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Improve hip fracture outcome in the elderly patient (iHOPE): a study protocol for a pragmatic, multicentre randomized controlled trial to test the efficacy of spinal versus general anaesthesia

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Improve hip fracture outcome in the elderly patient (iHOPE): a study protocol for a pragmatic, multicentre randomized controlled trial to test the efficacy of spinal versus general anaesthesia

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ABSTRACT

Introduction:

Hip fracture surgery is associated with high in-hospital and 30-day mortality rates and serious adverse patient outcomes. Evidence from randomized controlled trials regarding effectiveness of spinal versus general anaesthesia on patient-centred outcomes after hip fracture surgery is sparse.

Methods and analysis:

The iHOPE study is a pragmatic national, multicentre, randomized controlled, open label clinical trial with a two-arm parallel group design. In total 1032 hip fracture patients (>65 years) will be randomized in an intended 1:1 allocation ratio to receive spinal anaesthesia (n=516) or general anaesthesia (n=516). Outcome assessment will occur in a blinded manner after hospital discharge and if feasible also in-hospital. The primary endpoint will be assessed by telephone interview and comprises the time to the first occurring event of the binary composite outcome of all-cause mortality or new-onset serious cardiac and pulmonary complications within 30 postoperative days. In-hospital secondary endpoints, assessed via in-person interviews and medical record review, include mortality, perioperative adverse events, delirium, satisfaction, walking independently and hospital data like length of stays and discharge destination. Telephone interviews will be performed for long-term endpoints (all cause-mortality, independence in walking, chronic pain, ability to return home cognitive function and overall health and disability) at postoperative day 30±3, 180±45 and 365±60.

Ethics and dissemination:

iHOPE has been approved by the leading Ethics Committee of the Medical Faculty of the RWTH Aachen University on 14.03.2018 (EK 022/18). Approval from all other involved local Ethical Committees was subsequently requested and obtained. Study start is planned for April 2018 with a total recruitment period of 24 months. iHOPE will be disseminated via presentations at national and international scientific meetings or conferences and publication in peer-reviewed international scientific journals.

Trial registration number: German Clinical Trials Register DRKS00013644

ARTICLE SUMMARY

Strengths and limitations of this study

- iHOPE will confirm the effectiveness of standard care spinal and standard care general anaesthesia for hip fracture.
- Anaesthesia treatment will be performed according to the clinical routine (pragmatic approach) after randomization, which will enable more generalizable results for the iHOPE trial.
- iHOPE will help to optimize the efficacy, clinical and cost effectiveness of anaesthesia care.
- iHOPE will apply a consented core outcome set[41] and liaises with REGAIN trial,[23] which focuses on a different primary endpoint.
- We plan to combine data from iHOPE and the REGAIN trial[23] after publication in an individualized patient data (IPD) meta-analysis under a separate protocol in order to aid future guideline development.

INTRODUCTION

In Germany, the elderly population (>65 years) will grow from 27% of the total population in 2015 to 39% in 2040.[1] The recently published EuroHOPE patient database oversees 59,605 hip fracture patients across seven European countries. The hip fracture prevalence of patients older than 50 years ranged from 307/100,000 in Finland to 1,269/100,000 in Italy in the year 2007. The 30-day and one-year mortality rate peaked with 11.7 and 34.8% in Hungary and was lowest in Italy with 4.0 and 19.7% respectively.[2] The 2012 annual number of hip fractures in the UK was reported to be 77,000[3] and is projected to rise to 101,000 by 2020.[4] European data,[4-6] extrapolated to Germany´ s population, show that the 2013 incidence of hip fracture was 126 per 100,000 residents per year. The "Institut für Qualitätssicherung und Transparenz im Gesundheitswesen" (IQTIG) published recently its "2017 Hip Fracture" report covering 60,178 medical records of hip fracture patients who received surgical intervention from 1,215 German hospitals. The IQTIG report presented an in-hospital mortality rate of 4.8%.[7] A retrospective analysis of a level I trauma centre in Germany revealed an in-hospital mortality rate of even 8.2%. Postoperative cardiac and respiratory complications were observed in 21.5% of the patients, with an in-hospital mortality rate of 28.7% in this group.[8] In total, the one-month mortality rate after hip fracture ranges from 4 to 12% and reaches up to 35% after one year in Europe and the USA.[2,7,9,10] The aforementioned is associated with approximately 33,500 deaths in Germany, annually.[5] Hip fracture patients frequently present complex comorbidities including but not limited to impaired hepatic and renal function, diabetes mellitus, dementia, delirium, coronary artery disease, heart failure and patient poly-pharmacy. These are all individually linked to an increase in postoperative complications and mortality. The vast majority of the entire hip fracture patients (95%) arrives at hospital with at least one major comorbidity.[11] According to the IQTIG analysis, 63% of patients with hip fracture were presented in hospital with severe comorbidities (ASA III) and 8% with life threatening comorbidities (ASA IV).[7] It is not surprising that patients with multiple comorbidities are at highest risk of death.[11] Additional risk factors such as residential status, functional and cognitive impairment prior to fracture, male gender, poor nutrition status and anaemia have been identified and are associated with increased mortality.[5] Serious cardiac and pulmonary complications (pneumonia, pulmonary embolism, cardiac arrest and myocardial infarction) appear most frequent.[7] Furthermore, the number of comorbidities negatively influences the psychological outcomes of elderly patients with hip fracture.[12,13] Postoperative delirium is the most common complication in hospitalized elderly patients and is strongly associated with hip fracture surgery, with reported incidence rates of 13-50%.[7] Occurrence of post-surgery delirium is associated with a worse prognosis for recovery, posttraumatic stress disorder, depression and increased mortality.[14-18] The most

significant risk factors for delirium are age and pre-existing damage to the brain such as dementia or alcohol abuse.[15] On average, hip fracture patients in Germany spend 13 days in hospital (median 11 days).[7] There is an enormous humanitarian and socioeconomic need to improve quality and effectiveness of care for hip fracture patients.

So far, no specific anaesthesia management has been recommended for hip fracture surgery. The commonly most applied anaesthesia techniques for hip fracture surgery represent spinal and general anaesthesia.[19] A comparison of regional and general anaesthesia for hip fracture surgery from randomized controlled trials was summarized 2016 in a Cochrane review.[20] There was no difference in one-month mortality or in several serious adverse events e.g. pneumonia, myocardial infarction, and cerebrovascular events. Yet, the level of evidence in the reported studies was low, the power of the studies insufficient and the authors concluded that "due to the limited evidence, neither general nor regional anaesthesia seems to improve perioperative outcome".[20] However, in recent years several large non-randomized trials have been published. A matched retrospective cohort study including 56,729 patients analysed the association of regional anaesthesia (spinal or epidural) compared to general anaesthesia with the 30-day mortality and hospital length of stay. Regional anaesthesia was associated with a shorter length of hospital stay, but no difference was found between groups in the 30-day mortality.[21] In consequence, we performed a systematic review and meta-analysis that was not limited to randomized trials, comparing in-hospital and 30-day mortality rate, and length of hospital stay after regional or general anaesthesia undergoing hip fracture surgery.[22] The retrospective studies in this review included overall 413,245 patients. We found a significantly lower rate of in-hospital mortality in the regional anaesthesia group, but there was no difference between the groups with regard to the 30-day mortality. The length of hospital stay was significantly shorter and the incidence of myocardial infarction was significantly lower in the regional anaesthesia group. Of note, evidence in this meta-analysis was mainly limited to retrospective and highly heterogeneous data and the risk of bias within and across studies was high. At present insufficient evidence exists to characterize the comparative effectiveness of spinal versus general anaesthesia for hip fracture surgery among older patients. In this respect it is important to note that a large randomized controlled study of 1600 patients with >50 years of age, undergoing hip fracture surgery with general or spinal anaesthesia was launched in February 2016 in the USA and Canada.[23] The primary aim of the REGAIN study is to analyse the recovery of walking at 60 days after randomization and further patient-centred outcomes up to 1 year.

Objectives

iHOPE is composed to optimize the efficacy, clinical and cost effectiveness of anaesthesia care for hip fracture patients. iHOPE aims to compare the efficacy of two different standard anaesthesia care approaches (spinal versus general anaesthesia) for hip fracture surgery on the binary composite outcome of all-cause mortality or new-onset serious cardiac and pulmonary complications within 30 postoperative days. The primary hypothesis is, that spinal anaesthesia is superior to general anaesthesia with respect to the composite outcome.

Several secondary objectives will be studied during iHOPE.

METHODS AND ANALYSES

Trial design

iHOPE is designed as a pragmatic, multicentre, randomized controlled, open label clinical trial with a two arm parallel group design allocating patients in an intended 1:1 allocation ratio to proof the two sided hypothesis, whether one of the anaesthesia regimes is superior to the other one, with respect to the primary composite endpoint. iHOPE was composed as a more pragmatic than explanatory trial to yield results, which are more generalizable for the routine clinical practice. The PRECIS-2 tool[24] was used to determine the extent of our design as a pragmatic trial (Table 1)

Table 1. Score 1: very explanatory; Score 2: rather explanatory; Score 3: equally pragmatic/explanatory; Score 4: rather pragmatic; Score 5: very pragmatic

Domain	Score	Rationale
1. Eligibility Criteria	5	iHOPE will include a broad spectrum of elderly patients identical to the patients in the usual care. Legally not competent patients (due to e.g. dementia) will also be included in this trial.
2. Recruitment	5	iHOPE will recruit the patients during the clinical routine in the hospitals.
3. Setting	5	Identical setting to usual care setting. iHOPE will engage hospitals with tertiary as well as secondary care. This includes both academic and community hospitals.
4. Organisation intervention	5	Usual attending anaesthesia team will conduct the intervention. Care provider instructions regarding the study protocol will be provided, but there is no need for an advanced expertise for provision of the intervention.
5. Flexibility (delivery)	5	The intervention has to be provided according to the clinical routine. Co-treatment is not restricted and may be delivered as judged by the anaesthetist in charge.

6. Flexibility (adherence)	5	Treatment changes are allowed, if clinically necessary.
7. Follow-up	4	Brief in-hospital follow-up will occur during the first 4 postoperative days and at the discharge day. Blinding will be encouraged during the first 4 postoperative visits, but it is not mandatory. This will facilitate study conduction during the clinical routine in the different settings. The visit on the discharge day has not to be blinded, due to the requirement of extensive medical chart review. A blinded outcome assessor (e.g. study-nurse) will be required for the follow-up visits after hospital discharge at day 30 ± 3, day 180 ± 45 and day 365 ± 60. The follow-up will consist of a short telephone interview of the patient or the proxy.
8. Primary outcome	5	The primary outcome (binary composite outcome of all-cause mortality or new-onset serious cardiac and pulmonary events until postoperative day 30) is obviously relevant for the patients.
9. Primary analysis	4	An intention-to-treat analysis will be performed with all available data. A per-protocol analysis, sensitivity and pre-specified subgroup analyses will be performed in addition.

This study protocol is composed according to the SPIRIT statement. The SPIRIT checklist is provided in the Supplementary Table 1.

Setting and Duration

This study will be performed in at least 17 German secondary and tertiary hospitals. The full list of centres can be obtained at the corresponding author. Patient recruitment is planned to start April 2018. "Last patient in" is anticipated for March 2020. Last Follow-up is expected to be April 2021.

Eligibility criteria

Eligibility criteria for patients are presented in Table 2.

Table 2 Eligibility criteria for patients

Inclusion criteria	Patients ≥ 65 years with acute intra- / extracapsular hip fracture (e.g. femoral neck fracture, subtrochanteric or intertrochanteric fracture) requiring surgical intervention
	Planned surgical treatment via hemiarthroplasty, total hip arthroplasty or appropriate osteosynthetic procedure
	Written informed consent prior to study participation
Exclusion criteria	Patients who are institutionalized by court or administrate order
	Patients with planned concurrent surgery, which is not amenable to spinal anaesthesia
	Patients with absolute and relative contraindications to spinal anaesthesia, including but not limited to: Known or suspected congenital or acquired coagulopathy; active use of pharmacologic anticoagulants within timeframe, defined to contraindicate neuraxial block placement, as defined by the recommendations of the German Society of Anaesthesiology[25]; known or suspected unrepaired critical or severe aortic stenosis; known or suspected active skin infection at the planned needle insertion site; known or suspected elevated intracranial pressure contraindicating dural puncture
	Periprosthetic fracture
	Prior participation in the iHOPE study
	Determination by the attending surgeon, the attending anaesthesiologist, the site Principle Investigator or his designate, that the patient or the attending team in the operating room would not be suitable for a randomization procedure (e.g.: patients will be excluded, if one treatment has preferably to be used in this patient according to the clinical situation).

Eligibility criteria for centres

Participating centres are eligible, if they are willing to participate, have the appropriate infrastructure for trial performance, have the support of their surgeons and expect to recruit about a third of all presented hip fracture patients in their hospital.

Intervention

1032 patients will be randomly assigned to receive either spinal anaesthesia (n=516) or general anaesthesia (n=516). Beside this study treatment group allocation, complete perioperative patient care will be performed as per usual in the clinical routine of the attending anaesthesia team. There is no study-specific default regarding the concomitant care of the patients.

The attending anaesthesia team will apply the allocated treatment according to the instructions shown in Supplementary File 1, which comply with the standard care in Germany.

Participant timeline

Visits

All visits are presented in the Supplementary Table 2, which shows the schedule of enrolment, interventions, and assessments according to the SPIRIT Statement, and described in detail in the Supplementary File 1.

In brief, following a screening visit with seeking of an informed consent (Visit 0), an investigator will perform the baseline assessment (Visit 1). Randomization will occur after a re-evaluation of the eligibility criteria shortly before surgery (Visit 2). The routine attending anaesthesia team will be informed about the allocated treatment group by the investigator. The routine team will perform the study treatment during the clinical routine in accordance with the pragmatic study protocol. Thereafter, the patient will be visited daily on the first 4 postoperative days by an (if feasible blinded) investigator (Visit 3-6). The feasibility of in-hospital blinding will depend on the resources of the study team. It will be documented for each visit, if blinding was preserved. These visits will consist of an assessment of delirium, pain, mortality, adverse events and additionally patient satisfaction on the 4th day or if earlier at discharge. A further in-person patient visit and a medical records review will occur on the hospital discharge day by not blinded investigators (Visit 7). Assessments after hospital

discharge will be performed on postoperative day 30 ± 3, 180 ± 45 and 365 ± 60 via medical record review and telephone interview of the patient or rather the proxy by a blinded outcome assessor (Visits 8-10).

Outcome measures

Primary outcome measure

The primary endpoint is the time to the first occurring event of the binary composite outcome of all-cause mortality or new-onset (i.e. not pre-existing at time of surgery) serious cardiac and pulmonary events up to 30-days after randomization. Definitions of serious cardiac and pulmonary events are adapted from the definitions used by the National Surgical Quality Improvement Program (NSQIP).[26] These include cardiac arrest requiring CPR or defibrillation, myocardial infarction, pneumonia, pulmonary embolism, ventilator > 48 hours and unplanned intubation. The primary endpoint will be assessed via in-person visits and medical record review during hospitalization and via telephone interview after hospital discharge at day 30 after randomization. Events after hospital discharge will only be considered as present if they led to hospital re-admission or death. In case of hospital re-admission the family physician or the respective hospital will be contacted and the documentation of the event will be requested.

Our primary outcome was selected based on the results of previous trials, which showed a high postoperative 30 days mortality rate[2,10] and incidence of cardio-respiratory complications[8,27] in hip fracture patients.

Secondary outcome measures

The secondary endpoints include binary as well as continuous outcomes consisting of (but not limited to) the following:

- Difference in the proportion of patients alive and delirium free in the first 4 days after randomization. Delirium will be assessed via in-person interview by the validated, high sensitive and specific assessment tool 3D-Confusion Assessment Method (3D-CAM).[28] It will be applied at baseline and daily on the first 4 postoperative days.
- Difference in the proportion of patients with postoperative pain; and in the characteristics and duration of postoperative pain between the two treatment arms. Pain will be assessed via numeric rating scale (NRS 0-10) and questions derived from the Brief Pain Inventory[29] and the German pain questionnaire.[30] Assessment will be performed via in-

person interview at baseline and each postoperative visit during hospital stay. After discharge, it will be performed via telephone interview at each follow-up visit.

- Difference in the satisfaction with care between the two treatment arms, assessed at day 4 or the day of discharge (whichever occurs first). The Bauer Patient Satisfaction Questionnaire[31] will be used via in-person interview on postoperative day 4 or at discharge (whichever occurs first), to assess the patients´ satisfaction.
- Difference in the number of in-hospital events, which include (but not limited to): Planned and unplanned admission to critical care; length of hospital and intensive care stay; length of hospital stay longer than expected; independence in walking and the need for assistive devices for walking at hospital discharge; postoperative hospital discharge destination; in hospital all-cause mortality and severe new-onset complications as those used by the NSQIP.[26] These events will be assessed on the discharge day from hospital or at least at postoperative day 30 via in-person interview and medical record review.
- Difference in the proportion or means of long-term outcomes at day 30 ± 3, day 180 ± 45 and day 365 ± 60 after randomization will include: All cause-mortality, independence in walking and need for assistive devices for walking; chronic pain; ability to return home; cognitive function via Short blessed test (SBT)[32]; and overall health and disability via World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0)[33]. Except of the cognitive function and chronic pain, which could only be assessed via telephone interview of the patient, all other data could also be assessed via telephone interview of the proxy.
- Difference in the proportion of patients with perioperative serious adverse events like intraoperative cardiac arrest; malignant hyperthermia; intraoperative anaphylaxis; intraoperative aspiration; total spinal anaesthesia; epidural hematoma; paralysis of the lower extremities lasting greater than 24 hours following spinal anaesthesia; fall within 12 hours of anaesthesia care. These data will be assessed during the surgery and the postoperative in-hospital visits via in-person interview and medical record review.
- Sensitivity and subgroup analyses of the primary outcome will consider the baseline proportion of patients with depression and frailty. Depression will be assessed via the 15-items short version of the Geriatric Depression Scale (GDS) at baseline via in-person interview.[34] Frailty assessment will be performed according to phenotype-model of Fried at baseline via in-person interview.[35] Four of originally five Fried-criteria will be assessed: fatigue, maximal grip strength assessment of the dominant hand, physical activity (employing the Minnesota Leisure Time Activities Questionnaire) and weight loss in the past year. Gait velocity as the fifth Fried criterion will be omitted in this study for obvious reasons.

Sample size

The multicentre, randomized "hip fracture surgery in elderly patients (HIPELD)" study revealed an in-hospital event rate of 12.7% for cardiac and pulmonary complications and 3.8% for the 28-day mortality was revealed in the general anaesthesia group.[27] Of note, the HIPELD study included a strongly confined patient population. The recently published IQTIG report revealed an in-hospital mortality rate of 4.8% and a total reported complication rate of 16.3%.[7] The one-month mortality rate after hip fracture ranges from 4 to 12%.[2,7,9,10] Thus to the best of our knowledge a conservative event rate of 16% of the binary composite endpoint can be assumed for the general anaesthesia group in the iHOPE trial. Furthermore, HIPELD was able to detect a decrease from 15.9% to 8% for serious adverse events and 28-day mortality in the xenon intervention group. Based on the HIPELD data a restrictive, meaningful treatment difference of 6% in the event rate seems to be reasonable on a 5% significance level with a power of 80%. We assume an exponential dropout rate (e.g. loss to follow-up after hospital discharge) of 5%. Using the template STT2-1 from nQuery 7.0 advisory we calculated a sample size of 516 patients per group. It is assumed that the treatment differences are homogenous with respect to extend, variation and sample size per group across sites. Loss to follow-up may occur, but time to event analysis is carried out up to the last visit. No interim analysis of the trial is planned and will be conducted.

Dropout-handling

We will examine in a sensitivity analysis the dropout pattern with respect to treatment. Details are shown in Supplementary File 1

Recruitment

Patients, meeting the inclusion criteria, in absence of the exclusion criteria, will be recruited consecutively during the recruitment period of 24 months. A screening and enrolment log will be kept. The screening number will be coded independently from the randomization number. The Principle Investigators will check the actual recruitment rates weekly, by standardised enrolment reports. All subjects will be recruited in in-hospital settings between the time of presentation and surgery. Participating centres will use multiple strategies to identify potentially eligible patients, including interval calls to specific units, residents and nurses, reviews of inpatient census lists and operating room schedules, and requests to physicians, nurses and emergency room personnel to contact study site staff when a hip fracture patient is admitted to the hospital.

Allocation

Randomization procedure will be stratified by site. The intended allocation ratio is 1:1. The selection of the best practice randomization procedure to prevent selection and time trend bias will follow the ERDO.[36] Details, including the set of investigated randomization procedures, the amount of biases and the decision will be given in a Randomization Report (Department of Medical Statistics, University Hospital RWTH Aachen, Germany), which will be kept concealed up to closure of the database. The randomization list will be imported in an online data management system owned by the sponsor The Center for Translational & Clinical Research Aachen (CTC-A). The site research staff will enter patient´s baseline data in the database and request the randomization assignment via the online data management system, which will be available on a 24/7 basis. Treatment allocation will be reported centralized via the data management system. The site research staff will then communicate this information to the treating anaesthesia team immediately prior to surgery.

Blinding

iHope is composed as an open label trial. Intraoperative attending physicians and patients cannot be blinded, due to the nature of the intervention. In-hospital outcome assessors will be blinded as far as possible based on the site resources. There will be two case report forms (CRFs) for each patient. One will include the non-blinded visits 0-2 and visit 7. The second will include the visits 3-6 and 8-10 for the blinded investigators. Patients and attending physicians will strongly be inculcated not to disclose the allocation status at the follow-up assessments. Accidentally revealing the treatment assignment is possible but unlikely during the medical records review at follow-up, as the outcome assessor would have to seek and view the intraoperative anaesthesia protocol consciously. In any case, the outcome assessor will have to document each follow-up visit, if blinding was successfully performed.

Data collection

All data, which should be collected, are presented in the Supplementary File 1.

Training

Standardisation procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardisation among sites (e.g., training, telephone follow-up guideline for complete and standardised assessment, newsletters, investigator meetings, monitoring, centralised evaluations, and validation methods). The Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital RWTH Aachen, will offer a brief training on diagnosis and management of delirium (online-based) for

all participating centres. Furthermore, they will offer a central hotline for consultation on delirium diagnosis and management.

Bias

The extent of selection and time trend bias on the primary results will be minimized by application of the ERDO.[36] Performance bias will be minimized by adherence to the standard operating procedures for spinal and general anaesthesia in each centre, which are based on the recommendations of the German Society of Anaesthesiology,[25] and monitoring during the trial. Attrition bias will be minimized by strict follow-up of the patients due to the fact that most documentation will be carried out during patient´s hospital stay. Misclassification bias/ measurement bias will be minimized since we will apply simple measurements, which are used in daily practise or are easy to perform (e.g. WHODAS). It will be aimed to perform postoperative in-hospital outcome assessment in a blinded manner. However, all in-hospital outcomes will be documented with limited subjective influence due to standardized definition. Telephone follow-up for post-discharge outcomes assessment will be carried out blinded. The post-discharge assessors will be obliged not to open the electronic anaesthesia protocols which are filed in the hospital database or any paper-based anaesthesia files. Thus ascertainment bias will be kept to a minimum. Including all eligible patients for the particular centre within the recruitment period in addition to appropriate randomization procedure will minimize selection/ recruitment bias.

Data management

All collected data will be entered in a paper based case report form (CRF), which will be considered as source data. These include automatic print outs as well as paper-based patient records and electronic patients` data.

Investigators will enter the information required by the protocol into an online electronic case report form (eCRF). The CTC-A will develop in cooperation with the Department of Medical Informatics RWTH Aachen the web-based electronic data capture software OpenClinica,[37] which supports the Clinical Data Interchange Standards Consortium (CDISC).[38] The up-loaded data will be collected and preserved on servers of the CTC-A with optimal security and Good Clinical Practice compliance. Detailed information on the eCRF completion will be provided by an eCRF completion manual, an e-learning tool and during the site initiation visits. The access to the eCRF is password controlled. Plausibility checks will be performed according to a data validation plan, with automatically and manually generated queries. The database will be closed, after all data are entered and all queries are solved.

Direct access to source data

The investigator is obliged to allow study specific monitoring, auditing, and inspections with direct access to source data.

Statistical methods

Efficacy analysis: The time to the first occurring event of the binary composite of all-cause mortality or new-onset serious cardiac and pulmonary complications up to 30 days after surgery serves as primary endpoint and will be compared between the two treatment groups at the two sided global significance level of 5% using log rank-test stratified by centre. The primary analysis population will be the full analysis set, preserving the intention to treat principle (ICH E9). The two-sided 95% confidence interval for the hazard ratio will be computed for description of effects. Further in sensitivity analysis the treatment by site interaction will be evaluated by a Gail-Simon-test and the method of Branson and Whitehead[39] will be applied to adjust for treatment-cross-over. In further sensitivity analyses, we will study the effect of mortality alone ignoring serious cardiac and pulmonary complications with mortality as risk, which competes with occurrence of serious cardiac and pulmonary complications in a competing risk model. Ancillary analyses concerning the primary endpoint will be based on Cox-proportional Hazard models including further explanatory variables like age, comorbidities, depression, dementia, anaemia and pre-existing frailty. Moreover, exploratory tests regarding the secondary endpoints will be performed. Details of the statistical models will be given in the trial statistical analysis plan prior to database lock. Safety: All SAEs and predefined adverse events (AEs) will be recorded and handled in a safety database. Unscheduled visits may be performed at any time during the study, whenever necessary to assess or to follow-up on adverse or serious adverse events. Descriptive safety analyses regarding the number of adverse events in each group will be prepared for each Data Safety Monitoring Board (DSMB) meeting, to enable a risk-benefit assessment. The assessment will not result in a formal interim analysis affecting the error rates of the study and thus will not include information about the primary endpoint.

Monitoring

The Principle Investigator of each site has the responsibility for the safety of the study at the respective site. This safety monitoring will include careful assessment and appropriate reporting of AEs as noted below. The Study Director and the Data Safety Monitoring Board

(DSMB) will be responsible for monitoring the data quality and the ongoing safety of subjects in the entire trial.

Data Safety Monitoring Board (DSMB)

A formal DSMB will consist of three anaesthesia (CN, DH, TH), one geriatric (RD), one psychiatrics (MBa) and one statistics expert (MBo), with no competing interests and fully independent from the sponsor and investigators. The DSMB will oversee the data in particular with respect to safety and data integrity.
The DSMB roles, responsibilities, and operating procedures will be described in the iHOPE DSMB Charter. Four DSMB meetings are planned during the recruitment period.

Sponsor Monitoring

The CTC-A will be responsible for quality assurance through regular on-site monitoring, data and query management, reporting of AEs and annual safety reports. Details are presented in Supplementary File 1.

Auditing

Independent audits are possible at any time. This includes the possibility that a member of the CTC-A´s quality assurance function or of the funder, the Federal Ministry for Education and Research (BMBF), may arrange to visit the investigator in order to audit the study documents and performance of the study at the study site.

Harms

Safety assessments will consist of monitoring and recording all AEs and SAEs and the regular monitoring of intraoperative vital data by the attending anaesthetist. AEs in this study are defined according to the ICH-GCP guideline. AEs and SAEs will be recorded after randomization during the visits 2-7 via patient interviews and medical record reviews. After hospital discharge, we will only record SAEs related to the primary endpoint, which have to be confirmed by a hospital or the family physician of the patient. It is not planned to assess other AEs or SAEs via follow-up calls due to the lack of validation capacity. AEs will be followed until the event resolves or stabilises. The Principle Investigator of each centre will have to report all SAEs to the sponsor (CTC-A) within 24 hours of discovery or notification of the event. The sponsor will collect all SAE reports and provide an annual safety report to the Ethics Committees.

Study Termination

The study will be prematurely terminated for an "individual patient" in case of: their own request and withdrawal of consent; if, in the investigator´s opinion, continuation of the trial would be detrimental to the subject´s well-being; hip fracture surgery was not performed; or death before surgery.

The study will be prematurely terminated for a "participating centre" in case of substantial and irreparable deficiencies in data quality, inadequate compliance, subsequent protocol violations or deficient patient recruitment.

As spinal and general anaesthesia are universal standard care procedures for hip fracture surgery, there is no known or expected difference in overall risk or safety for patients between these two approaches, which would induce a prematurely termination of the "whole study". For this reason, we do not propose formal stopping rules based on demonstrated superiority or inferiority of either treatment with regard to the primary or secondary endpoints. However, the Study Director in consultation with the DMSB trial may prematurely close the trial, if an unexpected high numbers of SAEs occur in one of the treatment groups.

ETHICS AND DISSEMINATION

Ethical and Legal Aspects

iHOPE will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, GCP-guidelines, the Declaration of Helsinki, EU Commission Directive 2005/28, §15 of the German Medical Association's professional code of conduct "Berufsordnung für Ärzte, BOÄ", and the applicable data protection law.

Ethics Committee

The study received an ethical approval EK 022/18 from the leading Ethics Committee of the RWTH Aachen University on 14.03.2018. An approval form all other involved local Ethical Committees was subsequently requested. Inclusion of any subject into the study, will only occur after obtaining an ethical approval for the respective site.

Protocol amendments

Any change in the study protocol and/or informed consent form will be approved by the respective Ethics Committees (except for changes in logistics and administration or when necessary to eliminate immediate hazards).

Informed Consent

Written informed consent will be obtained from patients prior to study-participation, after comprehensive written and verbal information by an investigator. Patients will be informed about the study as well as the data protection and have to agree to the direct access to their individual data. The informed consent form has to be signed and personally dated by the patient and one of the Sub-Investigators. A copy will be provided to the patients.

To ensure that the study population is representative of a wider population of patients, and to avoid selection bias, it is important to include patients with lack of the capacity to consent. In these cases (e.g. emergency surgical population or dementia), either the legal representatives will be asked to give verbal and written informed consent, or a study-independent physician. The latter condition applies only to those patients, where a legal representative has not yet been appointed or is not available before surgery. A confirmation of the written consent by the independent physician, will be requested as soon as possible from the recovered patient or the legal representative.

Confidentiality

All subjects will be identified by a unique randomization number. Each Principle Investigator will safely keep a list, which will allow the identification of the pseudonymized patients. The patient's informed consent, with their printed name and signature will be filed separately in the investigators file.

Patients will be informed that their data will be pseudonymized and handed to a third party anonymized. Access to encoded data or source documents will only be given to authorised bodies or persons (sponsor, authorised staff, auditors, competent authorities or ethics commission) for validation of data. Confidentiality of collected data will be warranted, also in case of publications.

Source data will be stored in locked cabinets/ rooms with restricted access at each study site. Safe data storage will also be ensured for 10 years after completion of the trial.

Post-study treatment

No specific post-study arrangements or care will be performed after this study. All subjects will return to their standard medical care after the study, as needed.

A separate patient`s insurance has not been deemed necessary, since there is no specific, study intervention and patients are treated according to clinical standard and in accordance with §15 of the German Medical Association's professional code of conduct "Berufsordnung für Ärzte, BOÄ".

Patient and Public Involvement

HS (Aktionsbündnis Patientensicherheit e.V., Berlin, (German Coalition for Patient Safety)) and MS (Senior Consultant, Section Patient Safety, Medical Advisory Service of Social Health Insurance) support this trial within the Trial Steering Committee. They have reviewed the trial protocol in regard to patient safety aspects and will provide further input during the trial conduction, interpretation and dissemination of the results. Interviews of patients before and after hip fracture surgery in the University Hospital RWTH Aachen were performed before study conception. They aimed to elicit patients´ feedback on the major disadvantages and fears of anaesthesia for hip fracture surgery. The results of the interviews emphasized our commitment to understand patient perspectives on hip fracture outcomes and highlighted the pre-eminence of patient perspectives in the definition and selection of outcomes for iHOPE.

Strategies for disseminating and implementing of iHOPE results will address anticipated barriers at the level of the individual patient, the health care provider, and the health system. iHOPE will focus on educating patients and support patient empowerment via the iHOPE partners network with regard to anaesthesia options for hip fracture care and their demonstrated relative risk and benefits. The Study Director will organize “information days” for patients. Stakeholders will be invited to participate. Such “information days” may e.g. include “meet-the-expert” sessions, open forum discussions and public lectures. iHOPE will liaise to patients, patients´ advocacy groups, patient representative groups, caregivers, stakeholders and insurer, accordingly. Members of the patient partners will disseminate and communicate to other patients and patient groups.

Dissemination

Information about iHOPE will be spread via presentations at national and international scientific meetings, and conferences. Study results will be published in appropriate peer-reviewed international scientific journals with open access and in one or more public clinical study registry(ies). Publishing details will be given in the clinical study agreement.

In addition, iHOPE will use its advantage to disseminate results to trauma and orthopaedic surgery, to psychiatric and aging sciences via an established network and alliances of iHOPE investigators and partners. Furthermore iHOPE will liaise with the German Society of Trauma Surgery projects “German Geriatric Trauma Centre Certification” and the “Geriatric Trauma Registry”.

Also, iHOPE will closely cooperate with the REGAIN trial[23] and will use the dissemination platform of REGAIN to spread the study results not just nationally but also in the USA and Canada and vice versa.

Moreover, MS (Senior Consultant Section Patient Safety, Medical Advisory Service of Social Health Insurance) will strengthen effective dissemination and implementation of iHOPE results at the level of health policy and insurance providers. This will enable to mitigate or eliminate unintended disincentives for provision of high-quality care that may emerge from present healthcare reimbursement models, potentially including efforts to promote use of effective anaesthesia care.

DISCUSSION

At present, insufficient evidence exists to characterize the comparative effectiveness of spinal versus general anaesthesia for hip fracture surgery among elderly patients. Therefore, identification of the best anaesthesia technique with improvement of patient-centred outcomes after hip fractures is of greatest importance.

iHOPE employs treatment protocols which reflect “real world” approaches to general and spinal anaesthesia. The administration of anaesthesia will be carried out in the course of routine care by staff anaesthesiologists, who do not necessarily need to be part of the iHOPE study team. iHOPE does not require specialised techniques, drugs, or monitoring beyond those available and commonly used in standard care settings. This, and the multicentre character of iHOPE, with totally 1032 randomized patients, will enable us to generate more generalizable results, which are applicable for a large number of individuals with hip fractures.

Despite the parallel conduction of the REGAIN[23] study, iHOPE is justified as it focuses on a different primary endpoint. The primary endpoint in the REGAIN study is the independence of walking 60 days after hip-fracture surgery. Furthermore, REGAIN is conducted in Canada and the USA, while iHOPE is conducted in Germany. In spite of the different primary endpoint, most outcome variables in the REGAIN[23] and iHOPE study have been harmonized. This will enable us to carry out an individualized patient data (IPD) meta-analysis, which is considered as the “gold standard” of systematic reviews.[40] This creates a unique possibility to combine the original data from iHOPE and REGAIN after publication, which will improve guideline development to enhance outcome after hip fracture surgery. The similarity of other key aspects of study design, including eligibility criteria, treatment protocols and follow-up of 365 days in these two studies will further facilitate additional joint analyses.

Due to feasibility of the study one limitation is that data collection for several in-hospital adverse events will be performed via medical record review. This implies that not recorded events may not be detected.

REFERENCES

1. [Anteile der Altersgruppen unter 20, ab 65 und ab 80 Jahre in Deutschland, 1871 bis 2060 (Stand: 2015)]. Available from: http://www.bib-demografie.de/DE/ZahlenundFakten/02/Abbildungen/a_02_12_ag_20_65_80_d_1871_2060.html?nn=3074114. Accessed March 2018.

2. Medin E, Goude F, Melberg HO, et al. European Regional Differences in All-Cause Mortality and Length of Stay for Patients with Hip Fracture. *Health Econ* 2015; 24

3. The National Hip Fracture Database. The National Hip Fracture Database. Available from: http://www.europe.eu. Accessed February 2018

4. Holt G, Smith R, Duncan K, et al. Changes in population demographics and the future incidence of hip fracture. *Injury* 2009; 40:722-26.

5. Coburn M, Röhl AB, Knobe M, et al. [Anesthesiological management of elderly trauma patients]. *Anaesthesist* 2016; 65:98-106.

6. European State Population Numbers. Available from: http//www.europe.eu. Accessed September 2017

7. Hüftgelenknahe Femurfraktur mit osteosynthetischer Versorgung. Hüftgelenknahe Femurfraktur mit osteosynthetischer Versorgung. Available from https://www.iqtig.org/downloads/ergebnisse/qidb/2016/2017-04-26/QIDB_2016_INDIREKT_PDF/QIDB_2016_indirekte_Verfahren/QIDB_Referenzbereiche/QSKH_17n1-HUEFT-FRAK_2016_QIDB-DV_V01_2017-04-06.pdf

8. Carow J, Carow JB, Coburn M, et al. Mortality and cardiorespiratory complications in trochanteric femoral fractures: a ten year retrospective analysis. *Int Orthop* 2017; 41:2371–80

9. Boddaert J, Raux M, Khiami F, et al. Perioperative management of elderly patients with hip fracture. *Anesthesiology* 2014; 121:1336-341.

10. Brauer CA, Coca-Perraillon M, Cutler DM, et al. Incidence and mortality of hip fractures in the United States. *JAMA* 2009; 302:1573-79.

11. Coburn M, Sanders R, Neuman M, et al. We may have improved but we must get better still: The never-ending story of the elderly with fractured neck of femur. *Eur J Anaesthesiol* 2017; 34:115-17.

12. Coburn M, Fahlenkamp A, Zoremba N, et al. Postoperative cognitive dysfunction: Incidence and prophylaxis. *Anaesthesist* 2010; 59:177-84.

13. Huang Y-F, Liang J, and Shyu Y-IL. Number of Comorbidities Negatively Influence Psychological Outcomes of the Elderly Following Hip Fracture in Taiwan. *J Aging Health* 2016; 28:1343-361.

14. Härter M, Schorr S, Schneider F, et al.. Unipolare Depression : S3-Leitlinie/Nationale VersorgungsLeitlinie. Available from: http://www.leitlinien.de/mdb/downloads/nvl/depression/depression-2aufl-vers1-kurz.pdf. Accessed January 2018

15. Böhner H, Hummel TC, Habel U, et al. Predicting delirium after vascular surgery: a model based on pre- and intraoperative data. *Ann Surg* 2003; 238:149-156.

16. Böhner H, and Schneider F. *N Engl J Med.* 2006; 354: 2510

17. Drews T, Franck M, Radtke FM, et al. Postoperative delirium is an independent risk factor for posttraumatic stress disorder in the elderly patient: a prospective observational study. *Eur J Anaesthesiol* 2015; 32:147-151.

18. Sanders RD, Pandharipande PP, Davidson AJ, et al. Anticipating and managing postoperative delirium and cognitive decline in adults. *BMJ* 2011; 343:d4331.

19. White SM, Moppett IK, and Griffiths R. Outcome by mode of anaesthesia for hip fracture surgery. An observational audit of 65 535 patients in a national dataset. *Anaesthesia* 2014; 69:224-230.

20. Guay J, Parker MJ, Gajendragadkar PR, et al. Anaesthesia for hip fracture surgery in adults. *Cochrane Database Syst Rev* 2016; 2:CD000521.

21. Neuman MD, Rosenbaum PR, Ludwig JM, et al. Anesthesia technique, mortality, and length of stay after hip fracture surgery. *JAMA* 2014; 311:2508-517.

22. Van Waesberghe J, Stevanovic A, Rossaint R, et al. General vs. neuraxial anaesthesia in hip fracture patients: a systematic review and meta-analysis. *BMC Anesthesiol* 2017; 17:87.

23. Neuman MD, Ellenberg SS, Sieber FE, et al. Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN): protocol for a pragmatic, international multicentre trial. *BMJ Open* 2016; 6:e013473.

24. Loudon K, Treweek S, Sullivan F, et al. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ* 2015; 350:h2147.

25. Waurick K, Riess H, Van Aken H et al. S1-Leitlinie Rückenmarksnahe Regionalanästhesien und Thrombembolieprophylaxe/ antithrombotische Medikation. *Anästh Intensivmed* 2014; 55:464-92.

26. ACS NSQIP. Available from: https://www.facs.org/quality-programs/acs-nsqip. Accessed February 2018

27. Coburn M, Sanders RD, Maze M, et al. The hip fracture surgery in elderly patients (HIPELD) study to evaluate xenon anaesthesia for the prevention of postoperative delirium: a multicentre, randomized clinical trial. *Br J Anaesth* 2018; 120:127-137.

28. Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. *Ann Intern Med* 2014; 161:554-561.

29. Cleeland CS, and Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994; 23:129-138.

30. Nagel B, Gerbershagen HU, Lindena G, et al. Development and evaluation of the multidimensional German pain questionnaire. *Schmerz* 2002; 16:263-270.

31. Bauer M, Böhrer H, Aichele G, et al. Measuring patient satisfaction with anaesthesia: perioperative questionnaire versus standardised face-to-face interview. *Acta Anaesthesiol Scand* 2001; 45:65-72.

32. Kawas C, Karagiozis H, Resau L, et al. Reliability of the Blessed Telephone Information-Memory-Concentration Test. *J Geriatr Psychiatry Neurol* 1995; 8:238-242.

33. Ustün TB, Chatterji S, Kostanjsek N, et al. Developing the World Health Organization Disability Assessment Schedule 2.0. *Bull World Health Organ* 2010; 88:815-823.

34. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982; 17:37-49.

35. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56:M146-156.

36. Hilgers RD, Uschner D, Rosenberger WF, et al. ERDO - a framework to select an appropriate randomization procedure for clinical trials. *BMC Med Res Methodol* 2017; 17:159.

37. OpenClinca, available from http://openclinica.com. Accessed February 2018

38. CDISC, available from http://www.cdisc.org. Accessed February 2018

39. Branson M, and Whitehead J. Estimating a treatment effect in survival studies in which patients switch treatment. *Stat Med* 2002; 21:2449-463.

40. IPD MA chochrane. Available from: http://www.methods.cochrane.org/ipdma. Accessed February 2018

41. Haywood KL, Griffin XL, Achten J, Costa ML. Developing a core outcome set for hip fracture trials. *Bone Joint J* 2014 ;96:1016-23.

42. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol* 1990; 10:244-251.

Author Contributions

MC is the iHOPE Study Director and Coordinating Principal Investigator. He conceived the overall study and received the iHOPE grant (01KG1714 from the Federal Ministry for Education and Research (BMBF), Bonn, Germany). The iHOPE Clinical Project Management is allocated to AK. AK wrote the first draft of this manuscript and made substantial contributions to the conception of the study protocol together with MC. The iHOPE Trial Management (MC, RR, SI, AH, MDN), the Trial Statistician (RDH), the Data Monitoring and Safety Board (NC, TH, DH, MBa, MBo, RD), the investigators of the participating iHOPE centres (CA, JA, MD, PK, PKn, PKr, RL, CO, CR, RS, CS, OV, FW, MW, KZ, AZ) and other participating bodies (FH, HS, MS, DCW, MK, FS, CB, RDS) each made substantial contributions to the conception or design of the study protocol. All authors revised the protocol critically for important intellectual content, approved the final version and agree to be accountable for all aspects of the work. The iHOPE study group is listed as Collaborators. The Collaborators are substantially involved in carrying out the iHOPE study as Investigators of the recruiting centres, in the Project and Data Management and Monitoring. All Collaborators critically reviewed the study protocol and the manuscript.

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Competing interests

MC received a grant for this trial from the Federal Ministry for Education and Research (BMBF), Bonn, Germany. MDN is currently funded by the US Patient-Centered Outcomes Research Institute for related work (grant PCS 1406-18876) and he is the Principal Investigator of the REGAIN Trial (Clinicaltrials.gov number NCT02507505). AK, CA, JA, MBa, CB, MBo, RD, MD, TH, DH, FH, RDH, AH, SI, PK, MK, PKn, PKr, RL, CN, CO, CR, RR, RDS, RS, FS, HS, MS, CS, OV, FW, DCW, MW, KZ, AZ declare no competing interests.

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Ethical Approval

Ethical approval EK 022/18 was obtained from the leading Ethics Committee of the RWTH Aachen University on 14.03.2018 An approval form all other involved local Ethical Committees was subsequently requested.

Supplementary File 1

EXTENDED METHODS

Intervention

Provider instructions spinal anaesthesia

Spinal anaesthesia should be performed as a single-shot block. Supporting adapted sedation is permitted for block placement and intraoperative comfort of the patient. The level of sedation should be assessed by the Observer´s Assessment of Alertness/ Sedation Scale (OAAS) (Table 2), a simple, validated measure of alertness among sedated subjects[42]. The intraoperative alertness/ sedation depth should correspond to OAAS ≥2. Documentation of OAAS should be performed every 30 minutes or at least once during surgery, irrespective of the use of active sedation. If clinically required, conversion to general anaesthesia is permitted. All remaining aspects of anaesthesia care, e.g. monitoring, drugs and dosage, postoperative pain management, supplemental nerve blocks, and management of intraoperative events should be handled as per usual routine. Optional assessment: If a bispectral index (BIS)-monitoring is available and used at the institution.

Supplementary File Table 1: Observer's Assessment of Alertness/Sedation[42]

Score	Subject responsiveness	Sedation level
5	Responds readily to name spoken in normal tone	Alert
4	Lethargic response to name spoken in normal tone	Light sedation
3	Responds only after name is called loudly and/or repeatedly	Moderate sedation
2	Responds only after mild prodding or shaking	Moderate sedation
1	Does not respond to mild prodding or shaking	Deep sedation

Provider instructions general anaesthesia

Maintenance of general anaesthesia with an inhaled anaesthetic or continuous intravenous application of propofol: Intravenous opioids should be applied as needed for intraoperative analgesia. Airway management should be performed as usual in

the respective centre (e.g. via endotracheal tube, laryngeal mask airway, or other device). All remaining aspects of anaesthesia care, e.g. monitoring, drugs and dosage, postoperative pain management, supplemental nerve blocks, and management of intraoperative events should be handled as per usual routine. Optional assessment: If a BIS-monitoring is available and used at the institution.

Data collection

Visit 0 (Screening visit), pre-randomization phase

The investigator/ study staff will screen all potentially eligible patients between the time of presentation and surgery. This will be followed by a screening visit, to check if the patient meets inclusion criteria in the absence of exclusion criteria. Investigators will obtain written informed consent from eligible patients or their legal representatives, after study-specific patient information.

Visit 1 (Preoperative evaluation visit), pre-randomization phase

The pre-evaluation visit will also be conducted between the time of presentation and surgery via patient or proxy interview. It will comprise the assessment of the patient demographics, medical history, the most recent preoperative routine laboratory values, vital data, clinical data, residential and educational status and the overall health and disability assessment belonging to the study-specific baseline testing. Further study-specific baseline testing (cognition, delirium, pain, and depression) and frailty assessment will be performed directly via patient interview, independent of the cognitive status of the patient. Additionally, we will document the contact data of the patients and the proxy, as well as the "do not resuscitate" status of the patient.

Baseline data to be collected:

- Patient demographics (age, sex, race, weight, height, body mass index (BMI), American Society of Anaesthesiologists (ASA) physical status)
- Educational and residential status; patient and proxy contact information; do not resuscitate status
- Pre-existing diseases and medical history, including medication and risk factors (smoking status, alcohol status)

- Supplemental oxygen or mechanical ventilation, baseline vital data including blood pressure, heart rate and oxygen saturation.
- Ability of walking 3 m across the room prior to hip fracture
- Type of hip fracture and planned kind of surgery
- Most recent preoperative routine laboratory values, if done in the clinical routine: haemoglobin, haematocrit, MCV, white blood cells, serum creatinine, urea, albumin, protein (total), calcium (total), potassium, sodium, AST, alkaline phosphatase, TSH, platelets, INR and PTT

Study-specific testing: baseline assessment prior to surgery:

Cognition will be assessed by the validated Short blessed test (SBT), which enables a brief screen of cognition via in-person and telephone interview (5-10 minutes).[32]

Delirium will be assessed via in-person interview by the validated, high sensitive and specific assessment tool 3D-Confusion Assessment Method (3D-CAM) (3-5 minutes).[28]

The overall health and disability will be assessed via the 12-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0), which can be administered in person as well as via telephone interview in 5-10 minutes. The WHODAS 2.0 is a patient-reported outcome assessment tool, which comprises: cognition, mobility, self-care, interpersonal relationships, work and household roles, and participation in society.[33]

Depression will be assessed via the short version of the Geriatric Depression Scale (GDS) (5 min.).[34]

Frailty assessment will be performed according to phenotype-model of Fried at baseline via in-person interview.[35] Four of originally five Fried-criteria will be assessed: fatigue, maximal grip strength assessment of the dominant hand, physical activity (employing the Minnesota Leisure Time Activities Questionnaire) (5-10 min.) and weight loss in the past year. Gait velocity as the fifth Fried criterion will be omitted in this study for obvious reasons. We will also obtain laboratory results.

Pain will be assessed via numeric rating scale (NRS 0-10) and questions derived from the Brief Pain Inventory.[29] We will assess the average and worst pain within the past 2 weeks before hip-fracture and the actual pain level.

Visit 2 (Hip-fracture surgery), intervention phase

The investigator will randomize the patient, after a short re-evaluation of patient eligibility and the eligibility of the attending routine team in the operating room. The patient will not be randomized, if the attending anaesthesia and surgery team is unwilling or ineligible (as judged by the principle investigator) to treat study patients. The attending anaesthesia team will be informed by study staff about the assigned study group after randomization. The routine attending anaesthesia team (does not necessarily have to belong to the study team) will perform the study treatment during the clinical routine in accordance with the pragmatic study protocol. Sedation/ alertness level for patients in the spinal anaesthesia group will be documented according to the OAAS. BIS values will optionally be documented, if used in the clinical routine during both procedures. Other routine surgical- and anaesthesia-related data (e.g. monitoring-devices, patient vital data, used drugs, times, adverse events (AEs), discharge destination after surgery etc.) will be collected via medical record review.

Data to be collected:

- Observer's assessment of alertness scale (OAAS) (alertness/ sedation level), optional BIS-monitoring, other monitoring, clinical management
- Medical record review including but not limited to date of surgery, time to surgery, procedure type/ implant, anaesthesia and surgery time, use of a safe-surgery checklist, blood loss, transfusion, infusion, blood pressure, oxygen saturation, initial anaesthesia type, intrathecal agents administered, peripheral nerve blocks, benzodiazepines, iv. opioids, anaphylaxis, aspiration, orthogeriatric care available
- Adverse Events (AEs) and serious adverse events (SAEs) according to the patient interview and medical charts

Visit 3-5 (Postoperative day 1-3), in-hospital patient-centred outcome phase

Daily assessment of delirium, pain and mortality via patient visit and interview on ward, if the patient is still in hospital. Documentation of AEs will occur via additional medical record review. Blinding will be encouraged during the first 4 postoperative visits, but it is not mandatory. A second investigator will perform these visits in a

blinded manner as far as possible in the clinical routine. It will be documented for each visit, if blinding was preserved.

Study-specific in-person assessment on the 1st-3rd postoperative day, if the patient is still in hospital:

- Delirium (3D-CAM) assessment (3-5 min)
- Postoperative mortality assessment (2-5 min)
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 24 hours, quality of pain (5 min.) derived from the German pain questionnaire.[30]
- AEs and SAEs according to the patient interview and medical charts

Visit 6 (Postoperative day 4), in-hospital patient-centred outcome phase

Delirium, pain, mortality, and patient satisfaction will be assessed via patient visit and interview on ward, if the patient is still in hospital. If the patient is discharged before postoperative day 4, patient satisfaction will be assessed in addition to the respective visit 3-5. Documentation of AEs will occur via additional medical record review.

Blinding will be encouraged during the first 4 postoperative visits, but it is not mandatory. A second investigator will perform visit 6 in a blinded manner as far as possible in the clinical routine. It will be documented for this visit, if blinding was preserved.

Study-specific in-person assessment on the 4th postoperative day or at discharge (whatever occurs first), if the patient is still in hospital

- Delirium (3D-CAM) assessment (3-5 min)
- Postoperative mortality assessment (2-5 min)
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 24 hours. Pain quality (5 min.)
- Bauer Patient Satisfaction Questionnaire (3 min.)
- AEs and SAEs according to the patient interview and medical charts

Visit 7 (Hospital discharge day), in-hospital patient-centred outcome phase

All cause mortality, new-onset complications according to the NSQIP[26], other AEs, admission to Intensive Care Unit (ICU), length of stay in hospital and ICU, discharge destination, independence in walking, pain assessment, and medical pain management until postoperative day 4 will be assessed via medical record review and patient visit and interview on ward. This visit will be performed in addition to visit 3-6, if the hospital discharge occurs within the first 4 postoperative days. Blinding for Visit 7 will not be required.

Study-specific in-person and medical record assessment on the hospital discharge day

- In-hospital mortality (2-5 min); new-onset complications (bleeding requiring transfusion, myocardial infarction, congestive heart failure, stroke or transient ischemic attack, pneumonia, urinary tract infection, wound infection, systematic sepsis, thromboembolic complications, unplanned intubation, ventilator > 48 hours, acute renal failure, cardiac arrest requiring CPR or defibrillation, epidural haematoma requiring surgery, new paralysis of lower extremities, return to operating room, inpatient falls, unplanned postoperative mechanical ventilation, additional surgeries) (30-60 min)
- Assessment of admission to critical care, length of intensive care and hospital stay, discharge destination (5-10 min); Independence in walking (5 min)
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 24 hours, quality of pain (5 min.)
- Medical pain management until postoperative day 4
- AEs and SAEs according to the patient interview and medical charts

Visit 8 (Postoperative day 30 ± 3), post-discharge patient-centred primary outcome phase

Will be performed in a blinded manner via medical record review and telephone interview of the patient or rather the proxy. In case of serious cardiac or pulmonary complications, the family physician and / or the respective hospital will be contacted in addition. Assessment of all-cause mortality or new-onset (i.e. not pre-existing at time of surgery) serious cardiac and pulmonary complications as defined by the NSQIP[26]. Furthermore, assessment of the secondary outcomes: Recovery of walking, pain intensity and quality, residential status, cognition, overall health and disability assessment and pain.

Study-specific follow-up on the 30 ± 3th postoperative day (via telephone interview)

- All-cause mortality and new-onset serious cardiac and pulmonary complications (see 7.1) (10-15 min)
- Recovery of walking, residential status (5 min)
- WHODAS 2.0 (overall health and disability) (5-10 min)
- Short Blessed Test (cognition) (5-10min),
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 2 weeks, quality of pain, intake of pain medication (5 min.)

Visit 9 (Postoperative day 180 ± 45), post-discharge patient-centred long-term outcome phase

Assessment of mortality, recovery of walking, residential status, cognition, overall health and disability assessment and pain intensity and quality via telephone interview of the patient or rather the proxy in a blinded manner.

Study-specific follow-up on the 180 ± 45th postoperative day (via telephone interview)

- All cause mortality assessment (2-5 min)
- Recovery of walking, residential status (5min)
- WHODAS 2.0 (overall health and disability) (5-10 min)
- Short Blessed Test (cognition) (5-10 min)
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 2 weeks, quality of pain, intake of pain medication (5 min.)

Visit 10 (Postoperative day 365 ± 60), post-discharge patient-centred long-term outcome phase

Assessment of mortality, recovery of walking, residential status, cognition, overall health and disability assessment and pain intensity and quality via telephone interview of the patient or rather the proxy in a blinded manner.

Study-specific follow-up on the 365 ± 60th postoperative day (via telephone interview)

- All cause mortality assessment (2-5 min)
- Recovery of walking, residential status (5min)
- WHODAS 2.0 (overall health and disability) (5-10 min)

- Short Blessed Test (cognition) (5-10 min)
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 2 weeks, quality of pain, intake of pain medication (5 min.)

Dropout-handling

Patients who withdraw their consent after randomization or who cannot be contacted for follow-up assessments will be handled as dropouts. Patients who withdraw consent before randomization will be considered as screening failures. All randomized patients (also with protocol deviations) will be followed up as long as possible according the intention-to-treat concept. Particularly, patients, who receive a treatment change (protocol deviation) have also to be followed up and will not be considered as dropouts, but the reason has to be documented clearly.

Sponsor monitoring

The CTC-A will be responsible for quality assurance through regular on-site monitoring, data and query management, reporting of AEs and annual safety reports. The CTC-A maintains a Quality Management System (QMS) for Clinical Trials and regularly implements Quality Assurance and Quality Control measures alongside the development and design as well as performance and reporting of clinical trials. The quality management system of the CTC-A complies with all relevant guidelines and also comprises a data protection system according to the Act to Strengthen the Security of Federal Information Technology. The quality management system consists of the quality management handbook and the quality assurance handbook, comprising standard operating procedures (SOPs), working instructions, forms, templates and checklists for all relevant tasks in accordance with the Helsinki Declaration, International Conference on Harmonisation Guideline for Good Clinical Practice (ICH-GCP), German Medical and Medical Device Act.

Monitoring procedures include four visits per site designed to clarify all prerequisites before the study commences (including initiation visit and close-out visit). Interim monitoring visits will take place on a regular basis according to a mutually agreed schedule. During these visits, the monitor will check for 100% subject eligibility (informed consent form; in- and exclusion criteria). Risk-based monitoring will be used for completion of the entries on the eCRF/CRF and the integrity of the source

data with the eCRF/CRF entries. Furthermore the monitor will check the compliance with the clinical study protocol, ICH-GCP principles and the Declaration of Helsinki. Additionally, the monitor will check if all AEs and SAEs have been reported appropriately within the time periods required. The investigator and all staff will be expected to cooperate with the monitor by providing any missing information whenever possible. Further details of monitoring activities will be set forth in the monitoring manual.

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

Section/item	ItemNo	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	30
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	28
	5b	Name and contact information for the trial sponsor	16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17, 19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18, 19, Suppl. File 1

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6,7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11, 12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12, 13, Suppl. File 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12, Suppl. File 1, Table 1
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	17
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	17, Table 1 , Suppl. File 1

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13, 14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Supplementary Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16, Suppl. File 1
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16, Suppl. File 1

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	not necessary, somebody is always unblinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16, Supplementary File 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16, 17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17, 18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Suppl. File 1

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19,20
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18, 21
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19, 20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20, 21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	30
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	21
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21, 22
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not provided, only on request to the corresponding author
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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

Supplementary Table 2

Schedule of enrolment, interventions, and assessments according to the SPIRIT Statement

			Main STUDY PERIOD								
	Screening	Enrolment	Allocation	Post-allocation				Discharge	Follow-up		
TIMEPOINT/Visit**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
ENROLMENT:											
Eligibility screen	X		X§								
Informed consent	X										
Randomization			X								
INTERVENTIONS:											
Spinal anaesthesia				X							
General anaesthesia				X							
ASSESSMENTS:											
Screening for inclusion criteria:											
1. ≥ 65 years with intra/-extracapsular hip fracture (femoral neck fracture, subtrochanteric or intertrochanteric fracture) requiring surgical intervention	X		X								

Written informed consent												
Screening for exclusion criteria: *1. Institutionalisation by court or administrate order* *2. Concurrent surgery, which is not amenable to spinal anaesthesia* *3. Absolute contraindications to spinal anaesthesia* *4. Periprosthetic fracture* *5. Prior participation in the iHOPE study* *6. Exclusion as considered by any involved physician/ investigator regarding the patient or attending team*	X		X									
Patient demographics *(age, sex, race, weight, height, BMI, smoking status, alcohol status, ASA physical status*		X										
Residential status		X								X	X	X
Educational status		X										
Personnel data *(Contact information, do not resuscitate status)*		X										
Frailty assessment (*Short Minnesota Leisure Time Activities Questionnaire, weight loss, fatigue, grip strength)*		X										
Medical history		X										
Preoperative medication		X										
Most recent laboratory values from		X										

the clinical routine												
Most recent clinical data *(BP, HR, SpO_2, mechanical ventilation, oxygen requirement)*		X										
Ability/Recovery of walking		X							X	X	X	X
Type of hip fracture and planned kind of surgery		X										
Surgery- and anaesthesia related data acquisition				X								
Primary outcome variables												
• *All cause mortality*										X		
• *Serious cardiac and pulmonary complications*										X		
Assessment of secondary outcome variables												
• *Pain*		X			X	X	X	X	X	X	X	X
• *Medical pain management*									X			
• *Cognition (Short blessed test)*		X								X	X	X
• *Delirium (3D-Confusion Assessment Method)*		X			X	X	X	X				
• *Overall health and disability (WHODAS 2.0)*		X								X	X	X
• *Depression (Geriatric Depression Scale)*		X										

• *Bauer Patient Satisfaction Questionnaire*								X				
• *In-hospital events (Hospital and ICU-length of stay, outcomes according to the NSQIP, discharge destination)*									X			
• *Residential status*										X	X	X
• *All cause mortality*					X	X	X	X	X		X	X
• *Safety assessment (Intraoperative cardiac arrest; malignant hyperthermia; intraoperative anaphylaxis; intraoperative aspiration; total spinal anaesthesia; epidural hematoma; paralysis of the lower extremities lasting greater than 24 hours following spinal anaesthesia; fall within 12 hours of anaesthesia care)*				X	X				X			
• *Other adverse events*				X	X	X	X	X	X			

ASA, American Society of Anesthesiologists physical status; BMI, body mass index; BP, blood pressure; HR, heart rate; ICU, Intensive Care Unit; LOS, length of stay; NSQIP, National Surgical Quality Improvement Program; SpO2, peripheral oxygen saturation

§ Short re-evaluation of the eligibility before randomization

Specific time-points: ***Visit 0: Screening visit, conducted between the time of presentation and surgery via patient or proxy interview; **Visit 1: Preoperative evaluation visit**, conducted between the time of presentation and surgery via patient or proxy interview; **Visit 2: Hip-fracture surgery day**, conducted in the operating room; **Visit 3-6: In-hospital patient-centred outcome phase,** conducted on postoperative day 1-4; **Visit 7: Hospital discharge day.** Patient visit on ward and medical record review. This visit will be performed in addition to visit 3-6, if the hospital discharge occurs within the first 4 postoperative days; **Visit 8:** Postoperative day 30 ± 3. Medical record review and telephone interview of the patient or rather the proxy; **Visit 9**: Postoperative day 180 ± 45. Telephone interview of the patient or rather the proxy; **Visit 10:** Postoperative day 365 ± 60. Telephone interview of the patient or rather the proxy.*

BMJ Open

Improve hip fracture outcome in the elderly patient (iHOPE): a study protocol for a pragmatic, multicentre randomized controlled trial to test the efficacy of spinal versus general anaesthesia

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Geriatric medicine
Keywords:	ANAESTHETICS, GERIATRIC MEDICINE, Anaesthesia in orthopaedics < ANAESTHETICS

Improve hip fracture outcome in the elderly patient (iHOPE): a study protocol for a pragmatic, multicentre randomized controlled trial to test the efficacy of spinal versus general anaesthesia

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ABSTRACT

Introduction:

Hip fracture surgery is associated with high in-hospital and 30-day mortality rates and serious adverse patient outcomes. Evidence from randomized controlled trials regarding effectiveness of spinal versus general anaesthesia on patient-centred outcomes after hip fracture surgery is sparse.

Methods and analysis:

The iHOPE study is a pragmatic national, multicentre, randomized controlled, open label clinical trial with a two-arm parallel group design. In total 1032 hip fracture patients (>65 years) will be randomized in an intended 1:1 allocation ratio to receive spinal anaesthesia (n=516) or general anaesthesia (n=516). Outcome assessment will occur in a blinded manner after hospital discharge and in-hospital. The primary endpoint will be assessed by telephone interview and comprises the time to the first occurring event of the binary composite outcome of all-cause mortality or new-onset serious cardiac and pulmonary complications within 30 postoperative days. In-hospital secondary endpoints, assessed via in-person interviews and medical record review, include mortality, perioperative adverse events, delirium, satisfaction, walking independently, length of hospital stay and discharge destination. Telephone interviews will be performed for long-term endpoints (all cause-mortality, independence in walking, chronic pain, ability to return home cognitive function and overall health and disability) at postoperative day 30±3, 180±45 and 365±60.

Ethics and dissemination:

iHOPE has been approved by the leading Ethics Committee of the Medical Faculty of the RWTH Aachen University on 14.03.2018 (EK 022/18). Approval from all other involved local Ethical Committees was subsequently requested and obtained. Study started in April 2018 with a total recruitment period of 24 months. iHOPE will be disseminated via presentations at national and international scientific meetings or conferences and publication in peer-reviewed international scientific journals.

Trial registration number: German Clinical Trials Register DRKS00013644

ARTICLE SUMMARY

Strengths and limitations of this study

- iHOPE will confirm the effectiveness of standard care spinal and standard care general anaesthesia for hip fracture.
- Anaesthesia treatment will be performed according to the clinical routine (pragmatic approach) after randomization, which will enable more generalizable results for the iHOPE trial.
- iHOPE will apply a core outcome set[41] and liaises with REGAIN trial,[23] which focuses on a different primary endpoint.
- We plan to combine data from iHOPE and the REGAIN trial[23] after publication in an individualized patient data (IPD) meta-analysis under a separate protocol in order to aid future guideline development.

INTRODUCTION

In Germany, the elderly population (>65 years) will increase from 27% of the total population in 2015 to 39% in 2040.[1] The recently published EuroHOPE patient database oversees 59,605 hip fracture patients across seven European countries. The prevalence of hip fractures among patients older than 50 years ranged from 307/100,000 in Finland to 1,269/100,000 in Italy in the year 2007. The 30-day and one-year mortality rate peaked with 11.7 and 34.8% in Hungary and was lowest in Italy with 4.0 and 19.7% respectively.[2] The 2016 annual number of hip fractures in the UK was reported to be 65,645[3] and is projected to rise to 101,000 by 2020.[4] European data,[4-6] extrapolated to Germany' s population, show that the 2013 incidence of hip fracture was 126 per 100,000 residents per year. The "Institut für Qualitätssicherung und Transparenz im Gesundheitswesen" (IQTIG) published recently its "2017 Hip Fracture" report covering 60,178 medical records of hip fracture patients who received surgical intervention from 1,215 German hospitals. The IQTIG report presented an in-hospital mortality rate of 4.8%.[7] A retrospective analysis of a level I trauma centre in Germany revealed an in-hospital mortality rate of even 8.2%. Postoperative cardiac and respiratory complications were observed in 21.5% of the patients, with an in-hospital mortality rate of 28.7% in this group.[8] In total, the one-month mortality rate after hip fracture ranges from 4 to 12% and reaches up to 35% after one year in Europe and the USA.[2, 7, 9, 10] The aforementioned is associated with approximately 33,500 deaths in Germany, annually.[5] The vast majority of hip fracture patients (95%) arrive at hospital with at least one major comorbidity,[11] including hepatic and renal function, diabetes mellitus, dementia, delirium, coronary artery disease, heart failure and patient poly-pharmacy. These are all individually linked to an increase in postoperative complications and mortality. According to the IQTIG analysis, 63% of patients with hip fracture were presented in hospital with severe comorbidities (ASA III) and 8% with life threatening comorbidities (ASA IV).[7] Reports from the UK show higher numbers of ASA IV patients (12-14%).[12, 13] It is not surprising that patients with multiple comorbidities are at highest risk of death.[11] Additional risk factors such as residential status, functional and cognitive impairment prior to fracture, male gender, poor nutrition status and anaemia have been identified and are associated with increased mortality.[5] Serious cardiac and pulmonary complications (pneumonia, pulmonary embolism, cardiac arrest and myocardial infarction) appear most frequent.[7] Furthermore, the number of comorbidities negatively influences the psychological outcomes of elderly patients with hip fracture.[14, 15] On average, hip fracture patients in Germany spend 13 days in hospital (median 11 days).[7] There is an enormous humanitarian and socioeconomic need to improve quality and effectiveness of care for hip fracture patients.

So far, no specific anaesthesia management has been recommended for hip fracture surgery.[16] The commonly most applied anaesthesia techniques for hip fracture surgery represent spinal and general anaesthesia.[17] Several studies have reviewed the evidence for these two techniques and showed partially contradictory results with limited quality. One Cochrane review found no difference in 30-day mortality or in several serious adverse events e.g. pneumonia, myocardial infarction, and cerebrovascular events.[18] A secondary analysis of prospectively collected observational data confirmed the result for the 30-days mortality.[19] Another analysis showed a shorter length of hospital stay after regional anaesthesia and was in line regarding the 30-day mortality.[20] A large retrospective cohort study analysed the in-hospital mortality rate and found no difference among the groups.[21] This was contrary to our previously conducted meta-analysis, which included overall 413,245 patients and found a significantly lower rate of in-hospital mortality in the regional anaesthesia group, but likewise no difference with regard to the 30-day mortality.[22] The length of hospital stay was significantly shorter and interestingly the incidence of myocardial infarction was significantly lower in the regional anaesthesia group. A recently published meta-analysis, could not confirm the lower incidence of myocardial infarction.[23] Of note, the evidence in these reviews was influenced by observational studies and highly heterogeneous data.

At present insufficient evidence exists to characterize the comparative effectiveness of spinal versus general anaesthesia for hip fracture surgery among older patients. In this respect it is important to note that a large randomized controlled study of 1600 patients with >50 years of age, undergoing hip fracture surgery with general or spinal anaesthesia was launched in February 2016 in the USA and Canada.[24] The primary aim of the REGAIN study is to analyse the recovery of walking at 60 days after randomization and further patient-centred outcomes up to 1 year.

Objectives

iHOPE will compare the efficacy of two different standard anaesthesia care approaches (spinal versus general anaesthesia) for hip fracture surgery on a binary composite outcome of all-cause mortality or new-onset serious cardiac and pulmonary complications within 30 postoperative days. The primary hypothesis is that spinal anaesthesia is superior to general anaesthesia with respect to the composite outcome.

Several secondary objectives will be studied during iHOPE.

METHODS AND ANALYSES

Trial design

iHOPE is designed as a pragmatic, multicentre, randomized controlled, open label clinical trial with a two arm parallel group design allocating patients in an intended 1:1 allocation ratio to test the two sided hypothesis of whether one of the anaesthesia regimes is superior to the other one, with respect to the primary composite endpoint. iHOPE was composed as a pragmatic rather than an explanatory trial to yield results that are generalizable for routine clinical practice. The PRECIS-2 tool[25] was used to determine the extent of our design as a pragmatic trial (Table 1)

Table 1. Score 1: very explanatory; Score 2: rather explanatory; Score 3: equally pragmatic/explanatory; Score 4: rather pragmatic; Score 5: very pragmatic

Domain	Score	Rationale
1. Eligibility Criteria	5	iHOPE will include a broad spectrum of elderly patients identical to the patients in the usual care. Legally not competent patients (due to e.g. dementia) will also be included in this trial.
2. Recruitment	5	iHOPE will recruit the patients during the clinical routine in the hospitals.
3. Setting	5	Identical setting to usual care setting. iHOPE will engage hospitals with tertiary as well as secondary care. This includes both academic and community hospitals.
4. Organisation intervention	5	Usual attending anaesthesia team will conduct the intervention. Care provider instructions regarding the study protocol will be provided, but there is no need for an advanced expertise for provision of the intervention.
5. Flexibility (delivery)	5	The intervention has to be provided according to the clinical routine. Co-treatment is not restricted and may be delivered as judged by the anaesthetist in charge.

6. Flexibility (adherence)	5	Treatment changes are allowed, if clinically necessary.
7. Follow-up	4	Brief in-hospital follow-up will occur during the first 4 postoperative days and at the discharge day. Blinding will be encouraged during the first 4 postoperative visits, but it is not mandatory. This will facilitate study conduction during the clinical routine in the different settings. The visit on the discharge day has not to be blinded, due to the requirement of extensive medical chart review. A blinded outcome assessor (e.g. study-nurse) will be required for the follow-up visits after hospital discharge at day 30 ± 3, day 180 ± 45 and day 365 ± 60. The follow-up will consist of a short telephone interview of the patient or the proxy.
8. Primary outcome	5	The primary outcome (binary composite outcome of all-cause mortality or new-onset serious cardiac and pulmonary events until postoperative day 30) is obviously relevant for the patients.
9. Primary analysis	4	An intention-to-treat analysis will be performed with all available data. A per-protocol analysis, sensitivity and pre-specified subgroup analyses will be performed in addition.

This study protocol is composed according to the SPIRIT statement. The SPIRIT checklist is provided in the Supplementary Table 1.

Setting and Duration

This study will be performed in at least 17 German secondary and tertiary hospitals. The full list of centres can be obtained at the corresponding author. Patient recruitment started in April 2018. "Last patient in" is anticipated for March 2020. Last Follow-up is expected to be in April 2021.

Eligibility criteria

Eligibility criteria for patients are presented in Table 2.

Table 2 Eligibility criteria for patients

Inclusion criteria	Patients ≥ 65 years with acute intra- / extracapsular hip fracture (e.g. femoral neck fracture, subtrochanteric or intertrochanteric fracture) requiring surgical intervention
	Planned surgical treatment via hemiarthroplasty, total hip arthroplasty or appropriate osteosynthetic procedure
	Written informed consent prior to study participation
Exclusion criteria	Patients who are institutionalized by court or administrate order
	Patients with planned concurrent surgery, which is not amenable to spinal anaesthesia
	Patients with absolute and relative contraindications to spinal anaesthesia, including but not limited to: Known or suspected congenital or acquired coagulopathy; active use of pharmacologic anticoagulants within timeframe, defined to contraindicate neuraxial block placement, as defined by the recommendations of the German Society of Anaesthesiology[26]; known or suspected unrepaired critical or severe aortic stenosis; known or suspected active skin infection at the planned needle insertion site; known or suspected elevated intracranial pressure contraindicating dural puncture
	Periprosthetic fracture
	Prior participation in the iHOPE study
	Determination by the attending surgeon, the attending anaesthesiologist, the site Principal Investigator or his designate, that the patient or the attending team in the operating room would not be suitable for a randomization procedure (e.g.: patients will be excluded, if one treatment has preferably to be used in this patient according to the clinical situation).

Eligibility criteria for centres

Participating centres are eligible, if they are willing to participate, have the appropriate infrastructure for trial performance, have the support of their surgeons and expect to recruit about a third of all presented hip fracture patients in their hospital.

Intervention

1032 patients will be randomly assigned to receive either spinal anaesthesia (n=516) or general anaesthesia (n=516). Beside this study treatment group allocation, complete perioperative patient care will be performed as per usual in the clinical routine of the attending anaesthesia team. There is no study-specific default regarding the concomitant care of the patients.

The attending anaesthesia team will apply the allocated treatment according to the instructions shown in Supplementary File 1, which comply with the standard care in Germany.

Participant timeline

Visits

All visits are presented in the Supplementary Table 2, which shows the schedule of enrolment, interventions, and assessments according to the SPIRIT Statement, and described in detail in the Supplementary File 1.

In brief, following a screening visit with seeking of an informed consent (Visit 0), an investigator will perform the baseline assessment (Visit 1). Randomization will occur after a re-evaluation of the eligibility criteria shortly before surgery (Visit 2). The routine attending anaesthesia team will be informed about the allocated treatment group by the investigator. The routine team will perform the study treatment during the clinical routine in accordance with the pragmatic study protocol. Thereafter, the patient will be visited daily on the first 4 postoperative days by an (if feasible blinded) investigator (Visit 3-6). The feasibility of in-hospital blinding will depend on the resources of the study team. It will be documented for each visit, if blinding was preserved. These visits will consist of an assessment of delirium, pain, mortality, adverse events and additionally patient satisfaction on the 4th day or if earlier at discharge. A further in-person patient visit and a medical records review will occur on the hospital discharge day by not blinded investigators (Visit 7). Assessments after hospital

discharge will be performed on postoperative day 30 ± 3, 180 ± 45 and 365 ± 60 via medical record review and telephone interview of the patient or rather the proxy by a blinded outcome assessor (Visits 8-10).

Outcome measures

Primary outcome measure

The primary endpoint is the time to the first occurring event of the binary composite outcome of all-cause mortality or new-onset (i.e. not pre-existing at time of surgery) serious cardiac and pulmonary events up to 30-days after randomization. Definitions of serious cardiac and pulmonary events are adapted from the definitions used by the National Surgical Quality Improvement Program (NSQIP).[27] These include cardiac arrest requiring CPR or defibrillation, myocardial infarction,[28] pneumonia, pulmonary embolism, ventilator > 48 hours and unplanned intubation. The primary endpoint will be assessed via in-person visits and medical record review during hospitalization and via telephone interview after hospital discharge at day 30 after randomization. Events after hospital discharge will only be considered as present if they led to hospital re-admission or death. In case of hospital re-admission the family physician or the respective hospital will be contacted and the documentation of the event will be requested.

Our primary outcome was selected based on the results of previous trials, which showed a high postoperative 30 day mortality rate[2, 10] and incidence of cardio-respiratory complications[8, 29] in hip fracture patients.

All definitions of outcomes (including the secondary outcomes) and all explanations of study procedures and assessments are described in the iHOPE manual (in German language). The main outcome definitions are presented in Supplementary File 2.

Secondary outcome measures

The secondary endpoints include binary as well as continuous outcomes consisting of (but not limited to) the following:

- Difference in the proportion of patients alive and delirium free in the first 4 days after randomization. Delirium will be assessed via in-person interview by the validated, high sensitive and specific assessment tool 3D-Confusion Assessment Method (3D-CAM).[30] It will be applied at baseline and daily on the first 4 postoperative days.
- Difference in the proportion of patients with postoperative pain; and in the characteristics and duration of postoperative pain between the two treatment arms. Pain will be

assessed via numeric rating scale (NRS 0-10) and questions derived from the Brief Pain Inventory[31] and the German pain questionnaire.[32] Pain will be assessed at rest and as an average pain, which includes the pain at rest and movement during the last 24 hours and 2 weeks, respectively. Assessment will be performed via in-person interview at baseline and each postoperative visit during hospital stay. After discharge, it will be performed via telephone interview at each follow-up visit.

- Difference in the satisfaction with care between the two treatment arms, assessed at day 4 or the day of discharge (whichever occurs first). The Bauer Patient Satisfaction Questionnaire[33] will be used via in-person interview on postoperative day 4 or at discharge (whichever occurs first), to assess the patients' satisfaction.
- Difference in the number of in-hospital events, which include (but not limited to): Planned and unplanned admission to critical care; length of hospital and intensive care stay; length of hospital stay longer than expected; independence in walking and the need for assistive devices for walking at hospital discharge; postoperative hospital discharge destination; in hospital all-cause mortality and severe new-onset complications as those used by the NSQIP.[27] These events will be assessed on the discharge day from hospital or at least at postoperative day 30 via in-person interview and medical record review.
- Difference in the proportion or means of long-term outcomes at day 30 ± 3, day 180 ± 45 and day 365 ± 60 after randomization will include: All cause-mortality, independence in walking and need for assistive devices for walking; chronic pain; ability to return home; cognitive function via Short blessed test (SBT)[34]; and overall health and disability via World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0)[35]. Except of the cognitive function and chronic pain, which could only be assessed via telephone interview of the patient, all other data could also be assessed via telephone interview of the proxy.
- Difference in the proportion of patients with perioperative serious adverse events like intraoperative cardiac arrest; malignant hyperthermia; intraoperative anaphylaxis; intraoperative aspiration; total spinal anaesthesia; epidural hematoma; paralysis of the lower extremities lasting greater than 24 hours following spinal anaesthesia; fall within 12 hours of anaesthesia care. These data will be assessed during the surgery and the postoperative in-hospital visits via in-person interview and medical record review.
- Sensitivity and subgroup analyses of the primary outcome will consider the baseline proportion of patients with depression and frailty. Depression will be assessed via the 15-items short version of the Geriatric Depression Scale (GDS) at baseline via in-person interview.[36] Frailty assessment will be performed according to phenotype-model of Fried at baseline via in-person interview.[37] Four of originally five Fried-criteria will be assessed:

fatigue, maximal grip strength assessment of the dominant hand, physical activity (employing the Minnesota Leisure Time Activities Questionnaire) and weight loss in the past year. Gait velocity as the fifth Fried criterion will be omitted in this study for obvious reasons.

Sample size

The multicentre, randomized "hip fracture surgery in elderly patients (HIPELD)" study revealed an in-hospital event rate of 12.7% for cardiac and pulmonary complications and 3.8% for the 28-day mortality was revealed in the general anaesthesia group.[29] Of note, the HIPELD study included a strongly confined patient population. The recently published IQTIG report revealed an in-hospital mortality rate of 4.8% and a total reported complication rate of 16.3%.[7] The one-month mortality rate after hip fracture ranges from 4 to 12%.[2, 7, 9, 10] Thus to the best of our knowledge a conservative event rate of 16% of the binary composite endpoint can be assumed for the general anaesthesia group in the iHOPE trial. Furthermore, HIPELD was able to detect a decrease from 15.9% to 8% for serious adverse events and 28-day mortality in the xenon intervention group. Based on the HIPELD data, a restrictive, meaningful treatment difference of 6% in the event rate seems to be reasonable on a 5% significance level with a power of 80%. We assume an exponential dropout rate (e.g. loss to follow-up after hospital discharge) of 5%. Using the template STT2-1 from nQuery 7.0 advisory we calculated a sample size of 516 patients per group. It is assumed that the treatment differences are homogenous with respect to extend, variation and sample size per group across sites. Loss to follow-up may occur, but time to event analysis is carried out up to the last visit. No interim analysis of the trial is planned and will be conducted.

Dropout-handling and protocol deviations

We will examine in a sensitivity analysis the dropout pattern with respect to treatment. Details for dropout-handling and protocol deviations are shown in Supplementary File 1.

Recruitment

Patients who meet the inclusion criteria and have none of the exclusion criteria will be recruited consecutively during the recruitment period of 24 months. A screening and enrolment log will be kept. The screening number will be coded independently from the randomization number. The Principal Investigators will check the actual recruitment rates weekly, by standardised enrolment reports. All subjects will be recruited in in-hospital settings between the time of presentation and surgery. Participating centres will use multiple strategies to identify potentially eligible patients, including interval calls to specific units, residents and nurses, reviews of inpatient census lists and operating room schedules, and

requests to physicians, nurses and emergency room personnel to contact study site staff when a hip fracture patient is admitted to the hospital.

Allocation

Randomization procedure will be stratified by site. The intended allocation ratio is 1:1. The selection of the best practice randomization procedure to prevent selection and time trend bias will follow the ERDO.[38] Details, including the set of investigated randomization procedures, the amount of biases and the decision will be given in a Randomization Report (Department of Medical Statistics, University Hospital RWTH Aachen, Germany), which will be kept concealed up to closure of the database. The randomization list will be imported in an online data management system owned by the sponsor The Center for Translational & Clinical Research Aachen (CTC-A). The site research staff will enter patient's baseline data in the database and request the randomization assignment via the online data management system, which will be available on a 24/7 basis. Treatment allocation will be reported centralized via the data management system. The site research staff will then communicate this information to the treating anaesthesia team immediately prior to surgery.

Blinding

iHope is composed as an open label trial. Intraoperative attending physicians and patients cannot be blinded, due to the nature of the intervention. In-hospital outcome assessors will be blinded as far as possible based on the site resources. There will be two case report forms (CRFs) for each patient. One will include the non-blinded visits 0-2 and visit 7. The second will include the visits 3-6 and 8-10 for the blinded investigators. Patients and attending physicians will strongly be inculcated not to disclose the allocation status at the follow-up assessments. Accidentally revealing the treatment assignment is possible but unlikely during the medical records review at follow-up, as the outcome assessor would have to seek and view the intraoperative anaesthesia protocol consciously. In any case, the outcome assessor will have to document each follow-up visit, if blinding was successfully performed.

Data collection

All data, which should be collected, are presented in the Supplementary File 1.

Training

Standardisation procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardisation among sites (e.g., training,

telephone follow-up guideline for complete and standardised assessment, newsletters, investigator meetings, monitoring, centralised evaluations, and validation methods). The Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital RWTH Aachen, will offer a brief training on diagnosis and management of delirium (online-based) for all participating centres. Furthermore, they will offer a central hotline for consultation on delirium diagnosis and management.

Bias

The extent of selection and time trend bias on the primary results will be minimized by application of the ERDO.[38] Performance bias will be minimized by adherence to the standard operating procedures for spinal and general anaesthesia in each centre, which are based on the recommendations of the German Society of Anaesthesiology,[26] and monitoring during the trial. Attrition bias will be minimized by strict follow-up of the patients due to the fact that most documentation will be carried out during patient's hospital stay. Misclassification bias/ measurement bias will be minimized since we will apply simple measurements, which are used in daily practise or are easy to perform (e.g. WHODAS). Postoperative in-hospital outcome assessment will be conducted, wherever possible, in a blinded manner. All in-hospital outcomes will be documented using standardized definitions. Telephone follow-up for post-discharge outcomes assessment will be carried out in a blinded manner. The post-discharge assessors will be obliged not to open the electronic anaesthesia protocols which are filed in the hospital database or any paper-based anaesthesia files. Thus ascertainment bias will be kept to a minimum. Including all eligible patients for the particular centre within the recruitment period in addition to appropriate randomization procedure will minimize selection/ recruitment bias.

Data management

All collected data will be entered in a paper based case report form (CRF), which will be considered as source data. These include automatic print outs as well as paper-based patient records and electronic patients` data.

Investigators will enter the information required by the protocol into an online electronic case report form (eCRF). The CTC-A will develop in cooperation with the Department of Medical Informatics RWTH Aachen the web-based electronic data capture software OpenClinica,[39] which supports the Clinical Data Interchange Standards Consortium (CDISC).[40] The uploaded data will be collected and preserved on servers of the CTC-A with optimal security and Good Clinical Practice compliance. Detailed information on the eCRF completion will be

provided by an eCRF completion manual, an e-learning tool and during the site initiation visits. The access to the eCRF is password controlled. Plausibility checks will be performed according to a data validation plan, with automatically and manually generated queries. The database will be closed, after all data are entered and all queries are solved.

Direct access to source data

The investigator is obliged to allow study specific monitoring, auditing, and inspections with direct access to source data.

Statistical methods

Efficacy analysis: The time to the first occurring event of the binary composite of all-cause mortality or new-onset serious cardiac and pulmonary complications up to 30 days after surgery serves as primary endpoint and will be compared between the two treatment groups at the two sided global significance level of 5% using log rank-test stratified by centre. The primary analysis population will be the full analysis set, preserving the intention to treat principle (ICH E9). The two-sided 95% confidence interval for the hazard ratio will be computed for description of effects. Further in sensitivity analysis the treatment by site interaction will be evaluated by a Gail-Simon-test and the method of Branson and Whitehead[41] will be applied to adjust for treatment-cross-over. In further sensitivity analyses, we will study the effect of mortality alone ignoring serious cardiac and pulmonary complications with mortality as risk, which competes with occurrence of serious cardiac and pulmonary complications in a competing risk model. Ancillary analyses concerning the primary endpoint will be based on Cox-proportional Hazard models including further explanatory variables like age, comorbidities, depression, dementia, anaemia and pre-existing frailty. Moreover, exploratory tests regarding the secondary endpoints will be performed. Details of the statistical models will be given in the trial statistical analysis plan prior to database lock. Safety: All SAEs and predefined adverse events (AEs) will be recorded and handled in a safety database. Unscheduled visits may be performed at any time during the study, whenever necessary to assess or to follow-up on adverse or serious adverse events. Descriptive safety analyses regarding the number of adverse events in each group will be prepared for each Data Safety Monitoring Board (DSMB) meeting, to enable a risk-benefit assessment. The assessment will not result in a formal interim analysis affecting the error rates of the study and thus will not include information about the primary endpoint.

Monitoring

The Principal Investigator of each site has the responsibility for the safety of the study at the respective site. This safety monitoring will include careful assessment and appropriate reporting of AEs as noted below. The Study Director and the Data Safety Monitoring Board (DSMB) will be responsible for monitoring the data quality and the ongoing safety of subjects in the entire trial.

Data Safety Monitoring Board (DSMB)

A formal DSMB will consist of three anaesthesia (CN, DH, TH), one geriatric (RD), one psychiatrics (MBa) and one statistics expert (MBo), with no competing interests and fully independent from the sponsor and investigators. The DSMB will oversee the data in particular with respect to safety and data integrity. The DSMB roles, responsibilities, and operating procedures will be described in the iHOPE DSMB Charter. Four DSMB meetings are planned during the recruitment period.

Sponsor Monitoring

The CTC-A will be responsible for quality assurance through regular on-site monitoring, data and query management, reporting of AEs and annual safety reports. Details are presented in Supplementary File 1.

Auditing

Independent audits are possible at any time. This includes the possibility that a member of the CTC-A's quality assurance function or of the funder, the Federal Ministry for Education and Research (BMBF), may arrange to visit the investigator in order to audit the study documents and performance of the study at the study site.

Harms

Safety assessments will consist of monitoring and recording all AEs and SAEs and the regular monitoring of intraoperative vital data by the attending anaesthetist. AEs in this study are defined according to the ICH-GCP guideline. AEs and SAEs will be recorded after randomization during the visits 2-7 via patient interviews and medical record reviews. After hospital discharge, we will only record SAEs related to the primary endpoint, which have to be confirmed by a hospital or the family physician of the patient. It is not planned to assess other AEs or SAEs via follow-up calls due to the lack of validation capacity. AEs will be followed until the event resolves or stabilises. The Principal Investigator of each centre will have to report all SAEs to the sponsor (CTC-A) within 24 hours of discovery or notification of the event. The sponsor will collect all SAE reports and provide an annual safety report to the Ethics Committees.

Study Termination

The study will be prematurely terminated for an "individual patient" in case of: their own request and withdrawal of consent; if, in the investigator's opinion, continuation of the trial would be detrimental to the subject's well-being; hip fracture surgery was not performed; or death before surgery.

The study will be prematurely terminated for a "participating centre" in case of substantial and irreparable deficiencies in data quality, inadequate compliance, subsequent protocol violations or deficient patient recruitment.

As spinal and general anaesthesia are universal standard care procedures for hip fracture surgery, there is no known or expected difference in overall risk or safety for patients between these two approaches, which would induce a prematurely termination of the "whole study". For this reason, we do not propose formal stopping rules based on demonstrated superiority or inferiority of either treatment with regard to the primary or secondary endpoints. However, the Study Director in consultation with the DMSB trial may prematurely close the trial, if an unexpected high numbers of SAEs occur in one of the treatment groups.

ETHICS AND DISSEMINATION

Ethical and Legal Aspects

iHOPE will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, GCP-guidelines, the Declaration of Helsinki, EU Commission Directive 2005/28, §15 of the German Medical Association's professional code of conduct "Berufsordnung für Ärzte, BOÄ", and the applicable data protection law.

Ethics Committee

The study received an ethical approval EK 022/18 from the leading Ethics Committee of the RWTH Aachen University on 14.03.2018. An approval form all other involved local Ethical Committees was subsequently requested. Inclusion of any subject into the study, will only occur after obtaining an ethical approval for the respective site.

Protocol amendments

Any change in the study protocol and/or informed consent form will be approved by the respective Ethics Committees (except for changes in logistics and administration or when necessary to eliminate immediate hazards).

Informed Consent

Written informed consent will be obtained from patients prior to study-participation, after comprehensive written and verbal information by an investigator. Patients will be informed about the study as well as the data protection and have to agree to the direct access to their individual data. The informed consent form has to be signed and personally dated by the patient and one of the Sub-Investigators. A copy will be provided to the patients.

To ensure that the study population is representative of a wider population of patients, and to avoid selection bias, it is important to include patients with lack of the capacity to consent. In these cases (e.g. emergency surgical population or dementia), either the legal representatives will be asked to give verbal and written informed consent, or a study-independent physician. The latter condition applies only to those patients, where a legal representative has not yet been appointed or is not available before surgery. A confirmation of the written consent by the independent physician, will be requested as soon as possible from the recovered patient or the legal representative.

Confidentiality

All subjects will be identified by a unique randomization number. Each Principal Investigator will safely keep a list, which will allow the identification of the pseudonymized patients. The patient's informed consent, with their printed name and signature will be filed separately in the investigators file.

Patients will be informed that their data will be pseudonymized and handed to a third party anonymized. Access to encoded data or source documents will only be given to authorised bodies or persons (sponsor, authorised staff, auditors, competent authorities or ethics commission) for validation of data. Confidentiality of collected data will be warranted, also in case of publications.

Source data will be stored in locked cabinets/ rooms with restricted access at each study site. Safe data storage will also be ensured for 10 years after completion of the trial.

Post-study treatment

No specific post-study arrangements or care will be performed after this study. All subjects will return to their standard medical care after the study, as needed.

A separate patient`s insurance has not been deemed necessary, since there is no specific, study intervention and patients are treated according to clinical standard and in accordance with §15 of the German Medical Association's professional code of conduct "Berufsordnung für Ärzte, BOÄ".

Patient and Public Involvement

HS (Aktionsbündnis Patientensicherheit e.V., Berlin, (German Coalition for Patient Safety)) and MS (Senior Consultant, Section Patient Safety, Medical Advisory Service of Social Health Insurance) support this trial within the Trial Steering Committee. They have reviewed the trial protocol in regard to patient safety aspects and will provide further input during the trial conduction, interpretation and dissemination of the results. Interviews of patients before and after hip fracture surgery in the University Hospital RWTH Aachen were performed before study conception. They aimed to elicit patients' feedback on the major disadvantages and fears of anaesthesia for hip fracture surgery. The results of the interviews emphasized our commitment to understand patient perspectives on hip fracture outcomes and highlighted the pre-eminence of patient perspectives in the definition and selection of outcomes for iHOPE.

Strategies for disseminating and implementing of iHOPE results will address anticipated barriers at the level of the individual patient, the health care provider, and the health system. iHOPE will focus on educating patients and support patient empowerment via the iHOPE partners network with regard to anaesthesia options for hip fracture care and their demonstrated relative risk and benefits. The Study Director will organize "information days" for patients. Stakeholders will be invited to participate. Such "information days" may e.g. include "meet-the-expert" sessions, open forum discussions and public lectures. iHOPE will liaise to patients, patients' advocacy groups, patient representative groups, caregivers, stakeholders and insurer, accordingly. Members of the patient partners will disseminate and communicate to other patients and patient groups.

Dissemination

Information about iHOPE will be spread via presentations at national and international scientific meetings, and conferences. Study results will be published in appropriate peer-reviewed international scientific journals with open access and in one or more public clinical study registry(ies). Publishing details will be given in the clinical study agreement.

In addition, iHOPE will use its advantage to disseminate results to trauma and orthopaedic surgery, to psychiatric and aging sciences via an established network and alliances of iHOPE investigators and partners. Furthermore iHOPE will liaise with the German Society of Trauma Surgery projects “German Geriatric Trauma Centre Certification” and the “Geriatric Trauma Registry”.

Also, iHOPE will closely cooperate with the REGAIN trial[24] and will use the dissemination platform of REGAIN to spread the study results not just nationally but also in the USA and Canada and vice versa.

Moreover, MS (Senior Consultant Section Patient Safety, Medical Advisory Service of Social Health Insurance) will strengthen effective dissemination and implementation of iHOPE results at the level of health policy and insurance providers. This will enable to mitigate or eliminate unintended disincentives for provision of high-quality care that may emerge from present healthcare reimbursement models, potentially including efforts to promote use of effective anaesthesia care.

DISCUSSION

At present, insufficient evidence exists to characterize the comparative effectiveness of spinal versus general anaesthesia for hip fracture surgery among elderly patients. Therefore, identification of the best anaesthesia technique with improvement of patient-centred outcomes after hip fractures is of the greatest importance.

iHOPE employs treatment protocols which reflect “real world” approaches to general and spinal anaesthesia. The administration of anaesthesia will be carried out in the course of routine care by staff anaesthesiologists, who do not necessarily need to be part of the iHOPE study team. iHOPE does not require specialised techniques, drugs, or monitoring beyond those available and commonly used in standard care settings. This, and the multicentre character of iHOPE, with totally 1032 randomized patients, will enable us to generate more generalizable results, which are applicable for a large number of individuals with hip fractures. On the other hand we are aware of the risks of the "real world" approaches, due to the lack of standardisation for anaesthesia in hip fracture patients, which might introduce artificial variation.[42] To account for this issue, we will assess several factors that may be influenced by variations in "physician-individualised care".[43] These include among others (irrespective of the assigned anaesthesia method) the assessment of the total doses of the used drugs, haemodynamic values, the use of advanced intraoperative monitoring, the fluid

and transfusion management, the early postoperative haemoglobin level, and the intraoperative sedation level.

A recently published consensus paper with advices for basic standards of anaesthetic care in hip fracture patients has pointed out 7 important principles.[16] Several of these principles are already covered in the German national guidelines issued by the German Society for Anaesthesiology and Intensive Care Medicine (DGAI),[44] even if not specifically focused on hip fracture patients. This refers to the multidisciplinary care for all surgical patients, the principles that an appropriately experienced anaesthetist should perform anaesthesia,[45] the use of standard monitoring for each patient and advanced intraoperative monitoring (e.g. invasive blood pressure measurement) in high-risk patients. Furthermore, in accordance with the consensus paper, [16] anaesthesia in the iHOPE study will be administered according to agreed standards at each hospital. Other German guidelines are also in line with the consensus paper. All participating German centres have to follow the blood transfusion guideline of the German Medical Association[46] and the German Association for Trauma Surgery (DGU), which advises to perform hip-fracture surgery within 24 hours and encourages an early patient remobilisation.[47] The surgical technique will follow the standard national policies.[47]

Of note, the impact of sedation levels during spinal anaesthesia on hip fracture outcomes remains an active area of research and debate. Preliminary work by Sieber and colleagues have suggested higher rates of delirium after sedation with low intraoperative Bispectral Index (BIS) values,[48] and current trials are underway to validate these initial findings. While the iHOPE study does not specify a particular regimen for intraoperative sedation, anaesthesiologists are directed by protocol to avoid deep levels of sedation (i.e. OAA/S less than 2). Additionally, sites are instructed to monitor OAA/S values[49] along with BIS scores, depending on availability at participating sites. Despite the parallel conduction of the REGAIN[24] study, iHOPE is justified as it focuses on a different primary endpoint. The primary endpoint in the REGAIN study is the independence of walking 60 days after hip-fracture surgery. Furthermore, REGAIN is conducted in Canada and the USA, while iHOPE is conducted in Germany. In spite of the different primary endpoint, most outcome variables in the REGAIN[24] and iHOPE study have been harmonized. This will enable us to carry out an individualized patient data (IPD) meta-analysis, which is considered as the “gold standard” of systematic reviews.[50] This creates a unique possibility to combine the original data from iHOPE and REGAIN after publication, which will improve guideline development to enhance outcome after hip fracture surgery. The similarity of other key aspects of study design, including eligibility criteria, treatment protocols and follow-up of 365 days in these two studies will further facilitate additional joint analyses.

Due to feasibility of the study one limitation is that data collection for several in-hospital adverse events will be performed via medical record review. This implies that not recorded events may not be detected. Of note, all diagnoses will follow the routine care. Thus, serum troponin values will be measured at the attending physician's discretion. According to the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing non-cardiac surgery, it is not recommended to use a perioperative troponin screening systematically for all non-cardiac surgical patients.[51]

A further limitation of iHOPE is that patients who are explicitly choosing one of the techniques, or are considered ineligible for other reasons than contraindications by the investigators will be excluded and may represent a reasonable proportion of the elderly hip-fracture population. In consequence, there might arise a discrepancy between the totally eligible population (i.e. patients without contraindications for spinal anaesthesia) and successfully included patients in the iHOPE study. A feasibility calculation before the study design, has taken these patients as well as the patients who are ineligible due to the exclusion criteria like e.g. anticoagulation into account.

REFERENCES

1. [Anteile der Altersgruppen unter 20, ab 65 und ab 80 Jahre in Deutschland, 1871 bis 2060 (Stand: 2015)]. Available from: http://www.bib-demografie.de/DE/ZahlenundFakten/02/Abbildungen/a_02_12_ag_20_65_80_d_1871_2060.html?nn=3074114. Accessed March 2018.
2. Medin E, Goude F, Melberg HO, et al. European Regional Differences in All-Cause Mortality and Length of Stay for Patients with Hip Fracture. *Health Econ* 2015;24 Suppl 2:53-64.
3. Royal College of Physicians and the Association of Anaesthetists of Great Britain and Ireland. National Hip Fracture Database. NHFD-AnnualReport2017.pdf. available from: https://nhfd.co.uk/files/2017ReportFiles/NHFD-AnnualReport2017.pdf. Accessed June 2018.
4. Holt G, Smith R, Duncan K, et al. Changes in population demographics and the future incidence of hip fracture. *Injury* 2009;40:722-6.
5. Coburn M, Röhl AB, Knobe M, et al. [Anesthesiological management of elderly trauma patients]. *Anaesthesist* 2016;65:98-106.
6. European State Population Numbers. Available from: http//www.europe.eu. Accessed September 2017.
7. Hüftgelenknahe Femurfraktur mit osteosynthetischer Versorgung. Hüftgelenknahe Femurfraktur mit osteosynthetischer Versorgung. Available from https://www.iqtig.org/downloads/ergebnisse/qidb/2016/2017-04-26/QIDB_2016_INDIREKT_PDF/QIDB_2016_indirekte_Verfahren/QIDB_Referenzbereiche/QSKH_17n1-HUEFT-FRAK_2016_QIDB-DV_V01_2017-04-06.pdf. Accessed March 2018.
8. Carow J, Carow JB, Coburn M, et al. Mortality and cardiorespiratory complications in trochanteric femoral fractures: a ten year retrospective analysis. *Int Orthop* 2017; 41:2371–80.
9. Boddaert J, Raux M, Khiami F, et al. Perioperative management of elderly patients with hip fracture. *Anesthesiology* 2014;121:1336-41.
10. Brauer CA, Coca-Perraillon M, Cutler DM, et al. Incidence and mortality of hip fractures in the United States. *JAMA* 2009;302:1573-9.
11. Coburn M, Sanders R, Neuman M, et al. We may have improved but we must get better still: The never-ending story of the elderly with fractured neck of femur. *Eur J Anaesthesiol* 2017;34:115-117.

12. Johansen A, Tsang C, Boulton C, et al. Understanding mortality rates after hip fracture repair using ASA physical status in the National Hip Fracture Database. *Anaesthesia* 2017;72:961-966.
13. Tsang C, Boulton C, Burgon V, et al. Predicting 30-day mortality after hip fracture surgery: Evaluation of the National Hip Fracture Database case-mix adjustment model. *Bone Joint Res* 2017;6:550-556.
14. Coburn M, Fahlenkamp A, Zoremba N, et al. Postoperative cognitive dysfunction: Incidence and prophylaxis. *Anaesthesist* 2010;59:177-84.
15. Huang Y-F, Liang J, Shyu Y-IL. Number of Comorbidities Negatively Influence Psychological Outcomes of the Elderly Following Hip Fracture in Taiwan. *J Aging Health* 2016;28:1343-1361.
16. White SM, Altermatt F, Barry J, et al. International Fragility Fracture Network Delphi consensus statement on the principles of anaesthesia for patients with hip fracture. *Anaesthesia* 2018;73:863-874.
17. White SM, Moppett IK, Griffiths R. Outcome by mode of anaesthesia for hip fracture surgery. An observational audit of 65 535 patients in a national dataset. *Anaesthesia* 2014;69:224-30.
18. Guay J, Parker MJ, Gajendragadkar PR, et al. Anaesthesia for hip fracture surgery in adults. *Cochrane Database Syst Rev* 2016;2:CD000521.
19. White SM, Moppett IK, Griffiths R, et al. Secondary analysis of outcomes after 11,085 hip fracture operations from the prospective UK Anaesthesia Sprint Audit of Practice (ASAP-2). *Anaesthesia* 2016;71:506-14.
20. Neuman MD, Rosenbaum PR, Ludwig JM, et al. Anesthesia technique, mortality, and length of stay after hip fracture surgery. *JAMA* 2014;311:2508-17.
21. Patorno E, Neuman MD, Schneeweiss S, et al. Comparative safety of anesthetic type for hip fracture surgery in adults: retrospective cohort study. *BMJ* 2014;348:g4022.
22. Van Waesberghe J, Stevanovic A, Rossaint R, et al. General vs. neuraxial anaesthesia in hip fracture patients: a systematic review and meta-analysis. *BMC Anesthesiol* 2017;17:87.
23. O'Donnell CM, McLoughlin L, Patterson CC, et al. Perioperative outcomes in the context of mode of anaesthesia for patients undergoing hip fracture surgery: systematic review and meta-analysis. *Br J Anaesth* 2018;120:37-50.
24. Neuman MD, Ellenberg SS, Sieber FE, et al. Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN): protocol for a pragmatic, international multicentre trial. *BMJ Open* 2016;6:e013473.
25. Loudon K, Treweek S, Sullivan F, et al. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ* 2015;350:h2147.

26. Waurick K RHVAHKPGWVT. *Anästh Intensivmed* 2014;55:464-492.
27. ACS NSQIP. Available from: https://www.facs.org/quality-programs/acs-nsqip. Accessed February 2018.
28. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J* 2012;33:2551-67.
29. Coburn M, Sanders RD, Maze M, et al. The hip fracture surgery in elderly patients (HIPELD) study to evaluate xenon anaesthesia for the prevention of postoperative delirium: a multicentre, randomized clinical trial. *Br J Anaesth* 2018;120:127-37.
30. Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. *Ann Intern Med* 2014;161:554-61.
31. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994;23:129-38.
32. Nagel B, Gerbershagen HU, Lindena G, et al. [Development and evaluation of the multidimensional German pain questionnaire]. *Schmerz* 2002;16:263-70.
33. Bauer M, Böhrer H, Aichele G, et al. Measuring patient satisfaction with anaesthesia: perioperative questionnaire versus standardised face-to-face interview. *Acta Anaesthesiol Scand* 2001;45:65-72.
34. Kawas C, Karagiozis H, Resau L, et al. Reliability of the Blessed Telephone Information-Memory-Concentration Test. *J Geriatr Psychiatry Neurol* 1995;8:238-42.
35. Ustün TB, Chatterji S, Kostanjsek N, et al. Developing the World Health Organization Disability Assessment Schedule 2.0. *Bull World Health Organ* 2010;88:815-23.
36. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982;17:37-49.
37. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146-56.
38. Hilgers R-D, Uschner D, Rosenberger WF, et al. ERDO - a framework to select an appropriate randomization procedure for clinical trials. *BMC Med Res Methodol* 2017;17:159.
39. OpenClinca, available from http://openclinica.com. Accessed February 2018.
40. CDISC, available from http://www.cdisc.org. Accessed February 2018.
41. Branson M, Whitehead J. Estimating a treatment effect in survival studies in which patients switch treatment. *Stat Med* 2002;21:2449-63.
42. White SM, Griffiths R, and Moppett IK. Standardising anaesthesia for hip fracture surgery. *Anaesthesia* 2016;71:1391-5.
43. Moppett IK, White SM, and Griffiths R. Standards for hip fracture anaesthesia - a reply. *Anaesthesia* 2017;71:407-8.

44. DGAI Entschließungen, Empfehlungen, Vereinbarungen. Available from: https://www.dgai.de/publikationen/vereinbarungen.html#i__vereinbarungen_mit_anderen_fachgebieten. Accessed July 2018.
45. Beck G. Mindestanforderungen an den anästhesiologischen Arbeitsplatz* *Anaesth Intensivmed* 2013;54:39-42.
46. Querschnitts-Leitlinien (BÄK) zur Therapie mit Blutkomponenten und Plasmaderivaten. Available from: https://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/QLL_Haemotherapie_2014.pdf. Accessed July 2018.
47. Leitlinien der DGU. Available from: http://www.dgu-online.de/qualitaet-sicherheit/leitlinien/leitlinien-der-dgu.html. Accessed July 2018.
48. Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clin Proc* 2010;85:18-26.
49. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol* 1990;10:244-51.
50. IPD MA chochrane. Available from: http://www.methods.cochrane.org/ipdma. Accessed February 2018.
51. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;130:2215-45.

Author Contributions

MC is the iHOPE Study Director and Coordinating Principal Investigator. He conceived the overall study and received the iHOPE grant (01KG1714 from the Federal Ministry for Education and Research (BMBF), Bonn, Germany). The iHOPE Clinical Project Management is allocated to AK. AK wrote the first draft of this manuscript and made substantial contributions to the conception of the study protocol together with MC. The iHOPE Trial Management (MC, RR, SI, AH, MDN), the Trial Statistician (RDH), the Data Monitoring and Safety Board (NC, TH, DH, MBa, MBo, RD), the investigators of the participating iHOPE centres (CA, JA, MD, PK, PKn, PKr, RL, CO, CR, RS, CS, OV, FW, MW, KZ, AZ) and other participating bodies (FH, HS, MS, DCW, MK, FS, CB, RDS) each made substantial contributions to the conception or design of the study protocol. All authors revised the protocol critically for important intellectual content, approved the final version and agree to be accountable for all aspects of the work. The iHOPE study group is listed as Collaborators. The Collaborators are substantially involved in carrying out the iHOPE study as Investigators of the recruiting centres, in the Project and Data Management and Monitoring. All Collaborators critically reviewed the study protocol and the manuscript.

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Competing interests

MC received a grant for this trial from the Federal Ministry for Education and Research (BMBF), Bonn, Germany. MDN is currently funded by the US Patient-Centered Outcomes Research Institute for related work (grant PCS 1406-18876) and he is the Principal Investigator of the REGAIN Trial (Clinicaltrials.gov number NCT02507505). AK, CA, JA, MBa, CB, MBo, RD, MD, TH, DH, FH, RDH, AH, SI, PK, MK, PKn, PKr, RL, CN, CO, CR, RR, RDS, RS, FS, HS, MS, CS, OV, FW, DCW, MW, KZ, AZ declare no competing interests.

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Ethical Approval

Ethical approval EK 022/18 was obtained from the leading Ethics Committee of the RWTH Aachen University on 14.03.2018 An approval form all other involved local Ethical Committees was subsequently requested.

Supplementary File 1

EXTENDED METHODS

Intervention

Provider instructions spinal anaesthesia

Spinal anaesthesia should be performed as a single-shot block. Supporting adapted sedation is permitted for block placement and intraoperative comfort of the patient. The level of sedation should be assessed by the Observer´s Assessment of Alertness/ Sedation Scale (OAA/S) (Table 2), a simple, validated measure of alertness among sedated subjects.[49] The intraoperative alertness/ sedation depth should correspond to OAA/S ≥2. Documentation of OAA/S should be performed every 30 minutes or at least once during surgery, irrespective of the use of active sedation. If clinically required, conversion to general anaesthesia is permitted. All remaining aspects of anaesthesia care, e.g. monitoring, drugs and dosage, postoperative pain management, supplemental nerve blocks, and management of intraoperative events should be handled as per usual routine. Optional assessment: If a bispectral index (BIS)-monitoring is available and used at the institution.

Supplementary File Table 1: Observer's Assessment of Alertness/Sedation[49]

Score	Subject responsiveness	Sedation level
5	Responds readily to name spoken in normal tone	Alert
4	Lethargic response to name spoken in normal tone	Light sedation
3	Responds only after name is called loudly and/or repeatedly	Moderate sedation
2	Responds only after mild prodding or shaking	Moderate sedation
1	Does not respond to mild prodding or shaking	Deep sedation

Provider instructions general anaesthesia

Maintenance of general anaesthesia with an inhaled anaesthetic or continuous intravenous application of propofol: Intravenous opioids should be applied as needed for intraoperative analgesia. Airway management should be performed as usual in

the respective centre (e.g. via endotracheal tube, laryngeal mask airway, or other device). All remaining aspects of anaesthesia care, e.g. monitoring, drugs and dosage, postoperative pain management, supplemental nerve blocks, and management of intraoperative events should be handled as per usual routine. Optional assessment: If a BIS-monitoring is available and used at the institution.

Data collection

Visit 0 (Screening visit), pre-randomization phase

The investigator/ study staff will screen all potentially eligible patients between the time of presentation and surgery. This will be followed by a screening visit, to check if the patient meets inclusion criteria in the absence of exclusion criteria. Investigators will obtain written informed consent from eligible patients or their legal representatives, after study-specific patient information.

Visit 1 (Preoperative evaluation visit), pre-randomization phase

The pre-evaluation visit will also be conducted between the time of presentation and surgery via patient or proxy interview. It will comprise the assessment of the patient demographics, medical history, the most recent preoperative routine laboratory values, vital data, clinical data, residential and educational status and the overall health and disability assessment belonging to the study-specific baseline testing. Further study-specific baseline testing (cognition, delirium, pain, and depression) and frailty assessment will be performed directly via patient interview, independent of the cognitive status of the patient. Additionally, we will document the contact data of the patients and the proxy, as well as the "do not resuscitate" status of the patient.

Baseline data to be collected:

- Patient demographics (age, sex, race, weight, height, body mass index (BMI), American Society of Anaesthesiologists (ASA) physical status)
- Educational and residential status; patient and proxy contact information; do not resuscitate status
- Pre-existing diseases and medical history, including medication and risk factors (smoking status, alcohol status)

- Supplemental oxygen or mechanical ventilation, baseline vital data including blood pressure, heart rate and oxygen saturation.
- Ability of walking 3 m across the room prior to hip fracture
- Type of hip fracture and planned kind of surgery
- Most recent preoperative routine laboratory values, if done in the clinical routine: haemoglobin, haematocrit, MCV, white blood cells, serum creatinine, urea, albumin, protein (total), calcium (total), potassium, sodium, AST, alkaline phosphatase, TSH, platelets, INR and PTT

Study-specific testing: baseline assessment prior to surgery:

Cognition will be assessed by the validated Short blessed test (SBT), which enables a brief screen of cognition via in-person and telephone interview (5-10 minutes).[34]

Delirium will be assessed via in-person interview by the validated, high sensitive and specific assessment tool 3D-Confusion Assessment Method (3D-CAM) (3-5 minutes).[30]

The overall health and disability will be assessed via the 12-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0), which can be administered in person as well as via telephone interview in 5-10 minutes. The WHODAS 2.0 is a patient-reported outcome assessment tool, which comprises: cognition, mobility, self-care, interpersonal relationships, work and household roles, and participation in society.[35]

Depression will be assessed via the short version of the Geriatric Depression Scale (GDS) (5 min.).[36]

Frailty assessment will be performed according to phenotype-model of Fried at baseline via in-person interview.[37] Four of originally five Fried-criteria will be assessed: fatigue, maximal grip strength assessment of the dominant hand, physical activity (employing the Minnesota Leisure Time Activities Questionnaire) (5-10 min.) and weight loss in the past year. Gait velocity as the fifth Fried criterion will be omitted in this study for obvious reasons. We will also obtain laboratory results.

Pain will be assessed via numeric rating scale (NRS 0-10) and questions derived from the Brief Pain Inventory.[31] We will assess the average and worst pain within the past 2 weeks before hip-fracture and the actual pain level.

Visit 2 (Hip-fracture surgery), intervention phase

The investigator will randomize the patient, after a short re-evaluation of patient eligibility and the eligibility of the attending routine team in the operating room. The patient will not be randomized, if the attending anaesthesia and surgery team is unwilling or ineligible (as judged by the principle investigator) to treat study patients. The attending anaesthesia team will be informed by study staff about the assigned study group after randomization. The routine attending anaesthesia team (does not necessarily have to belong to the study team) will perform the study treatment during the clinical routine in accordance with the pragmatic study protocol. Sedation/ alertness level for patients in the spinal anaesthesia group will be documented according to the OAA/S. BIS values will optionally be documented, if used in the clinical routine during both procedures. Other routine surgical- and anaesthesia-related data (e.g. monitoring-devices, patient vital data, used drugs and dosages, times, adverse events (AEs), discharge destination after surgery etc.) will be collected via medical record review.

Data to be collected:

- Observer's assessment of alertness scale (OAA/S) (alertness/ sedation level), optional BIS-monitoring, other monitoring, clinical management
- Medical record review including but not limited to date of surgery, time to surgery, procedure type/ implant, anaesthesia and surgery time, use of a safe-surgery checklist, blood loss, transfusion, infusion, blood pressure (including pre-induction blood pressure, lowest intraoperative blood pressure, and the duration of a systolic blood pressure less than 20% from baseline), oxygen saturation, initial anaesthesia type, intrathecal agents administered, peripheral nerve blocks, benzodiazepines, intravenous opioids, anaphylaxis, aspiration, orthogeriatric care available
- Adverse Events (AEs) and serious adverse events (SAEs) according to the patient interview and medical charts

Visit 3-5 (Postoperative day 1-3), in-hospital patient-centred outcome phase

Daily assessment of delirium, pain and mortality via patient visit and interview on ward, if the patient is still in hospital. Documentation of AEs will occur via additional medical record review. Blinding will be encouraged during the first 4 postoperative visits, but it is not mandatory. A second investigator will perform these visits in a blinded manner as far as possible in the clinical routine. It will be documented for each visit, if blinding was preserved.

Study-specific in-person assessment on the 1st-3rd postoperative day, if the patient is still in hospital:

- Delirium (3D-CAM) assessment (3-5 min)
- Postoperative mortality assessment (2-5 min)
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 24 hours, quality of pain (5 min.) derived from the German pain questionnaire.[32]
- AEs and SAEs according to the patient interview and medical charts

Visit 6 (Postoperative day 4), in-hospital patient-centred outcome phase

Delirium, pain, mortality, and patient satisfaction will be assessed via patient visit and interview on ward, if the patient is still in hospital. If the patient is discharged before postoperative day 4, patient satisfaction will be assessed in addition to the respective visit 3-5. Documentation of AEs will occur via additional medical record review.

Blinding will be encouraged during the first 4 postoperative visits, but it is not mandatory. A second investigator will perform visit 6 in a blinded manner as far as possible in the clinical routine. It will be documented for this visit, if blinding was preserved.

Study-specific in-person assessment on the 4th postoperative day or at discharge (whatever occurs first), if the patient is still in hospital

- Delirium (3D-CAM) assessment (3-5 min)
- Postoperative mortality assessment (2-5 min)
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 24 hours. Pain quality (5 min.)
- Bauer Patient Satisfaction Questionnaire (3 min.)

- AEs and SAEs according to the patient interview and medical charts

Visit 7 (Hospital discharge day), in-hospital patient-centred outcome phase

All cause mortality, new-onset complications according to the NSQIP[27], other AEs, admission to Intensive Care Unit (ICU), length of stay in hospital and ICU, discharge destination, independence in walking, pain assessment, and medical pain management until postoperative day 4 will be assessed via medical record review and patient visit and interview on ward. This visit will be performed in addition to visit 3-6, if the hospital discharge occurs within the first 4 postoperative days. Blinding for Visit 7 will not be required.

Study-specific in-person and medical record assessment on the hospital discharge day

- In-hospital mortality (2-5 min); new-onset complications (bleeding requiring transfusion, myocardial infarction, congestive heart failure, stroke or transient ischemic attack, pneumonia, urinary tract infection, wound infection, systematic sepsis, thromboembolic complications, unplanned intubation, ventilator > 48 hours, acute renal failure, cardiac arrest requiring CPR or defibrillation, epidural haematoma requiring surgery, new paralysis of lower extremities, return to operating room, inpatient falls, unplanned postoperative mechanical ventilation, additional surgeries) (30-60 min)
- Assessment of admission to critical care, length of intensive care and hospital stay, discharge destination (5-10 min); Independence in walking (5 min)
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 24 hours, quality of pain (5 min.)
- Medical pain management until postoperative day 4
- AEs and SAEs according to the patient interview and medical charts

Visit 8 (Postoperative day 30 ± 3), post-discharge patient-centred primary outcome phase

Will be performed in a blinded manner via medical record review and telephone interview of the patient or rather the proxy. In case of serious cardiac or pulmonary complications, the family physician and / or the respective hospital will be contacted

in addition. Assessment of all-cause mortality or new-onset (i.e. not pre-existing at time of surgery) serious cardiac and pulmonary complications as defined by the NSQIP[27]. Furthermore, assessment of the secondary outcomes: Recovery of walking, pain intensity and quality, residential status, cognition, overall health and disability assessment and pain.

Study-specific follow-up on the 30 ± 3th postoperative day (via telephone interview)

- All-cause mortality and new-onset serious cardiac and pulmonary complications (see 7.1) (10-15 min)
- Recovery of walking, residential status (5 min)
- WHODAS 2.0 (overall health and disability) (5-10 min)
- Short Blessed Test (cognition) (5-10min),
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 2 weeks, quality of pain, intake of pain medication (5 min.)

Visit 9 (Postoperative day 180 ± 45), post-discharge patient-centred long-term outcome phase

Assessment of mortality, recovery of walking, residential status, cognition, overall health and disability assessment and pain intensity and quality via telephone interview of the patient or rather the proxy in a blinded manner.

Study-specific follow-up on the 180 ± 45th postoperative day (via telephone interview)

- All cause mortality assessment (2-5 min)
- Recovery of walking, residential status (5min)
- WHODAS 2.0 (overall health and disability) (5-10 min)
- Short Blessed Test (cognition) (5-10 min)
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 2 weeks, quality of pain, intake of pain medication (5 min.)

Visit 10 (Postoperative day 365 ± 60), post-discharge patient-centred long-term outcome phase

Assessment of mortality, recovery of walking, residential status, cognition, overall health and disability assessment and pain intensity and quality via telephone interview of the patient or rather the proxy in a blinded manner.

Study-specific follow-up on the 365 ± 60th postoperative day (via telephone interview)

- All cause mortality assessment (2-5 min)
- Recovery of walking, residential status (5min)
- WHODAS 2.0 (overall health and disability) (5-10 min)
- Short Blessed Test (cognition) (5-10 min)
- Pain assessment via numeric rating scale (0-10). The average and worst pain within the past 2 weeks, quality of pain, intake of pain medication (5 min.)

Dropout-handling and protocol deviations

Patients who withdraw their consent after randomization or who cannot be contacted for follow-up assessments will be handled as dropouts. Patients who withdraw consent before randomization will be considered as screening failures. All randomized patients (also with protocol deviations) will be followed up as long as possible according the intention-to-treat concept. Particularly, patients, who receive a treatment change (protocol deviation) have also to be followed up and will not be considered as dropouts, but the reason has to be documented clearly.

Sponsor monitoring

The CTC-A will be responsible for quality assurance through regular on-site monitoring, data and query management, reporting of AEs and annual safety reports. The CTC-A maintains a Quality Management System (QMS) for Clinical Trials and regularly implements Quality Assurance and Quality Control measures alongside the development and design as well as performance and reporting of clinical trials. The quality management system of the CTC-A complies with all relevant guidelines and also comprises a data protection system according to the Act to Strengthen the Security of Federal Information Technology. The quality management system consists of the quality management handbook and the quality assurance handbook, comprising standard operating procedures (SOPs), working instructions, forms, templates and checklists for all relevant tasks in accordance with the Helsinki Declaration, International Conference on Harmonisation Guideline for Good Clinical Practice (ICH-GCP), German Medical and Medical Device Act.

Monitoring procedures include four visits per site designed to clarify all prerequisites before the study commences (including initiation visit and close-out visit). Interim monitoring visits will take place on a regular basis according to a mutually agreed schedule. During these visits, the monitor will check for 100% subject eligibility (informed consent form; in- and exclusion criteria). Risk-based monitoring will be used for completion of the entries on the eCRF/CRF and the integrity of the source data with the eCRF/CRF entries. Furthermore the monitor will check the compliance with the clinical study protocol, ICH-GCP principles and the Declaration of Helsinki. Additionally, the monitor will check if all AEs and SAEs have been reported appropriately within the time periods required. The investigator and all staff will be expected to cooperate with the monitor by providing any missing information whenever possible. Further details of monitoring activities will be set forth in the monitoring manual.

Supplementary File 2

Main outcome definitions:

Myocardial infarction

1. Definition according to the European Society of Cardiology:[28]

Increase in serum cardiac biomarker (preferably cardiac troponin) values AND at least one of the following:

a) Symptoms of ischemia

b) New ST-segment or T-wave ECG changes or new left bundle branch block c) Pathological Q-waves

d) Radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality

e) Identification of an intracoronary thrombus

Pneumonia

Definition according to the definition of the REGAIN[24] and the ISOS trial[52]:

Criteria from **BOTH** Radiology and Signs/Symptoms/Laboratory evidence as listed below:

Radiology: One definitive chest radiological exam (X-ray or CT) with at least one of the following:

• New or progressive and persistent infiltrate

• Consolidation or opacity

• Cavitation

Signs/Symptoms/Laboratory:

At least one of the following:

• Fever (>38 °C or >100.4 °F) with no other recognized cause

• Leukopenia (<4000 WBC/mm3) or leukocytosis (≥12,000 WBC/mm3)

• For adults ≥ 70 years old, altered mental status with no other recognized cause and at least two of the following:

- new onset of purulent sputum or change in character of sputum, or increased respiratory
- secretions, or increased suctioning requirements
- new onset or worsening cough, or dyspnoea, or tachypnoea
- rales or bronchial breath sounds
- worsening gas exchange (hypoxia, increased oxygen or ventilator demand)

Pulmonary embolism

Definition according to the definition of the REGAIN[24] and ISOS trial:[52]

Diagnosis of a new blood clot or thrombus within the pulmonary arterial system confirmed by high probability V-Q scan, CT angiography, TEE, pulmonary arteriogram, or positive findings at autopsy.

Additional reference:

52. International Surgical Outcomes Study group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. Br J Anaesth 2016;117:601-9.

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

Section/item	ItemNo	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	31
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	29-30
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16, 18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17, 18, Suppl. File 1

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6,7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10, 11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11, 12, Suppl. File 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14, Suppl. File 1, Table 1
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11, Table 1 , Suppl. File 1

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11, Supplementary Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15, Suppl. File 1
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15, Suppl. File 1

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	not necessary, somebody is always unblinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15, Supplementary File 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16, 17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16, 17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18, Suppl. File 1

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18,20
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19, 20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	30/31
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21-22

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20-21
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21, 22
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not provided, only on request to the corresponding author
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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

Supplementary Table 2

Schedule of enrolment, interventions, and assessments according to the SPIRIT Statement

			Main STUDY PERIOD								
	Screening	Enrolment	Allocation	Post-allocation				Discharge	Follow-up		
TIMEPOINT/Visit**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
ENROLMENT:											
Eligibility screen	X		X§								
Informed consent	X										
Randomization			X								
INTERVENTIONS:											
Spinal anaesthesia				X							
General anaesthesia				X							
ASSESSMENTS:											
Screening for inclusion criteria: *1. ≥ 65 years with intra/-extracapsular hip fracture (femoral neck fracture, subtrochanteric or intertrochanteric fracture) requiring surgical intervention*	X		X								

Written informed consent												
Screening for exclusion criteria: *1. Institutionalisation by court or administrate order* *2. Concurrent surgery, which is not amenable to spinal anaesthesia* *3. Absolute contraindications to spinal anaesthesia* *4. Periprosthetic fracture* *5. Prior participation in the iHOPE study* *6. Exclusion as considered by any involved physician/ investigator regarding the patient or attending team*	X		X									
Patient demographics *(age, sex, race, weight, height, BMI, smoking status, alcohol status, ASA physical status*		X										
Residential status		X								X	X	X
Educational status		X										
Personnel data *(Contact information, do not resuscitate status)*		X										
Frailty assessment *(Short Minnesota Leisure Time Activities Questionnaire, weight loss, fatigue, grip strength)*		X										
Medical history		X										
Preoperative medication		X										
Most recent laboratory values from		X										

the clinical routine												
Most recent clinical data *(BP, HR, SpO_2, mechanical ventilation, oxygen requirement)*		X										
Ability/Recovery of walking		X							X	X	X	X
Type of hip fracture and planned kind of surgery		X										
Surgery- and anaesthesia related data acquisition				X								
Primary outcome variables												
• *All cause mortality*										X		
• *Serious cardiac and pulmonary complications*										X		
Assessment of secondary outcome variables												
• *Pain*		X			X	X	X	X	X	X	X	X
• *Medical pain management*									X			
• *Cognition (Short blessed test)*		X								X	X	X
• *Delirium (3D-Confusion Assessment Method)*		X			X	X	X	X				
• *Overall health and disability (WHODAS 2.0)*		X								X	X	X
• *Depression (Geriatric Depression Scale)*		X										

• *Bauer Patient Satisfaction Questionnaire*								X				
• *In-hospital events (Hospital and ICU-length of stay, outcomes according to the NSQIP, discharge destination)*									X			
• *Residential status*										X	X	X
• *All cause mortality*					X	X	X	X	X		X	X
• *Safety assessment (Intraoperative cardiac arrest; malignant hyperthermia; intraoperative anaphylaxis; intraoperative aspiration; total spinal anaesthesia; epidural hematoma; paralysis of the lower extremities lasting greater than 24 hours following spinal anaesthesia; fall within 12 hours of anaesthesia care)*				X	X				X			
• *Other adverse events*				X	X	X	X	X	X			

ASA, American Society of Anesthesiologists physical status; BMI, body mass index; BP, blood pressure; HR, heart rate; ICU, Intensive Care Unit; LOS, length of stay; NSQIP, National Surgical Quality Improvement Program; SpO2, peripheral oxygen saturation

§ Short re-evaluation of the eligibility before randomization

Specific time-points: ***Visit 0: Screening visit, conducted between the time of presentation and surgery via patient or proxy interview; **Visit 1: Preoperative evaluation visit**, conducted between the time of presentation and surgery via patient or proxy interview; **Visit 2: Hip-fracture surgery day**, conducted in the operating room; **Visit 3-6: In-hospital patient-centred outcome phase,** conducted on postoperative day 1-4; **Visit 7: Hospital discharge day.** Patient visit on ward and medical record review. This visit will be performed in addition to visit 3-6, if the hospital discharge occurs within the first 4 postoperative days; **Visit 8:** Postoperative day 30 ± 3. Medical record review and telephone interview of the patient or rather the proxy; **Visit 9**: Postoperative day 180 ± 45. Telephone interview of the patient or rather the proxy; **Visit 10:** Postoperative day 365 ± 60. Telephone interview of the patient or rather the proxy.*