PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Kowark, Ana; Adam, Christian; Ahrens, Jörg; Bajbouj, Malek; Bollheimer, Cornelius; Borowski, Matthias; Dodel, Richard; Dolch, Michael; Hachenberg, Thomas; Henzler, Dietrich; Hildebrand, Frank; Hilgers, Ralf-Dieter; Hoeft, Andreas; Isfort, Susanne; Kienbaum, Peter; Knobe, M; Knuefermann, Pascal; Kranke, Peter; Laufenberg-Feldmann, Rita; Nau, Carla; Neuman, Mark; Olotu, Cynthia; Rex, Christopher; Rossaint, Rolf; Sanders, Robert; Schmidt, Rene; Schneider, Frank; Siebert, Hartmut; Skorning, Max; Spies, Claudia; Vicent, Oliver; Wappler, Frank; Wirtz, Dieter; Wittmann, Maria; Zacharowski, Kai; Zarbock, Alexander; Coburn, Mark; iHOPE study group, Collaborators

VERSION 1 – REVIEW

REVIEWER	Martyn Parker Peterborough city hospital, UK
REVIEW RETURNED	27-Apr-2018

GENERAL COMMENTS	Essentially this is an excellent protocol and study with no specific issue A few small issues that I have but should not alter the course of the study or acceptance of this protocol for publication Like many I am never happy with composite outcomes which are used to make the study statistically significant but I can see why the titlists devise these for the power calculation. As long as all outcomes are also reported separately for the systematic reviews this is OK and I much rather see such trials than no trials. The definition of outcomes such as cardiac and pulmonary events is not given in the protocol. For example ‘pneumonia’ may be just a few crackles in the chest to some. Important and relevant outcomes such as this need a clearly defined definition, ideally in the protocol and throughout the study so we all know what is being measured. For example below are those of the hip attack study Pneumonia Any one of the following: 1. Rales or crackles or dullness to percussion on physical examinations of chest AND any of the following: a. New onset of purulent sputum or change in character of sputum

	b. Isolation of organism from blood culture c. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy d. Isolation of virus or detection of viral antigen in respiratory c. Respiratory rate >20 breaths/min d. White blood cell count >12x109/L or , 4x109/L 2. Chest radiography showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following: a. New onset of purulent sputum or change in character of sputum b. Isolation of organism from blood culture c. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy d. Isolation of virus or detection of viral antigen in respiratory secretions or immunological pathogen identification (IgM titer) e. Histopathologic evidence of pneumonia Pulmonary embolism Any one of the following: 1. A high probability ventilation/perfusion lung scan 2. An intraluminal filling defect of segmental or larger artery on a helical CT scan 3. An intraluminal filling defect on pulmonary angiography 4. A positive diagnostic test for a deep venous thrombosis (i.e., positive compression ultrasound or venogram) and one of the following: a. non-diagnostic (i.e., intermediate probability) ventilation/perfusion lung scan b. non-diagnostic (i.e., subsegmental defects) helical CT scan Appendix to: The Hip Fracture Accelerated Surgical Treatment and Care Track (HIP ATTACK) Investigators. Accelerated care versus standard care in patients with hip fracture: the HIP ATTACK pilot trial. CMAJ 2013. DOI: 10.1503/cmaj.130901. Copyright © 2013 Canadian Medical Association and its licensors

REVIEWER	Iain Moppett University of Nottingham, UK
REVIEW RETURNED	30-Apr-2018
GENERAL COMMENTS	The authors describe the protocol for a large multicentre RCT of GA vs spinal anaesthesia for hip fracture. In general the study is well described and justification provided for the choices made. My comments are all relatively minor. ASA distribution: 8% ASA4 feels quite low - the UK data are a bit higher - around 12-14%. Tsang C, Boulton C, Burgon V, Johansen A, Wakeman R, Cromwell DA. 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. Johansen A, Tsang C, Boulton C, Wakeman R, Moppett I. Understanding mortality rates after hip fracture repair using ASA physical status in the National Hip Fracture Database. Anaesthesia. 2017;72:961-966.

	The more recent analysis fo GA vs spinal from NHFD is: 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;71:506-514. The NHFD has it's own website: NHFD.co.uk (Reference 3). I can't see the Patorno study mentioned. Patorno E, Neuman MD, Schneeweiss S, Mogun H, Bateman BT. Comparative safety of anesthetic type for hip fracture surgery in adults: retrospective cohort study. BMJ. 2014;348:g4022. Mention should probably be made of the REGARD study - although much smaller it is an ongoing GA vs spinal hip fracture study. http://www.isrctn.com/ISRCTN15165914 Have the authors considered approaching the PI to include this in the IPD meta-analysis? Pain - it is unclear whether this is at rest or on movement. Sedation - this issue has bedevilled hip fracture studies. Perhaps some discussion of the merits or otherwise of allowing sedation (and some reference to Sieber's work?) Similarly, the issue of what 'good' GA or spinal anaesthesia is needs some discussion. (I am of course conflicted in this - I have written and published on the topic). Perhaps also some reference to the recent FFN consensus (which steered clear of suggesting GA or spinal). How will patients allocated to spinal who require intra-op GA be assigned? Recruiting 1/3 patients feels quite optimistic. Do the authors have pilot data to support this? Given a free choice, how many patients do they think will choose one or the other technique and therefore be ineligible? It will be important to understand something about those patients not included. By definition the study only includes those where the clinicians and the patient have equipoise - which isn't the same as the total population. Some more information about time to theatre, orthopaedic management, haemoglobin management etc. might be helpful. I appreciate that centres will vary, but there should be a cor set of standards. Power analysis: I might be helpful to see the range of power analyses based on expected power, and a range of plausible and / or clinically significant differences in event rates. Outcomes - the Belfast group have been working on a core outcome set for anaesthesia studies: https://www.ncbi.nlm.nih.gov/pubmed/29397135 https://www.sciencedirect.com/science/article/pii/S0007091217540453 It might be worth contacting them to see what they found.

	Patient choice - this trial is written by researchers / anaesthesiologists. There is little mention of what patients might want. Very minor point: it should be the Principal Investigator (not principle). There are few English issues which will probably get sorted as the manuscript is revised. There are native English speakers on the author list who will be able to advise. My comments are intended to be constructive - some of the references are to work that I have been involved with, but I would not wish the authors to feel that they have to cite these works - they are for reference and information. I hope these comments are helpful and that the study goes well. Iain Moppett Nottingham, UK

REVIEWER	Dr Stuart M White Royal Sussex County Hospital, Brighton, East Sussex, BN2 5BE, UK
REVIEW RETURNED	30-Apr-2018

GENERAL COMMENTS	This is a well-designed study protocol. It's very similar to what the US/Canadians are attempting with their ongoing REGAIN study. I'm not confident, however, that the results will tell us anything new. Either there won't be a difference (due mainly to the vast number of variables operating within each group and/or the temporal disconnection between the moment of anaesthesia and the time-distant recording of outcomes) or there will be a difference (which will be more difficult to explain, given that no other studies have found much of a difference, and will suggest mainly that German anaesthetists are better at giving either spinal or general anaesthesia). Instead, could I implore the authors to consider spending their research money on comparing specific, evidence-based 'best practice' techniques of spinal (low dose, + block, minimal/monitored sedation, managed hypotension/cement insertion) vs general (spontaneously breathing, depth monitored, + block, managed hypotension/cement insertion) anaesthesia, to give a better idea of exactly what anaesthetic should be given to best ease these vulnerable patients through surgery and onto recovery?

REVIEWER	Lasocki, Sigismond Centre Hospitalier Universitaire d'Angers, Département Anesthésie Réanimation
REVIEW RETURNED	15-May-2018

GENERAL COMMENTS	Dr Kowark et al proposed a very interesting and fully detailed study protocol, for the iHOPE trial (Improve hip fracture outcome in the elderly patient). The study protocol is well written and detailed. The rational for the study and its design are valuable.

	Only few points deserve slight modifications/clarifications: - The introduction may be shortened. Notably the point regarding post-operative delirium is too much emphasized, since it is not a primary endpoint of the study. - The main comments concern the primary composite endpoint: the definition for myocardial infarction should be mentioned. Will troponin be measured systematically in each patient? If yes, at which time point? If it is not the case, this could be regarded as a limitation of the study and should be mentioned. - The authors promote a “pragmatic” study, to increase the external validity of the results. However, one point is very important to underscore: patients under anticoagulation will be excluded and they may represent a high proportion of these elderly population. This will certainly limit the number of eligible patients and could be pointed out in the limitations. - I’m not sure that the description of the objectives (ie: “iHOPE is composed to optimize the efficacy, clinical and cost effectiveness of anaesthesia care for hip fracture patients….”) corresponds exactly to the design and the primary outcome. Indeed, no costs analysis is scheduled, isn’t? Please reword it.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: martyn parker
Institution and Country: Peterborough city hospital, UK
Please state any competing interests or state ‘None declared’: none

Please leave your comments for the authors below
Essentially this is an excellent protocol and study with no specific issue

A few small issues that I have but should not alter the course of the study or acceptance of this protocol for publication

Like many I am never happy with composite outcomes which are used to make the study statistically significant but I can see why the titlists devise these for the power calculation. As long as all outcomes are also reported separately for the systematic reviews this is OK and I much rather see such trials than no trials.

Response: Thank you for your comment. Indeed, all our outcomes are also assessed separately.

The definition of outcomes such as cardiac and pulmonary events is not given in the protocol. For example ‘pneumonia’ may be just a few crackles in the chest to some. Important and relevant outcomes such as this need a clearly defined definition, ideally in the protocol and throughout the study so we all know what is being measured.

For example below are those of the hip attack study
Pneumonia
Any one of the following:

1. Rales or crackles or dullness to percussion on physical examinations of chest AND any of the following:
a. New onset of purulent sputum or change in character of sputum
b. Isolation of organism from blood culture c. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy d. Isolation of virus or detection of viral antigen in respiratory
c. Respiratory rate >20 breaths/min
d. White blood cell count >12x109/L or , 4x109/L

2. Chest radiography showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following:
a. New onset of purulent sputum or change in character of sputum
b. Isolation of organism from blood culture
c. Isolation of pathogen from specimen obtained by
transtracheal aspirate, bronchial brushing, or biopsy
d. Isolation of virus or detection of viral antigen in respiratory
secretions or immunological pathogen identification (IgM
titer)
e. Histopathologic evidence of pneumonia

Pulmonary embolism
Any one of the following:
1. A high probability ventilation/perfusion lung scan
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan
3. An intraluminal filling defect on pulmonary angiography
4. A positive diagnostic test for a deep venous thrombosis (i.e., positive compression ultrasound or venogram) and one of the following:
a. non-diagnostic (i.e., intermediate probability) ventilation/perfusion lung scan
b. non-diagnostic (i.e., subsegmental defects) helical CT scan

Appendix to: The Hip Fracture Accelerated Surgical Treatment and Care Track (HIP ATTACK) Investigators. Accelerated care versus standard care in patients with hip fracture: the HIP ATTACK pilot trial. CMAJ 2013. DOI: 10.1503/cmaj.130901. Copyright © 2013 Canadian Medical Association and its licensors

Response:

Thank you very much for your helpful and encouraging comments.

All centres received in addition to the study protocol a German-language manual of procedures. This manual explains required data collection for each visit in detail and provides detailed definitions for all study outcomes.

Outcome definitions for postoperative events have been harmonized with definitions used in the REGAIN trial, as we aim to combine our results later in the individualized patient data meta-analysis. All these applied outcome definitions were already used in the ISOS trial (http://isos.org.uk).

To address the reviewer's comments, we have added to our METHODS section under "primary outcome measure" new text, which appears below. Additionally, the main outcome definitions are now presented in a supplement to the manuscript, as described here:

"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. "

Furthermore, we have added our reference for the definition of myocardial infarction to the main text. On our iHOPE website (www.ihope-trial.org), which will be launched soon, we will have a public and a password secured area for the participating centres. All study documents, including the iHOPE manual and a detailed instruction video for delirium assessment, will be accessible by the iHOPE investigators in this secured area.

Reviewer: 2
Reviewer Name: Iain Moppett
Institution and Country: University of Nottingham, UK
Please state any competing interests or state 'None declared': I am a researcher in peri-operative care of hip fracture. I am a member of the Trial Management Group for REGARD - a study of GA vs spinal in hip fracture (focussed on delirium): https://warwick.ac.uk/fac/med/research/ctu/trials/regard/ I am a grant co-applicant with one of the many (middle) authors. We have not discussed this study and it is unrelated to our grant application. I have been a co-applicant for an unsuccessful international grant with the chief investigator some years ago, concerning hip fracture, but unrelated to this study.

Please leave your comments for the authors below
The authors describe the protocol for a large multicentre RCT of GA vs spinal anaesthesia for hip fracture.

In general the study is well described and justification provided for the choices made. My comments are all relatively minor.

ASA distribution: 8% ASA4 feels quite low - the UK data are a bit higher - around 12-14%.

Tsang C, Boulton C, Burgon V, Johansen A, Wakeman R, Cromwell DA. 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.
Johansen A, Tsang C, Boulton C, Wakeman R, Moppett I. Understanding mortality rates after hip fracture repair using ASA physical status in the National Hip Fracture Database. Anaesthesia. 2017;72:961-966.

Response: Thank you for this advice, we referred in this sentence to the German "Institut für Qualitätssicherung und Transparenz im Gesundheitswesen" (IQTIG) report. We have added now to the introduction that the numbers in the UK are even higher and have cited your proposed references.

The more recent analysis fo GA vs spinal from NHFD is:
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;71:506-514.

Response: According to the suggestions of reviewer #4, we have shortened our introduction and rephrased the summary about the available evidence. We have added text on page 7 to refer specifically to this reference as follows:

"*A secondary analysis of prospectively collected observational data confirmed the result for the 30-days mortality.*[19] "

The NHFD has it's own website: NHFD.co.uk (Reference 3).

Response: Thank you very much for your advice. We have corrected the reference and refer now in the INTRODUCTION text to the annual report 2017 as follows: "*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] "

I can't see the Patorno study mentioned.
Patorno E, Neuman MD, Schneeweiss S, Mogun H, Bateman BT. Comparative safety of anesthetic type for hip fracture surgery in adults: retrospective cohort study. BMJ. 2014;348:g4022

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Response: Thank you for this comment. This reference was already included in our meta-analysis [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].

But, we have added this reference to our INTRODUCTION on page 7 as follows:

"... 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] "

Mention should probably be made of the REGARD study - although much smaller it is an ongoing GA vs spinal hip fracture study. http://www.isrctn.com/ISRCTN15165914
Have the authors considered approaching the PI to include this in the IPD meta-analysis?

Response: Thank you for your advice. We didn`t have contact to the PI, yet. We will look into it and explore whether it might be feasible to combine the results of all three studies.

Pain - it is unclear whether this is at rest or on movement.

Response: We have added to the METHODS section on page 13 the following:

"*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.*"

Sedation - this issue has bedevilled hip fracture studies. Perhaps some discussion of the merits or otherwise of allowing sedation (and some reference to Sieber's work?)

Response: Thank you for your suggestion. We allowed a degree of flexibility in sedation to ensure feasibility of implementation across a diverse group of sites. Though, we did not make any defaults for

the exact performance of sedation during spinal anaesthesia, we have specified in our supplementary data file 1 that the target level of the OAA/S should not be less than 2.

We have added the following to our DISCUSSION part on page 23 "*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.*"

Validation work in this area is ongoing (see https://clinicaltrials.gov/ct2/show/NCT00590707) results are expected soon.

Similarly, the issue of what 'good' GA or spinal anaesthesia is needs some discussion. (I am of course conflicted in this - I have written and published on the topic).

Response: Thank you. We have added the following to our discussion part on page 22-23:

"*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]"

Additionally, in our supplementary data file 1 on page 4 we have specified clearer, which kinds of haemodynamic values are assessed in our study: *"... blood pressure (including pre-induction blood pressure, lowest intraoperative blood pressure, and the duration of a systolic blood pressure less than 20% from baseline)*"

Perhaps also some reference to the recent FFN consensus (which steered clear of suggesting GA or spinal).

Response: Thank you for your suggestion. Please see also our response to your previous question.

Additionally, we have added the reference to the FFN consensus paper to our sentence in the INTRODUCTION on page 7: "*So far, no specific anaesthesia management has been recommended for hip fracture surgery.*[16]" This refers to the following sentence in the FFN consensus paper: "The Committee's preferred recommendation, that either regional or general anaesthesia should be offered to patients, reflects current evidence, although it is worth noting that no Committee member agreed that general anaesthesia was usually preferable to regional anaesthesia."

How will patients allocated to spinal who require intra-op GA be assigned?

Response: All patients will be analysed according to their original allocation. These patients with change in the allocated treatment will be considered as patients with protocol deviation. All patients (also patients with protocol deviations) will be analysed according to the Intention-To-Treat principle. This was presented in the Supplementary File 1 under the section on handling dropouts. We have rephrased the heading of this section now into "Dropout-handling and protocol deviations" and we refer now to them in the METHODS section of the main manuscript on page 14.

Recruiting 1/3 patients feels quite optimistic. Do the authors have pilot data to support this?
Given a free choice, how many patients do they think will choose one or the other technique and therefore be ineligible? It will be important to understand something about those patients not included.

Response: The iHOPE trial will enrol 1032 patients across at least 17 sites over 24 months. A feasibility calculation was performed in initially 15 of these hospitals before submission of the grant application for this trial to the BMBF (German Federal Ministry for Education and Research).

Results of the feasibility calculation: The expected combined total hip fracture volume across 15 sites during the recruitment phase is approximately 4668 patients. Patients fulfilling the inclusion criteria during the recruitment phase account for about 3210 patients (69% of all hip fracture patients). The aforementioned estimates are based on the site's hospital data management systems. The site's PIs expected to be capable of randomising 1275 patients within the recruitment period, which accounts for 28% of all hip fracture patients and 40% of the patients fulfilling the inclusion criteria. The potential "over-recruitment" gives the iHOPE trial a 25% safety margin in the expected enrolment estimates. Without safety margin iHOPE would need to randomize 32% of the patients meeting the inclusion criteria. Additionally we have later decided to recruit two more centres for the trial. The iHOPE recruitment estimates are underlined by the REGAIN trial. The REGAIN trial obtained consent for 46% of screened patients meeting inclusion criteria over the first 6 months of accrual and randomised 36%. In addition, the recently published FOCUS trial enrolled 2016 out of 3132 eligible patients (64%) in a multicentre randomized trial assessing the transfusion management strategies in hip fracture patients using similar criteria as iHOPE. In addition, we have coordinated the European, multicentre, randomised trial to evaluate the incidence of postoperative delirium in the elderly hip fracture patient with xenon- or sevoflurane-based anaesthesia (HIPELD trial). Yet, an array of strict inclusion and exclusion criteria (e.g. patients without severe mental disorders, depression, preoperative delirium, or a score of < 24 in the Mini-Mental State Examination) lead to an inclusion rate of only 15% of all hip fracture patients in the total recruitment period. As a consequence, iHOPE aims to include all patients ≥ 65 years with acute hip fracture requiring surgical intervention within the inclusion period of two years and who gave signed informed consent to minimize recruitment delay. The study director of iHOPE will check weekly the actual recruitment rates within the centre by standardised enrolment reports, so that remedial action can be undertaken immediately. 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 site study staff when a hip fracture patient is admitted to the hospital.

We have added the following at the end of our DISCUSSION on page 24: "*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.* "

A screening list will capture all hip fracture patients during the recruitment period in each centre. Therefore, we will be able to identify the reasons for exclusion from the study.

By definition the study only includes those where the clinicians and the patient have equipoise - which isn't the same as the total population.

Response: Please see our response to your previous question. We refer to this limitation in our DISCUSSION on page 24 now.

Some more information about time to theatre, orthopaedic management, haemoglobin management etc. might be helpful. I appreciate that centres will vary, but there should be a cor set of standards.
Response: As explained above, we have added that the minimum standards of the participating centres adhere to the German national guidelines.

Time to theatre: According to the German Association for Trauma Surgery, hip-fracture surgery should be performed within 24h after hospital admission. We assess in our CRF the following times: Time to surgery after hospital admission, the exact anaesthesia induction time, incision time or procedure start time, end surgery or procedure (closure) time, anaesthesia cessation time (In case of spinal anaesthesia: permission to leave operating room by the attending anaesthesist/ In case of general anaesthesia: Cessation of the hypnotic agent).

Orthopaedic management: The surgical technique will be in line with the standard national policies. We assess the exact surgery type according to the German OPS codes (operation and procedure keys), which includes the question, if cement was used.

Regarding the haemoglobin management: We assess the amount of intraoperative transfusion of blood products, the preoperative haemoglobin level and the postoperative haemoglobin level within

the first two hours after wound closure. All centres have to follow the blood transfusion guideline of the German Medical Association.

In our manuscript we refer to our Supplemental File 1, where we present several data, which will be collected during surgery and after surgery.

"...*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*"

Power analysis:
I might be helpful to see the range of power analyses based on expected power, and a range of plausible and / or clinically significant differences in event rates.
Response: Thank you for your comment. Knowing that the estimated sample size is very sensitive to the different assumptions such as accrual time, duration of follow-up, the parameter for the dropout rate and the location of the difference between the groups, we have chosen all these parameters after careful consideration. Deviations from the assumptions can equally lead to an increased or reduced sample size. For example, if we assumed 7% instead of 6% difference between the groups. Then we would need 394 per group instead of 516 if all other assumptions remained the same. At 5% instead of 6% we would need 713 per group.

Outcomes - the Belfast group have been working on a core outcome set for anaesthesia studies:
https://www.ncbi.nlm.nih.gov/pubmed/29397135
https://www.sciencedirect.com/science/article/pii/S0007091217540453
It might be worth contacting them to see what they found.

Response: Thank you for your suggestion. We have been in contact with them during the FFN meeting. Yet, their article was published after we had finished and submitted our study protocol to the ethics committee and the funder. The iHOPE study is already recruiting. All iHOPE outcome measures are in accordance with the previously agreed core outcome set (COS) for hip fracture patients [Haywood KL et al. Developing a core outcome set for hip fracture trials. BJJ 2014; 96-B: 1016-23].

Patient choice - this trial is written by researchers / anaesthesiologists. There is little mention of what patients might want.

Response: As pointed out in our ETHICS AND DISSEMINATION section under the subheading "**Patient and Public Involvement"** the trial protocol was reviewed and modified by two representatives of the patients. These are the authors Hartmut Siebert (Aktionsbündnis Patientensicherheit e.V., Berlin, (German Coalition for Patient Safety)) and Max Skorning (Senior Consultant, Section Patient Safety, Medical Advisory Service of Social Health Insurance). Furthermore, we have conducted interviews with patients after their hip-fracture surgery, to retrieve their opinion about the hip-fracture surgery before finalisation of the study protocol.

Very minor point: it should be the Principal Investigator (not principle). There are few English issues which will probably get sorted as the manuscript is revised. There are native English speakers on the author list who will be able to advise.
Response: Thank you for your advice. Our native speaking co-authors have entirely revised the manuscript.

We have also replaced "Principle investigator" by "Principal Investigator" throughout the manuscript.

My comments are intended to be constructive - some of the references are to work that I have been involved with, but I would not wish the authors to feel that they have to cite these works - they are for reference and information.

I hope these comments are helpful and that the study goes well.

Reviewer: 3
Reviewer Name: Dr Stuart M White
Institution and Country: Royal Sussex County Hospital, Brighton, East Sussex, BN2 5BE, UK
Please state any competing interests or state ‘None declared’: Mark Coburn was a co-author on recently (2018)published Consensus Guidelines on the Anaesthetic management of patients with Hip Fracture, that I convened

Please leave your comments for the authors below
This is a well-designed study protocol. It's very similar to what the US/Canadians are attempting with their ongoing REGAIN study.

Response: Thank you for your comment.

I'm not confident, however, that the results will tell us anything new. Either there won't be a difference (due mainly to the vast number of variables operating within each group and/or the temporal disconnection between the moment of anaesthesia and the time-distant recording of outcomes) or there will be a difference (which will be more difficult to explain, given that no other studies have found much of a difference, and will suggest mainly that German anaesthetists are better at giving either spinal or general anaesthesia).

Response: Thank you very much for this comment. We agree that interpretation of any randomized study, particularly one conducted in the context of clinical practice, may be complicated. However, one strength of the proposed study is the randomized design, which will offer substantial advantages for assessment of causal effects over available non-randomized studies in this area. In this way, it will represent an important means of validating and extending ongoing work in the US and Canada.

Instead, could I implore the authors to consider spending their research money on comparing specific, evidence-based 'best practice' techniques of spinal (low dose, + block, minimal/monitored sedation, managed hypotension/cement insertion) vs general (spontaneously breathing, depth monitored, + block, managed hypotension/cement insertion) anaesthesia, to give a better idea of exactly what

anaesthetic should be given to best ease these vulnerable patients through surgery and onto recovery?
Response: Thank you for this comment. We do not disagree that potential insight could be gained from a less pragmatic design (i.e. one that specifies aspects of intraoperative care more tightly than is done in iHOPE or REGAIN). At the same time, we respectfully submit that the proposed design will provide important insights regarding the outcomes of spinal versus general anaesthesia as applied in daily clinical practice that such a „best practice“ trial could not provide.

Reviewer: 4
Reviewer Name: lasocki
Institution and Country: Département Anesthésie Réanimation, CHU Angers, Angers F-49000, France
Please state any competing interests or state ‘None declared’: None with this subject

Please leave your comments for the authors below
Dr Kowark et al proposed a very interesting and fully detailed study protocol, for the iHOPE trial (Improve hip fracture outcome in the elderly patient).

The study protocol is well written and detailed. The rational for the study and its design are valuable. Only few points deserve slight modifications/clarifications:

- The introduction may be shortened. Notably the point regarding post-operative delirium is too much emphasized, since it is not a primary endpoint of the study.

Response: Thank you for your advice. We have deleted the "delirium" part in our introduction and shortened the part about actual evidence for general vs. regional anaesthesia on page 7 as follows:

"*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.*"

- The main comments concern the primary composite endpoint: the definition for myocardial infarction should be mentioned. Will troponin be measured systematically in each patient? If yes, at which time point? If it is not the case, this could be regarded as a limitation of the study and should be mentioned.

Response: Thank you for this important point of view. Please refer also to our second response to reviewer #1. We have added now in the Supplementary File 2 the main outcome definitions, which include the myocardial infarction.

According to the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing non-cardiac surgery, it is not recommended to measure the perioperative troponin values for all patients. As we intend to receive results from the "real-world", the serum troponin concentration will be measured at attending physician's discretion. We have added this to our DISCUSSION on page 24 as follows: "*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] "

- The authors promote a "pragmatic" study, to increase the external validity of the results. However, one point is very important to underscore: patients under anticoagulation will be excluded and they may represent a high proportion of these elderly population. This will certainly limit the number of eligible patients and could be pointed out in the limitations.

Response: Thank you for your advice. Please refer also to our response #11 to Reviewer #2, regarding our pre-study feasibility analysis.

The following was added to the DISCUSSION on page 24: "*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."*

- I'm not sure that the description of the objectives (ie: "iHOPE is composed to optimize the efficacy, clinical and cost effectiveness of anaesthesia care for hip fracture patients….") corresponds exactly to the design and the primary outcome. Indeed, no costs analysis is scheduled, isn't? Please reword it.

Response: Thank you very much for your comment! We have rephrased it as follows: "*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....*"

VERSION 2 – REVIEW

REVIEWER	Lasocki, Sigismond Centre Hospitalier Universitaire d'Angers, Département Anesthésie Réanimation

REVIEW RETURNED	30-Jul-2018

GENERAL COMMENTS	All my points have been addressed