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Improve hip fracture outcome in the elderly patient (iHOPE): a study protocol for a pragmatic, multicentre randomised 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 randomised 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, randomised controlled, open-label clinical trial with a two-arm parallel group design. In total, 1032 patients with hip fracture (>65 years) will be randomised 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 inhospital. 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 March 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 DRKS00013644; Pre-results

Strengths and limitations of this study

- ► Improve hip fracture outcome in the elderly patient (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 randomisation, which will enable more generalisable results for the iHOPE trial.
- ► iHOPE will apply a core outcome set and liaises with REGAIN (A Randomized Controlled Trial of Regional versus General Anesthesia to Promote Independence after Hip Fracture trial, which focuses on a different primary endpoint.
- ► We plan to combine data from iHOPE and the REGAIN trial after publication in an individualised patient data 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 patients with hip fracture across seven European countries. The prevalence of hip fractures among patients older than 50 years ranged from 307/100 000 in Finland to 1269/100 000 in Italy in the year 2007. The 30-day and 1-year mortality rates 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) recently published its '2017 Hip Fracture' report covering 60 178 medical records of patients with hip fracture who received surgical intervention from 1215 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 1-month mortality rate after hip fracture ranges from 4% to 12% and reaches up to 35% after 1 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 patients with hip fracture (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 polypharmacy. 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 American Society of Anaesthesiologists (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 patients with hip fracture.

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 (SAEs), for example, pneumonia, myocardial infarction and cerebrovascular events.[18] A secondary analysis of prospectively collected observational data confirmed the result for the 30-day 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 characterise 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 randomised 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 randomisation and further patient-centred outcomes up to 1 year.

OBJECTIVES

iHOPE will compare the efficacy of two different standard anaesthesia care approaches (spinal vs 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, randomised 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 generalisable for routine clinical practice. The

Table 1 Score 1: very explanatory; score 2: rather explanatory; score 3: equally pragmatic and 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, eg, 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. Cotreatment 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 four postoperative days and at the discharge day. Blinding will be encouraged during the first four 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 (eg, 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 prespecified subgroup analyses will be performed in addition.

iHOPE, Improve hip fracture outcome in the elderly patient.

pragmatic-explanatory continuum indicator summary-2 (PRECIS-2) tool[25] was used to determine the extent of our design as a pragmatic trial (table 1).

This study protocol is composed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. The SPIRIT checklist is provided in the online supplementary table 1.

Setting and duration

This study will be performed in at least 17 German secondary and tertiary hospitals. The list of centres can be obtained from 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.

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

A total of 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 online supplementary file 1, which comply with the standard care in Germany.

Participant timeline

Visits

All visits are presented in the online supplementary table 2, which shows the schedule of enrolment, interventions and assessments according to the SPIRIT statement, and described in detail in the online 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). Randomisation 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

Table 2 Eligibility criteria for patients

Inclusion criteria	Patients aged ≥65 years with acute intracapsular/extracapsular hip fracture (eg, 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 institutionalised 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 pharmacological anticoagulants within time frame, defined to contraindicate neuraxial block placement, as defined by the recommendations of the German Society of Anaesthesiology[38]; known or suspected unrepaired critical or severe aortic stenosis; known or suspected active skin infection at the planned needle insertion site; and 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 randomisation procedure (eg, patients will be excluded, if one treatment has preferably to be used in this patient according to the clinical situation).

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 four 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 (AEs) and additionally patient satisfaction on the fourth 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 (ie, not pre-existing at time of surgery) serious cardiac and pulmonary events up to 30 days after randomisation. 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,[27] pneumonia, pulmonary embolism, ventilator >48 hours and unplanned intubation. The primary endpoint will be assessed via in-person visits and medical record review during hospitalisation and via telephone interview after hospital discharge at day 30 after randomisation. Events after hospital discharge will only be considered as present if they led to hospital readmission or death. In case of hospital readmission, 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 cardiorespiratory complications[8 28] in patients with hip fracture.

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 online 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 randomisation. Delirium will be assessed via in-person interview by the validated, high sensitive and specific assessment tool 3D-Confusion Assessment Method.[29] It will be applied at baseline and daily on the first four 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 (0–10) and questions derived from the Brief Pain Inventory[30] and the German pain questionnaire.[31] 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[32] 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 randomisation 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[33]; and overall health and disability via WHO Disability Assessment Schedule 2.0 (WHODAS 2.0).[34] 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 SAEs like intraoperative cardiac arrest; malignant hyperthermia; intraoperative anaphylaxis; intraoperative aspiration; total spinal anaesthesia; epidural haematoma; paralysis of the lower extremities lasting greater than 24 hours following spinal anaesthesia; and 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-item short version of the Geriatric Depression Scale at baseline via in-person interview.[35] Frailty assessment will be performed according to phenotype-model of Fried at baseline via in-person interview.[36] 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, randomised '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.[28] 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 1-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 SAEs 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 (eg, 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 online 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 randomisation 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

Randomisation procedure will be stratified by site. The intended allocation ratio is 1:1. The selection of the best practice randomisation procedure to prevent selection and time trend bias will follow the Evaluation of Randomization procedures for Design Optimization (ERDO).[37] Details,

including the set of investigated randomisation procedures, the amount of biases and the decision will be given in a randomisation report (Department of Medical Statistics, University Hospital RWTH Aachen, Germany), which will be kept concealed up to closure of the database. The randomisation 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 randomisation assignment via the online data management system, which will be available on a 24/7 basis. Treatment allocation will be reported centralised 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 online supplementary file 1.

Training

Standardisation procedures will be implemented to ensure accurate, consistent, complete and reliable data, including methods to ensure standardisation among sites (eg, 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 minimised by application of the ERDO.[37] Performance bias will be minimised 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,[38] and monitoring during the trial. Attrition bias will be minimised 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 minimised since we will apply simple measurements, which are used in daily practise or are easy to perform (eg, WHODAS). Postoperative in-hospital outcome assessment will be conducted, wherever possible, in a blinded manner. All in-hospital outcomes will be documented using standardised definitions. Telephone follow-up for postdischarge outcomes assessment will be carried out in a blinded manner. The postdischarge assessors will be obliged not to open the electronic anaesthesia protocols that 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 randomisation procedure will minimise selection/recruitment bias.

Data management

All collected data will be entered in a paper-based 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 CRF (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.[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 International Council for Harmonisation (ICH E9).

The two-sided 95% CI for the HR 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 crossover. 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 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 AEs or SAEs. Descriptive safety analyses regarding the number of AEs 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 DSMB will be responsible for monitoring the data quality and the ongoing safety of subjects in the entire trial.

Data Safety Monitoring Board

A formal DSMB will consist of three anaesthesia (CN, DH and TH), one geriatric (RD), one psychiatrics (MalB) and one statistics expert (MatB), 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 online 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, 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 randomisation 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

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 subinvestigators. 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 (eg, 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 randomisation number. Each principal investigator will safely keep a list, which will allow the identification of the pseudonymised patients. The patient's informed consent, with their printed name and signature, will be filed separately in the investigator's file.

Patients will be informed that their data will be pseudonymised and handed to a third party anonymised. 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.

Poststudy treatment

No specific poststudy 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 emphasised 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 healthcare 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 organise 'information days' for patients. Stakeholders will be invited to participate. Such 'information days' may, for example, 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 ageing 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 nationally and 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 characterise 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 that 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 a total of 1032 randomised patients, will enable us to generate more generalisable results, which are applicable for a large number of individuals with hip fractures. However, we are aware of the risks of the 'real world' approaches, due to the lack of standardisation for anaesthesia in patients with hip fracture, 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 patients with hip fracture has pointed out seven 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,[44] even if not specifically focused on patients with hip fracture. 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 (eg, 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, 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[48] have suggested higher rates of delirium after sedation with low intraoperative Bispectral Index (BIS) values, 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 (ie, Observer's Assessment Of Alertness/Sedation Scale (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 harmonised. This will enable us to carry out an individualised patient data 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 AEs 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 American College of Cardiology/American Heart Association (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 (ie, 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, for example, anticoagulation into account.

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Contributors 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 and MDN), the Trial Statistician (R-DH), the Data Monitoring and Safety Board (CN, TH, DH, MalB, MatB and RD), the investigators of the participating iHOPE centres (CA, JA, MD, PetK, PasK, PetK, RL-F, CO, CR, RS, CS, OV, FW, MW, KZ and AZ) and other participating bodies (FH, HS, MS, DCW, MK, FS, CB and 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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Ethics approval Ethical approval EK 022/18 was obtained from the leading Ethics Committee of the RWTH Aachen University on 14 March 2018. An approval from all other involved local ethical committees was subsequently requested.

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