Trial Protocol

Liberal transfusion strategy to prevent mortality and anaemia-associated, ischaemic events in elderly non-cardiac surgical patients

[LIBERAL-Trial]

Funded by the German Research Foundation (Deutsche Forschungsgemeinschaft)
Reference: ME 3559/3-1

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Synopsis

Title of the trial	Liberal transfusion strategy to prevent mortality and anaemia-associated, ischaemic events in elderly non-cardiac surgical patients (LIBERAL-Trial)
Acronym	LIBERAL
Indication	Elderly patients (≥ 70 years) undergoing intermediate- or high-risk non-cardiac surgery
Primary goal of the trial/primary end point	Primary efficacy endpoint: Composite of death from any cause and anaemia-associated, ischaemic events (defined as acute myocardial infarction, acute ischaemic stroke, acute kidney injury stage III, acute mesenteric ischaemia, acute peripheral vascular ischaemia) within 90 days after surgery. After hospital discharge, events will only be considered as present if they lead to hospital re-admission or death.
Secondary goals of the trial/ secondary end points	Key secondary endpoints: percentage of patients transfused, number of RBC units, length of stay in hospital, length of stay on intensive care unit, acute kidney injury stage I-II, infections, re-hospitalisation, functional status (Barthel index), health-related quality of life, and composite components with 90 days follow-up. Composite components with 1 year follow-up.
Trial design	The study is a prospective, multicentre, open, randomised, controlled clinical trial.
Trial population	Inclusion criteria for registration: Patients ≥ 70 years of age scheduled for intermediate- or high-risk non-cardiac surgery. Exclusion criteria: preoperative Hb level ≤ 9 g/dl, chronic kidney disease requiring dialysis, suspected lack of compliance with follow-up procedures, participation in other interventional trials, expected death within 3 months, inability to provide informed consent with absence of a legally authorised representative/ legal guardian, temporary inability to provide informed consent, previous participation in our trial, patients who are prevented from having blood and blood products according to a system of beliefs (e.g. Jehovah's Witnesses), preoperative autologous blood donation. Inclusion criteria for randomisation: Registered patients will be randomised only if they indeed develop severe anaemia (if Hb level falls ≤ 9 g/dl) during surgery (=day 0) or day 1, 2, or 3 after surgery. Exclusion criteria for randomisation: Occurrence of a component of composite endpoint, transfusion of allogeneic blood after registration
Sample size	N=2,470 patients
Therapy	Experimental intervention: Liberal group (patients receive a RBC unit each time Hb falls ≤ 9 g/dl (≤ 5.6mmol/l) with a target range for the post-transfusion Hb level of 9-10.5 g/dl (5.6-6.5 mmol/l)). Control intervention: Restrictive group (patients receive a single RBC unit each time Hb falls ≤ 7.5 g/dl (≤ 4.7 mmol/l) with a target range for the post-transfusion Hb level of 7.5-9 g/dl (4.7-5.6 mmol/l). Follow-up per patient: Discharge, 90 days, and 1 year Duration of intervention per patient: intra-/postoperative until hospital discharge or 30 days, whichever occurs first.
Biometry	The primary endpoint will be analysed by a generalised linear mixed model, namely logistic regression adjusting for age, cancer surgery (y/n), type of surgery (intermediate- or high-risk), and incorporating centres as random effect.

	The treatment effect will be quantified on the odds ratio scale with two-sided 95% confidence intervals provided. Secondarily, also point estimates and confidence intervals for the rate difference and the relative risk will be provided.
Trial Duration	**Duration of intervention:** from randomisation (which is within 3 days after surgery) until hospital discharge or up to 30 days, whichever occurs first **Individual trial duration:** from randomisation (which is within 3 days after surgery) until follow-up visits 90 days and 1 year after surgery **Planned recruitment period:** 60 months **Duration of the entire trial:** First patient in to last patient out (60 months' recruitment + 1 year follow-up). The trial formally starts with the randomisation of the first patient (FPI = first patient in), and the formal end of the study is the last Follow-up visit of the last patient included (LPO = last patient out).

Schedule of Assessments and Procedures

X: assessments for all registered patients / ●: additional assessments for randomised patients

Examinations	Screening	Surgery	Observation before randomisation	Randomisation[1]	Intervention/Observation after randomisation	Discharge	Day 90 after surgery	Follow up 1 year after surgery
	14 days up to 1 day before surgery	Day 0	During surgery (=day 0) or day 1, 2, or 3 after surgery	During surgery (=day 0) or day 1, 2, or 3 after surgery	Up to discharge or 30 days after surgery	Within 2 days before or on day of discharge	Day 87 – Day 111	Day 350 - Day 400
Visits	V1	V2	V3	V4	V5	V6	V7	V8
Inclusion criteria	X			●[1]				
Exclusion criteria	X			●[1]				
Informed consent	X							
Registration	X							
Demographic data, medical history	X							
Physical examination	X							
Laboratory (haemoglobin, creatinine)	X	X[2a,c]	X[2a]		●[2b]			
Surgery		X[2c]						
Functional status (Barthel index)	X						●	
Health-related quality of life							●	
Randomisation				●[1]				
Intervention [3] incl. time and number of transfused RBC units					●[3]			
Anaemia-associated ischaemic events (components of primary endpoint)					●	●	●	●
ICU and hospital stay						●		
Infection requiring i.v. antibiotics					●	●	●	
Re-hospitalisation for any cause							●	
Acute kidney injury stage I-II					●	●		
All-cause mortality							X	●
AE/SAE-Monitoring					●	●		

[1] Randomisation: as soon as haemoglobin falls ≤9 g/dl during surgery (=day 0) or day 1, 2, or 3 after surgery, registered consenting patients will be randomised. Re-evaluation of inclusion-/exclusion criteria before randomisation only refers to obvious occurrence of any component of the composite endpoint and any allogeneic blood transfusion after registration (chapter 4.2.2.). No specified diagnostics are scheduled.

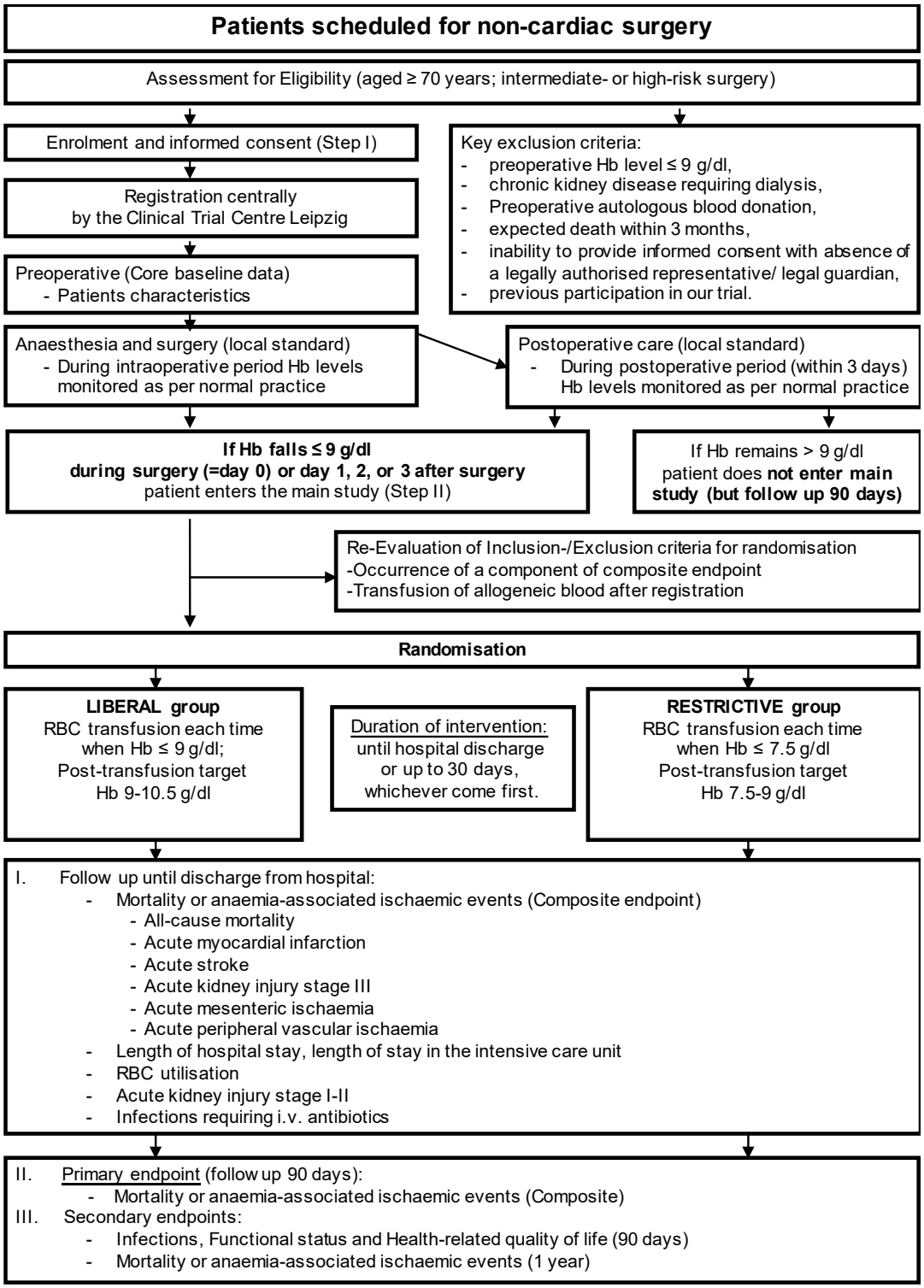
[2a] Haemoglobin levels will be determined from blood samples (mainly as part of the patient's usual care) at least daily before randomisation.

[2c] Mild drop of haemoglobin < 9 g/dl due to induction of anaesthesia and infusion-related dilution before skin incision is permitted and not an exclusion criteria

[2b] Haemoglobin levels will be determined from blood samples (mainly as part of the patient's usual care) at any time during or after randomisation until hospital discharge (up to 30 days after surgery; at least every 3 days), and after each transfused unit. Creatinine levels will be determined as part of the patient's usual care at any time during or after randomisation until hospital discharge (or up to 30 days after surgery; at least every 7 days).

[3] Intra-/Postoperative Intervention: Duration of intervention per patient: from intra-/postoperative randomisation until hospital discharge or 30 days after surgery, whichever occurs first. Physicians will be instructed to transfuse RBC units each time Hb is lower than the randomised threshold and as soon as possible. The randomised target post-transfusion Hb level needs to be reached each time within 24 hours upon receipt of lab result at the latest.

Flow Chart



Patients scheduled for intermediate- or high-risk non-cardiac surgery will be included in two steps. Before surgery we will check eligibility and obtain informed consent from patients or legally authorised representative/legal guardian (step I). Registered patients will be randomised only as soon as Hb falls ≤ 9 g/dl during surgery (=day 0) or day 1, 2, or 3 after surgery. Physicians will be instructed by the investigator to transfuse as soon as possible, and the target post-transfusion Hb level needs to be reached within 24 hours upon receipt of lab result at the latest. The assigned transfusion rules remain in force until discharge or 30 days after surgery, whichever occurs first. The occurrence of any individual anaemia-associated ischaemic event will be documented at all trial visits up to 90 days and 1 year after surgery.

1 RATIONALE

1.1 Medical Background

Perioperative anaemia leads to impaired oxygen supply with a risk of vital organ ischaemia, particularly of the heart, brain, kidney, and gut, resulting in perioperative myocardial ischaemia, stroke, kidney injury, and mesenteric ischaemia, respectively. In healthy and fit individuals, perioperative anaemia can be compensated by several mechanisms that preserve oxygen transport. Therefore, current guidelines recommend restrictive RBC transfusion after non-cardiac surgery.

Trials showing that restrictive transfusion is as safe as compared to a liberal strategy however typically including only a limited proportion of elderly patients. The compensatory mechanisms, however, are impaired in old and frail patients. Thus, it is unclear whether these guidelines apply in a geriatric population. Accordingly, major uncertainties exist among clinicians, and current clinical practice is variable. Noteworthy, clinicians have to deal with a large number of elderly non-cardiac surgical patients with significant perioperative anaemia and relevant need for RBC transfusion. More than 50% of all RBC transfusions are used in elderly patients in daily practice, and current population dynamics will lead to an increasing demand for RBC transfusions in the old-age patient group.

We identified evidence by searching the Cochrane Central Register of Controlled Trials, MEDLINE 1995 to January 2017, reference lists of published reviews and relevant papers. We focused on the latest published randomised controlled trials or meta-analyses in which intervention groups were assigned on the basis of a clear transfusion 'trigger'. Moreover, possible unpublished clinical trials were searched through ClinicalTrials.gov.

In 10% of elderly patients, preoperative anaemia is present and characterised by multiple pathologies.[1,2] After hospital admission, incidence of anaemia further increases dramatically due to additional diagnostic- and surgery-related blood loss.[3] To correct anaemia, transfusion of RBC units is widely used.

However, several studies have indicated that a restrictive RBC transfusion strategy with tolerating lower haemoglobin (Hb) levels is as safe as a liberal one while it reduces RBC utilisation, particular in critically ill patients,[4] patients with acute upper gastrointestinal bleeding,[5] and brain trauma patients.[6] Based on these findings, most international guidelines recommend restrictive indication for RBC transfusion,[7-11] and two US health care organizations (American Medical Association Physician Consortium for Performance Improvement® and The Joint Commission[12]) and the Choosing Wisely® campaign[13] have previously recommended strategies to minimise overuse in blood products.

As recent trials included only a limited proportion of elderly patients, it is unclear whether these guidelines apply in a geriatric population. Accordingly, major uncertainties exist among clinicians, and current clinical practice varies significantly.[14,15] Aging is associated with an increasing prevalence of cardiovascular comorbidities and decline of functional reserve. In 70 year old patients, e.g. arterial hypertension is present in 75%,[16] diabetes mellitus in 25%,[17] and atrial fibrillation in 10%.[18] Therefore, normal anaemia-related compensatory mechanisms are severely impaired in elderly patients, which may result in greater vulnerability to anaemia-related ischaemic events and perioperative complications.[19,20]

In addition, recent trials increase the uncertainty: Carson et al. studied 110 patients with acute coronary syndrome with a mean age of 71 years and found fewer major cardiac events and deaths if RBC transfusion increased Hb > 10 g/dl compared to a restrictive strategy (10.9% vs. 25.5%).[21] Murphy et al. randomised 2,007 cardiac surgical patients with a median age of 70 years and found fewer deaths 90 days after surgery in the liberal group (RBC transfusion if Hb

< 9 g/dl) compared to the restrictive (if Hb < 7.5 g/dl) group (2.6% vs. 4.2%), however data about the clinical significance in the elderly patients (≥ 70 years) still remain sparse.[22] One small trial including 40 patients with hip fracture compared a liberal (RBC transfusion if Hb <10 g/dl) and a restrictive group (if Hb < 8 g/dl), and demonstrated a 2.5-times higher 30-day mortality in the restrictive group.[23] The same group performed a subsequent trial enrolling 2,016 patients older than 50 years of age, who had either a history of or a risk factors for cardiovascular disease, and whose Hb level were < 10 g/dl after hip-fracture surgery. A restrictive strategy (Hb < 8 g/dl) was not superior to a liberal transfusion strategy (Hb < 10 g/dl) regarding rates of death or inability to walk on 60-days follow-up.[24] De Almeida et al. randomised 198 patients with a mean age of 64 years undergoing major cancer surgery, and found that a liberal transfusion strategy (if Hb < 9 g/dl) was associated with fewer major postoperative complications (19.6 vs. 35.6%) compared with a restrictive strategy (if Hb < 7 g/dl).[25]

In summary, more than 50% of all RBC transfusions are used in in old and frail patients, and current population dynamics in most developed countries will lead to an increasing demand for RBC transfusions in this specific group of patients.[26] The available evidence for transfusion criteria is not sufficient for the elderly.

1.2 Rationale

1.2.1 Hypothesis and Experimental Aspects of the Clinical Trial

In Germany, 18 million patients undergo surgery per year; of those 3 to 4 million are older than 70 years. At the age of 70 years, life expectancy add up to 15 years (80 year old patients can expect 10 years).[27] The literature shows that half of all RBC transfusions are used in elderly patients and the ratio is growing due to current population dynamics.[26] Thus, evidence-based perioperative care for these elderly patients is highly important.

However, recent transfusion studies included only a limited proportion of elderly patients, were not sufficiently powered or did not cover the relevant broad spectrum of surgical procedures including visceral, trauma, orthopaedic, vascular, and neurosurgery in elderly patients.[28] Thus, the lack of recruitment of elderly patients into clinical trials is relevant and the available evidence for optimal treatment is not sufficient for the elderly patient. Conclusions of methodologically sound clinical investigations in non-elderly patients do not apply to the geriatric population. Thus, the proposed study is of major clinical importance and urgently needed.

In this LIBERAL-Trial, patients will be randomised either to the LIBERAL group receiving a single RBC unit each time Hb falls less or equal 9 g/dl with a target range for the post-transfusion Hb level of 9-10.5 g/dl or to the RESTRICTIVE group receiving a single RBC unit each time Hb falls less or equal 7.5 g/dl with a target range for the post-transfusion Hb level of 7.5-9 g/dl.

Hb thresholds for transfusion are controversial and different people will argue for different thresholds. Considering the most recent meta-analysis, Hb transfusion thresholds used in previous studies varied from 7 to 10 g/dl for the restrictive and from 9 to 13 g/dl for the liberal group, respectively.[29] In the LIBERAL-Trial, we adopt thresholds similar to those used in the most recent large prospective trials.[4,22,24] The proposed thresholds span the range of contemporary international practice.[7]

Irrespective of the group assignment, physicians will be allowed to transfuse patients in exceptional cases, e.g. symptomatic anaemia with physiological triggers of anaemic hypoxia, or massive/life-threatening bleeding.

We hypothesise that a liberal strategy reduces the occurrence of major adverse events defined as the composite of all-cause mortality, acute myocardial infarction, acute stroke, acute kidney

injury, acute mesenteric ischaemia and/or acute peripheral vascular ischaemia within 90 days after non-cardiac surgery compared to a restrictive transfusion strategy.

1.3 Risk-Benefit Considerations

All patients will receive standard perioperative care.

The patients in neither/none of both groups will be exposed to additional risk since the transfusion strategies studied do not transgress the variability seen in clinical routine and recent trials. Hb transfusion thresholds used in previous studies varied from 7 to 10 g/dl for the restrictive and from 9 to 13 g/dl for the liberal group, respectively.[9,15,21,22,24,25,29,30] RBC transfusion is the main treatment option for anaemia due to surgical blood loss.

With respect to equipoise about the main research questions there is evidence from surveys of diverse practice between clinicians and centres,[15] and reported benefits using a liberal[22] or restrictive transfusion thresholds.[31]

In non-elderly patients, the restrictive transfusion strategy is standard.

In elderly patients, however, major uncertainties exist about best transfusion triggers. All potential investigators had agreed to use these two threshold levels for the purpose of this study even if they would not generally use either of these levels in normal care. Given that there is not enough evidence for either the liberal or the restrictive strategy in elderly, we feel that a randomised trial is ethically rather warranted than inacceptable.

All patients benefit from intensive monitoring and consequently early detection of any decrease of Hb.

Patients with legally authorised representative/legal guardian will represent a relevant proportion of fragile patients, thus generalizability for elderly patients will be ensured.

2 OBJECTIVES

2.1 Primary Objective

To evaluate if in a geriatric population, a liberal strategy reduces the occurrence of major adverse events after non-cardiac surgery compared to a restrictive transfusion strategy within 90 days after surgery.

The primary efficacy outcome is defined as a composite of:

I. **All-cause mortality** defined as death from any cause.
II. **Acute myocardial infarction** confirmed by a cardiologist
III. **Acute ischaemic stroke** confirmed by a neurologist
IV. **Acute kidney injury (stage III)** defined according to the Kidney Disease Improving Global Outcomes criteria: Increase of plasma creatinine level ≥ 3 times within a time window of 7 days or initiation of renal replacement therapy.[32]
V. **Acute mesenteric ischaemia** defined as ischaemia confirmed by intervention (abdominal surgery or mesenteric angiography).
VI. **Acute peripheral vascular ischaemia** defined as a new non-thrombotic compromised circulation in a limb confirmed by angiography and/or leading to surgery.

After hospital discharge, events of composite outcome will only be considered as present if they lead to **hospital re-admission** or **death.**

2.2 Secondary Objectives

To evaluate if:

A liberal transfusion strategy reduces the occurrence of any individual component of the composite of primary objectives at discharge, 90 days and 1 year after surgery.

A liberal strategy results in shorter total hospital stay and a shorter length of stay on the intensive care unit, and improves functional status and health-related quality of life at 90 days after surgery.

A liberal transfusion strategy reduces the occurrence of acute kidney injury stage I-II defined according to the Kidney Disease Improving Global Outcomes criteria[32] (stage I: increase of plasma creatinine level ≥ 1.5-1.9 times baseline or ≥ 0.3mg/dl within 48 hours; stage II: increase of plasma creatinine level ≥ 2-2.9 times baseline within a time window of 7 days) during the initial hospital stay.

The re-hospitalisation rate within 90 days after surgery is reduced by liberal transfusion strategy.

A liberal transfusion strategy does not increase occurrence of infections requiring therapeutic intravenous antibiotic treatment (pneumonia, wound infection, sepsis, central line associated blood stream infection) during the initial hospital stay or leading to hospital re-admission within 90 days after surgery.

In addition, the proportion of patients receiving RBC transfusion and the number of units transfused are evaluated.

3 TRIAL DESIGN AND DESCRIPTION

3.1 Trial Design

The study is a prospective, multicentre, open, randomised, controlled clinical trial.

3.2 Requirements at the Trial Sites regarding Personnel and Equipment

3.2.1 Qualification of investigator/deputy and medical staff in the study team

Investigators and deputies are licenced to practice medicine (specialist in anaesthesiology, internal medicine, surgery, transfusion medicine or advanced residency).

They have theoretical and practical experience in conducting clinical trials. Their qualification is defined as follows

- Documented proof of the conduct of several clinical trials after August 2004 (12. Amendment of German Drug Law) incl. proof of GCP training

AND

- Updates of GCP knowledge and revisions of German Drug Law every two to three years, if necessary

The Investigator is responsible for selecting and assembling the study team members (especially the medical staff) according to the requirements of this trial protocol. At least one transfusion physician should be part of each study team. Furthermore, the investigator is

responsible for training and supervision of the study team and providing all necessary information. This has to be documented.

Medical staff is licenced to practice and has at least theoretical experience in conducting clinical trials. The qualification is defined as follows

- Certification of successful participation in an investigator course incl. GCP training **OR** Documented proof of conducting clinical trials after August 2004 (12. Amendment of German Drug Law) incl. proof of GCP training

AND

- Updates of GCP knowledge and revisions of German Drug Law every two to three years, if necessary

Other medical staff of general ward is responsible for RBC transfusion after transfer to general ward. The investigator is responsible for training in trial protocol and especially in investigational product. This has to be documented.

3.2.2 Essential technical equipment at the trial sites and involvement of other facilities in the trial

Specific requirements at study centres will include:

- PC for electronic registration/randomisation and data entry (electronic CRF)

3.3 Trial Sites and Number of Trial Subjects

The study is planned to be conducted in about 15 - 25 study centres in Germany. The aim is to include a total number of 2.352 patients evaluable for the primary analysis. Assuming a drop-out rate of about 5%, a total of 2.470 patients are to be randomised.

3.4 Expected Duration of Trial

Duration of intervention: from randomisation (which is within 3 days after surgery) until hospital discharge or up to 30 days, whichever occurs first

Individual trial duration: from randomisation (which is within 3 days after surgery) until follow-up visit 90 days and 1 year after surgery

Planned recruitment period: 60 months

Duration of the entire trial: First patient in to last patient out (60 months' recruitment + 1 year follow-up).

The trial formally starts with the randomisation of the first patient (FPI = first patient in), and the formal end of the study is the last Follow-up visit of the last patient included (LPO = last patient out).

3.5 Premature Termination of the Trial

3.5.1 Termination of the Trial at a Single Site

The trial can be aborted at a single site if

- the protocol is not adhered to,
- the quality of data is deficient,
- there is inadequate recruitment.

The coordinating investigator decides whether or not to exclude the site, together with the sponsor and biometrician if appropriate.

Investigators and sites no longer participating in the trial must inform the coordinating investigator immediately and should provide justification for the decision.

Further treatment of patients still involved in the study is to be arranged together with the investigator.

3.5.2 Termination of the Whole Trial or of Individual Arms of the Trial

The trial can be terminated prematurely by the coordinating investigator if there are

- changes in the risk-benefit considerations, e.g. as a result of unexpected adverse events or other safety concerns regarding trial specific therapy (after consultation of the DSMB)
- proven superiority of one therapy arm (in the interim analysis)
- new insights from other trials
- an insufficient recruitment rate.

The final decision regarding the premature termination of the trial will be made by the sponsor or his authorised representative (coordinating investigator).

Since the trial is subject to German drug law, the approval can be rescinded or the study can be terminated by the responsible federal authority (Paul-Ehrlich-Institut) or the responsible ethics committee.

4 TRIAL SUBJECTS

4.1 Inclusion Criteria

4.1.1 Inclusion Criteria for Registration (Step I)

1. Elderly patients (≥ 70 years)
2. Undergoing intermediate- or high-risk non-cardiac surgery (according to the ESC/ESA Guidelines: surgery-related risk of cardiovascular death and myocardial infarction:[33])
    a. **Intermediate risk** (30-day risk 1-5%): e.g., intraperitoneal (splenectomy, hiatal hernia), peripheral arterial angioplasty, endovascular aneurysm repair, head and neck, major neurological/orthopaedic (hip and spine), major urological, major gynaecological, intra-thoracic surgery
    b. **High-risk** (30-day risk > 5%): e.g., aortic and major vascular, open limb revascularisation, (partial) duodeno-pancreatic, (partial) liver resection, oesophagectomy, adrenal or (partial or radical) renal resection, total cystectomy
3. Written informed consent; obtained before surgery from the patients or from their legally authorised representative (authorisation including clinical research/clinical trials)/legal guardian, if the patient is unable to provide informed consent.

4.1.2 Inclusion Criteria for Randomisation (Step II)

Registered patients will be randomised only if and as soon as Hb falls ≤ 9 g/dl (in spite of possible autologous transfusion) during surgery (=day 0) or day 1, 2, or 3 after surgery. If Hb remains > 9 g/dl (even after a two-stage surgery) patient does not enter the main study but vital status (all-cause mortality) will be determined 90 days after surgery.

4.2 Exclusion Criteria

4.2.1 Exclusion Criteria for Registration (Step I)

1. preoperative Hb level ≤ 9 g/dl
2. chronic kidney disease requiring dialysis
3. suspected lack of compliance with follow-up procedures
4. participation in other interventional trials
5. expected death within 3 months
6. inability to provide informed consent with absence of a legally authorised representative/ legal guardian
7. temporary inability to provide informed consent
8. previous participation in our trial
9. Patients who are prevented from having blood and blood products according to a system of beliefs (e.g. Jehovah's Witnesses)
10. preoperative autologous blood donation

4.2.2 Exclusion Criteria for Randomisation (Step II)

1. Occurrence of any component of composite endpoint after registration:

    - Acute myocardial infarction
    - Acute ischaemic stroke
    - Acute kidney injury (stage III)
    - Acute mesenteric ischaemia
    - Acute peripheral vascular ischaemia

2. Any allogeneic blood transfusion after registration

NOTE: any previous allogeneic blood transfusion before registration is NOT an exclusion criteria as long as preoperative Hb level is > 9 g/dl.

4.3 Justification for the Inclusion of vulnerable Populations

We assume that approximately 10-20% of patients are unable to provide informed consent and are represented by a legally authorised representative/legal guardian.

All patients benefit from closer observation before and after any RBC transfusion within the study. The study tries to show that anaemia associated risks can be reduced by a liberal transfusion strategy leading to potential benefit from participating in the trial.

LIBERAL is a patient-oriented study in the geriatric patient population. Excluding vulnerable patients would compromise the generalisability of the study results.

The proportion of vulnerable patients will increase due to the demographic shift. So these patients are an integral part of the LIBERAL target population. Evidence on transfusion triggers is particularly sparse in this subpopulation.

If a legal representative is established and the authorisation also covers medical treatment including clinical research/clinical trials, then the legal representative is to be contacted immediately and informed about the trial. The legal representative then decides whether or not the patient will participate.

Patients with inability to provide informed consent and with absence of a legally authorised representative/legal guardian will be not included.

Patients who are only temporarily not able to provide informed consent will also be not included.

4.4 Participation in more than one Clinical Trial

During the verification of the inclusion and exclusion criteria the investigator/his deputy or authorised medical staff of the study team checks if the patient is currently participating in any other interventional clinical trial. Should this be the case, the patient will not be included. Moreover, by signing the informed consent form, the patient confirms that he/she is not participating in any other interventional clinical trial simultaneously.

4.5 Statement on the Inclusion of Dependent Individuals

During the screening procedure, all patients will be interviewed concerning any potential relationship to the investigator/his deputy or to medical staff of the study team, the coordinating investigator or the sponsor.

4.6 Rationale for Gender Distribution

All elderly patients undergoing intermediate- or high-risk non-cardiac surgery that fulfil the inclusion and exclusion criteria will be informed about the clinical trial and asked to participate. We expect the gender ratio in the study to mirror the gender ratio in the target population.
An explorative sub-group analysis by gender is part of the planned analysis.

5 INVESTIGATIONAL PRODUCT

5.1 Trial Drugs

The strategies under evaluation use different haemoglobin levels as trigger for red blood cells (RBC) transfusions and aim at different target ranges of haemoglobin levels to be maintained. The trial drug will be used as a means to the end and they will be manufactured and used as in standard care.

Only commercially available approved Red Blood Cell Concentrates (RBCs) units will be used within this clinical trial. A list of these approved RBCs is available online at http://www.pei.de/DE/arzneimittel/blutprodukte/blutkomponenten-zur-transfusion/erythrozytenkonzentrate/erythrozytenkonzentrate-node.html

The sponsor maintains a list of all approved RBCs including Name, Marketing Authorisation Holder, Licence Number, Licence Date, link to SmPC and Date of SmPC as a separate document. There are copies of the list in each investigators site file. **Only RBCs listed in this document will be used within this clinical trial.** The sponsor must report all changes of this document (e.g. newly approved and used RBCs) to PEI as amendment.

The RBCs are provided by the local blood bank according to clinical routine considering the requirements of §63i AMG. This will assure the participants' safety, the traceability and identification of the RBCs given. Therefore, a special labelling of the RBCs for the trial according to § 42 AMG and § 5 GCP-V is not necessary.

5.2 Drug Accountability

Information about RBCs given to trial participants is documented in the patient file as in standard clinical routine.

The drug accountability documentation in the eCRF includes the following:

- Hb levels triggering the transfusions and Hb levels reached after transfusion to verify protocol compliance
- Time/date, unit number and volume of each RBC unit given to trial participants
- Batch Number of the used RBC

Consistency checks of these data are part of statistical monitoring. Inconsistencies in the documentation will trigger monitoring of this patient on-site.

5.3 Administration of the Study Drug

5.3.1 Procedures/Intervention

If Hb intra- or postoperatively falls $\leq$ 9 g/dl (in spite of possible autologous transfusion) mainly as part of the patient's standard care at any time during surgery (=day 0) or day 1, 2, or 3 after surgery, registered patients will be randomised either to

- **LIBERAL group:** patients receive a single RBC unit each time Hb falls ≤ 9 g/dl (≤ 5.6mmol/l) with a target range for the post-transfusion Hb level of 9-10.5 g/dl (5.6-6.5 mmol/l), or

- **RESTRICTIVE group:** patients receive a single RBC unit each time Hb falls ≤ 7.5 g/dl (≤ 4.7 mmol/l) with a target range for the post-transfusion Hb level of 7.5-9 g/dl (4.7-5.6 mmol/l).

The intervention per patient will be followed until hospital discharge or up to 30 days after surgery, whichever occurred first. Thus our study essentially covers the whole risk period for anaemia-associated complications during and after surgery.

Physicians will be allowed to refuse to transfuse, or transfuse patients irrespective of the group assignment in exceptional cases, e.g. hypervolaemia, symptomatic anaemia with physiological triggers of anaemic hypoxia, or massive/life-threatening bleeding, but must document the reason(s) why on the study eCRF (note: this does NOT constitute a patient withdrawal).

All registered patients will receive standard perioperative care. Other aspects of perioperative care will be provided in accordance with local standard. It is not practicable to insist that perioperative protocols are rigidly controlled. Stratification of randomisation by centre will ensure that variations in such protocols by centre do not introduce bias. Variations in transfusion regimes between centres are always likely to occur in the provision of usual care and, therefore, they can also be considered to enhance the applicability of the trial findings.

Local instructions for haemotherapy are valid for the trial.

5.3.2 Compliance

The RBCs will be administered by trained medical staff and must be documented as in clinical routine. Therefore, patient's treatment compliance should easily be observed.

5.3.3 Dealing with Side-effects

The following typical side-effects are known:

- acute or delayed haemolytic transfusion reaction
- anaphylactic transfusion reaction
- febrile transfusion reaction
- post transfusion purpura
- transfusion-related respiratory insufficiency
- transfusion-related circulatory overload
- transfusion-related hypothermia
- transmission of infections or bacterial contamination cannot be excluded

Transfusion must be stopped immediately in case of an emergency. The intravenous access must remain open. Further treatment is performed according to the severity of symptoms and guidelines for emergency treatment.

5.3.4 Alternative/Permitted Medication

Continuation of patient's usual care. Autologous red blood cell (re-)transfusion and respective transfusion triggers will be followed according to local standards, irrespective of group allocation.

5.3.5 Counter indicated/Forbidden Concomitant Medication

None.

5.3.6 Overdose and Abuse

Not applicable.

6 INDIVIDUAL TRIAL PROCEDURES

6.1 Patient Information and Informed Consent

The investigator/deputy of investigator or authorised medical staff will explain to each trial patient the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort that may be caused to each trial subject. Each trial subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship to the treating physician. The patient will be provided with enough time to think about the participation in the study.

No patient will be included before written informed consent is obtained. The informed consent will be given by means of a standard written statement, written in German in a non-technical language. The informed consent will be signed and dated by both patient/or legally authorised representative/legal guardian and treating investigator. The original document is kept by the investigator in the investigator site file (ISF), whereas the patient receives a copy.

The patient's consent must refer explicitly to the collection and processing of health-related data. Therefore, the patient should be informed explicitly about the purpose of collecting the data and scope of what is to be collected and that personal data, in particular those related to health, will be used.

6.1.1 Informed Consent in Patients not able to give Informed Consent by themselves

If a legal representative is established and the authorisation also covers medical treatment including clinical research/clinical trials, then the legal representative has to be contacted immediately and informed about the trial. The legal representative then decides whether or not the patient will participate.

Further details of the procedures for patients who are not able to provide informed consent in person are described in section 4.3.

Patients who are only temporarily not able to provide informed consent will also be not included.

6.1.2 Withdrawal of Informed Consent

Patients may withdraw their consent to participate at any time without giving reasons. Nevertheless, the patient should be asked for the reason of the premature termination after being informed that he/she does not need to do so. Information as to when and why a patient was registered/randomised and when he/she withdrew consent must be retained in the documentation.

The patient is to be informed that in case of revocation of his/her consent, the stored data may be used further, as may be necessary to

- assess effects of the drug being tested,
- guarantee that the patient's personal interests are not adversely affected,
- comply with the requirement to provide complete authorisation documentation.

6.2 Enrolment in the Trial

Patients scheduled for intermediate- or high-risk non-cardiac surgery will be included in two steps, to make sure that non-informative patients are not randomised and do not dilute the treatment effect under investigation.

Step I: Screening and registration (- 14 days up to -1 day before surgery):

Generally, the investigator or authorised qualified members of the study group in the trial site screen potential patients eligible for recruitment up to 14 days before surgery for general participation on the basis of pre-existing data (e.g., as available in medical records).

The investigator or authorised qualified members of the study group (physicians) will check eligibility and obtain informed consent from the patient or his/her legally authorised representative/ legal guardian within the preoperative patient education. Eligible patients with informed consent will be registered with the Clinical Trial Centre Leipzig into the central study database (password controlled process) (step I). On registration the patient will be allocated a unique study ID number from Patient-Identification-List (located in the Investigator Site File) which will be used throughout the patient's participation in the study.

For registration, a basic patient data set need to be recorded: demographic data, type of surgery, Hb level, informed consent, study eligibility according to inclusion/exclusion criteria.

Step II: Randomisation (during surgery (=day 0) or day 1, 2 or 3 after surgery):

As soon as Hb falls ≤ 9 g/dl during surgery (= day 0) or day 1, 2 or 3 after surgery and there is no obvious occurrence of composite components, registered patients will be randomised via internet at the Clinical Trial Centre Leipzig, Germany (step II).

Qualified medical staff in participating centres will gain limited access to the system using a personal password. Information to identify a participant uniquely and to confirm eligibility must be entered before the system will assign the randomised treatment allocation.

An intraoperative randomisation might be necessary if Hb falls ≤ 9 g/dl during surgery. If it is not possible to randomise the patient via internet during surgery, the patient can be randomised intraoperatively by opening a sealed envelope. The envelope contains the assigned transfusion protocol. If the intraoperative randomisation via envelope was done by a physician who is not member of the study group, the randomisation has to be confirmed by the investigator or study clinician. The randomisation form has to be sent to the Clinical Trial Centre Leipzig via Fax (+49 (0)341 9716259) immediately after surgery.

The sealed envelope can also be used if it is not possible to randomise the patient via internet for technical reasons.

The (intraoperative) randomisation via envelope is entered into the randomisation tool by Clinical Trial Centre Leipzig staff after receipt of the fax.

The Randomisation form must be stored in the investigator site file. Randomisation has to be documented in the patient's medical record.

Medical staff and attending physicians will be instructed to transfuse as soon as possible after the respective trigger has been reached. The target post-transfusion Hb level needs to be reached at latest within 24 hours upon receipt of the triggering lab result. The assigned transfusion rules remain in force until hospital discharge or up to 30 days after surgery, whichever occurs first.

Additional patient-related data will be recorded:

Hb levels (including measurement method: blood gas analysis; capillary blood; central laboratory)

NOTE: any lowest haemoglobin measurements determined either by BGA or central laboratory testing should be used as transfusion.

Planned two-stage surgery:

Registration can either be done at the day of informed consent, at the day of first or second surgery before or even after skin incision, but latest before Hb drops.

In planned two-stage surgical procedures with a time period of several days between surgeries, screening and registration can either be done before the first or the second surgery as long as Hb is ≥ 9 g/dl, but informed consent is suggested to be obtained before the first operation.

Randomisation needs to be done as soon as Hb falls ≤ 9 g/dl

- at the day of first surgery (= day 0) or day 1, 2 or 3 after first surgery, or
- at the day of second surgery (= day 0) or day 1, 2 or 3 after second surgery.

6.2.1 Discovery of a Violation of the Eligibility Criteria

In general, the violation of eligibility criteria is not a reason for premature withdrawal of the patient from the trial therapy or from the whole trial.

If after registration/randomisation it is discovered that the patient was not eligible at the time of registration/randomisation, this has to be reported to the Clinical Trial Centre Leipzig Data Management as soon as possible. The Clinical Trial Centre Leipzig Data Management informs the investigator/his deputy or authorised medical staff immediately as to what is to be done with the patient. The patient's study related documentation will be continued as described in the schedule of assessments.

6.3 Description of the Procedures/Intervention

6.3.1 Screening (Visit 1: - 14 days up to -1 day before surgery)

All registered patients:

- inclusion and exclusion criteria for registration (step I; see also chapter 4.1.1 and 4.2.1)
- baseline variables / patient's characteristics / demographic data (incl. type of surgery and medical history)
- informed consent
- physical examination
- laboratory tests (small blood count including haemoglobin, clinical chemistry including creatinine)
- measurement of haemoglobin including measurement method (BGA, central laboratory
- functional status (Barthel index)

6.3.2 Surgery (Visit 2: day 0)

All registered patients:

- day 0: skin incision until 23:59 of the same day
- at least one measurement of haemoglobin including measurement method (BGA, central laboratory, capillary blood)
- minimal documentation concerning surgery

6.3.3 Observation before randomisation (Visit 3: during surgery (= day 0) or day 1, 2 or 3 after surgery)

All registered patients:

- day 1, 2, or 3: 24 hours from 00:00 – 23:59
- course of haemoglobin (at least daily) including measurement method (BGA, central laboratory, capillary blood)

6.3.4 Randomisation (Visit 4 – during surgery (=day 0) or day 1, 2, 3 after surgery)

- see also chapter 6.2 – Randomisation
- Re-evaluation of inclusion-/exclusion criteria before randomisation only refers to obvious occurrence of any component of the composite endpoint and any allogeneic blood transfusion after registration. No specified diagnostics are scheduled (see also chapter 4.1.2 and 4.2.2)
- **Randomisation** according to protocol (Step II)

6.3.5 Intervention/ Observation after randomisation (Visit 5; up to discharge or 30 days after surgery)

Randomised patients only:

- duration of observation after randomisation: intra-/postoperative until hospital

discharge or 30 days after surgery, whichever occurs first

- intervention: liberal or restrictive transfusion strategy
- investigator is responsible for instruction of physicians to transfuse RBC units each time Hb is lower the randomised threshold and as soon as possible. The target post-transfusion Hb level needs to be reached within 24 hours upon receipt of triggering lab result at the latest. The investigator is responsible that the randomised intervention is followed for each patient.
- laboratory test: haemoglobin levels will be determined from blood samples mainly as part of the patient's usual care at any time during or after surgery (up to 30 days after surgery; at least every 3 days), and after each transfused unit. In the case of a prolonged stay at the intensive care unit, Hb levels should be documented at least every 6 hours.
- laboratory tests: mainly routine laboratory check-up (blood count, clinical chemistry); creatinine plasma level will be measured at least every 7 days;
- any blood sampling, and any start of a RBC transfusion will be documented
- Occurrence of any individual anaemia-associated ischaemic event, defined as a composite of
    - all-cause mortality
    - acute myocardial infarction confirmed by a cardiologist

      Investigators should involve a cardiologist in case of
        - either observing **relevant symptoms**:
            - Ischaemic symptoms including any of the following: chest discomfort, arm discomfort, neck discomfort, jaw discomfort, shortness of breath, or pulmonary oedema, OR
            - Ischaemic electrocardiography findings including any of the following: new or presumed new pathologic Q waves, left bundle branch block, or ST segment elevation (≥ 2 mm), OR
            - Ischaemic myocardial infarction confirmed by coronary angiography
        - or noting an **acute elevation of troponin** (Serum troponin concentration will be measured at attending physician's discretion)
            - troponin values ≥ 2 times 99th percentile upper reference limit in patients with normal values before randomisation, OR
            - elevation of troponin values ≥ 2 times the baseline value if the baseline values are elevated,[34,35] unless clearly explained by non-ischemic aetiology (e.g., pulmonary embolism, sepsis, cardioversion)
    - acute ischaemic stroke confirmed by a neurologist
    - acute kidney injury (stage III)
    - acute mesenteric ischaemia defined as ischaemia confirmed by intervention
    - acute peripheral vascular ischaemia confirmed by angiography and/or leading to surgery.
- infection requiring intravenous (i.v.) antibiotics
- acute kidney injury stages I-II

- AE/SAE-Monitoring

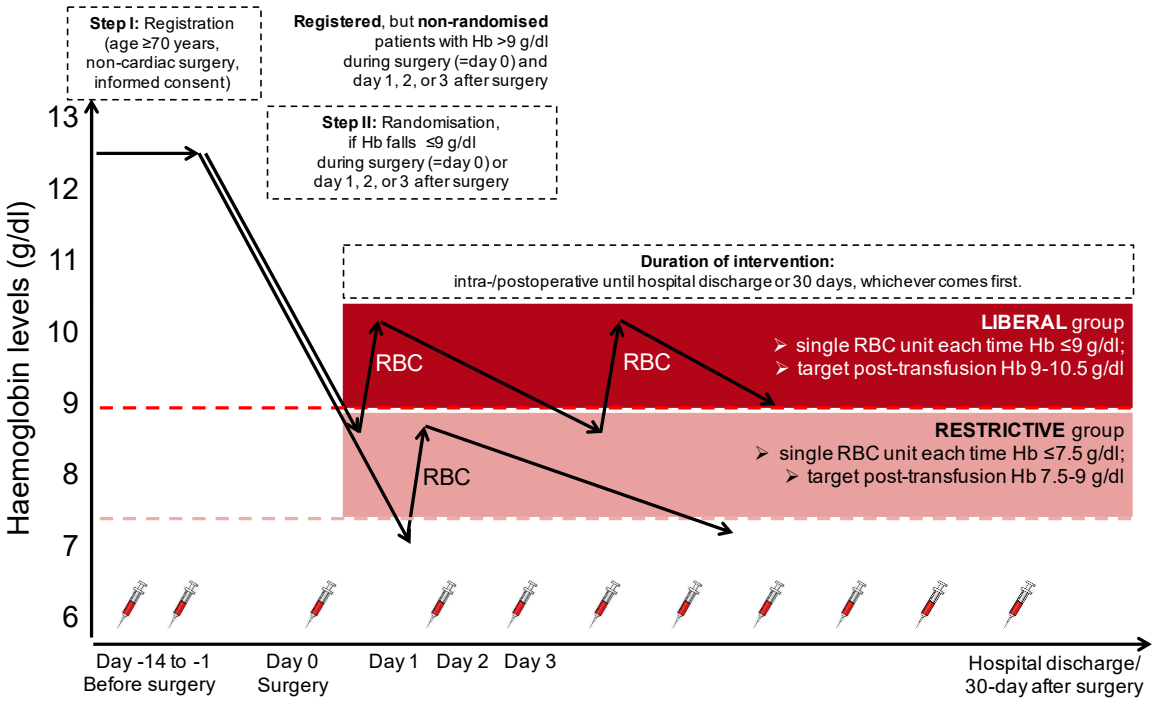


Figure 2 shows scheme of study intervention. Hb levels will be determined from blood samples (syringe symbol) mainly as part of the patient's usual care at any time during or after surgery (up to 30 days after surgery; at least every 3 days), and after each transfused unit. Consenting patients will be registered (Step I) and will be randomised as soon as Hb falls ≤ 9 g/dl during surgery (=day 0) or day 1, 2, or 3 after surgery. Physicians will be instructed to transfuse RBC units each time Hb is lower the defined threshold and as soon as possible. The target post-transfusion Hb level needs to be reached within 24 hours upon receipt of lab result at latest. The intervention per patient will be followed until hospital discharge or up to 30 days, whichever occurred first, comparable to recent large trials.[4,5,22,24]
In case of any massive or life-threatening bleeding, the single-unit policy should be paused.

6.3.6 Discharge (Visit 6 - within 2 days before or on day of discharge)

Randomised patients only:

- Occurrence of any individual anaemia-associated ischaemic event, defined as a composite of all-cause mortality, acute myocardial infarction, acute stroke, acute kidney injury stage III, acute mesenteric ischaemia, and/or acute peripheral vascular ischaemia until hospital discharge (more details in 6.3.5 and 8.2)
- hospital stay/stay on the intensive care unit,
- utilisation of RBC units
- acute kidney injury stages I-II
- infections requiring i.v. antibiotics
- AE/SAE-Monitoring
- Discharge: physician's letter to treating physicians including information about the trial and the planned follow-up

6.3.7 Follow-up (Visit 7) (Day 90 (Day 87 – Day 111) after surgery) by telephone

questionnaire

6.3.7.1 Registered, but non-randomised patients

- all-cause mortality (yes/no; specific cause) at 90 days (Day 87 – Day 111) after surgery (by telephone; relatives, family doctor, physicians, hospitals where necessary)

6.3.7.2 Randomised patients only

Primary outcome:

Occurrence of any individual anaemia-associated ischaemic event, defined as a composite of:

- all-cause mortality, acute myocardial infarction, acute stroke, acute kidney injury stage III, acute mesenteric ischaemia, and/or acute peripheral vascular ischaemia until hospital discharge (more details in 8.2.) at 90 days (primary endpoint) after surgery.

After hospital discharge, events will only be considered as present if they lead to hospital re-admission or death.

Hospital re-admission requires at least one overnight stay in an acute hospital.

An ambulatory hospital visit or an admission to a rehabilitation facility or day hospital is not regarded as hospital readmission.

To reduce possible loss to follow-up after hospital discharge, the composite endpoint will be identified following a structured assessment procedure:

- telephone interview of the trial site personnel with the patient, their relatives or legal representatives, inquiring about
    - Vital status of the patient (if death occurred; documentation of date and cause of death)
    - Any hospital re-admissions
    - ➔ In case of hospital re-admission, the family doctor and / or the respective hospital is contacted, and a detailed documentation on the hospital stay is requested
- If direct contact with the patient / his family fails, the family doctor is contacted directly
    - ➔ In case of hospital re-admission, a detailed documentation on the hospital stay is requested

Secondary outcomes:

- infections requiring i.v. antibiotics with re-hospitalisation
- re-hospitalisation for any cause
- Functional status (assessed with Barthel Index[36] by telephone questionnaire; a scoring model that measures the patient's performance in 10 activities of daily life, focusing on items that are related to self-care and mobility. The maximal score is 100 (5-point increments), indicating that the patient is fully independent in physical functioning. The lowest score is 0, representing a totally dependent bedridden state (Appendix 18.3.1).
- Health-related quality of life (assessed by EuroQoL EQ-5D and WHODAS 2.0 by telephone questionnaire; please see Appendix 18.3.2 and 18.3.3)

A detailed, trial-specific working instruction and a questionnaire to be used as source document for the results of the telephone interview will be provided.

NOTE: Any temporary functional inability or reduced quality of life following acute illness or re-

admission to hospital will be assessed by current Barthel index and current EuroQoL EQ-5D and WHODAS 2.0 without any adjustments.

6.3.8 Follow-up (Visit 8) (1 year (Day 350 – Day 400) after surgery) by telephone questionnaire

Randomised patients only:

Occurrence of any individual anaemia-associated ischaemic event, defined as a composite of:

- all-cause mortality, acute myocardial infarction, acute stroke, acute kidney injury stage III, acute mesenteric ischaemia, and/or acute peripheral vascular ischaemia until hospital discharge (more details in 8.2.) at 1 year after surgery.

After hospital discharge, events will only be considered as present if they lead to hospital re-admission or death.

To reduce possible loss to follow-up after hospital discharge, the composite endpoint will be identified following a structured assessment procedure:

- telephone interview of the trial site personnel with the patient, their relatives or legal representatives, inquiring about
    - Vital status of the patient (if death occurred; documentation of date and cause of death)
    - Any hospital re-admissions
    - ➔ In case of hospital re-admission, the family doctor and / or the respective hospital is contacted, and a detailed documentation on the hospital stay is requested
- If direct contact with the patient / his family fails, the family doctor is contacted directly
    - ➔ In case of hospital re-admission, a detailed documentation on the hospital stay is requested

A detailed, trial-specific working instruction and a questionnaire to be used as source document for the results of the telephone interview will be provided.

6.4 Premature Termination of the Intervention Phase or Follow-up

The date (as exactly as possible) and if possible the circumstances and reasons for every premature termination of the intervention phase or follow-up will be recorded by the site where the patient was being treated and will be communicated to the Clinical Trial Centre Leipzig - Data Management.

6.4.1 Premature Termination of the Intervention Phase for Individual Patients

The trial intervention phase may be terminated prematurely in case:

1. a patient has an adverse event (e.g. transfusion incident) that would, in the investigator's judgement, make continued intervention as per protocol an unacceptable risk
2. at the judgement of the investigator for any other reason of medical prudence
3. on request of the patient

In case of premature termination of intervention phase, it is necessary to document the reason of termination and the current condition of the patient.

All further study visits until visit 8 (1 year after surgery) will take place as planned and described above. **Termination of trial intervention does not mean that the patient is off-study.**

Our primary statistical analysis follows the intention to treat principle as close as possible. For a valid analysis, it is of major importance to minimise the rate of drop-outs. Therefore, in patients which do not withdraw their consent, all study visits shall be performed as scheduled.

6.4.2 Premature Termination of the Follow-up for Individual Patients

Premature termination of trial intervention phase does not lead to individual study termination (see chapter 6.4 for explanation).

The only circumstances in which a premature study termination (i.e. no further study visits) in a randomised patient is unavoidable are:

- withdrawal of informed consent,
- complete loss of contact to the patient or
- death of the patient.

Each premature termination of the trial has to be documented by the responsible investigator. If possible date, circumstances of, reason for the termination, and - if applicable - the final status of patient should be documented in detail and communicated to the Clinical Trial Centre Leipzig - Data Management.

6.5 Plan for Further Treatment

Patients will be treated as usual after the individual treatment period of the clinical trial.

7 ADVERSE EVENTS (AE/SAE)

The focus of this clinical trial is to find an appropriate transfusion strategy to prevent mortality and anaemia-associated, ischaemic events in elderly non-cardiac surgical patients. The strategies under evaluation are specified by different haemoglobin levels triggering the application of red blood cells (RBC) with **different target ranges of haemoglobin levels** to be reached.

LIBERAL investigates different transfusion strategies concerning the risk of ischaemic events. Efficacy or immediate safety of RBC transfusions are not in the primary focus of the trial. RBCs will be manufactured and used as in standard care.

Therefore, the collection, documentation and notification of safety relevant events are adapted for this clinical trial. Following data are of special interest:

- **haemovigilance data,** i.e. haemolytic transfusion reaction, allergic reactions, transfusion-transmitted infections according to §63i AMG (Arzneimittelgesetz, German Medicinal Products Act) and
- data defined as **end points** (primary and secondary)

7.1 Safety Surveillance

During the course of the trial, every patient will be monitored closely. This encompasses documenting Adverse Events as well as the following parameters:

- routine laboratory check-up; creatinine plasma level will be measured at least every 7 days (Visit 5)
- haemoglobin levels will be determined from blood samples mainly as part of the patient's usual care at any time during or after surgery (up to 30 days after surgery; at least every 3 days), and after each transfused unit (Visit 5)

- occurrence of any individual anaemia-associated ischaemic event, defined as a composite of all-cause mortality, acute myocardial infarction, acute stroke, acute kidney injury stage III, acute mesenteric ischaemia, and/or acute peripheral vascular ischaemia (hospital discharge and FU).

7.2 Concomitant Diseases

Concomitant diseases characterising the patient's actual health status will be recorded at registration.

7.3 Definition of (serious) adverse events

According to the ICH-Guideline E2A[37,38], (serious) adverse events are defined as follows.

7.3.1 Adverse Events (AE)

According to ICH Guideline E6 an Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Adverse Events encompass any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease that arise newly or worsen after first application of RBC.

7.3.2 Serious Adverse Events

An Adverse Event is defined to be serious according to ICH-Guideline E2A, paragraph IIB, if it

- **results in death**,
- **is life-threatening**,
- **requires in-patient hospitalization or prolongation of existing hospitalization**,
- **results in persistent or significant disability/incapacity**

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death had it been more severe.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

7.4 Documentation and Reporting of (serious) adverse events

7.4.1 Documentation

Haemovigilance data

Haemovigilance data, i.e. haemolytic transfusion reaction, allergic reactions, transfusion-transmitted infections according to §63i AMG and as well as all other adverse events deemed possibly related to the RBC application will be documented on the AE-form of the CRF.

These adverse events are classified by their seriousness, intensity and relationship to the IMP (see also 18.1).

Within this trial all **haemovigilance data meeting the definition of SAE** will have to be

documented in addition on the SAE-forms and reported as SAE following the requirements described below (see 7.4).

Efficacy endpoints

The following events meeting the SAE-Definition above will be documented on the Endpoint assessment form of the eCRF. The eCRF has to be filled in shortly after each study visit. A reminder system will be established by the Data Management staff of the Clinical Trial Centre Leipzig in order to ensure timely documentation.

- Any component of the composite primary outcome, including:
  - death
  - acute myocardial infarction
  - acute stroke
  - acute kidney injury stage III
  - acute mesenteric ischaemia
  - acute peripheral vascular ischaemia

Additional documentation of any of these events on the AE and SAE form and reporting following the requirements described below (see 7.4) is only necessary if there is a possible relationship of the event with the RBC application.

Participants in the trial are undergoing intermediate or high-risk surgery. Therefore, many Adverse Events are expected. The following potential adverse events are typical symptoms or results of the **underlying diseases** or the **surgical procedures**. **These events must <u>only</u> be documented on the AE and SAE form if they fulfil the definition of seriousness and there is a possible <u>relationship of the event with the RBC application</u>.**

- Gastro-intestinal complication, including
  - pancreatitis
- Postoperative haemorrhage
- Pulmonary complications, including
  - acute respiratory distress syndrome
  - re-intubation and ventilation
  - tracheostomy
  - pleural effusion requiring drainage
- Arrhythmias, including
  - Supraventricular tachycardia or
  - atrial fibrillation
- Re-operation for any reason
- Infectious events, including
  - Sepsis
  - Pneumonia
- Thromboembolic complications, including
  - deep vein thrombosis
  - pulmonary embolus

7.4.2 Documentation period

Start of the collection of data on adverse events will be first application of RBC and the end will be at hospital discharge.

7.4.3 Reporting Obligations: INVESTIGATOR

Serious Adverse Events (as outlined in 7.3.2) have to be documented on the SAE-forms and the investigator must report them to the sponsor immediately. If more information about the SAE becomes available later, it must also be reported to the sponsor immediately.

In all the reports, personal data are to be pseudonymised by using the patient's identification code. It must be possible to relate the initial and all follow-up reports to each other by means of the patient identification number.

In the event of a patient's death, the investigator/the deputy or the authorised medical staff provide the leading ethics committee(s), all involved ethics committees in multi-centred trials, the responsible federal authorities and the sponsor with all further information needed to fulfil their tasks **upon request**.

The investigator or the authorised medical staff must report every Serious Adverse Event as soon as it is known to the following address:

ZKS Leipzig - KKS/Arzneimittelsicherheit
Universität Leipzig
Zentrum für Klinische Studien Leipzig – KKS
Härtelstr. 16-18, 04107 Leipzig
Telefon: +49/341/97-16129
E-Mail: pharmacovigilance@zks.uni-leipzig.de

Fax: +49/341/97-16278

7.4.4 Documentation and Reporting Obligations: SPONSOR

After the Clinical Trial Centre receives the SAE, it is immediately passed on to the coordinating investigator/ responsible person for the medical assessment.

The coordinating investigator/responsible person forms a second medical opinion of the SAE with respect to causal relationships and the decision as to whether or not it was expected, as described in Chapter 18.1.3 and 18.1.4 and forwards the assessment to the KKS within two days of its arrival.

In the Clinical Trial Centre, the SAE data are entered into the SAE database immediately and the MedDRA coding takes place simultaneously.

Then forwarding as per law and as described in Chapter 7.6 only for Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) takes place.

Details of the sponsor's documentation and reporting obligations will be specified in a special, trial-specific pharmacovigilance plan, which will be written and finalised alongside with this protocol, if possible.

7.5 Periodic Reports

7.5.1 Annual Safety Report

The sponsor writes a safety report annually or upon request (Annual Safety Report, ASR[1]). The sponsor sends the report about the safety of the trial medication to the leading ethics committee and the federal authorities.

[1] See "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use").

The key date is the date of the first authorization of the clinical trial by the federal authority. All data obtained up to this date (each year) will be included in the ASR. Beginning with the key date, there is a time-limit of 60 days for the preparation and submission of the ASR.

The ASR is written by the coordinating investigator in cooperation with the project manager at the Clinical Trial Centre and the responsible biometrician.

7.6 Suspected Unexpected Serious Adverse Reactions (SUSAR)

7.6.1 Definition

Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) are side-effects (probably or definitely associated with the administration of the investigational product), the nature or severity of which are inconsistent with the information available about the product. Information about the trial product is contained in the Investigator's Brochure or the SmPC (Summary of medicinal Product Characteristics).

7.6.2 Documentation und Reporting Obligations

Information for SPONSOR

The sponsor submits all information available about a SUSAR immediately to the leading ethics committee, the responsible federal authorities, and to all participating primary investigators, at the latest within 15 calendar days after the event becomes known.

For every SUSAR that results in death or a life-threatening condition, the leading ethics committee, the federal authority, and all participating investigators must be informed by the sponsor within 7 calendar days after the event becomes known. Additional information has to be given within 8 further calendar days

Details of the sponsor's documentation and reporting obligations will be specified in a special, trial-specific pharmacovigilance plan which will be written and finalised alongside with this protocol, if possible.

Information for INVESTIGATOR

The investigator passes down all relevant information concerning the SUSAR to all participating trial investigators at his/her trial centre. This has to be confirmed by the investigator by signing an acknowledgement document.

7.7 Other Safety Relevant Issues

Other safety issues also qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an investigational medicinal product or would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial, for instance:

New events related to the conduct of a trial or the development of an IMP likely to affect the safety of subjects, such as:

- a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
- a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,
- a major safety finding from a newly completed preclinical study (such as carcinogenicity),

- a temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor
- Recommendations of the DSMB, if any, where relevant for the safety of subjects.

The sponsor, together with the DSMB (see also chapter 12.5) if appropriate, decides if the number of events or qualitative changes in the expected SARs comprise a safety issue and must be reported.

7.8 Therapeutic Procedures

If a patient requires treatment as a result of an Adverse Event, then it must meet the recognised standards of medical care in order to restore the patient's health. Appropriate resuscitation devices and medication must be available in order to treat the patient as quickly as possible in the event of an emergency.

The action taken to treat the AE/SAE must be documented by the investigator either in the appropriate CRF and/or using additional documents.

7.9 Dealing with Pregnancy

As recruitment is limited to patients ≥ 70 years of age scheduled for intermediate- or high-risk non-cardiac surgery, no pregnancy is expected.

8 BIOMETRY

8.1 Biometrical Aspects of the Trial Design

LIBERAL is a prospective, multicentre, open, randomised, controlled clinical trial.

Patients are included in two steps in order to avoid randomisation of patients for whom the clinical question concerning transfusion strategy is not pertinent:

1. Patients meeting inclusion/exclusion criteria give informed consent and are registered before their surgery (step I).
2. Registered patients are randomised if and only if a Hb value of 9 mg/dl or below is documented during surgery (=day 0) or day 1, 2, or 3 after surgery (step II).

Registration for LIBERAL stops as soon as the sample size of randomised patients suffices for 80% power or the planned interim analysis shows superiority. Patients already registered at termination of accrual can still be randomised (except in case of superiority).

Some post registration data of registered, but not randomised patients will be collected and analysed:

- Course of Hb (at least daily) during surgery (=day 0) or day 1, 2, or 3 after surgery (as a quality endpoint to describe compliance with the protocol) and delta Hb (Difference pre-op Hb and Hb d3).
- Type and date of surgery
- Vital status up to d90

8.1.1 Measures to Prevent Bias

<u>Randomisation</u>

Randomisation to the liberal or restrictive group will be stratified by centre.

Allocation concealment will be warranted. Randomisation will be performed centrally by block randomisation with variable block length. After written informed consent the randomisation will be done via an internet-based randomisation tool. For urgent intra-operative randomisation or

in case of internet unavailability randomisation can be performed using sealed envelopes. Envelope randomisations will be checked during monitoring.

Blinding

Perioperative care will be provided for all patients according to local standards. Blinding of the patient and involved physicians is not feasible: Staff and study personnel involved in perioperative care cannot be blinded, as the clinicians themselves will determine whether or not a participant meets the requirements for a RBC transfusion according to the study protocol.

Blinded Evaluation

Assessment of some components of the primary endpoint may require an endpoint committee in exceptional, particularly difficult cases. If such an endpoint committee is needed it will be blinded to the study arm.

8.2 Endpoints

8.2.1 Primary Endpoint

Justification

The primary efficacy outcome is a binary composite of mortality from any cause and anaemia-associated, ischaemic events (defined as acute myocardial infarction, acute stroke, acute kidney injury stage III, acute mesenteric ischaemia, acute peripheral vascular ischaemia) within 90 days after surgery.

With the proposed composite, we assess relevant anaemia-associated ischaemic events encompassing five different organs (brain, heart, kidney, gut, limbs) where the assigned Hb level/transfusion strategy will likely have an effect.

We want to show that a liberal transfusion strategy prevents **anaemia-associated, ischaemic events and mortality**.

Other important events such as infections are unlikely to be triggered by anaemia-associated ischaemia. Infections are therefore not included in the primary composite endpoint, but documented as a secondary endpoint.

Operational definition

The primary efficacy outcome is defined as a composite of (within 90 days after surgery):

I. **All-cause mortality** is defined as death from any cause.

II. **Acute myocardial infarction** confirmed by a cardiologist.

III. **Acute ischaemic stroke** confirmed by a neurologist.

IV. **Acute kidney injury (stage III)** is defined according to the Kidney Disease Improving Global Outcomes criteria: Increase of plasma creatinine level ≥ 3 times within a time window of 7 days or initiation of renal replacement therapy.[32]
(Serum creatinine concentration will be measured at least every 7 days until hospital discharge. Urine output criteria will not be used to define acute kidney injury because most of hospital do not mandate hourly urine output measurements on all patients, and

because of the likelihood of inaccurate measurement in the substantial number of patients without urinary catheters.)

V. **Acute mesenteric ischaemia** is defined as ischaemia confirmed by intervention (abdominal surgery or mesenteric angiography).

VI. **Acute peripheral vascular ischaemia** is defined as a new non-thrombotic compromised circulation in a limb confirmed by angiography and/or leading to surgery.

After hospital discharge, events will only be considered as present if they lead to **hospital re-admission** or **death**. Direct transfer to another hospital will not be defined as re-admission. Hospital re-admission requires at least one overnight stay in an acute hospital.

An ambulatory hospital visit or an admission to a rehabilitation facility or day hospital is not regarded as hospital readmission.

After hospital discharge, the composite endpoint will be assessed by a telephone interview (see 6.3.7). In cases of inability to follow by telephone, the primary endpoint will be ascertained from participant's family doctor, or hospital files, respectively.

8.2.2 Secondary Endpoints

Secondary outcome measures are the following:

- The occurrence of any **individual component of the composite** of all-cause mortality, acute myocardial infarction, acute stroke, acute kidney injury stage III, acute mesenteric ischaemia, and/or acute peripheral vascular ischaemia at hospital discharge, at 90 days, and 1 year after surgery.
- **Proportion of patients receiving RBC** transfusion and the **number of units transfused**.
- Total **length of stay** in the intensive care unit and in hospital from randomisation to discharge (for strategy comparison); in addition, total length of stay in the intensive care unit and in hospital from admission to discharge will be used for descriptive purposes.
- The occurrence of **acute kidney injury (stage I or II)** defined according to the Kidney Disease Improving Global Outcomes criteria[32] (stage I: increase of plasma creatinine level ≥ 1.5-1.9 times baseline or ≥ 0.3mg/dl within 48 hours; stage II: increase of plasma creatinine level ≥ 2-2.9 times baseline within a time window of 7 days) during the initial hospital stay
- **Time to (first) infection** (infection requiring therapeutic intravenous antibiotic treatment (pneumonia, wound infection, sepsis, central line associated blood stream infection[31,32,39])) during the initial hospital stay or leading to hospital re-admission within 90 days after surgery.
- **Time to (first) re-hospitalisation** within 90 days.
- **Functional status** (assessed by Barthel Index[36,40] by telephone questionnaire; Appendix 18.3.1).
- **Health-related quality of life** (assessed by EuroQoL EQ-5D[41,42] and 12-item World Health Organisation Disability Assessment Schedule WHODAS 2.0[43]) by telephone questionnaire; Appendix 18.3.2 and 18.3.3).

8.3 Statistical Description of the trial hypothesis

8.3.1 Statistical Hypotheses/Statistical Estimation Method

We aim at showing superiority of liberal over restrictive transfusion thresholds regarding anaemia-associated risk of organ ischaemia and death for elderly patients.

8.4 Sample Size Discussion

Expected overall composite complication rate in randomised patients

We expect an overall composite complication rate (OCCR) of about 25% in LIBERAL. The OCCR is a crucial ingredient for the sample size calculation. Remaining uncertainty concerning OCCR reflects the need for a study focusing on the old age group.

Justification: The guestimate relies on the following evidence:

In the first round funding application, we guestimated an OCCR of 15% mainly based on a literature review of studies including a mixture of elderly and (in a larger proportion) non-elderly patients.

A better guestimate can be derived from outcome data of elderly non-cardiac surgery patients from our own large observational database. Our group recently finished recruitment of 129,719 surgical patients in four University Hospitals within 30 months into an observational study in the field of Patient Blood Management.[44]
A total of 29,748 patients were 70 years or older, and underwent low (ca. 50%), intermediate (ca. 40%), or high-risk (ca. 10%) non-cardiac surgery. Overall, 20% of patients received RBC transfusion with a mixed but more restrictive transfusion strategy (each time Hb fell ≤ 7-8.5 g/dl). Types of surgery were 18% trauma/orthopaedic, 11% neurosurgery, 13% general/ visceral/endocrine, 12% neck, 9% urology, and 8% vascular surgery.

In-hospital event rates (%)	Mortality	Myocardial infarction	Ischaemic stroke	Acute renal failure
Patients ≥ 70years (n=29,748)	6.25	1.34	1.10	4.86
Subgroup 0 RBC units (n=23,666)	1.65	0.49	0.36	0.90
Subgroup 1-2 RBC units (n=2,664)	7.51	2.14	0.94	4.35
Subgroup 2-4 RBC units (n=1,356)	11.36	3.69	1.55	7.01
Subgroup ≥ 5 RBC units (n=2,062)	25.41	6.40	2.76	19.40

These data do not directly inform the proposed LIBERAL trial since they include about 50% low risk patients, which would not qualify for the proposed LIBERAL trial. Risk classification of the performed surgery is not available. In addition, detailed data on Hb course was not documented, so that we cannot exactly determine the number of patients that would have received a RBC with the liberal transfusion strategy investigated in the proposed LIBERAL trial.

After careful discussion of plausible scenarios our best guestimate is that 5,500 - 6,500 of the 29,748 patients would have qualified for randomisation in LIBERAL. Their OCCR is projected to lie between 18 and 19% with the definitions used for in-hospital events.

Please note that for patients randomised in LIBERAL, the expected event rate will increase due to the following reasons:

- complications for primary endpoint will be counted not only until hospital discharge, but up to 90 days after surgery,
- only patients with intermediate or high surgical risk and Hb values ≤ 9 g/dl will be randomised, and
- acute mesenteric ischaemia and acute peripheral vascular ischemia will additionally be counted.

Proportion of registered patients that qualify for randomisation

We assume conservatively that 25-40% of the registered patient can actually be randomised after a Hb drop ≤ 9g/dl.

Justification: In the table above about 20% of the patients got transfusions. But in this rate low risk surgery was included. Pilot data of N=38 patients from Frankfurt meeting the inclusion criteria showed that 55% fulfilled the criteria for randomisation (Hb ≤ 9 mg/dl).

Effect size

The primary endpoint will be analysed by logistic regression adjusting for age, cancer surgery (y/n), type of surgery (intermediate- or high-risk), [33] and incorporating centres as random effect. The treatment effect will be quantified on the odds ratio scale with two-sided 95% confidence intervals provided.

The effect size to be detected is set to an odds ratio of OR=0.765.

Justification: The available evidence on treatment differences from randomised trials concerning the old age group is sparse and inconsistent. Therefore, we choose an effect size, which would clinically be worth to detect. Assuming an OCCR of 25%, an odds ratio of OR=0.765 corresponding to a 5% reduction in OCCR from 27.5% to 22.5% or risk reduction of 18% would justify switching to the liberal transfusion strategy.

Statistical requirements

We use a two sided significance level α=0.05 and require 80% power to detect the effect size specified above.

Drop-outs

We expect less than 5% drop-outs or non-informative patients.

Justification: Loss to follow up will mainly be due to withdrawal of consent by individual patients or inability to contact the patient.

Intra-hospital losses to follow up are negligible due to close monitoring by members of the study team. Perioperative blood samples will mainly be taken together with routine laboratory controls. To minimise drop out in connection with protocol violations, we defined several pragmatic exceptions regarding RBC transfusion strategy (i.e. clinicians will be allowed to transfuse in case of symptomatic anaemia, massive or live-threatening bleeding, patient's request, but must document the reason).

After discharge, the primary endpoint will be assessed within 90 days after surgery. In cases of inability to follow by telephone, the primary endpoint will be ascertained from participant's family doctor, or hospital files, respectively.

Based on our positive experience from a recent multicentre trial including 1,400 cardiac surgical patients with only 1.4% loss to follow-up,[45] we expect a dropout rate of less than 5%.

Sample size

We plan randomising n=2,470 patients.

For the above scenario, enrolment of 2 x 1,176=2,352 patients is required using a two-sided significance level of 5% and requiring power of 80% for a test of the null-hypothesis OR=1 versus OR=0.765 based on the normal approximation to log(OR). We expect a dropout rate of less than 5% (see section 3.7.4). Thus, we plan randomising n=2,470 patients.

If the OCCR turned out to be above 25%, power to detect the specified odds ratio would increase.

8.5 Statistical Methods

8.5.1 Analysis Population

The full analysis set will be as close as possible to the ideal implied by the intention-to-treat-principle. Subjects allocated to a specific group will be followed up, and analysed as members of that group irrespective of the intervention received.

The Full Analysis Set (FAS*)* for the primary efficacy analysis includes all randomised subjects.

A secondary per-protocol analysis of the primary outcome will be performed in all patients without major protocol violations, e.g.:

- haemoglobin levels below the target range for more than 24 hours
- haemoglobin level drop to less than 6 g/dl (3.7 mmol/l)
- RBC transfusion of two instead of a single unit without medical indication

This list may be extended during the conduct of the trial.

A detailed statistical analysis plan will be provided before the planned interim analysis.

8.5.2 Planned Methods for Analysis

A flowchart according to the CONSORT statement will describe the disposition of all patients registered to the trial detailing screening failure before randomisation, withdrawals, drop-outs and inclusion in the analyses sets defined above. Respective listing will be provided. In addition, patients with major protocol violations will be listed.

Standard methods of descriptive statistics will be used always indicating the number of valid and missing values. Summary statistic will be reasonably rounded to avoid pseudo-precision.

General on the planned confirmatory analyses:
Each treatment comparison will be reported as a point estimate of the intervention effect on a meaningful scale, its 95% confidence interval and a respective p-value.
For each treatment comparison in the primary and secondary endpoints both a simple and a model based analysis will be provided.

- The simple, easy to communicate analyses will use widely known standard methods like the chi^2-test or t-test and the associated confidence intervals for the underlying measure of difference.
- Advanced analyses will use generalised linear mixed models to adjust the treatment comparison for relevant covariates and possible random centre effects.

If a relevant discordance between simple and advanced analysis arises, the model based approach is given preference in general; but the conflict has to be explored and the statistical report and any publication will mention and discuss the discrepancy.

Demographic and other baseline parameter will be described for the whole FAS and by randomisation arm using standard methods appropriate to the scale.

Patients will be listed on whom no intervention or an intervention not corresponding to the randomisation arm was performed.

We will describe the frequencies of the observed patterns of components of the primary endpoint in cases with at least one complication. A Venn diagram will be used for illustration.

8.5.3 Primary endpoint

The primary endpoint will be analysed by a generalised linear mixed model, namely logistic regression adjusting for age, cancer surgery (y/n), type of surgery (intermediate- or high-risk),[33] and incorporating centres as random effect.

The treatment effect will be quantified on the odds ratio scale with two-sided 95% confidence intervals provided. Secondarily, also point estimates and confidence intervals for the rate difference and the relative risk will be provided.

The test of the null hypothesis that the odds ratio concerning the composite endpoint is equal to one will be tested using the Wald statistic for the coefficient of the treatment effect in the logistic regression.

If a relevant number of randomised patients (> 1%) have missing information for 90-day, a sensitivity analysis of estimated 90-day time to composite event rates will be performed using an analogously structured proportional hazard regression model censoring these patients at their time of last information and thus including all randomised patients.

The general linear mixed model is fitted using R package “lme4” with option: Gauss-Hermit Quadrature as integration method. For testing we used R package “lmerTest” using the Kenward & Roger method to determine the appropriate degrees of freedom, which is also used in SAS1. This choice of methodological details and software is in line with current published recommendations.

8.5.4 Secondary endpoints

8.5.4.1 Analysis of binary components of the composite endpoint

The same logistic regression model as for the primary endpoint is used in the analysis of the treatment effect in the separate binary components of the composite endpoint.

A table and a Forest plot of the confidence intervals of the intervention effect (both for model based odds ratios and crude differences in complication rates) for the primary composite endpoint and its binary components will be provided.

8.5.4.2 Analysis of time to composite endpoint and Overall survival

Time to event data will be described using Kaplan-Meier product limit estimator. The intervention effect will be analysed with a Cox regression including the same covariates as in the analysis of the primary endpoint and including Centre as random effect.

Validity of the proportional hazard assumption will be checked by graphical methods.

Impact of further covariates can be explored in supplementary analyses.

8.5.4.3 Analysis of time to occurrence of non-fatal endpoint components

Death from other causes is treated as a competing risk. Standard methods of Gray for competing risk analysis as implemented in R package “cmprsk” will be used.

Cumulative incidence rates at d90 and at 1year will be estimated.

The intervention effect will be analysed with the proportional sub distribution hazards regression model described by Fine and Gray including the same covariates as in the analysis of the primary endpoint.

Impact of further covariates can be explored in supplementary analyses.

8.5.5 Sub-group analyses

We hypothesise that the benefit from a liberal transfusion strategy increases with declining anaemia compensatory capacity.

We will therefore perform **exploratory** subgroup analyses by

- Age (< 80 versus ≥ 80 years),
- Gender (male/female),
- American Society of Anaesthesiology Physical Status classification,[46]
- presence of cancer (y/n),
- ischaemic heart disease (y/n),
- heart failure (y/n),
- peripheral vascular disease (y/n),
- previous stroke (y/n),

Any resulting hypothesis requires confirmation in independent data.

Formally powering the study for subgroup analyses would have inflated the necessary sample size by a factor of more than four.

8.5.6 Analysis in all registered patients

For all registered patients, we will collect course of haemoglobin during surgery (= day 0) or day 1, 2, 3 after surgery and the vital status at day 90 (all-cause mortality).

The prognostic value of delta Hb (Difference pre-op Hb and Hb d3) and Barthel index on short term mortality will be analysed adding these factors to the standard generalised linear mixed model specified above.

Assessment of prognostic impact of developing anaemia later than immediately after surgery is conceptually complicated because whether a patient will become anaemic lies in the future and can thus not serve as a prognostic factor. Thus no defined time point of prognostication is available.

However, we will investigate, whether the fact/information that a patient needs a transfusion within the first 3 days after surgery means his hazard for death or composite endpoint increases, using “Transfusion received” as time dependent covariate in a COX regression.

8.6 Statistical Monitoring

We will monitor **accrual rates** for registration and randomisation as well as the randomisation rate among registered patients both overall and by trial site.

Drop-outs and protocol violations will be listed and reasons analysed. Cross-checks of these events with **SAE-reports** will be performed.

The quality of the trial intervention depends on performing of Hb measurements and promptly reacting to them:

We will monitor adequacy in the frequency of Hb measurements overall and by trial-site.

We require **prompt randomisation as soon as relevant anaemia emerges** and thus will statistically monitor the

- Time interval from taking the blood sample that qualifies the patient for randomisation to time of randomisation.

In particular, we will list registered patients that could have been randomised based on their course of haemoglobin, but were not.

We will assess **adherence to the assigned transfusion strategy** and thus will statistically monitor the

- Time interval from taking a blood sample that leads to a transfusion indication to taking the blood sample, which documents that, the respective post-transfusion Hb target was indeed reached. This delay should be less than 24 hours.

In addition, we will monitor the number of patients with **exceptional RBC transfusion** interventions and analyse the reason given.

Data from statistical monitoring will be used to trigger on-site monitoring and identify patients for SDV. The results will also be included into reports for the Data Monitoring Safety Board.

8.7 Interim Analyses

8.7.1 Formal interim analysis for early superiority

Additionally, we schedule one formal unblinded interim analysis after about 1,450 patients with 90-day endpoint information in order to detect early superiority. Stopping for futility is not envisaged because a sufficiently narrow confidence interval for the treatment effect would be important evidence in case of a negative study outcome.

This interim analysis will use a significance level of alpha=0.001 such that the final analysis does not require adjusting for multiple testing.[47] With this interim analysis, we will have 80% power to detect an odds ratio of 0.6, which corresponds to an OCCR difference in the order of 10%.

If the interim analysis turns out significant, the trial will be stopped, unless the Data Monitoring Safety Board (DMSB) recommends otherwise.

The responsible study biometrician will perform the formal interim analysis, write a strictly confidential report and discuss the results exclusively with the Data Monitoring Safety Board. If the DSMC recommends continuing with the trial, the Sponsor, the steering committee, the investigators, and the study team will only receive the information that the interim analysis for early superiority was performed and discussed with the DSMC and that the trial continues. All respective documents and analysis scripts are kept on a dedicated file system to which only the biometrician and his assistant have access rights.

8.8 Final Analysis

The final analysis can be performed as soon as treatment and d90 follow-up of all randomised patients is documented.

9 CONCOMITANT SCIENTIFIC PROJECTS

There are no concomitant scientific projects.

10 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 GCP-Statement

All persons participating in the conduct of the trial (sponsor, authorised representative of the sponsor, investigators, etc.) commit themselves to observe the Declaration of Helsinki (Version Fortaleza 2013),[48] as well as all pertinent national laws and the current ICH guidelines for Good Clinical Practice (GCP).[49-51]

10.2 Initial Submission

10.2.1 General considerations

General ethical considerations also include the consideration and compliance with the following standards, laws and provisions: Declaration of Helsinki,[48] EU Commission directive 2005/28/EC “Good clinical practice” (GCP), Medicinal Products Act (AMG),[52] Proposal for Safeguarding Good Scientific Practice, and the EU Directive 95/46/EC (Data protection).

10.2.2 Submission to the Ethics Committee and Federal Authority

Prior to submitting the trial related documents to the leading (and involved) ethics committee(s) and the responsible federal authority, the sponsor must enter the trial into the European database for clinical trials (EudraCT).

Afterwards, the protocol and all other associated documents according to GCP-V § 7 will be submitted to the leading ethics committee of the University of Wuerzburg and of all participating centres for appraisal. Parallel to the submission to the leading ethics committee (EC), each participating EC is informed of the submission and also receives a copy of the documents including those of the trial sites, which they have to approve. At the same time the study documents will be submitted to the responsible federal authority (PEI) according to the requirements of GCP-V § 7.

The trial can start only after obtaining a positive appraisal by the leading ethics committee and approval from the responsible federal authority. All documentation regarding the submissions and their results must be filed in the trial master file (TMF). Additionally, every participating centre must receive a copy of the relevant documents to be filed in the investigator site file (ISF).

10.3 Protocol Amendments

Changes made to the protocol that was appraised positively by the ethics committee and approved by the responsible federal authority must be positively reappraised and approved if the changes

- are such that they may affect the subjects' safety, e.g. fundamental changes to the therapeutic procedures
- result in further data collection that necessitates changes to the patient information and/or informed consent form,
- affect the interpretation of the scientific documents upon which the trial is based or the significance of the results of the trial,
- significantly affect the leadership or conduct of the trial,
- concern the quality or the innocuousness of the investigational drug, or

- in clinical trials with drugs containing genetically modified organism affect the risk-benefit considerations for the environment at large.

In order to ensure most comparable conditions during trial conduct and in the interest of valid statistical analyses, the investigators, the coordinating investigator or any other person involved in the trial conduct may not alter the study conditions agreed upon and set out in this protocol.

Amendments should be made only in exceptional cases. Any amendment must be set out in writing, at the same time giving the reasons, and signed by all parties concerned. The amendment then becomes part of the study protocol, and is to be filed in the Trial Master File (TMF).

Amendments which might have an impact on the well-being of the subject (major amendments) such as the use of additional invasive procedures require an additional approval by the Ethics Committee (EC) and by the competent authority. In addition, a further informed consent form is to be signed by all trial subjects enrolled in the trial who might be affected by the amendment. In case of substantial changes new approvals of the leading ethics committee and approval of the competent authority are required before the changes become effective. Minor changes will only be submitted to the Ethics Committee and the competent authority in a written form.

The investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior EC approval opinion. As soon as possible, the implemented deviation or change, the reason for it, and if appropriate, the proposed protocol amendment(s) should be submitted to the coordinating investigator for agreement.

11 DOCUMENTATION

11.1 Case Report Forms (CRF)

The Case Report Form (CRF) will be designed by the Clinical Trial Centre Leipzig in cooperation with the coordinating investigator and provided as electronic form (eCRF).

The questionnaire of quality of life will be provided as paper form.

The Investigator or an authorised member of the study team for this task will connect to the database via internet and enter data directly into the database via eCRF data entry masks.

In order to facilitate the documentation as per protocol in case of malfunction of the electronic system or any of its components, a paper version of the CRF will be additionally provided. The content of this paper version will be transferred to the eCRF as soon as the electronic system is available again.

The eCRF has to be filled in shortly after each study visit.

Each eCRF page will be signed electronically by the investigator. This represents the electronic equivalent of a signature on paper and confirms that all data on the eCRF is correct and hasn't been changed. If a value gets changed on the eCRF later on, the electronic signature will be set back automatically and has to be signed again by the principal investigator or an authorised member of the study team. This ensures that changes on the eCRF will be dated and signed as well. All entries and data changes will be tracked automatically including date, time and person who entered/changed information (audit trail). Major correction or major missing data have to be explained.

If the Principal Investigator authorises other members of the study team to enter and sign CRF data, their name, initials, position, signature must be supplied to the Sponsor or its authorised representative via Staff Signature und Delegation Log.

However, the **investigator has final responsibility** at all times for the accuracy and authenticity of all clinical and laboratory data entered in the CRF.

An eCRF will be provided for each patient. The patient will only be identified with the Patient-ID. All information required by the protocol and therefore collected during the clinical trial must be recorded by the Investigator or an authorised member of the study team as source data in the source documentation for the study.

Source data according to ICH-GCP E6 are defined as any information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

We expect source data for all items documented on the electronic CRFs. A paper questionnaire will be provided to document the 90 day and 1 year FU as a telephone interview.

On-site staff performing remote data entry will be trained by the Clinical Trial Centre Leipzig.

11.2 Data Management

For creation of the study database the EDC Tool (secuTrial®) will be used. The database will be validated according to the Standard Operating Procedures (SOPs) of the Clinical Trial Centre Leipzig prior to data capture.

The information entered into the eCRF is systematically checked for completeness, consistency and plausibility by rules implemented in the EDC Tool such that discrepancies can dealt with at data entry. Errors and Warnings are listed in a validation report and can be resolved at any time during entry process. On completion of the data entry the site staff flags the eCRF-pages as 'data entry completed' (DEC).

During on-site monitoring or central statistical monitoring, the monitor or the data manager at the Clinical Trial Centre may create a manual query for discrepancies that are identified after DEC. All eCRF-pages with queries are marked in the system and a report with all queries listed is available. The site staff is responsible for data correction and resolves queries directly in the eCRF-page.

The Clinical Trial Centre Leipzig will supervise and support the solution of the queries and will close all correctly resolved queries. In case a query cannot be solved, the data management staff may close the query in agreement with the study biometrician.

During the whole course of the study, a backup of all data is made on a daily basis. Unauthorised access to patient data is prevented by the access concept of the study database which is based on a strict hierarchy and role model. Any change of data (e.g. when data is changed in the database during query management) is recorded automatically via audit trail within the database.

At the end of the study, once the database has been declared complete and accurate, the database will be locked. Thereafter, any changes to the database are possible only by joint written agreement between coordinating investigator, biometrician and data manager.

11.3 Archiving

All relevant trial documentation (Trial Master File) and the electronically stored data will be stored for at least 10 years by the sponsor after the trial's completion.

At the trial sites, the investigators' files, patient identification lists, signed written consent forms, electronic copies of all eCRFs and the patients' files will be stored for at least 10 years after the trial's completion. If local rules or other legal requirements (e.g. German Transfusion Law) require longer periods of archiving, then these are to be met especially for the local patient files.

12 SUPERVISION OF THE CLINICAL TRIAL

General: All study procedures, including development of the protocol, case report form and investigator site file, content of patient information and consent, application for ethics and authority's approval, data processing, central and on-site monitoring, and evaluation will follow the Standard Operating Procedures (SOP) of the Clinical Trial Centre Leipzig (ZKS Leipzig).

12.1 Access to Source Data

According to ICH-GCP and the applicable German laws, the investigator must permit all authorised third parties access to the trial site and the medical records of the trial subjects (source data). These include the clinical trial monitors, auditors and other authorised employees of the sponsor, as well as members of the local or federal authorities. All these persons are sworn to secrecy.

12.2 Monitoring

Risk-adapted on-site Monitoring: The Clinical Trial Centre Leipzig will be responsible for trial monitoring. Pre-study, initiation, regular and close-out visits will be performed in all centres. All trial sites will be visited regularly depending on the results of the risk assessment performed during development of trial protocol as well as risk-analysis and subsequently at the basis of the monitoring plan.

Central/statistical monitoring: A risk-based monitoring strategy will be implemented. During trial conduct, central monitoring procedures will be combined with on-site monitoring visits in order to achieve high protocol compliance and data quality, as well as to ensure patients' safety and rights. Central/statistical monitoring will include a timely query management process based on consistency and plausibility checks supervised by the trial biometrician, combined with a dunning process for missing documentation. These processes are supported by automatic routines implemented in the trial database. Prior to every scheduled on-site visit, the data management will provide the monitor with patient synopses summarising the data already available in the database, and indicating possible protocol deviations or inconsistencies.
Details regarding the clinical monitoring will be specified in a special, trial-specific monitoring plan which will be written and finalised alongside with this protocol.

12.3 Audits

In order to guarantee that the conduct of the study is in accordance with ICH-GCP[50] and the national laws, the sponsor reserves the right to audit selected trial sites. The auditor will be independent from the staff involved in the proceedings of this clinical study.

The investigator agrees to give the auditor access to all relevant documents for review.

12.4 Inspections

According to German drug law (AMG) and the corresponding GCP-guidelines (GCP-V), inspections of the trial sites may be performed by the local or federal authorities at any time during or after completion of the trial.

The investigator agrees to give the inspectors access to all relevant documents for review.

12.5 Independent Supervision of the Trial

A Data Monitoring Safety Board (DMSB) consisting of two physicians and one biostatistician will be set-up. Envisaged members of the DSMB are listed in the General information. The

DMSB is responsible for safeguarding the interests of trial subjects, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial.

The DMSB will assess the progress of the trial at regular intervals and will evaluate all safety data. In addition, the DSMB will evaluate the results of the blinded interim analysis to check the design assumptions as well as results of the formal interim efficacy analysis. It will recommend to the coordinating investigator and the sponsor whether to continue, modify, or stop the trial.

A DSMB charter will describe the role of the DSMB and processes of its interaction with the study team in detail.

13 DATA PROTECTION AND CONFIDENTIALITY

Within this study, personal data from the trial subjects incl. data regarding the therapy and the course of disease (medical results) will be collected locally at the trial site.

The data for the trial will be stored and processed in pseudonymised form (i.e. without reference to the patient's name) with the aid of an identification number. The patient's name will not appear on any case report form or in any other trial document submitted to the data management at ZKS Leipzig. All collected data will be kept confidential.

Trial data will be analysed at the Clinical Trial Centre Leipzig. The safety concept ensures amongst other things that data access is limited to authorised persons, that measures are taken to prevent loss of data and that the laws pertaining to data protection are observed. The data are protected from third party access and only members of the trial are permitted to have access. These members are sworn to secrecy.

In the event of withdrawal of consent, the necessity for storing data will be evaluated. Data not needed will be deleted immediately. Personal data will be stored in an anonymous manner after reaching the study aim/after finishing of all concomitant scientific projects 10 years at the latest, if there are no other regulatory or contractual time periods for archiving.

13.1 Declaration regarding Data Protection

During data entry, processing and analysis in the Clinical Trial Centre Leipzig, Universität Leipzig, Härtelstr. 16-18, 04107 Leipzig, all requirements of the data protection act will be taken into account. Access to the data is strictly limited to authorised persons. Data are protected against unauthorised access.

13.2 Declaration regarding the Pseudonymised Transfer of Personal Data

The sponsor certifies herewith that the transfer of pseudonymised personal data will take place according to the documentation and communication regulations in §§ 12 und 13 of the GCP-guidelines. Moreover, the sponsor certifies that trial participants who do not permit the transfer of data will not be admitted to the trial.

13.3 Declaration regarding Data-Sharing

The data on which the primary publication of the LIBERAL trial results was based will be shared with interested scientists on request (e.g. for meta-analyses, health related registers or other scientific questions) if the LIBERAL steering committee agrees. Shared data will be anonymized. This offer extends for at least five years.

14 ADMINISTRATIVE AGREEMENTS

14.1 Adherence to the Protocol

The clinical trial described here will be conducted and analysed in accordance with local laws (AMG/GCP-Verordnung)[49,52] and ICH guidelines for Good Clinical Practice (GCP).[50]

Protocol violations are all deviations from the procedures outlined in this document.

Major protocol violations are defined in section 8.5.1.

After a patient has been enrolled, it is the investigator's responsibility to avoid protocol violation in order to obtain unbiased data for the trial. Major protocol violations will be reported to the coordinating investigator/sponsor as soon as possible. All protocol violations will be documented and discussed with the responsible biometrician before closing the data base and carrying out the statistical analysis.

The investigator must ensure that the recorded data are documented as per protocol. Minor variations are an inevitability, but must be documented together with a justification.

Protocol violations are documented in the e-CRF.

14.2 Funding and Insurance

The LIBERAL-Trial is funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), Reference ME 3559/3-1.

Patients are insured at the CNA Insurance Company Limited, Köln.

The number of the insurance policy is: 10235943.

Copies of both insurance policies and the insurance conditions will be filed in the investigators file. A copy of insurance conditions will be handed over to the patient during informed consent process.

14.3 Notification of the Local Authorities

Prior to enrolment of the first patient in the trial, the sponsor, his/her legal representatives/ contractors and all investigators and their deputies are responsible according to German drug law AMG § 67 (1) and the requirements of the GCP-V § 12 and 13 for notifying the local regulatory authority of their participation in the trial.

According to § 67 (3) AMG and §§ 12,13 GCP-V the sponsor, his/her legal representatives/ contractors and all investigators and their deputies are also responsible for notifying the local regulatory authority of amendments, premature termination of trial arms or of the whole study and the regular trial termination.

14.4 Publication Policy and Registration

The LIBERAL-Trial shall be published under the lead of the coordinating investigator together with contributing partners in a peer-reviewed journal, irrespective of the trial results. The publication policy will follow the recommendations of Good Scientific Practice (GSP) of the Deutsche Forschungsgemeinschaft (DFG, http://www.dfg.de) and will meet the criteria of the International Committee of Medical Journal Editors (http://www.icmje.org).

Prior to study start, the clinical trial will be registered in a public trial registry (ClinicalTrials.gov).

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16 PROTOCOL SIGNATURES

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Coordinating investigator:		
Prof. Dr. P. Meybohm	Date	Signature
Biometrician:		
Dr. D. Hasenclever	Date	Signature

17 PROTOCOL AGREEMENT

Herewith I declare that I have read and understood the present protocol and agree to honour each part of it. I will ensure that all the patients enrolled in the trial by my site will be treated, observed and documented in accordance with this protocol. I will ensure that all persons assisting with the study under my supervision are adequately informed about the protocol, the investigational product and their duties.

Date: _____

Signature of local Investigator: _____

Affiliation/address (stamp): _____

_____

_____

_____

18 APPENDIX

18.1 Classification of Adverse Events

18.1.1 Degree of seriousness

The degree of seriousness of an Adverse Events will be determined in accordance with the definitions in 7.3.1 and 7.3.2.

18.1.2 Assessment of Intensity

The assessment of the intensity accords with CTCAE V4.0[37]

Mild Adverse Event	• asymptomatic or mild symptoms; • clinical or diagnostic observations only; • intervention not indicated.
Moderate Adverse Event	• minimal, local or non-invasive intervention indicated; • limiting age-appropriate instrumental ADL*[2].
Severe Adverse Event	• medically significant but not immediately life-threatening; • hospitalization or prolongation of hospitalization indicated; • disabling; • limiting self care ADL**
Life-threatening Adverse Event	• Life-threatening consequences; • urgent intervention indicated
Death related to Adverse Event	

18.1.3 Determining the Causal Relationship

The investigator/the deputy or the authorised medical staff must assess whether or not the Adverse Event is causally related to the administration of the trial medication. The following classification is to be used.

- Reasonable possibility
- No reasonable possibility

A reasonable possibility exists, if one of the following WHO-UMC criteria is met:

- occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be

[2] **Activities of Daily Living (ADL):**
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

- with a reasonable time, sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
- with a reasonable time, sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- more data is essential for a proper assessment or the additional data are under examination
- cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified

No reasonable possibility exists, if the following WHO-UMC criterion is met:

- with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

18.1.4 Expected/Unexpected

Adverse Events are unexpected if they do not occur in the manner or with the intensity described in the SmPC (see investigator's files).

18.1.5 Outcome of an Adverse Event

The outcome of an Adverse Event is classified as follows:

- recovered/resolved
- recovering/resolving
- not recovered/not resolved
- recovered/resolved with sequelae
- fatal*
- unknown

*Note: A patient's death is not in itself an event, but the consequence of one. The event that led to the patient's death must be documented completely and reported even if death occurs four weeks after stopping medication and independent of whether or not there is a relation to the therapy or not.

18.2 Definitions/Abbreviations

18.2.1 Acronym

AE	Adverse Event
AMG	Arzneimittelgesetz
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BGA	Blood Gas Analysis
BOB	Bundesoberbehörde
GCP	Good Clinical Practice
GCP-V	GCP-Verordnung
ICH	International Conference on Harmonisation
MPG	Medizinproduktegesetz
PEI	Paul-Ehrlich-Institut
RBC	Red blood cells
SAE	Serious adverse event
SAR	Serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
WHO-UMC	World Health Organization – Uppsala Monitoring Centre

18.3 Functional Status and Health-related Quality of life

18.3.1 Barthel Index (Hamburger Manual[40])

Bewertet wird nur, was der Patient tatsächlich aus eigenem Antrieb in seiner aktuellen Situation tut, nicht was er von seiner Motorik theoretisch oder unter anderen äußeren Bedingungen könnte!
Sollten (z.B. je nach Tagesform) stets unterschiedliche Einstufungskriterien zutreffen, ist die niedrigere Einstufung zu wählen.

	ESSEN
10	komplett selbständig oder selbständige PEG-Beschickung/-Versorgung
5	Hilfe bei mundgerechter Vorbereitung, aber selbständiges Einnehmen oder Hilfe bei PEG-Beschickung/-Versorgung
0	kein selbständiges Einnehmen und keine Magensonde/PEG-Ernährung
	AUFSETZEN & UMSETZEN
15	komplett selbständig aus liegender Position in (Roll-)Stuhl und zurück
10	Aufsicht oder geringe Hilfe (ungeschulte Laienhilfe)
5	erhebliche Hilfe (geschulte Laienhilfe oder professionelle Hilfe)
0	wird faktisch nicht aus dem Bett transferiert
	SICH WASCHEN
5	vor Ort komplett selbständig incl. Zähneputzen, Rasieren und Frisieren
0	erfüllt „5“ nicht
	TOILETTENBENUTZUNG
10	vor Ort komplett selbständige Nutzung von Toilette oder Toilettenstuhl incl. Spülung / Reinigung
5	vor Ort Hilfe oder Aufsicht bei Toiletten- oder Toilettenstuhlbenutzung oder deren Spülung / Reinigung erforderlich
0	benutzt faktisch weder Toilette noch Toilettenstuhl
	BADEN / DUSCHEN
5	selbständiges Baden oder Duschen incl. Ein-/Ausstieg, sich reinigen und abtrocknen
0	erfüllt „5“ nicht
	AUFSTEHEN & GEHEN
15	ohne Aufsicht oder personelle Hilfe vom Sitz in den Stand kommen und mindestens 50 m ohne Gehwagen (aber ggf. Stöcken/Gehstützen) gehen
10	ohne Aufsicht oder personelle Hilfe vom Sitz in den Stand kommen und mindestens 50 m mit Hilfe eines Gehwagens gehen
5	mit Laienhilfe oder Gehwagen vom Sitz in den Stand kommen und Strecken im Wohnbereich bewältigen; alternativ: im Wohnbereich komplett selbständig mit Rollstuhl
0	erfüllt „5“ nicht
	TREPPENSTEIGEN
10	ohne Aufsicht oder personelle Hilfe (ggf. incl. Stöcken/Gehstützen) mindestens ein Stockwerk hinauf und hinuntersteigen
5	mit Aufsicht oder Laienhilfe mind. ein Stockwerk hinauf und hinunter
0	erfüllt „5“ nicht
	AN- & AUSKLEIDEN
10	zieht sich in angemessener Zeit selbständig Tageskleidung, Schuhe (und ggf. benötigte Hilfsmittel z.B. ATS, Prothesen) an und aus
5	kleidet mindestens den Oberkörper in angemessener Zeit selbständig an und aus, sofern die Utensilien in greifbarer Nähe sind
0	erfüllt „5“ nicht
	STUHLKONTINENZ
10	ist stuhlkontinent, ggf. selbständig bei rektalen Abführmaßnahmen oder AP-Versorgung
5	ist durchschnittlich nicht mehr als 1x/Woche stuhlinkontinent oder benötigt Hilfe bei rektalen Abführmaßnahmen / AP-Versorgung
0	ist durchschnittlich mehr als 1x/Woche stuhlinkontinent
	HARNKONTINENZ
10	ist harnkontinent oder kompensiert seine Harninkontinenz / versorgt seinen DK komplett selbständig und mit Erfolg (kein Einnässen von Kleidung oder Bettwäsche)
5	kompensiert seine Harninkontinenz selbständig und mit überwiegendem Erfolg (durchschnittlich nicht mehr als 1x/Tag Einnässen von Kleidung oder Bettwäsche) oder benötigt Hilfe bei der Versorgung seines Harnkathetersystems
0	ist durchschnittlich mehr als 1x/Tag harninkontinent

18.3.2 Quality of live (EQ-5D)

Bitte geben Sie an, welche Aussagen Ihren heutigen Gesundheitszustand am besten beschreiben, indem Sie ein Kreuz in ein Kästchen jeder Gruppe machen.

Beweglichkeit / Mobilität

Ich habe keine Probleme herumzugehen ❑

Ich habe einige Probleme herumzugehen ❑

Ich bin ans Bett gebunden ❑

Für sich selbst sorgen

Ich habe keine Probleme, für mich selbst zu sorgen ❑

Ich habe einige Probleme, mich selbst zu waschen oder mich anzuziehen ❑

Ich bin nicht in der Lage, mich selbst zu waschen oder anzuziehen ❑

Alltägliche Tätigkeiten *(z.B. Arbeit, Studium, Hausarbeit, Familien- oder Freizeitaktivitäten)*

Ich habe keine Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑

Ich habe einige Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑

Ich bin nicht in der Lage, meinen alltäglichen Tätigkeiten nachzugehen ❑

Schmerzen / Körperliche Beschwerden

Ich habe keine Schmerzen oder Beschwerden ❑

Ich habe mäßige Schmerzen oder Beschwerden ❑

Ich habe extreme Schmerzen oder Beschwerden ❑

Angst / Niedergeschlagenheit

Ich bin nicht ängstlich oder deprimiert ❑

Ich bin mäßig ängstlich oder deprimiert ❑

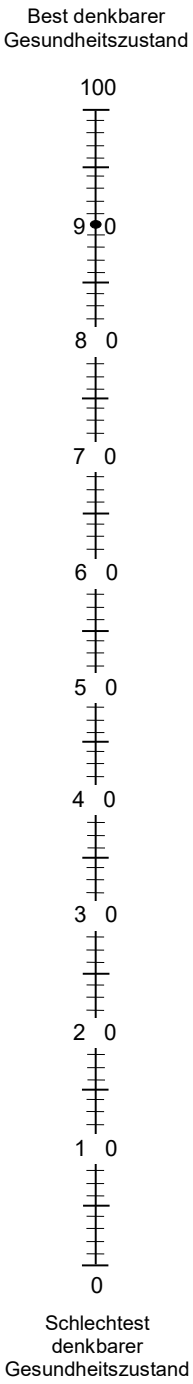
Ich bin extrem ängstlich oder deprimiert ❑

2

Um Sie bei der Einschätzung, wie gut oder wie schlecht Ihr Gesundheitszustand ist, zu unterstützen, haben wir eine Skala gezeichnet, ähnlich einem Thermometer. Der best denkbare Gesundheitszustand ist mit einer “100” gekennzeichnet, der schlechteste mit “0”.

Wir möchten Sie nun bitten, auf dieser Skala zu kennzeichnen, wie gut oder schlecht Ihrer Ansicht nach Ihr persönlicher Gesundheitszustand heute ist. Bitte verbinden Sie dazu den untenstehenden Kasten mit dem Punkt auf der Skala, der Ihren heutigen Gesundheitszustand am besten wiedergibt.

Ihr heutiger Gesundheitszustand



3

18.3.3 WHODAS 2.0

WHODAS 2.0

WORLD HEALTH ORGANIZATION
DISABILITY ASSESSMENT SCHEDULE 2.0

12
Interview

Abschnitt 4 Kernfragen

Zeigen Sie Lernkarte #2

Wie viele Schwierigkeiten hatten Sie in den letzten 30 Tagen:		Keine	Geringe	Mäßige	Starke	Sehr starke/ nicht möglich
S1	Eine längere Zeit (ca. 30 Minuten) zu stehen?	1	2	3	4	5
S2	Ihren Haushaltspflichten nachzukommen?	1	2	3	4	5
S3	Neue Aufgaben zu lernen (z.B. erlernen an einem neuen Ort zu gelangen, den Sie nicht kannten)	1	2	3	4	5
S4	Wie viele Schwierigkeiten hatten Sie, an gesellschaftlichen Aktivitäten (wie z.B. Festlichkeiten, religöse oder andere Aktivitäten) in der gleichen Art und Weise teilzunehmen, wie jeder andere?	1	2	3	4	5
S5	Wie sehr wurden Sie durch Ihren gesundheitlichen Zustand emotional belastet?	1	2	3	4	5

Wie viele Schwierigkeiten hatten Sie in den letzten 30 Tagen:		Keine	Geringe	Mäßige	Starke	Sehr starke/ nicht möglich
S6	Sich für 10 Minuten auf etwas zu konzentrieren?	1	2	3	4	5
S7	Eine längere Strecke (ca. einen Kilometer) zu Fuss zu gehen?	1	2	3	4	5
S8	Ihren gesamten Körper zu waschen?	1	2	3	4	5
S9	Sich anzuziehen?	1	2	3	4	5
S10	Im Umgang mit Personen, die Sie nicht kennen?	1	2	3	4	5
S11	Eine Freundschaft aufrechtzuerhalten?	1	2	3	4	5
S12	Bei der Bewältigung Ihres Arbeits-/Schulalltags?	1	2	3	4	5

H1	An wie vielen Tagen traten diese Schwierigkeiten während der letzten 30 Tage auf?	***Anzahl der Tage*** _____
H2	An wie vielen Tagen in den letzten 30 Tagen waren Sie aufgrund Ihrer Gesundheitsprobleme absolut unfähig, alltägliche Aktivitäten oder Ihre Arbeit zu verrichten?	***Anzahl der Tage*** _____
H3	An wie vielen Tagen in den letzten 30 Tagen mussten Sie aufgrund Ihrer Gesundheitsprobleme alltägliche Aktivitäten oder Ihre Arbeit reduzieren?	***Anzahl der Tage*** _____