica© Community Edition, Version 3.12). Data input requires an internet connection and a browser. Authorization and the electronic signature of users is granted via a login and password. To ensure the security of the data entered, web access is encrypted via SSL certificates. All data collected throughout the study period will be stored in a secure server at the Leibniz Supercomputing Centre of the Bavarian Academy of Sciences and Humanities (Leibniz-Rechenzentrum, LRZ). A secure file folder will be constructed before initiation of the trial. Access is limited to the PI and the data manager. Study participants will be identifiable through their study-specific screening number. Data routinely collected from patients, including questionnaire data, will be stored at the trial site up to T1 and at the coordinating trial center in Munich at T1 and T2, using eCRFs.

Any changes made during data collection will be documented using audit trails in OpenClinica. Data integrity is enforced by referential data rules, valid values, range checks, and consistency checks against data already stored in the database. Plausibility checks will be applied during data entry and before the data are transferred to the database. To ensure valid comparable data, data cleaning is carried out according to a data validation plan. After the database is locked, all study data will be exported from OpenClinica© for statistical analyses using SAS (Institute Inc., Cary, NC, USA) or the software package R, version 3.5.0 or higher (www.R-project.org).

#### *Monitoring*

An independent clinical monitor will check for accuracy, completeness, consistency, and reliability of the eCRFs by comparing documented data with source data. The monitor will check that data are collected, stored, and managed appropriately at all trial sites. Additionally, the monitor will check SAE documentation and status as well as documentation and follow-up of protocol deviations. Monitoring visits will be carried out regularly according to the standard operating procedures at each trial site independently, to ensure the trial procedure is executed according to good clinical practice [26].

### Data safety and monitoring board

An independent DSMB has been established to monitor the course of the study, recruitment, patient safety, the integrity of the trial, and if necessary to give a recommendation to the coordinating investigator and sponsor for discontinuation, modification, or continuation of the study. Furthermore, the DSMB will periodically review the safety-relevant events reported to this board. The members of the DSMB are Dr. Jochem König (Mainz), Dr. Andreas Linde (Königsfelden), Prof. Wolfgang Miltner (Jena), and Prof. Frank Schneider (Aachen).

## Discussion

The aim of the PICTURE trial is to evaluate the effect of a multicomponent primary-care-based intervention for ICU survivors suffering from posttraumatic stress. Since PTSD after critical illness is still an underestimated problem and PCPs are the first point of contact for providing health care to these patients, it might be beneficial to investigate this disease in ICU survivors and for the PCP to acquire new non-pharmacological treatment options to help these patients quickly during the typically long waiting periods for specialist support and therapy. Therefore, it is important to assess the effects of NET adapted to the primary care setting. The patient and the attending PCP are the information units within this trial. A single PCP will treat only one ICU patient (i.e. the first to be randomized). Therefore, all conclusions from the PICTURE trial will be limited to the pair of patient and PCP.

Assuming a representative population of PTSD patients and a representative population of ICU patients, the effect may be interpretable in a generalizable way, and it may reflect a general statement about the efficacy of a German, randomly chosen PCP who meets a randomly chosen patient. This generalizability might be reduced by specific selection processes (e.g., PCPs eager to join the trial, the long-term effect of the training, whether the PCP is eager to learn more about NET, whether there is a declining efficacy curve for PCPs, or how MAs deliver the phone support, which is the second component of the experimental intervention). These also need to be elucidated in specific sensitivity and process analyses.

Furthermore, this is a complex intervention and claims cannot be linked or partitioned into specific components. However, the involvement of physicians in primary care also poses certain challenges, as doctors

usually have no experience in conducting clinical trials, which might make it difficult to implement certain study procedures. For this reason, before the beginning of the intervention phase, the participating physicians will be trained not only in study-specific procedures but also in the basics of good clinical practice as prescribed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

PICTURE may have further limitations. A selection bias of participating PCPs and patients may limit the generalizability of the results. The control group delivers iTAU, which might not be representative for usual care in general but might be more thorough and conscientious. Even though the applied NET is adapted to the primary care setting, there may still be barriers to implementation in daily clinical practice, e.g. due to limited time resources in PCP practices. If two or more participating PCPs from the same practice have patients assigned to different treatment groups, there may be contamination between the intervention and control participants. If a PCP has more than one relevant patient, only the first patient randomized will be included in the full analysis data set. We expect this scenario to be rather unlikely, and it would lead to individual randomization instead of a cluster randomized design.

A major risk in the execution of the study could be insufficient recruitment due to the gradual integration of patients. To reduce this risk, we intensified the screening and recruitment procedure carried out in the SMOOTH trial, which was performed in and around Jena and Berlin, by increasing the number of recruitment areas to Berlin, Dresden, Hamburg, Tübingen, and Munich. In each catchment area, we employ study nurses to monitor and support screening and recruitment. The risk of adoption (learning) of the intervention by PCPs may lead to heterogeneity in intervention delivery. We may be able to reduce heterogeneity in the intervention by limiting the number of patients for each PCP (one patient per PCP).

### Trial status

At the time of manuscript submission, the study design has been evaluated by an independent international reviewer and has been approved by the ethics committee of LMU Munich. The first patient was pre-screened at an ICU at the end of October 2017 with the opening of the trial site of the PI (start of patient recruitment) in Munich. Until 26 April 2018, no study participants have been randomized. We expect enrolment of the first patient in summer 2018.

### Protocol version

Version 3.0, 14 March 2018.

## Additional file

**Additional file 1:** SPIRIT 2013 Checklist. (DOC 120 kb)

#### Abbreviations

(e)CRF: (Electronic) case report form; AE: Adverse event; CSSRI: Client Sociographic and Service Inventory; DSM: Diagnostic and Statistical Manual; DSMB: Data safety and monitoring board; EQ-5D-5L: Five-dimension Five-level EuroQol; EQ-VAS: EuroQol Visual Analog Scale; IBE: Institute for Medical Information Processing, Biometry and Epidemiology; ICU: Intensive care unit; iTAU: Improved treatment as usual; ITC: Investigational trial center; ITT: Intention to treat; LMU Munich: Ludwig Maximilian University of Munich; MA: Medical assistant; NET: Narrative exposure therapy; OASIS: Overall Anxiety Severity and Impairment Scale; PAM: Patient Activation Measure; PCP: Primary care physician; PC-PTSD: Primary Care PTSD Screen; PDS: Posttraumatic Stress Diagnostic Scale; PHQ: Patient Health Questionnaire; PI: Principal investigator; PTSD: Posttraumatic stress disorder; QALY: Quality-adjusted life year; S: Session; SAE: Serious adverse event; SIS: Six-item Screener; SOFA: Sequential Organ Failure Assessment; TFA: Theoretical framework of acceptability; VAS: Visual analogue scale; WHODAS: World Health Organization Assessment Schedule

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#### Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study (study protocol).

#### Authors' contributions

JG and TE initiated the study concept and design of the PICTURE trial. JG is the sponsor, and principal and coordinating investigator. JG and TE are responsible for the implementation of the study. JG, TE, SS, KS, HK, CA, and A Scherag made substantial contributions to conception and trial design, wrote the study protocol or the preceding research proposals for funding. JG, SS, CA, KS, M Scherer, D Lindemann, NU, RPK, A Scherag, HK, CB, TGS, and UM drafted the manuscript. JG, SS, CA, KS, M Schauer, RPK, A Scherag, M

Scherer, AB, CH, SJ, JB, TGS, KL, D Lindemann, KV, SG, RK, BZ, GS, HG, SK, TK, AW, OA, JO, JS, and TE critically reviewed the manuscript for medical and methodical content. CA and A Scherag developed the statistical concept and performed the sample size calculation. All authors provided feedback on drafts of this paper and read and approved the final manuscript.

### Ethics approval and consent to participate

The screening and enrolment of participants did not start until the written and unrestricted positive vote of the local ethics committee was obtained. The ethics committee of the Medical Faculty of LMU Munich, Germany, approved the study protocol on 20 September 2017 (approval number 17–436) covering all participating sites. Modifications to the protocol will be submitted to the ethics committee for review. Written informed consent will be obtained from all participating patients and PCPs in the trial.

### Consent for publication

Consent forms for the trial include consent for publication of results in peer-reviewed journals.

### Competing interests

All authors have completed the uniform disclosure form of the International Committee of Medical Journal Editors at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). The authors declare that they have no competing interests.

## Publisher's Note



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# 3. DISKUSSION

## 3.1 Einordnung der Ergebnisse

Wie eingangs ausgeführt und in der Literatur mehrfach angemahnt [25, 26, 50] besteht für Patienten nach kritischer Erkrankung eine relevante Versorgungslücke. Die vorliegende Habilitationsschrift widmet sich daher der Frage, wie die hausärztliche Versorgung von Patienten nach Intensivtherapie verbessert werden kann.

Ausgangspunkt der Arbeit war ein eigener systematischer Literaturreview zur Evidenz bisheriger Nachsorgekonzepte: Nur wenige Interventionen erwiesen sich hier als wirksam, primär hausärztliche Ansätze waren nicht verfügbar. Auch die Evidenz für die an die stationäre Versorgung angegliederten *post-ICU* Ambulanzen ist bislang heterogen [21], siehe 1.4.

Da die meisten Patienten nach kritischer Erkrankung langfristig in der Hausarztpraxis nachbehandelt [51] werden, lag es nahe, das nach Kenntnis des Autors erste hausärztlich basierte Nachsorgeprogramm zu entwickeln und in einer randomisiert-kontrollierten Interventionsstudie zu überprüfen. Den theoretischen Rahmen hierzu stellte das *Chronic Care Model* dar: ein umfassendes Konzept zur Versorgung chronisch Kranker, welches sowohl strukturierte Arbeitsabläufe, das Selbstmanagement des Patienten als auch die Koordination verschiedener Berufsgruppen verbindet [52]. Eingebettet in den integrierten Forschungs- und Behandlungsschwerpunkt „Sepsis und Sepsisfolgen“ am Universitätsklinikum Jena wurde mit der schweren Sepsis/ dem septischen Schock als Indikatorerkrankung eine komplexe Nachsorge-Intervention erfolgreich in fast 150 Hausarztpraxen implementiert. Die geringe Ablehnungsrate der angefragten Praxen kann als Indikator für eine hohe hausärztliche Bereitschaft gewertet werden, sich in dieser Thematik zu engagieren (siehe 2.3). Dies kann als positiver Indikator für die Machbarkeit zukünftiger Studien zur ambulanten Nachsorge kritischer Erkrankungen gewertet werden.

Die vergleichsweise globale primäre Zielgröße „mentale gesundheitsbezogene Lebensqualität“ zeigte in der Auswertung der multizentrischen SMOOTH-Studie keinen signifikanten Wirksamkeitsnachweis. Jedoch gaben die sekundären Zielgrößen Hinweise darauf, dass auch schwerste und komplex chronische Mehrfacherkrankungen, wie sie bei Patienten nach schwerer Sepsis oft vorliegen, durch ein praxisbasiertes *Case Management* in funktionellen Parametern positiv beeinflussbar sein könnten: Möglicherweise wurde die funktionelle Rehabilitation durch eine gesteigerte hausärztliche Aufmerksamkeit sowie die mobilisierende Aktivierung der Patienten durch die *Case Manager* unterstützt, sichtbar an verbesserten Ergebnissen der motorischen Funktion und der Tätigkeiten des alltäglichen Lebens. Auch die Reduktion von posttraumatischen Beschwerden 24 Monate nach Entlassung von der ITS kann mit der erhöhten hausärztlichen Aufmerksamkeit erklärt werden, ist doch soziale Unterstützung als Resilienzfaktor für posttraumatische Beschwerden gut untersucht [37]. Darüber hinaus hilft eine Schilderung des Traumas – wie es im Kontakt zwischen Patient und Hausarzt möglich war – intrusive, traumatische Erinnerungen in die persönliche Erinnerungsstruktur zu integrieren [47].

## 3.2 Implikationen

Ein wesentliches Ergebnis der qualitativen Interviews (siehe Kapitel 2.4) war der sowohl von Patienten als auch von Hausärzten geäußerte Wunsch, Früherkennung und Behandlung von Komplikationen nach Intensivtherapie in der Primärversorgung strukturell zu stärken. Dies betont die Notwendigkeit zur Entwicklung weiterer Interventionen und Studien. Für deren konkretes Design können aus SMOOTH mehrere Lehren gezogen werden:

- Vermutlich waren sowohl die primäre Zielgröße als auch das Interventionsdesign zu unspezifisch gewählt, um die heterogenen Beschwerden der eingeschlossenen Patienten nachweisbar zu adressieren. Somit erscheint die Fokussierung auf eine spezifische Komplikation nach Sepsis bzw. nach kritischer Erkrankung ratsam, gemessen mit einer sensitiven Zielgröße. Aus der Identifikation von spezifischen Verlaufstypen motorischer Rehabilitation von Sepsis-Überlebenden konnten bereits Empfehlungen für die Wahl künftiger Zielgrößen generiert werden (siehe 2.5).

- Dazu ist denkbar, dass auch die Erhöhung der Interventions-Intensität zu einer verbesserten Wirksamkeit führen kann – sei es in Dauer der Schulung von Hausärzten und *Case Managern* oder in Frequenz und Dauer der Patientenkontakte. Auch dies sollte in zukünftigen Studiendesigns Beachtung finden.

Darüber hinaus können die Ergebnisse dazu beitragen, die primärärztliche Nachsorge von Patienten nach Intensivtherapie strukturell weiter zu entwickeln, entsprechend des *ChronicCare* Modells nach Wagner [32] bzw. dem *teamlet*-Modell nach Bodenheimer [33]:

- Die Akzeptanz eines externen ärztlichen Beraters im Rahmen der Intervention (des Liaisonarztes, siehe 2.2) durch den Großteil der teilnehmenden Hausärzte zeigt Potential für weitere Akteure in der Hausarztpraxis zur Steuerung und Implementierung neuer evidenzbasierter Versorgungskonzepte.

- Die Einbeziehung von medizinischen Fachangestellten im Rahmen des beschriebenen *Case Managements* trägt zur Entlastung der Hausärzte bei, denen häufig Ressourcen für ihre medizinischen Kernaufgaben fehlen [53]. So kann die vorliegende Arbeit auch Impulse für die strukturelle Organisation der Hausarztpraxis geben.

## 3.3 Weiterentwicklung

Ein Teil der o.g. Implikationen konnte bereits im Anschluss-Projekt PICTURE realisiert werden: Mit der Beschränkung auf posttraumatische Beschwerden wurden Intervention und Zielgröße auf einen Teilbereich des PICS spezifiziert. Nicht nur für das Auftreten nach Intensivtherapie, sondern auch nach anderen Psychotraumata scheint hier für die Primärversorgung eine Evidenzlücke zu bestehen: Ein systematischer Literaturreview fand weder eindeutig hausärztlich dominierte Interventionen noch klare Wirksamkeitsnachweise (siehe 2.6). Dazu bestehen sogar in Ballungsräumen lange Wartezeiten für eine psychotherapeutische Traumatherapie [54], die in der Regel nur hausärztlich überbrückt werden kann.

Gleichzeitig wurde die Interventionsintensität in Dauer und Frequenz im Vergleich zu SMOOTH erhöht (siehe 2.7). Auf eine intensivmedizinische Indikatordiagnose wurde verzichtet, um die Anzahl potenziell eligibler Patienten nicht zu sehr einzuschränken. Bei positivem Wirksamkeitsnachweis könnte die in der PICTURE-Studie geprüfte Intervention perspektivisch für die primärmedizinische, überbrückende Versorgung von posttraumatischen Beschwerden jedweder Genese eingesetzt werden.

## 3.4 Disseminierung

Die erfolgreiche Durchführung einer multizentrischen klinischen Studie unter Einbeziehung von fast 300 Hausarztpraxen, 30 Kliniken, zehn akademischen Institutionen und mehreren internationalen Projektpartnern hat die Aufmerksamkeit für die Thematik in der klinischen Versorgung gewiss gefördert. Dazu wurden durch den Autor sowohl zur Intensivnachsorge generell als auch spezifisch zu posttraumatischen Beschwerden Lehrbuchkapitel [55, 56] und mehrere Artikel zur klinischen Handlungsrelevanz in nationalen und internationalen Fachzeitschriften veröffentlicht, die sich vor allem an praktisch tätige Kollegen richten [1, 2, 57–60].
Auch die Öffentlichkeit wurde in die Disseminierung einbezogen, unter anderem durch Produktion eines Erklärvideos, einem Stand auf der „Jenaer Nacht der Wissenschaft“ 2013, einem Interview in der Zeitschrift „Apothekenrundschau“ [61] oder der Verbreitung der SMOOTH-Studie innerhalb der Patientenorganisation „Deutsche Sepsis Hilfe e.V.“ [62].

Die wissenschaftliche Wahrnehmung sowohl der Studienergebnisse als auch der in Deutschland noch jungen akademischen Disziplin der Allgemeinmedizin wurde vor allem durch die Publikation in dem renommierten *Journal of the American Medical Association* (JAMA) [63] unterstützt, was sich auch in der internationalen Diskussion abbildet, wie im hochrangigen Review von Prescott und Angus [64]. Dazu wurden die Studienergebnisse auf bislang über 20 nationalen und internationalen Kongressen präsentiert [65–72].

Zusätzliche Aufmerksamkeit erhielten die Studienergebnisse durch die Auszeichnung mit mehreren Wissenschaftspreisen, darunter mit dem Hufeland-Preis der Deutschen Ärzteversicherung, einem der bedeutendsten deutschen Medizinpreise.

## 3.5 Limitationen

Die spezifischen Limitationen der einzelnen Teilprojekte wurden bereits ausführlich in den jeweiligen Abschnitten beschrieben. Als generelle Limitation lässt sich die begrenzte Repräsentativität der Studienkohorte für die Gesamtheit aller Patienten nach Intensivtherapie nennen, da

a) sie in ihren Charakteristika nur teilweise großen, populationsbezogenen Erhebungen von Sepsispatienten entspricht. Dies wird unter anderem deutlich an den überdurchschnittlich langen stationären Liegezeiten [63], welche als Indikator eines erhöhten Schweregrades verstanden werden können.

b) die Komplikationen und Verläufe nach Sepsis nur begrenzt auf andere kritische Erkrankungen übertragbar sind. Jedoch zeigt die Literatur Hinweise auf eine hohe Übereinstimmung in Pathophysiologie und klinischem Erscheinungsbild der Spätfolgen nach Sepsis und den Verläufen nach intensivmedizinischer Behandlung anderer Diagnosen [73].

## 3.6 Ausblick

Die Notwendigkeit für eine strukturierte ambulante Nachsorge nach Intensivtherapie wird in Zukunft vermutlich durch mehrere Faktoren an Bedeutung zunehmen: Kurz- und mittelfristig durch die SARS-CoV-2-Pandemie sowie langfristig durch den demographischen Wandel und dem damit verbundenen Anstieg chronischer Erkrankungen ist von einer wachsenden Anzahl von überlebenden Patienten nach Intensivtherapie auszugehen [60]. Dazu werden die weiter ansteigenden Kosten im Gesundheitswesen vermutlich eine zunehmende Verlagerung von Versorgungsleistungen in den ambulanten Sektor beschleunigen [74], zumal die an die stationäre Versorgung angeschlossenen *post-ICU* Ambulanzen den einleitend beschriebenen strukturellen und regionalen Limitationen unterliegen.

So wird die Rolle des Hausarztes als Begleiter, primärer Therapeut und „Lotse“ in einem fragmentierten Versorgungsprozess für vormals kritisch erkrankte Patienten eine wachsende Bedeutung erfahren.

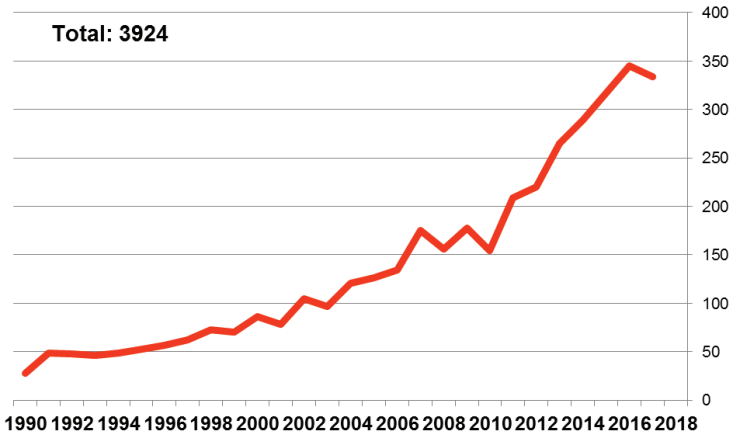


**Abb. 1:** Anzahl der Einträge in PubMed unter „ICU survivor“

Noch ist die Untersuchung von Spätfolgen nach Intensivtherapie und ihrer Behandlung eine junge Forschungsdisziplin. Auch wenn die Anzahl der Publikationen exponentiell zunimmt (siehe Abb. 1), sind viele der komplexen physiologischen und psychologischen Prozesse nach kritischer Erkrankung noch zu wenig verstanden, um von Interventionen effektiv adressiert zu werden. Seit Veröffentlichung des unter 2.1 beschriebenen Reviews im Jahr 2014 hat sich der Forschungsstand zur Effektivität von Nachsorge-Interventionen nicht grundsätzlich verändert [21]. Bevor gesundheitspolitische Entscheidungsträger etwa ein DMP zur primärärztlichen Nachsorge von Intensivpatienten in die Regelversorgung implementieren können, ist neben Grundlagenforschung zur Pathophysiologie vor allem die weitere Entwicklung und Schärfung von Interventionen, Parametern und Zielgruppen erforderlich.

# 4. ZUSAMMENFASSUNG

Spätfolgen nach Intensivtherapie – wie nach überlebter Sepsis – rücken zunehmend in den Fokus der Primärversorgung, da ein Großteil der betroffenen Patienten im Langzeitverlauf hausärztlich behandelt wird. Zwar besteht in der Hausarztpraxis viel Erfahrung im evidenzbasierten Umgang mit komplexer Multimorbidität. Mit einer zukünftig wachsenden Zahl von Überlebenden nach kritischer Erkrankung von ergibt sich jedoch die Notwendigkeit von spezifischen und strukturierten Versorgungskonzepten.

Im Rahmen der vorliegenden Habilitationsschrift wird am Beispiel der Indikatorerkrankung Sepsis/ septischer Schock ein solches hausärztliches Nachsorgeprogramm beschrieben. Die quantitative Auswertung dieses Programms zeigte keinen eindeutigen Wirksamkeitsnachweis: Möglicherweise waren die Beschwerden der komplex und schwer erkrankten Patienten zu heterogen, um von einer globalen Intervention adressiert werden zu können. Hinweise auf partielle Effekte ergaben sich jedoch bei Auswertung der sekundären Endpunkte. Dazu unterstreichen die Durchführbarkeit der Studie und die Ergebnisse der qualitativen Begleitevaluation die Bedeutung der Hausarztpraxis in der Langzeitversorgung von Patienten nach kritischer Erkrankung.

Zukünftige Forschung sollte sich auf ausgewählte Krankheitsbilder und Zielgrößen in der Intensivnachsorge fokussieren. Dieser Ansatz wurde in dem derzeit noch laufenden Folgeprojekt PICTURE für den Teilaspekt der posttraumatischen Beschwerden nach Intensivtherapie bereits realisiert.

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# 6. ANHANG

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## 6.2 Erläuterungen zur SMOOTH-Studie

Die englischsprachige Publikation des Studienprotokolls (siehe 2.2) ermöglicht nur eine orientierende Zusammenfassung des Designs der SMOOTH-Studie. Deswegen sollen die drei zentralen Interventionselemente sowie die wichtigsten Zielgrößen hier zusätzlich erläutert werden:

### *6.2.1 Entlassmanagement*

Um eine Kontinuität der transsektoralen Versorgung zu gewährleisten, wurde den Patienten der Interventionsgruppe bei Entlassung von der Intensivstation eine Informationsmappe ausgehändigt. Dieses Kompendium begleitete sie auf dem Weg über Normalstation und Rehabilitationseinrichtung in die ambulante Versorgung mit relevanten Informationen an die jeweils weiterversorgenden ärztlichen Kollegen: Unter anderem fanden sich hier Informationen zu sepsistypischen Folgeerkrankungen, erforderlichen Hilfsmitteln, häuslicher Krankenpflege und therapeutischen Empfehlungen, jeweils mit möglichen Ergänzungen durch jeden durchlaufenen Versorgungssektor.

### *6.2.2 Monitoring*

Das Monitoring zu den sechs Hauptkomplikationen der Sepsis wurde in Form einer telefonischen Kontaktaufnahme bei den Patienten durch die *Case Manager* durchgeführt, unter Verwendung eines Monitoring-Bogens: Um Repetitionseffekte zu vermeiden, wurden hier zur Qualitätssicherung von der Zielgrößenerfassung differente, jedoch ebenfalls etablierte Instrumente verwendet. Das Monitoring erfolgte nach Entlassung von der Intensivstation

- im ersten Halbjahr monatlich und
- im zweiten Halbjahr einmal pro Quartal.

Das Ergebnis wurde dem Hausarzt schriftlich und nach Dringlichkeit stratifiziert übermittelt (Ampel-Schema). Bei neu aufgetretenen klinischen Auffälligkeiten/*red flags* erfolgte eine umgehende telefonische Information des Hausarztes durch den Liaisonarzt mit einer kurzen Therapieempfehlung/Nachschulung zu den aufgetretenen Komplikationen. Der Liaisonarzt stand den Hausärzten zusätzlich bei Rückfragen und zur Supervision zur Verfügung. Individuelle Therapieentscheidungen wurden jedoch nicht übermittelt, die Therapieverantwortung verblieb bei dem behandelnden Hausarzt.

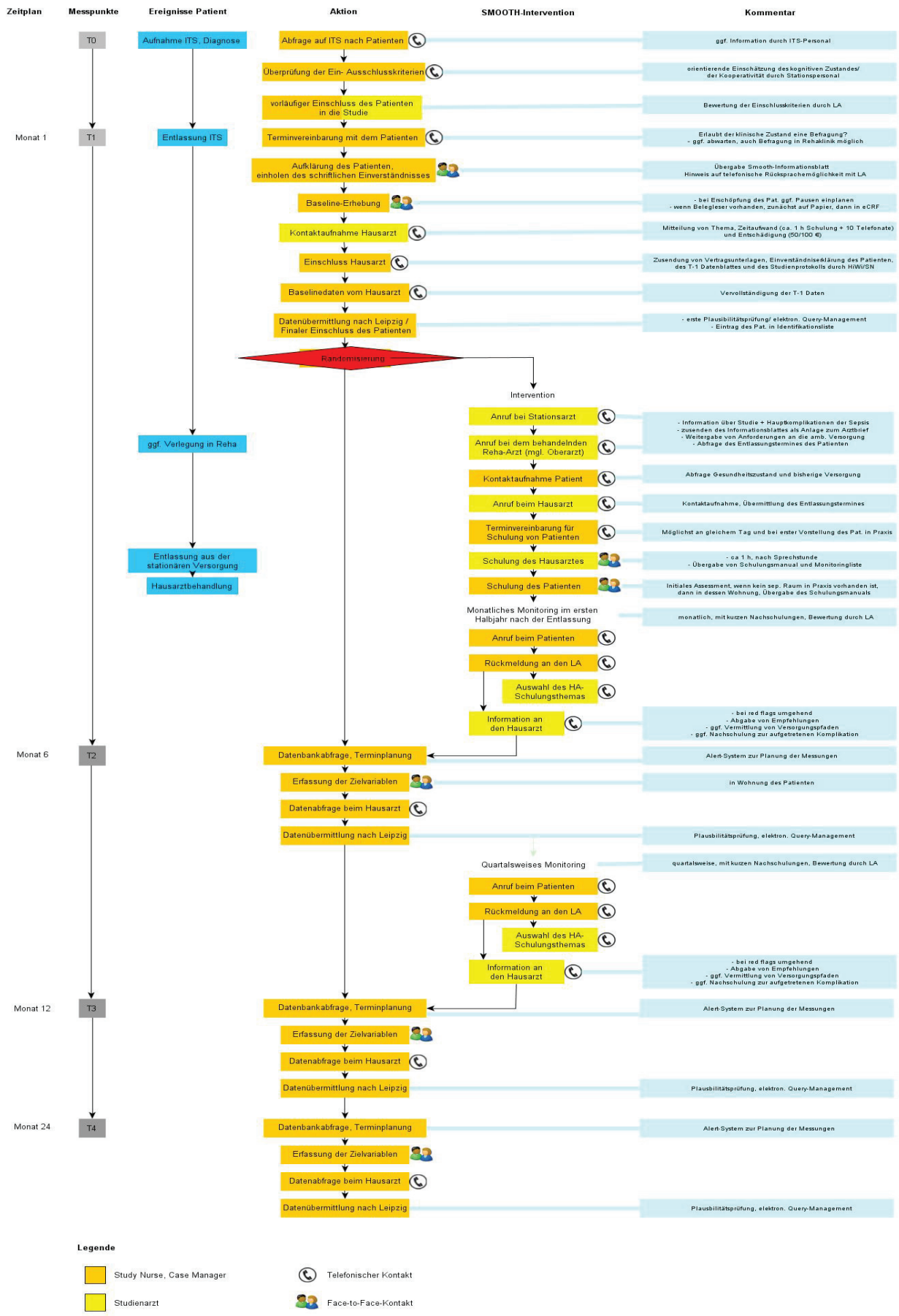


**Abb.2**: Ablaufschema der Smooth-Studie

Auch der Patient erhielt bei der folgenden Befragung eine Auswertung mit der möglichen Empfehlung, sich demnächst oder auch umgehend ärztlich vorzustellen. Auf Grundlage der beim Monitoring aufgefallenen Komplikationen wurden durch den Liaisonarzt die Themen der Nachschulung festgelegt, welche sich an die folgende Monitoring-Befragung anschloss.

### *6.2.3 Schulung*

Sowohl die Patienten- als auch die Hausarztschulung enthielten als Kernelemente die sechs wichtigsten Sepsis-Komplikationen Polyneuropathie, chronischer Schmerz, Kachexie, Depression, PTBS und kognitives Defizit (*Sepsis Six*). Die Schulung der Hausärzte des Interventionsarmes erfolgte einmalig durch den Liaisonarzt im Rahmen eines Präsenztermins in dessen Praxis unter Verwendung auch audiovisuellen Schulungsmaterials. Neben evidenzbasierten Diagnostik- und Therapieoptionen wurden auch kommunikative Techniken wie das motivierende Interview vermittelt. Der Hausarzt erhielt bei diesem Termin ein eigens hierzu zusammengestelltes Kompendium, eine Kurzversion für die Kitteltasche sowie die Originalfassung der beim Monitoring verwendeten Instrumente.

Die Patienten der Interventionsgruppe wurden nach Entlassung in die ambulante Versorgung ebenfalls im Rahmen eines Präsenztermins durch den *Case Manager* geschult. Die Schulung begann mit einer Kurzversion der Monitoring-Befragung (s.o.) zu gegenwärtigen Beschwerden, um Therapieziele formulieren zu können. Möglicherweise bereits aufgetretene Komplikationen wurden daraufhin ausführlich, weitere Komplikationen hingegen nur skizzierend behandelt.

Besonderes Augenmerk lag auf der Vermittlung eines effektiven Selbst-Managements, hat sich doch die persönliche Motivationslage als valider Prädiktor für die gesundheitsbezogene Lebensqualität ehemaliger Intensivpatienten erwiesen [75]. Den Abschluss der Schulung bildeten Hinweise auf Selbsthilfegruppen sowie eine Übersicht zu möglichen Pflegedienstleistungen, Hilfsmitteln und Rentenansprüchen. Auch Angehörige wurden hier ggf. mit eingebunden. Auch die Patienten erhielten ein umfassendes Manual, das den DISCERN-Kriterien für Patienteninformationen [76] entsprechend erstellt wurde. Beide Manuale finden sich in englischer Übersetzung im Anhang der Hauptpublikation [63]. Abbildung 2 zeigt den Studienablauf im Detail.

### *6.2.4 Zielgrößen*

Als primäre Zielgröße wurde der übergreifende Parameter „(mentale) gesundheitsbezogene Lebensqualität“ gewählt, um die Multidimensionalität der geplanten Intervention auf die vielfältige Symptomatik der Sepsis-Komplikationen am besten abbilden zu können. Dazu ist die gesundheitsbezogene Lebensqualität (HRQoL) neben der Mortalität ein verbreiteter Parameter für entlassene Intensiv-Patienten [77]. Als Messinstrument wurde der *Short Form 36 Health Survey* (SF-36) gewählt, der sowohl für somatische als auch für psychische Erkrankungen validiert ist [78]. Aufgrund seiner vielfachen Übersetzung und Veröffentlichung sind hier am ehesten international vergleichbare Ergebnisse zu erwarten [79]. Das Instrument zeigt eine hohe interne Konsistenz (*Cronbach's alpha* zwischen 0,65 und 0,94) und eine exzellente Re-test Stabilität (Intraklassen-Koeffizient von 0,75 bis 0,97). Eine Summendifferenz ab 5 Punkten wird klinisch und sozial als relevant behandelt [36]. Die sekundären Zielgrößen wurden entsprechend der Häufigkeit bislang beschriebener Komplikationen nach Sepsis gewählt, siehe Kapitel 1.2. Klinische Merkmale bei Studieneinschluss und Versorgungsparameter wurden – nach Literaturlage – als potentielle Einflussgrößen auf den späteren Verlauf erhoben. Wo keine etablierten Instrumente zur Verfügung standen, wurden schematisierte *items* erstellt, wie zur Beschreibung von Einschränkungen im HNO-Bereich unter Verwendung einer vierstufigen Likert-Skala. Tabelle 1 zeigt eine Auswahl der erhobenen Parameter mit Zeitpunkt und Ort ihrer Erfassung:

| Parameter | Zeit | Instrument (*Anzahl der Items*) | Erfassung durch |
|---|---|---|---|
| **Klinische Merkmale** | | | |
| Gesundheitsbezogene Lebensqualität | **$T_{-1-4}$** | *Short Form 36 Health Survey* (SF-36) *(36)* [36] | Befragung der Patienten |
| Depressivität | **$T_{1-4}$** | *Major Depression Inventory* (MDI) *(12)* [80] | |
| Posttraumatische Belastung | **$T_{1-4}$** | *Post-Traumatic Stress Scale*-10 (PTSS-10) *(10)* [81] | |
| Motorische Funktion | **$T_{2-4}$** | *Extra Short Musculoskeletal Function Assessment* (XSFMA-D) *(16)* [41] | |
| | | *(Instrumental) activities of daily life* (ADL/IADL) *(11)* [82] | |
| Schluck-, Schmeck-, Hör- und Riechstörungen | **$T_{-1-4}$** | 4-stufige Likertskala *(4)* | |
| Chronischer Schmerz | **$T_{1-4}$** | *Graded Chronic Pain Scale* (GCPS) *(7)* [83] | |
| Neuropathische Symptome | **$T_{1-4}$** | *Neuropathie-Symptom Score* (NSS) *(6)* [84] | |

| | | | |
|---|---|---|---|
| Ernährungszustand | $T_{-1-4}$ | *Malnutrition Universal Screening Tool* (MUST) *(4)* [85] | Befragung der Patienten |
| Kognitiver Status | $T_{1-4}$ | *Telephone Interview of Cognitive Status* (TICS-M) *(21)* [86] | |
| Schlaf | $T_{2-4}$ | Regensburger Insomniebogen (RIS) *(15)* [87] | |
| Medikamenten-abhängigkeit | $T_{2-4}$ | KFM (Kurzfragebogen zum Medikamentengebrauch) | |
| Mortalität | $T_{1-4}$ | Tod seit letzter Abfrage | Dokumentation des Hausarztes |
| **Versorgungsparameter** | | | |
| Stationärer Aufenthalt bei Sepsis-Diagnose | $T_1$ | Anzahl der Tage | Dokumentation der stationären Versorgung |
| Aufenthalt auf der Intensivstation | | | |
| Mechanische Beatmung | | | |
| Nierenersatztherapie | | schematisiert | |
| Infektionsfokus | | | |
| Einsatz von Sedativa und Steroiden | | | |
| Diagnosen stationär | | ICD-10 | |
| Hausarztkontakte | $T_{2-4}$ | Anzahl der Besuche beim Hausarzt seit letzter Messung | Dokumentation des Hausarztes |
| Krankenhausaufenthalte | $T_{2-4}$ | Tage stationärer Aufenthalt seit letzter Messung | |
| Arbeitsunfähigkeit | $T_{2-3}$ | AU-Tage seit letzter Messung | |
| Medikation | $T_{-1, 2-4}$ | Wirkstoff, Dosierung, Einnahmemodus, PZN | |
| Aufenthalt in Rehabilitations-einrichtungen | $T_{2-4}$ | Stationärer Aufenthalt (Tage) seit letzter Messung | |
| Facharztkontakte | | Anzahl der Facharztbesuche seit letzter Messung | |
| Pflegestufe, Heil- und Hilfsmittel | | schematisiert | |

T-1=3 Monate vor, T1=Monat 1, T2=Monat 6, T3= Monat 12, T4=Monat 24, jeweils nach Entlassung von der Intensivstation

**Tabelle 1: Auswahl erfasster Parameter der Smooth-Studie**

## 6.3 Erklärung gemäß § 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,
- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

15.12.2021

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