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A patient cohort on long-term sequelae of sepsis survivors: study protocol of the Mid-German Sepsis Cohort

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ABSTRACT

Introduction An increasing number of patients survive sepsis; however, we lack valid data on the long-term impact on morbidity from prospective observational studies. Therefore, we designed an observational cohort to quantify mid-term and long-term functional disabilities after intensive care unit (ICU)-treated sepsis. Ultimately, findings for the Mid-German Sepsis Cohort (MSC) will serve as basis for the implementation of follow-up structures for patients with sepsis and help to increase quality of care for sepsis survivors.

Methods and analysis All patients surviving ICU-treated sepsis are eligible and are recruited from five study centres in Germany (acute care hospital setting in Jena, Halle/Saale, Leipzig, Bad Berka, Erfurt; large long-term acute care hospital and rehabilitation setting in Klinik Bavaria Kreischa). Screening is performed by trained study nurses. Data are collected on ICU management of sepsis. On written informed consent provided by patients or proxies, follow-up is carried out by trained research staff at 3, 6 and 12 months and yearly thereafter. The primary outcome is functional disability as assessed by (instrumental) activities of daily living. Other outcomes cover domains like mortality, cognitive, emotional and physical impairment, and resource use. The estimated sample size of 3000 ICU survivors is calculated to allow detection of relevant changes in the primary outcome in sepsis survivors longitudinally.

Ethics and dissemination The study is conducted according to the current version of the *Declaration of Helsinki* and has been approved by four local/federal responsible institutional ethics committees and by the respective federal data protection commissioners. Results of MSC will be fed back to the patients and published in peer-reviewed journals.

Trial registration number German Clinical Trials Registry DRKS00010050.

Strengths and limitations of this study

► More patients survive sepsis but data on mid-term and long-term consequences is scarce. The Mid-German Sepsis Cohort (MSC) is designed to close this gap by a rather comprehensive assessment of sepsis sequelae in a sample of n=3000 patients.

► Coverage of the majority of intensive-care-treated patients with sepsis with limited inclusion and exclusion criteria in Mid-Germany.

► MSC ascertainment is compatible with the new SEPSIS-3 definition.

► MSC is a non-interventional cohort, while some of the patients will require tailored postacute support.

INTRODUCTION

Patients with sepsis experience life-threatening organ dysfunctions caused by a dysregulated host response to infection.[1] Recent estimates of population incident rates from high-income countries ranged between 148 and 288 hospital-treated sepsis cases per 100 000 person-years depending on disease severity; hospital mortality amounted to 26% for patients with (severe) sepsis during this period.[2] Survivorship from sepsis is increasing, but the burden of survivorship is high: among 3 years' (severe) sepsis survivors, up to 75% suffer from functional disability and about 17% suffer from cognitive impairment.[3] Survivors also experience mortality rates, which are increased compared with propensity-score-matched cohorts of other hospitalised patients.[4] A worldwide survey of sepsis survivors found that respondents suffered a range of impairment covering virtually every organ system and ability and deplored lack of services after acute care.[5] There is a need for specific treatment strategies and rehabilitation concepts to deal with the long-term consequences of sepsis.[6] However, such concepts are missing mainly because we lack prospectively collected and representative data on the nature, extent and impact of sepsis sequelae. Sepsis has therefore been called a 'hidden' healthcare disaster.[7]

A systematic review of long-term outcomes after sepsis included 30 studies up to February 2009.[8] The studies identified focused on mortality and health-related quality of life (HRQOL) but did not cover a broader range of outcomes. Overall, the study quality of assessed studies was found to be low to moderate based on the US Preventive Task Force criteria. Specifically, it was impossible to determine to what degree the outcomes were attributable to sepsis rather than to comorbidities. The authors conclude that future observational and interventional studies should include longer follow-up periods and later endpoints to better understand the natural history of sepsis and the effect of interventions on patient morbidities. Despite new insights,[4 9] these general remarks still apply.[10]

Consequently, we designed the Mid-German Sepsis Cohort (MSC) as a patient cohort to better and more completely quantify mid-term and long-term functional disabilities resulting from intensive care unit (ICU)-treated sepsis. Ultimately, findings for MSC will serve as basis for the implementation of follow-up structures for sepsis patients and help to increase quality of care for sepsis survivors.

METHODS AND ANALYSIS
Study design and setting
MSC is designed as a patient multicentre cohort. Patients will be recruited from ICUs with minimal inclusion and no exclusion criteria to cover a wide scope of mid-term and long-term functional disabilities and consequences after ICU/hospital discharge.

After the initiation in March 2016, recruitment started aiming at including 3000 patients during a period of 3 years from ICUs in five study centres in Germany (acute care hospital setting in Jena, Halle/Saale, Leipzig, Bad Berka, Erfurt); in addition, we will recruit patients by a modified protocol in the setting of a large long-term acute care hospital and rehabilitation centre (Klinik Bavaria Kreischa). Patients are screened for eligibility on a daily basis by a team of trained ICU study nurses. Documentation using routine hospital data includes three assessments: T_0 (onset of sepsis), T_1 (ICU discharge) and T_2 (hospital discharge). The follow-ups are planned after 3 (FU_1), 6 (FU_2) and 12 (FU_3) months and yearly thereafter up to 5 years (depending on additional funding) after ICU discharge. The follow-ups are conducted by trained study nurses, physicians or experienced medical students by phone call or face-to-face consultations by the study teams in Jena and Kreischa. Before the first follow-up at 3 months, survivors or their consenting proxies are sent an invitation letter; subsequently, a date is set up for a telephone interview. If the survivor is not able to participate in the interview because of cognitive impairment, the interview is performed with the legal proxy or main caregiver. If survivors or proxies cannot be contacted in time to participate at the first 3-month follow-up (FU_1), the subsequent interviews are nevertheless scheduled given that consent is not withdrawn. If possible, survivors are examined once over the study period in person.

Eligibility criteria
Patients aged ≥18 years (at ICU discharge) with diagnosed (severe) sepsis and septic shock are enrolled. (Severe) sepsis is defined as clinically suspected or microbiologically proven infection and presence of at least one organ dysfunction due to infection. Septic shock is defined as persistent hypotension despite adequate volume resuscitation. Organ dysfunction and shock were diagnosed according to the current definitions of the German Sepsis Society,[11] but documentation is such that the new SEPSIS-3 criteria[1] can also be applied.

Prior MSC enrolment is the only exclusion criterion in the ICU. Patients or proxies who are not fluent in German are excluded from the follow-up interviews.

Acute hospital and follow-up assessments and outcomes
Primary outcome is the change score (T_1 to FU_3) of functional capacity assessed by activities of daily living (ADLs) and instrumental ADLs, which are valid instruments for the evaluation of the patients' self-care capacity. Secondary outcomes are related to changes or associations in the domains of HRQOL, cognitive dysfunction, post-traumatic stress symptoms, depression, fatigue, pain, insomnia, medication, use of medical services (rehabilitation, hospitalisation, out-patient therapy), recurrent infections and sepsis, reintegration and return to work, presumed cause of death and other long-term effects like dialysis, long-term ventilation and nursing care.

Table 1 is a summary of the documentation of acute care (T_0, T_1 and T_2). It includes diagnostic and therapeutic measures, comorbidities, severity of illness scores ('Sequential Organ Failure Assessment' score), end-of-life decisions, length of ICU/hospital stay and time and cause of death if applicable.

A comprehensive list of physical, functional, emotional and mental sepsis outcomes documented at the follow-up appointments (FU_1, FU_2, FU_3, etc) was put together by the use of several sources (see table 2 for an overview). We performed a comprehensive literature search and used instruments of the German National Cohort.[12] In addition, we drew on other Center for Sepsis Control and Care (CSCC) postacute experiences[13 14] and refined the list by obtaining feedback from sepsis survivors and relatives from the German Sepsis Aid[15] who advised on the comprehensiveness as well as relevance and also translated the final list of symptoms into lay terms (for instance, 'tingling' for paraesthesia, 'weakness of memory' or 'difficulty to concentrate' for cognitive impairments, etc). These lay terms are also used during the follow-up interview. We were also advised by Wes Ely (Vanderbilt University School of Medicine, Nashville, USA) on delirium monitoring and management in the ICU and assessment of pre-ICU cognitive functioning. All outcomes—except for hearing, tasting, smelling and swallowing—are measured by established and validated questionnaires. Depression

Table 1	On-site ICU and hospital documentation of MSC
Time of assessment and domain	**Documented items/content**
T_0 (on ICU, onset of sepsis)	
Demographic data	Age
	Gender
	Height
	Weight
	Insurance status
Admission status	Date of hospital admission
	Date of ICU admission
	Admission type
	Location prior to ICU admission
	Prior ICU admission
	Current participation in an intervention trial
	Prior dialysis
	Prior tracheostomy
	Prior long-term ventilation
	Prior dementia
(Severe) sepsis/ septic shock criteria	Presence of infection (community/ hospital acquired, focus)
	Presence of SIRS criteria
	Presence of organ dysfunction
	Septic shock
	Date of sepsis onset
Further information	Charlson Comorbidity Index
	Glasgow Coma Scale
	Selected vital signs (mean arterial blood pressure, Fio_2, Pao_2, urine output)
	Administration of vasopressors (dose)
	Selected lab results (creatinine, bilirubin, lactate, thrombocytes)
T_1 (ICU discharge)	
Patient status	Time/cause of death
	Date of ICU discharge
	Presence of end-of-life care
	Presence/duration of delirium
	Presence/duration of ventilation
	Presence/duration of replacement therapy (lung, kidney, other organs)
	Vasopressor treatment
	Presence/duration of tracheostomy
	Presence/number of CPR
	Presence/number of physiotherapeutic treatment

Continued

Table 1	Continued
Time of assessment and domain	**Documented items/content**
	Presence/number of erythrocyte concentrate treatment
	Invasive focus reconstruction
	Maximal Sequential Organ Failure Assessment score
Microbiology	Existence of positive blood cultures
	Existence of relevant pathogens
	Existence of multi-resistant pathogens
Further information	Early Rehabilitation Index
	Barthel Index
T_2 (hospital discharge)	
Patient status	Time/cause of death
	Date of hospital discharge
	Number of ICU episodes during hospital stay
	Discharge to
	Weight at discharge
	Presence of tracheostomy at discharge
	Presence of ventilation at discharge
	Presence of kidney replacement therapy at discharge

ICU, intensive care unit; MSC, Mid-German sepsis cohort; SIRS, systemic inflammatory response syndrome; CPR, cardiopulmonary resuscitation

and post-traumatic stress symptoms are measured by BSI-18[16] and PTSS-10.[17] Cognitive function is assessed by a telephone version of the MoCA[18–20] or IQCODE[21] in proxy interviews. Fatigue and pain are measured by the Chalder Fatigue Scale[22 23] and the Graded Chronic Pain Scale.[24] EQ-5D-5L[25] is used for assessment of the HRQOL prior to and after sepsis. Furthermore, survival status and other more specific domains of morbidity (eg, effects on tasting or sleeping) and healthcare utilisation as well as socio-economic effects and reintegration after sepsis are documented. Readmissions to hospitals, recurrent sepsis episodes, occurrence of infections, data on immunisation habits and persistence of multi-resistant infections are recorded. We aim for face-to-face contacts at least once during the study period to assess the Timed Up and Go test[26] and hand grip strength.[27] We developed a written interview guide and refined the interview during a pilot test.

Sample size calculation and data analysis plan
We calculated the sample size necessary to detect relevant changes in the primary outcome in sepsis survivors longitudinally. In detail, we assumed a range of possible mean differences Δ in {0.5, 0.6, 0.7, 0.8, 0.9, 1} in a paired t-test

Table 2 Central follow-up documentation and assessment tools of MSC

Domain	Documented items/content
Sepsis perception	"Do you know what sepsis is?"
	"Do you know that you were treated for sepsis?"
Current situation	Living conditions (location, change compared with prior to sepsis, care-giving needs)
	Hospital readmissions
	Recurrence of sepsis or severe infections
	Use of rehabilitation or ambulant therapies
	Medication
	Presence of dialysis, tracheostomy, ileostomy, urinary catheter
	Amputation of limbs due to sepsis
	Vaccination status
Medical information and socio-economic status	Employment status (prior to sepsis, currently)
	School education with graduation marks
	Professional education
	Family (marital status, spouse, children, siblings)
	Rough estimate of (premorbid) general cognitive performance based on the study of Jahn *et al*[29]
	Tobacco and alcohol consumption (prior to sepsis, currently)
	Splenectomy/asplenia
List of potential sepsis sequelae in patient-reported terms	Cognitive disabilities (attention deficit, disturbance of memory, speech disorder, impaired consciousness, lack of concentration)
	Muscle and nerve weakness, stumbling, walking disability
	Breathing problems
	Weight loss
	Depression, anxiety attacks, nightmares
	Fatigue, listlessness
	Personality changes
	Sleep problems
	Tingling in hands or feet
	Multi-resistant pathogens
	Need of care
	Incontinence, dribbling
	Mastery of daily life
	Sexual problems
	Ear, nose and throat symptoms (swallowing, smelling, hearing, tasting)
	Other symptoms
Validated questionnaires related to specific domains	Quality of life (EQ-5D-5L) (prior to sepsis and currently)
	ADL, (instrumental) ADL (prior to sepsis and currently)
	Fatigue (Chalder Fatigue Scale)
	Cognitive function (t-MoCA, IQCODE)
	Post-traumatic stress disorder (PTSS 10)
	Depression/anxiety/somatisation (BSI-18)
	Pain (Graded Chronic Pain Scale according to Korff)
	Sleep disorder (RIS)
	In case of face-to-face consultation:
	Physical mobility (Timed Up and Go test)[26]
	Cognitive function (MoCA)
	Hand grip strength[27]

Note that static items/content (like socio-economic status) is not again asked at subsequent follow-up assessments.
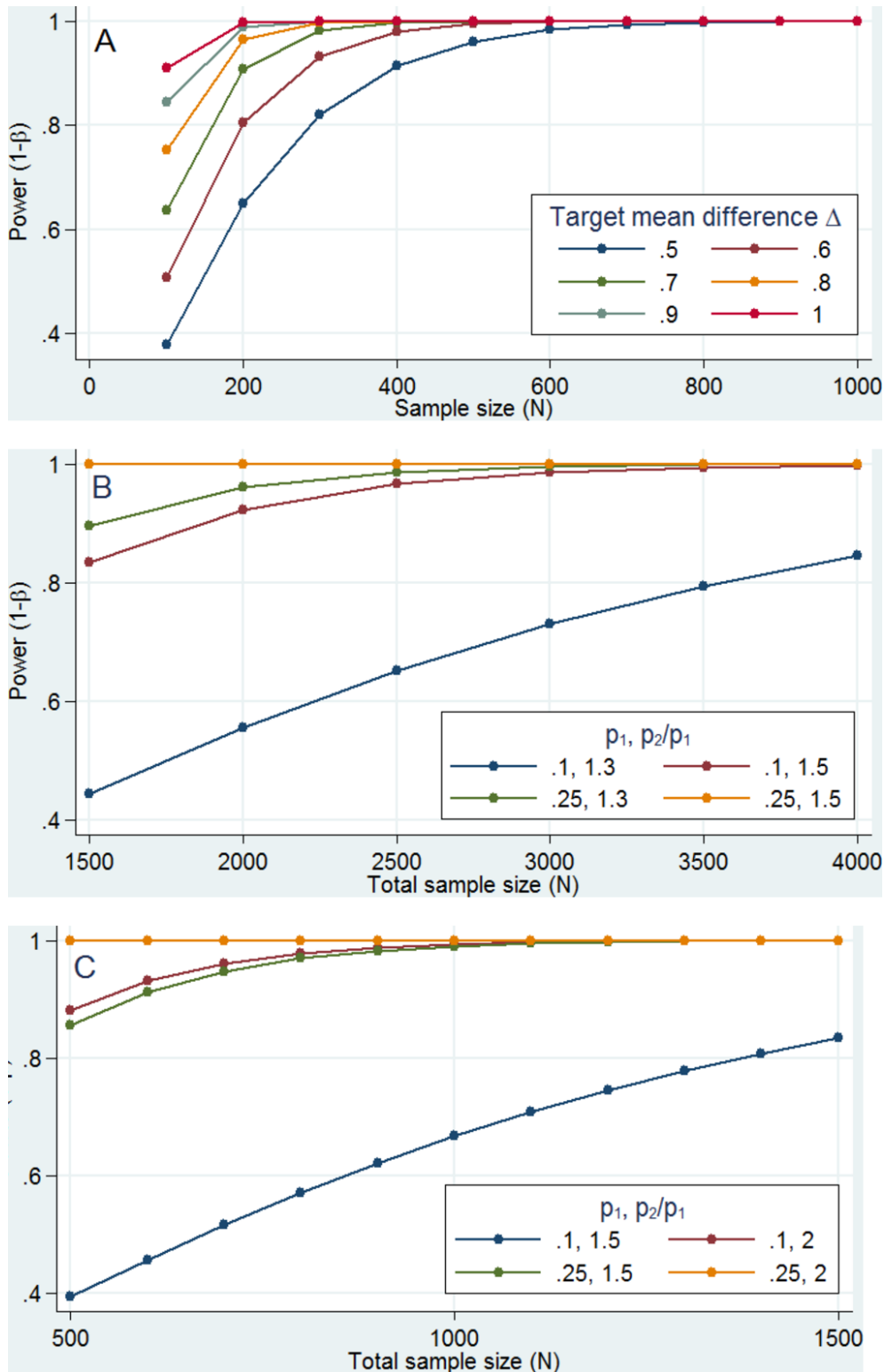ADL, activities of daily living.

Figure 1 Power considerations for MSC. (A) Power for longitudinal changes against N. (B) Power for associations against N at baseline (T_0, T_1). (C) Power for associations against N at 12-month follow-up (FU_3).

situation with a between-measure correlation of $\rho=0.5$ (H_0: $\Delta=0$ against H_1: $\Delta\neq0$ tested with $\alpha=0.05$; two sided) for a pretest mean of 8 (SD=3) for ADLs based on the data provided by Iwashyna et al.[28] We then varied the sample size that might be available for follow-ups from 100 to 1000 and plotted it against the comparison-wise power

(figure 1A). In addition and more generally, we display a range of generic exposure–outcome associations (eg, prognostic factors to outcomes) for the initial ICU part of MSC (figure 1B) and expected proportion of survivors after 12 months (figure 1C) for varying rates in exposed (p_2) relative to unexposed (p_1) patients (we assume a 1:1

distribution of a binary exposure and applied a significance level of $\alpha = 0.05$ (two sided) to a χ^2-test) and realistic sample sizes. These considerations underline that about 3000 patients should be recruited to detect moderate and clinically relevant cross-sectional and longitudinal effects.

The main objective of MSC is to describe the course (distributions, prevalences) and potential prognostic factors of mortality, morbidity (including functional (dis) ability as well as physical, neuropsychological and neuromuscular disability) and postsepsis infection-related complications. Analyses of the main paper will therefore be explorative and more descriptive, applying state-of-the-art methods (continuous variables, quartiles; count variables, absolute and relative frequencies; adequate regression models). All future analyses projects have to provide a precise research question and an analysis plan linked to it.

ETHICS AND DISSEMINATION
Informed consent
No informed consent is required to collect routine documentation of acute care (T_0, T_1 and T_2). Local study physicians obtain written informed consent for follow-up interviews from eligible patients (or their legal proxies) during the ICU or subsequent hospital stay. Patients or proxies are provided with written information about study aims and funding, study design and follow-up intervals, approximate duration of interviews, data protection and Institutional Review Board approval. Patients are assured that participation is voluntary and can be withdrawn at any time and that refusal to participate has no impact on medical treatment. If no legal proxy was established and written informed consent cannot be obtained during the acute hospital stay, family members receive a brochure with detailed information about MSC and are kindly asked to provide consent that the patient's contact information may be forwarded to the study centre so that the patient may be contacted later to obtain informed consent.

Study registration, ethics review and data protection
MSC is registered at the German Clinical Trials Register (DRKS00010050). It is conducted according to the current version of the *Declaration of Helsinki* and has been approved by four local/federal responsible institutional ethics committees and by the respective federal data protection commissioners. All data are collected with pseudonyms on electronic case report forms. Data capture takes place on the servers of Centre for Clinical Studies Jena at Jena University Hospital with 'OpenClinica', a validated study management software. OpenClinica meets all regulatory requirements (GCP, 21CFRPart11). By applying a hierarchical, role-based access control, an unauthorised access to patient data is impossible. Data are recorded in the study database via an encrypted data link (HTTPS) by use of data entry masks. It has an integrated audit trail that records any

kind of data changes automatically. In order to ensure a pseudonymised analysis of data, each patient data set is given a unique patient identification number when being entered into the study data base. There is a backup of all data at regular intervals. During the study period, data quality is checked for errors electronically (eg, range checks) and on-site by experienced monitors.

Access to data and dissemination
Data access to the final cleaned data set is provided to all project applicants (primarily within the MSC investigator group) along with written use and access rules of the CSCC. To ensure confidentiality, data distributed to project applicants will be double pseudonymised and any directly identifying patient information will not be provided.

Results of this study will be presented at scientific conferences and published in peer-reviewed journals. Reporting will be in line with the STROBE statement. Authorship is granted according to the guidelines of the German Research Foundation. Furthermore, there will be patient meetings to disseminate study results.

Perspective
Survivorship after sepsis is an emerging problem. Sepsis outcomes are a complex interplay between patient demographics, co-morbidities, predisposition and risk factors, treatment in the ICU and sepsis-related organ dysfunction. Data from MSC may help to elucidate whether these are causal factors or confounders. While older age, gender and comorbidities have been described as risk factor for mortality after sepsis, it is unclear which risk factors drive the prolonged morbidity observed after sepsis. MSC will also provide data on readmissions and healthcare utilisation, thereby allowing estimation of the socio-economic dimension of sepsis sequelae. Lastly, the comprehensive and functional assessment of physical, mental and emotional symptoms will contribute to characterise the postsepsis syndrome and develop targeted interventions for rehabilitation and aftercare.

study design, data collection and analysis, decision to publish or preparation of the future manuscripts.

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