SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Impact of carbohydrate reduced nutrition in septic patients on ICU - a prospective randomized controlled trial ***(page 1)***
Trial registration	2a	German trial register (DRKS.de) identifier is DRKS00017710 ***(page 6)***
	2b	Universal Trial Number (UTN) is U1111-1237-2493 ***(page 6)***
Protocol version	3	July 7th, 2019; version 1.1
Funding	4	We acknowledge support by the DFG Open Access Publication Funds of the Ruhr-University Bochum (Ref. No. IN-1214264), just for financial support for publication costs. This will have no impact on our study design or collection, analysis and interpretation of our data. ***(page 19)***

Roles and responsibilities	5a	Dr. med. Tim Rahmel[1] and Dr. med. Max Hübner[2]: Main authors of this manuscript, written and revised the manuscript, responsible for study conceptualization and statistical analysis plan Dr. med. Björn Koos[1]: Supported methodical description and laboratory experiments, participated in the design of this study, and revised the manuscript Dr. med. Alexander Wolf[1] and Katrin-Maria Willemsen[1]: Contributed to study design and conceptualisation of the methodical approach, supports patient recruitment, and revised the manuscript Dr. med. Gabriele Strauss[2]: Supports data collection and laboratory analysis, participated in the design of this study, and revised the manuscript David Efflinger[2]: Supports laboratory analysis, participated in the design of this study, and revised the manuscript Prof. Dr. med. Michael Adamzik[1]: Supports data collection, reviewed the statistical analysis plan, participated in the design of this study, and revised the manuscript Prof. Dr med. Simone Kreth[2]: Supporting study conceptualization, drafted the design of this study, reviewed the statistical analysis plan, wrote and revised the manuscript All authors read and approved the final manuscript. [1] Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie, Universitätsklinikum Knappschaftskrankenhaus Bochum, D-44892 Bochum, Germany [2] Walter-Brendel Center of Experimental Medicine, Faculty of Medicine, Marchioninistrasse 27, D-81377 München ***(page 20/21)***
	5b	n/a
	5c	We acknowledge support by the DFG Open Access Publication Funds of the Ruhr-University Bochum (Ref. No. IN-1214264), just for financial support for publication costs. This will have no impact on our study design or collection, analysis and interpretation of our data. ***(page 17)***
	5d	n/a

Introduction

Background and rationale	6a	Sepsis is defined as detrimental immune response to an infection. This overwhelming immune reaction often abolishes proper reconstitution of the immune cell homeostasis and in turn increases the risk for further complications. Recent studies suggest a favourable impact of ketone bodies on resolution of inflammation. Thus, a ketogenic diet started within the first days of sepsis may provide a beneficial, easy to apply and cost effective treatment option. Therefore, this study is designed to assess the feasibility, efficiency and safety of a ketogenic diet in septic patients. ***(page 4/5)***

	6b	This trial contributes to assess the feasibility and safety of low carb nutrition compared to standard enteral nutrition (comparator) in septic patients on the intensive care unit. ***(page 6-8)***
Objectives	7	The primary endpoint of the study is to assess if a low-carb diet in septic patients can increase the levels of ketone bodies within 14 days. The secondary objectives will be to compare safety, feasibility and immunologic patterns between the intervention group and the control group. ***(page 10)***
Trial design	8	This study is a randomized, open-label superiority trial, investigating in septic patients regarding the impact of low carb nutrition (intervention) compared to standard nutrition (control). ***(page 6)***

Methods: Participants, interventions, and outcomes

Study setting	9	This study will be conducted at the interdisciplinary, operative intensive care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum, a university hospital of Ruhr-University Bochum in Bochum, Germany. ***(page 6)***
Eligibility criteria	10	Inclusion criteria are age ≥ 18 years, written informed consent of the patient or their guardian, study enrollment within 36 hours after diagnosis of sepsis, and mechanical ventilation for less than 72 hours on study inclusion. Exclusion criteria are pregnancy or lactation, hemoglobin concentration < 8g/dl, insulin-dependent diabetes, severe and persistently health compromising metabolic disorders or autoimmune diseases, severe liver dysfunction or liver failure, refractory metabolic acidosis, invasive ventilation >72h, diagnosis of sepsis >36h at study enrollment, and contraindications against an enteral nutrition. ***(page 6)***
Interventions	11a	After study inclusion and randomization, the intervention group will receive a low carb nutritional solution (KetoCal 4:1, Nutricia, Erlangen, Germany) with 0.61g carbohydrates per 100mL. The controls will receive a standard enteral nutritional solution with 17.0g carbohydrates per 100mL (Fresubin HP Energy, Fresenius Kabi, Bad Homburg Deutschland) likewise started after randomization. As soon as the patients are capable of consuming oral food, the intervention group receives special ketogenic drinking solutions and also an individually adapted ketogenic diet plan provided by the hospital's kitchen. The control group will receive a standardized wholesome diet according to the common hospital's menu. ***(page 8)***

	11b	Hypoglycaemia, liver failure, metabolic acidosis, and any other kind of suggested severe adverse event, decision of to withdrew from the ketogenic diet ***(page 8)***
	11c	Control of the electronic patient data management system (PDMS) regarding protocol deviations.
	11d	n/a => There are no relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	The primary endpoint of the study is to assess if a low-carb diet in septic patients can increase the levels of ketone bodies within 14 days. The secondary objectives will be to compare safety, feasibility and immunologic patterns between the intervention group and the control group. ***(page 10)***

- Questionary "SF 36"			X		X		X	X
- 30-day mortality								X

Participant timeline 13

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation				End of study intervention	Close out
TIMEPOINT	Prior randomisation	Randomisation	Baseline (day 1)	Day 2 to 6	Day 7	Day 8 to 13	Day 14	Day 30
ENROLMENT								
- Eligibility screen	X							
- Informed consent	X							
- Randomisation		X						
STUDY INTERVENTIONS								
- Enteral nutrition			X	X	X	X	X	
ASSESSMENTS								
- Biometrical and demographic data			X					
- Clinical parameter			X	X	X	X	X	
- Ketone body concentration (in blood)			X	X	X	X	X	
- $CD4^+$ and $CD8^+$ T-cell isolation			X				X	
- Whole blood RNA isolation (Pax gene®)			X				X	
- Immunophenotyping (TrueCulture®)			X				X	
- Cytomegalovirus reactivation			X		X		X	
- Questionary "SF 36"			X		X		X	X
- 30-day mortality								X

(see Figure 3)

Sample size 14 In this randomized-controlled study, a total of 40 patients, i.e. 20 patients in the intervention group and 20 patients in the control group, will be enrolled. ***(page 7)***

Recruitment 15 We will ensure patient recruitment by screening patients on ICU daily. Eligible patients will be approached by the principal investigator and/or one of the eligible physicians.

Methods: Assignment of interventions (for controlled trials)

Allocation:		Block-balanced randomization, in a 1:1 ratio, will be computer-generated by StatsDirect (StatsDirect Ltd., Cambridge, United Kingdom) with random block sizes between n = 10 and n = 20, additionally using random permutations of treatments within each block. Investigators will be blinded to the allocation according to the randomization list until the study patient has been included. ***(page 8)***
Sequence generation	16a	Concealment of allocation mechanism will be performed by using sealed envelopes. For each patient included, a sealed envelope will be drawn and opened.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	The block-balanced randomization list will provide trial group allocation sequence.
Blinding (masking)	17a	n/a - no blinding will be performed.
	17b	n/a

Methods: Data collection, management, and analysis

Data collection methods	18a	The documentation of the data will be pseudonymized and computer-assisted from our patient data management system (PDMS) (Dräger ICM, Dräger Medical, Lübeck, Germany) in a central offline database. ***(page 11)***
	18b	All above mentioned parameters will be collected during the patients stay in hospital until discharge, death or 30th day of stay on ICU. In case of discharge from ICU, follow-up to evaluate 30-days survival will be performed by visit on normal ward or a phone call by one of the investigators. ***(page 11)***
Data management	19	All collected data will solely be provided in pseudonymized form for further study analyzation. Access to the pseudonymization key is only available to the principal investigator of this study. ***(page 11)***

Statistical methods	20a	Since this is a study designed to demonstrate superiority of the primary endpoint, whether a low-carb diet in septic patients can increase the levels of ketone bodies within 14 days, we will perform an intention-to-treat analysis as recommended by the Consolidated Standards of Reporting Trials guidelines. The per-protocol population will be defined as randomised patients without major protocol deviations, such as non-considerations of exclusion criteria or missing data for the primary endpoint. The per protocol analysis will also be made available along with the publication as supplementary material as appropriate. Baseline characteristics of all patients will be described per group. Qualitative data will be described as frequencies and percentages. Continuous variables are presented as mean ± standard deviation in case of normal distribution and as median and IQR (25th and 75th percentile) in case of non-normally distributed variables. Continuous variables will be compared using para- metric Student's t-test or non-parametric Mann-Whitney U test. Categorical variables will be characterised by numbers with percentages and will be compared using the $\chi 2$ test or a Fisher's exact test. Superiority will be assumed, if the 95% CI for the difference between the means excludes zero or p values are statistically significantly different at an a priori alpha error of less than 0.05.The graphical processing of variables will be performed depending on the measurement level of the variables as histograms, mean value curves with corresponding SD or box whisker plots. ***(page 11+12)***
	20b	N/A
	20c	We will perform an intention-to-treat and additionally a per-protocol analysis as recommended by the CONSORT guidelines. ***(page 11+12)***

Methods: Monitoring

Data monitoring	21a	Data entered in the central offline database will be monitored by an independent clinical research associate and checked for consistency and missing values. ***(page 11)***
	21b	No interim analyses are planned.
Harms	22	During study conduct and follow-up patients will be continuously monitored for possible adverse events. Those will be recorded in the database.
Auditing	23	n/a

Ethics and dissemination

Research ethics approval	24	This study was reviewed and approved by the Ethics Committee of the Medical Faculty of Ruhr-University Bochum (18-6657). ***(page 6)***

Protocol amendments	25	Principal investigator will communicate all important modifications to study personal.
Consent or assent	26a	Informed consent will be obtained by principal investigator and/or eligible physicians. ***(page 6)***
	26b	n/a
Confidentiality	27	All records, subjects' identities and data management will remain confidential with the General Data Protection Regulation (GDPR) of the European Parliament and the Council of the European Union. ***(page 11)***
Declaration of interests	28	None to declare ***(page 19)***
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	n/a
	31c	A publication of this study protocol in BMJ Open is submitted.
Appendices		
Informed consent materials	32	An informed consent form is available as translated copy as supplementary material. The original in German language can be obtained from the authors.
Biological specimens	33	n/a - all specimens will be discarded after study-related analysis

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.