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Evaluation of the geriatric co-management for patients with fragility fractures of the proximal femur (geriatric fracture center (GFC) concept): protocol for a prospective multicenter cohort study

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TITLE: Evaluation of the geriatric co-management for patients with fragility fractures of the proximal femur (geriatric fracture center (GFC) concept): protocol for a prospective multicenter cohort study

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ABSTRACT

Introduction

Treatment of fractures in the elderly population is a clinical challenge due partly to the presence of comorbidities. In Geriatric Fracture Centers (GFC) patients are co-managed by a geriatrician in an attempt to improve clinical outcomes and reduce morbidity and mortality. Until now the beneficial effect of orthogeriatric co-management has not been definitively proven. The primary objective of this study is to determine the effect of GFC on predefined major adverse events related to a hip fracture compared to usual care centers (UCC). The secondary objectives include assessments in quality of life, patient reported outcomes and cost-effectiveness.

Methods and analysis

Two hundred and sixty-six elderly hip fracture patients planned to be treated with osteosynthesis or endoprosthesis in either a GFC or UCC study site will be recruited, 133 per type of center. All procedures and management will be done according to the site's standard of care. Study-related visits will be performed at the following timepoints: preoperative, intraoperative, discharge from the orthopedic/trauma department, discharge to definite residential status, 12 weeks and 12 months post-surgery. Data collected include demographics, residential status, adverse events, patient reported outcomes, fall history, costs and resources related to treatment. The risk of major adverse events at 12 months will be calculated for each center type; patient reported outcomes will be analyzed by mixed effects regression models to estimate differences in mean scores between baseline and follow-ups whereas cost-effectiveness will be assessed using the incremental cost-effectiveness ratio.

Ethics and dissemination

Ethics approval for this study was granted from the local Ethics committees or Institutional Review Board from each of the participating sites prior to patient enrollment. The results of this study will be published in peer-reviewed journals and presented at different conferences.

Trial registration number: ClinicalTrials.gov: NCT02297581

STRENGHTS

- Study design: international multicenter observational cohort study
- Ability to provide real world data
- Well defined and assessable primary objective
- Comprehensive multidimensional approach to the problem combining objective and patient reported outcomes with health economic aspects

LIMITATIONS

- Dropouts due to loss of follow up or deaths might be a source of bias
- Reliable assessment of patient reported outcomes require compliant patients
- Assessment with a longer follow up might be required

INTRODUCTION

The number of geriatric trauma patients is steadily increasing worldwide due to a longer life expectancy. Older adults with osteoporotic fractures tend to have one or more comorbidities and therefore the treatment of geriatric fractures is complex. Increased mortality, disability, complications and high health care costs are some of the consequences of this problem (1, 2). To improve treatment outcomes in patients with osteoporotic fractures, multidisciplinary treatment approaches have been implemented. The principle of involving a geriatrician into the integral management of elderly patients, referred to as orthogeriatric co-management, was first introduced in Australia and the United Kingdom in the 1950s, but has rarely been applied until today (3). Few models testing different elements of specific geriatric care have led to inconclusive data. The latest Geriatric Fracture Centers (GFC) improved the principles of geriatric co-management by working in interdisciplinary teams and starting their interventions already preoperatively to achieve improved clinical outcomes. In this latest setting, the orthopedic surgeon and the geriatrician manage the patient together in an orthopedic ward and standardized treatment paths are implemented (4-6).

Less sophisticated models include geriatric consultant services in an orthopedic ward or orthopedic consultant service in a geriatric and rehabilitation ward (7-9). Overall, the main goals of an orthogeriatric co-management are reduction of complications, readmission and mortality, return to pre-fracture status, improvement of patient and family satisfaction, provision of best value of care to the health system and secondary fracture prevention (10). In 2013, an expert consensus (10) suggested 12 outcome parameters and assessment tools for the evaluation of different orthogeriatric co-management models in hip fracture treatment, which included: mortality, length of stay (midnight census method), time to surgery, complications, readmission rate, mobility (Parker Mobility Score, Timed Up and Go [TUG] test), quality of life (EQ-5D), pain (Verbal Rating Scale [VBS]), activities of daily living (Barthel Index), medication use (adverse drug reactions), place of residence and costs.

To achieve improved clinical outcomes in the elderly, the following key principles have been suggested (4, 11): Prioritization of the geriatric patient, which results in shorter time to surgery, early surgical stabilization of the fracture, frequent communication to avoid iatrogenic problems, estimation of the risk of developing delirium, attention to comorbidity, consideration to nutritional aspects, prevention of falls and osteoporosis care, early mobilization of the patient with weight bearing as tolerated, begin discharge planning at admission and use of standardized protocols.

Despite some research in the area, until now the beneficial effect of orthogeriatric co-management has not been definitively proven. A systematic literature review (7) identified 21 studies and grouped them into four treatment models. The integrated care model showed the lowest mean values regarding in-hospital mortality rate (1.14%), the lowest length of stay (7.39 days) and the lowest mean time to surgery (1.43 days). Although different outcome parameters were reported in different studies, a later systematic literature review and metaanalysis (12) showed no significant improvement for length of stay after specialized geriatric care and the relative risk of intrahospital and one year mortality seemed to be reduced, but without statistical significance (p = 0.34, p = 0.17, respectively). Care pathways and co-management of geriatric hip fracture patients need to be further evaluated in order to determine the value of interdisciplinary geriatric interventions on care quality and cost-effectiveness.

OBJECTIVES:

The primary objective of the study is to determine the effect of GFC on predefined major adverse events (AEs) that have a relationship to the treatment, immobilization or residential status within the 12 months following a fracture fixation surgery compared to usual care centers (UCC).

The secondary objectives include comparison between the two types of care in quality of life, activities of daily living, AEs of any kind, hospital readmissions, mobility status, falls, pain level, return to pre-injury status, time from admission to surgery, medications, adaptation to nutritional status, cost-effectiveness and the validation of a model to predict the risk of sustaining a contralateral hip fracture.

TRIAL DESIGN AND METHODS

Study design

This is a prospective, international, multicenter, observational cohort study to test the superiority of GFC over UCC.

The definition of a GFC is based on clear and objective criteria for a geriatric co-management program which are as follow: general geriatrician or orthogeriatrician available in trauma/orthopedic department, patient is seen by the geriatrician prior to surgery (except if the patient is admitted over night or during weekends), existence of local medical guidelines consented by orthopedic surgeons and geriatrician, predefined order set for assessing laboratory values, predefined patient pathway to guarantee a fast

track in the emergency room, daily communication among involved specialists from the postoperative phase until discharge from orthopedic/ trauma department and daily visits to the patient by the following specialists: geriatrician, orthopedic surgeon in combination with nurse, physiotherapists (except weekends) and social workers if required.

A UCC is defined as a center in which: No geriatrician is available in trauma/orthopedic department, preoperative visit by a geriatrician is not a standard, there are no predefined medical guidelines for geriatric fracture patients and daily visits to the patient from the postoperative phase until discharge from orthopedic / trauma department by a geriatrician are not standard.

Any other postoperative treatment not specifically described in this investigation is performed according to the standard of care at the study site.

A world wide open call was launched to invite interested sites to participate. A total of 12 sites are participating in this study. In order to account for local differences in health care systems and to allow comparisons based on geographic regions as well as globally, a GFC and a UCC within each participating country were selected. The site selection process has been described in detail in the accompanying publication (insert ref).

Participants

Eligible patients must meet the following inclusion criteria:

1) Age 70 years and older

2) Diagnosis of hip fracture treated either with osteosynthesis or endoprosthesis

3) Ability of the patient or assigned representative to understand the content of the patient information/Informed Consent Form

4) Signed and dated IRB/EC-approved written informed consent

Exclusion criteria:

1) Recent history of substance abuse (ie, recreational drugs, alcohol) that would preclude reliable assessment

2) Prisoner

3) Participation in any other medical device or medicinal product study within the previous month that could influence the results of the present study

Procedures

Recruitment

The assessment of eligibility will be performed by the investigator or a study coordinator, who will approach each potential study patient and inquire about their interest and eligibility in participating in this study. If the patient wishes to participate, a legally eligible member of the research team will go through the informed consent process, explaining the purpose of the study, procedures, risk/benefits, alternatives to participation, and data protection. Each patient choosing to participate will sign and date an Informed Consent Form. A copy of the signed Informed Consent Form will be placed into the patient's medical record, the Investigator Site File or the patient binder and one copy will be handed over to the patient. All patients with written informed consent will be allocated to a unique patient trial number. The date of informed consent and the recruitment information is entered in the study database. All patients who commence treatment within the study are considered as enrolled and all enrolled patients should be followed up within the study, except if their study participation is prematurely terminated. All patients recruited in a GFC or UCC are automatically allocated to the GFC and UCC analysis group, respectively.

Baseline assessment

All patients that were screened for the inclusion and exclusion criteria are entered on the patient pre-screen and enrollment log maintained at each study site. Demographical data, comorbidities, cognitive status/dementia, and psychological situation will be assessed. The Parker Mobility Score, modified Barthel Index and residential status are assessed referring to the patient's pre-injury status. Details relative to the injury (side affected, fracture classification, concomitant fractures), surgery (surgical time, type of implant, anesthesia), comorbidities, nutritional status, intake of relevant medication will be documented as well.

Interventions

All treatments and follow-up (FU) visits received in either GFC or UCC will be according to the hospital's standard of care. Study-related assessments will be performed at discharge from the orthopedic trauma/department (Discharge 1), discharge to definite residential status (Discharge 2), 12 weeks and 12 months post-surgery. Number of visits by a geriatrician, orthopedic surgeon and physiotherapist from surgery to discharge will be documented, as well as involvement of social workers and interventions aimed to prevent secondary fractures. The study-related assessments are summarized in Table 1.

Assessment parameters	Pre- intra- and postoperative visits **						
	Screening / Preoperative	Intraoperative (day 0)	Discharge 1 (± 3 days)	Discharge 2 (± 3 days)	12 (± 4) weeks	12 (± 1) months	
Patient information / consent	X						
Eligibility	X						
Demographics	X						
Charlson Comorbidity Index	X						
Screening assessments	X						
Pre-injury residential status	X*						
Clinic organization	X		X				
Timing of baseline activities	X	X					
Nutrition status evaluation			X	X	X	X	
Cognitive status			X	X			
Injury and surgical details		X					
Activities of daily living:							
Pre-injury Modified Barthel Index			X*				
Modified Barthel Index			X	X	X	X	
EQ-5D					X	X	
Pain			X	X	X	X	

Readmission					X	X
Residential status			X	X	X	X
Mobility:						
Pre-injury Parker Mobility Score			X*			
Parker Mobility Score				X	X	X
TUG test				X	X	X
Falls			X	X	X	X
Contralateral hip fracture				X	X	X
Pre-injury analgesics			X*			
Medication details	X		X	X	X	X
Major adverse events		X	X	X	X	X
Other adverse events		X	X	X	X	X
Direct and indirect costs	X	X	X	X	X	X

§ Discharge 1 and 2 may occur on the same date

* Data are retrospectively assessed referring to the pre-injury status.

** All postoperative FUvisits with the defined time windows are calculated from the day of surgery (i.e. day 0).

Outcome measures

Primary outcome measure

The major predefined AEs related to treatment / residential status / immobilization include and are limited to:

- Delirium (acute confusional state): common, serious, and potentially preventable source of morbidity and mortality for older hospitalized patients and is determined based on the Confusion Assessment Method (CAM). CAM was originally validated for use based on observations made during a brief, structured interview that included the Mini-Mental State Examination and Digit Span Test (13). In this study, the Mini-Mental State Examination (MMSE) will be used to assess the cognitive status of the patient

- Congestive heart failure: clinical disorder that results in pulmonary vascular congestion and reduced cardiac output (14). Congestive heart failure should be considered in the differential diagnosis of any adult patient who presents with dyspnea and/or respiratory failure. The diagnosis of heart failure is determined based on the Modified Framingham Criteria (15)
- Pneumonia: is an inflammation of the lung that is most often caused by infection with bacteria, viruses, or other organisms. Diagnosis of pneumonia is done according to the local standard of care through imaging or body fluid laboratory testing
- Deep venous thrombosis is evaluated by the local investigator based on clinical examination and confirmed using any of the following techniques, as per local standard of care through ultrasound, phlebography or other techniques
- Pulmonary embolism: is evaluated by the local investigator based on clinical examination and confirmed using any of the following techniques, as per local standard of care through CT scans, angiography, radionuclide examination
- Pressure ulcers are defined as a localized injury of ≥ 2 cm diameter to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear
- Myocardial infarction is defined as evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia

Secondary outcome measures

- Any other AEs not mentioned under the predefined major AE. Of special interest are new fractures resulting from a fall in particular contralateral hip fractures
- Mortality: will be assessed in 4 time frames: perioperative (from admission until 72 hrs post-surgery), and within the first 14, 30 and 365 days after surgery
- Activities of daily living measured using the modified Barthel Index
- Quality of life using EuroQoL5 (EQ-5D)
- Pain using the numerical rating scale (NRS)
- Timing of baseline activities: defined as time elapsed to surgery, start of pain management, fluid management and acute care since admission

- Hospital readmissions: is defined as any admission to a hospital (whether or not the study site) after the baseline visit up to the 12-month FU. As not all readmissions occur in the same initial hospital, the patient or proxy is asked at the FU time points whether any readmission has occurred
- Residential status: will be defined within the next 4 categories: living alone at their own home (or with a roommate), living with a spouse/partner at their own home, living with children or sibling and living in a facility, defined as a non-family environment such as a nursing home or supervised residential setting. Details of care provided by family members and/or professional staff (physician, nurse, geriatrician) will be recorded as one of the following categories: 24 hour care, daily, irregular and no care
- Mobility assessed with the Parker Mobility Score and TUG test
- Secondary fracture prevention: are strategies to avoid secondary fractures, which include strength and balance training, home hazard assessment, vision assessment and medication review. The participation of the patient in such a program will be documented
- Medications: number and type of medications. Of particular interest are the use of analgesics, osteoporosis treatment, drugs that increase the risk of delirium (neuroleptics, benzodiazepines, morphine and derivates)
- Cost-effectiveness: costs and resources related to the treatment will be assessed for the in-hospital stay. After discharge, the patient will document all direct and indirect resources in a Cost Diary that will include number of days the patient is unable to perform usual activities and lost work productivity by family members taking care of the patients. The cost of the geriatric co-management will be collected from each participating clinic. Quality-adjusted life years (QALYs) will be derived from the EQ-5D

Instruments

- Mini Mental State Examination (MMSE): is a tool that can be used to systematically and thoroughly assess mental status. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. The MMSE is effective as

a screening tool for cognitive impairment with older, community dwelling, hospitalized and institutionalized adults (16).

- Confusion assessment method (CAM): was originally developed in 1988-1990 to improve the identification and recognition of delirium. The CAM was intended to provide a new standardized method to enable non-psychiatrically trained clinicians to identify delirium quickly and accurately in both clinical and research settings. The CAM is usually rated by a clinical or trained lay interviewer on the basis of an interview with the patient that includes at least a brief cognitive assessment.
- Barthel Index: is an ordinal scale and each performance item is rated with a given number of points assigned to each level or ranking. It uses 10 variables describing activities of daily living and mobility. A higher number is associated with a greater likelihood of being able to live at home with a degree of independence following discharge from hospital. The score has been used extensively to monitor functional changes in individuals receiving in-patient rehabilitation, mainly in predicting the functional outcomes related to stroke. The modified Barthel Index (17, 18) has demonstrated high inter-rater reliability (0.95) and test-retest reliability (0.89) as well as high correlations (0.74–0.8) with other measures of physical disability.
- EQ-5D: standardized instrument that was designed for self-completion. It has five items (mobility, self-care, usual activities, pain/discomfort anxiety/depression) with a categorical response scale where health today is assessed. A good evidence for reliability, validity and responsiveness both for SF36 and EQ-5D has been shown (19, 20).
- Numerical rating scale (NRS): self-reported score based on a numerical rating scale that ranges from 0 to 10 to evaluate the presence and intensity of pain. A higher value implies greater pain.
- Parker Mobility Score: is a functional assessment with three walking ability questions that can each attain a maximum of 3 points. The final calculated score ranges from a minimum of 0 points to 3 or 9 points at maximum. The higher the score, the higher the function (21).
- Timed Up and Go test (TUG): is a commonly used screening tool to assist clinicians to identify patients at risk of falling. It measures the time (in seconds) that it takes for an individual to rise from an armchair (chair seat height = 45 cm / 1.5 feet), walk 3 meters (= 10 feet) to a line drawn on the floor, turn around and return to the chair. The total time taken for the patient to complete the entire task is the outcome measure. Those who complete the test in less than 10 seconds are freely mobile, patients completing the test between 10 and 19 seconds are independent for basic

transfers, and those who need 20-29 seconds to complete the test often use a cane. Patients with 30 seconds and more are much more dependent on walking aids and typically they need help with chair or toilet transfer (22, 23).

Sample size estimation

The sample size calculation has been performed on the basis of difference in the risk of major AEs. At one year following surgery, the risk of at least one major adverse event was estimated at 35% for GFC group and at 55% for the UCC Group. With a significance level of 5%, a power of 80%, and equal treatment groups, a sample size of 212 patients (106 per group) was calculated. This total was adjusted for an expected loss of patients of about 20%, giving an estimated total sample size of 266 patients (133 per group).

Statistical analyses

The primary analysis will be conducted using firstly the full analysis population ("enrolled" patients), and subsequently the per-protocol population. The risk of major AEs related to the treatment, hospitalization and/or immobilization occurring from surgery to the 1-year FU and regardless of time point of data collection will be reported at the patient level along with the 95% confidence intervals according to each treatment group. In addition, univariable and multivariable Poisson regression models will be used whereby the outcome will be the actual number of major AEs related to the treatment, hospitalization and/or immobilization.

Secondary analyses will be conducted using the per-protocol population. Initially, univariable statistical tests (e.g. Chi-square test or Fisher's exact test for categorical variables; t-test or Wilcoxon rank-sum test for continuous variables) will be used to evaluate differences in clinical and administrative parameters between the two treatment groups. Subsequently, longitudinal data will be analyzed by means of mixed effects regression models to estimate differences in mean scores (e.g. EQ-5D, modified Barthel Index, TUG, Parker Mobility Score, pain NRS) between FU and the respective baseline assessment by treatment group. The proposed cost-utility analysis will use decision modelling and sensitivity analysis techniques to ensure the robustness of the study's conclusions. Cost-effectiveness will be assessed using the incremental cost-effectiveness ratio, which is

determined by calculating the difference in costs divided by the difference in QALYs between the GFC and the UCC groups.

Enrolled patients who withdraw from study FU for any reason (withdrawal of consent, death, loss to FU, etc.) will be included in the analysis until the time at which they withdrew.

Data collection and management

Data handling and protection are conducted according to the ISO 14155 guidelines and ICH-GCP and applicable regulations. An electronic Case Report Form (eCRF) in REDCap (24) will be designed to accommodate the specific features of the study. Modifications of the eCRF will be made only if deemed necessary and in accordance with any amendment to the study protocol. Access to the eCRF is password protected and specific functions are assigned (e.g. study coordinator, investigator, monitor, etc.). The eCRF is to be completed in a timely manner after a patient's visit (i.e. 14 days after occurrence of a documentable event). During the site initiation visit and prior to recruiting the first patient, the research team at each site will undergo a defined training program that will include explanations on inclusion and exclusion criteria, study procedures, how to use the eCRF and general aspects of ISO 14155 and GCP. Monitoring visits will be performed as frequently as required to guarantee the completeness and accuracy of the information in the eCRF. At the end of the study, a site close out visit will be performed and all final clarifications will be done. Source data and any other essential documents have to be archived according to the legal requirements at the study site. Clinical study data (i.e. eCRF) and essential documents will be archived by the sponsor according to legal requirements.

Premature termination

Due to the nature and design of the study there are no stopping rules defined. All treatments are per standard of care and no additional or investigational medical device or medication is applied during the investigation.

Reporting of adverse events

All AEs are collected. In case of a serious adverse event, the sponsor is immediately notified. AEs and serious adverse events need to be reported by the investigator to the EC/IRB according to their regulatory requirements.

ETHICAL CONSIDERATIONS AND DISSEMINATION

This is an observational study in which vulnerable patients who are in an emergency situation, mentally incompetent (temporarily or permanently) or able to give oral consent only might be included. In these cases, surrogate consent will be obtained according to the local regulation and the patient's informed consent will be obtained as soon as possible. This study has been registered in Clinical Trials.gov under registration number NCT02297581. Ethics approval for this study was granted from the local Ethics committees or Institutional Review Board from each of the 12 participating sites prior to patient enrollment commenced at each site. The results of this study will be published in peer-reviewed journals and presented at different conferences.

DISCUSSION

Fragility fractures and their care are an increasing challenge to health care systems and societies. Due to the great number of comorbidities present in elderly patients, geriatric fractures and their treatment present several complications. Different orthogeriatric concepts have been developed to improve patient's outcome but until now, the beneficial effect of these models could not be proven. The results of this study are expected to give important evidence on the impact of geriatric co-management for patients with fragility fractures regarding the quality of life, outcomes in the elderly and cost-effectiveness. As we increase our life expectancy and the demographic pyramid continues to shift, these problems will be an increasing economic and social burden in particular in industrialized countries.

CURRENT STUDY STATUS

Patient recruitment started in June 2015 and will continue until October 2016. Data collection will be completed (last patient last visit) on November 2017.

AUTHORS' CONTRIBUTIONS

AJ, DH, VK, MB: Conception and design of the study, development and approval of original study protocol, revision and approval of final manuscript.

AH-Ch: Data collection, manuscript drafting, revision and approval of final manuscript.

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COMPETING INTERESTS

AH-Ch, AJ, DH and VK are AOCID employees and receive salary from the AO Foundation.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	☒
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	☒
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	☒
Objectives	3	State specific objectives, including any prespecified hypotheses	☒
Methods			
Study design	4	Present key elements of study design early in the paper	☒
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	☒
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	☒
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	☒
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	☒
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	☒
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	☒
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	☒
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	☒
		(*e*) Describe any sensitivity analyses	☒

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	☒
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	☒

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Evaluation of the geriatric co-management for patients with fragility fractures of the proximal femur (geriatric fracture center (GFC) concept): protocol for a prospective multicenter cohort study

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TITLE: Evaluation of the geriatric co-management for patients with fragility fractures of the proximal femur (geriatric fracture center (GFC) concept): protocol for a prospective multicenter cohort study

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ABSTRACT

Introduction

Treatment of fractures in the elderly population is a clinical challenge due partly to the presence of comorbidities. In Geriatric Fracture Centers (GFC) patients are co-managed by a geriatrician in an attempt to improve clinical outcomes and reduce morbidity and mortality. Until now the beneficial effect of orthogeriatric co-management has not been definitively proven. The primary objective of this study is to determine the effect of GFC on predefined major adverse events related to a hip fracture compared to usual care centers (UCC). The secondary objectives include assessments in quality of life, patient reported outcomes and cost-effectiveness.

Methods and analysis

Two hundred and sixty-six elderly hip fracture patients planned to be treated with osteosynthesis or endoprosthesis in either a GFC or UCC study site will be recruited, 133 per type of center. All procedures and management will be done according to the site's standard of care. Study-related visits will be performed at the following time points: preoperative, intraoperative, discharge from the orthopedic/trauma department, discharge to definite residential status, 12 weeks and 12 months post-surgery. Data collected include demographics, residential status, adverse events, patient reported outcomes, fall history, costs and resources related to treatment. The risk of major adverse events at 12 months will be calculated for each center type; patient reported outcomes will be analyzed by mixed effects regression models to estimate differences in mean scores between baseline and follow-ups whereas cost-effectiveness will be assessed using the incremental cost-effectiveness ratio.

Ethics and dissemination

Ethics approval for this study was granted from the local Ethics committees or Institutional Review Board from each of the participating sites prior to patient enrollment. The results of this study will be published in peer-reviewed journals and presented at different conferences.

Trial registration number: ClinicalTrials.gov: NCT02297581

STRENGTHS

- Observational cohort study design provides real world data about geriatric care
- International multicenter setting provides a better picture of the status of geriatric fractures around the world
- Broad inclusion criteria is more representative of the population under study
- Well defined and assessable primary objective
- Comprehensive multidimensional approach to the problem combining objective and patient reported outcomes with health economic aspects

LIMITATIONS

- Reliable assessment of patient reported outcomes require compliant patients
- Assessment with a longer follow-up might be required
- Lack of randomization might induce bias due to the influence of uncontrolled or unbalanced variables or due to differences in co-management among countries
- Dropouts due to loss of follow-up or deaths might be a source of bias
- Risk of recall bias might occur for items assessed retrospectively

INTRODUCTION

The number of geriatric trauma patients is steadily increasing worldwide due to a longer life expectancy. Older adults with osteoporotic fractures tend to have more comorbidities and therefore the treatment of geriatric fractures is complex. Increased mortality, disability, complications and high health care costs are some of the consequences of this problem [1, 2]. To improve treatment outcomes in patients with osteoporotic fractures, multidisciplinary treatment approaches have been implemented. The involvement of a geriatrician into the integral management of elderly patients is referred as orthogeriatric co-management [3]. A systematic literature review [4] grouped the orthogeriatric care into four treatment models but could not identify the best one. The efficacy of orthogeriatric management is contradictory [5-10]. A Cochrane review from 2001, updated in 2009 found substantial heterogeneity in trial interventions and although there was a tendency to a better overall result in patients with a multidisciplinary treatment, the results were not statistically significant [11]. Kammerlander [4] concluded that integrated care resulted in better outcomes regarding mortality and length of stay; however a later systematic literature review and metaanalysis [12] showed no significant improvement on these parameters. Three manuscripts published after the registration and start of the present study found better mobility [13, 14] and a high probability of cost-effectiveness [14] with comprehensive geriatric care however they found no difference on cognitive function, delirium, mortality or complications [10, 13].

To improve clinical outcomes in the elderly, the following key principles have been suggested [15, 16]: Prioritization of the geriatric patient resulting in shorter time to surgery, early surgical stabilization of the fracture, frequent communication to avoid iatrogenic problems, estimation of the risk of developing delirium, attention to comorbidity, consideration to nutritional aspects, prevention of falls and osteoporosis care, early mobilization of the patient with weight bearing as tolerated, begin discharge planning at admission and use of standardized protocols. Overall, the main goals of an orthogeriatric co-management are reduction of complications, readmission and mortality, return to pre-fracture status, improvement of patient and family satisfaction, provision of best value of care to the health system and secondary fracture prevention [17]. In 2013, an expert consensus [17] suggested 12 outcome parameters and assessment tools for the evaluation of different orthogeriatric co-management models in hip fracture treatment, which included: mortality, length of stay, time to surgery, complications, readmission rate, mobility (Parker Mobility Score, Timed Up and Go [TUG]

test), quality of life (EQ-5D), pain (Verbal Rating Scale [VBS]), activities of daily living (Barthel Index), medication use (adverse drug reactions), place of residence and costs.

The Geriatric Fracture Center (GFC) study was designed to evaluate the impact of standardized treatment pathways and geriatric interdisciplinary co-management on all the above mentioned parameters, focusing on complications and their cost-effectiveness.

OBJECTIVES:

The primary objective of the study is to determine the effect of GFC on predefined major adverse events (AEs) that have a relationship to the treatment, immobilization or residential status within the 12 months following a fracture fixation surgery compared to Usual Care Centers (UCC).

The secondary objectives include comparison between the two types of care in quality of life, activities of daily living, AEs of any kind, hospital readmissions, mobility status, falls, pain level, return to pre-injury residential status, mortality, time from admission to surgery, medications, adaptation to nutritional status, cost-effectiveness and the validation of a model to predict the risk of sustaining a contralateral hip fracture.

TRIAL DESIGN AND METHODS

Study design

This is a prospective, international, multicenter, observational cohort study to test the superiority of GFC over UCC.

The definition of a GFC is based on clear and objective criteria for a geriatric co-management program which are as follow: general geriatrician or orthogeriatrician available in trauma/orthopedic department, patient is seen by the geriatrician prior to surgery (except if the patient is admitted over night or during weekends), existence of local medical guidelines consented by orthopedic surgeons and geriatrician, predefined order set for assessing laboratory values, predefined patient pathway to guarantee a fast track in the emergency room, daily communication among involved specialists from the postoperative phase until discharge from orthopedic/ trauma department and daily visits to the patient by the

following specialists: geriatrician, orthopedic surgeon in combination with nurse, physiotherapists (except weekends) and social workers if required.

A UCC is defined as a center in which: No geriatrician is available in trauma/orthopedic department, preoperative visit by a geriatrician is not a standard, there are no predefined medical guidelines for geriatric fracture patients and daily visits to the patient from the postoperative phase until discharge from orthopedic / trauma department by a geriatrician are not standard.

Any other postoperative treatment not specifically described in this investigation is performed according to the standard of care at the study site.

A world wide open call was launched to invite interested sites to participate. In order to account for local differences in health care systems and to allow comparisons based on geographic regions as well as globally, a GFC and a UCC within each participating country were selected. The site selection process has been described in detail elsewhere ([18] intended to be a joint publication with this protocol). A total of 12 sites in 6 different countries are participating in this study: in Austria, the Medizinische Universitästklinik (Innsbruck) and the Allgemeines Krankenhaus (Linz); in Thailand, Bangkok Hospital and Bhumibol Adulyadej Hospital (Bangkok); in Netherlands, Ziekenhisgropt Twente (Almelo) and Academisch Ziekenhuis (Maastrich); in Spain Hospital Universitario Costa del Sol (Marbella) and Hospital Son Llatzer (Palma de Mallorca); in the United States, Saint Louis University Hospital (Saint Louis) and Elmhurst Hospital (New York) and in Singapore, Singapore General Hospital and Singapore Tan Tock Seng.

Participants

Eligible patients must meet the following inclusion criteria:

1) Age 70 years and older

2) Diagnosis of hip fracture treated either with osteosynthesis or endoprosthesis

3) Ability of the patient or assigned representative to understand the content of the patient information/Informed Consent Form

4) Signed and dated IRB/EC-approved written informed consent

Exclusion criteria:

1) Recent history of substance abuse (ie, recreational drugs, alcohol) that would preclude reliable assessment

2) Prisoner

3) Participation in any other medical device or medicinal product study within the previous month that could influence the results of the present study

Procedures

Recruitment

The assessment of eligibility will be performed by the investigator or a study coordinator, who will approach each potential study patient and inquire about their interest and eligibility in participating in this study. All sites will be informed and trained about the importance of recruiting consecutive patients. If the patient wishes to participate, a legally eligible member of the research team will go through the informed consent process, explaining the purpose of the study, procedures, risk/benefits, alternatives to participation, and data protection. Each patient choosing to participate will sign and date an Informed Consent Form. Although local regulations vary between countries, if approved by the local ethics committee, a surrogate will be able sign the informed consent on behalf of patients unable to do it for themselves. Whenever possible the consent of the patient will be acquired as soon as he is able to sign for himself. A copy of the signed Informed Consent Form will be placed into the patient's medical record, the Investigator Site File or the patient binder and one copy will be handed over to the patient. All patients with written informed consent will be allocated to a unique patient trial number. The date of informed consent and the recruitment information is entered in the study database. All patients who commence treatment within the study are considered as enrolled and all enrolled patients should be followed up within the study, except if their study participation is prematurely terminated. All patients recruited in a GFC or UCC are automatically allocated to the GFC and UCC analysis group, respectively.

Baseline assessment

All patients that were screened for the inclusion and exclusion criteria are entered on the patient pre-screen and enrollment log maintained at each study site. Demographical data, comorbidities, cognitive status/dementia, and psychological situation will be assessed. The Parker Mobility Score, modified

Barthel Index and residential status are assessed referring to the patient's pre-injury status. Details relative to the injury (side affected, fracture classification, concomitant fractures), surgery (surgical time, type of implant, anesthesia), comorbidities, nutritional status, intake of relevant medication will be documented as well.

Interventions

All treatments and follow-up (FU) visits received in either GFC or UCC will be according to the hospital's standard of care. Study-related assessments will be performed at discharge from the orthopedic trauma/department (Discharge 1), discharge to definite residential status (Discharge 2), 12 weeks and 12 months post-surgery. Number of visits by a geriatrician, orthopedic surgeon and physiotherapist from surgery to discharge will be documented, as well as involvement of social workers and interventions aimed to prevent secondary fractures. The study-related assessments are summarized in Table 1.

Table 1: Overview of the outcome measures and time points of assessment

Assessment parameters	Pre- intra- and postoperative visits **					
	Screening / Preoperative	Intraoperative (day 0)	Discharge 1 (± 3 days)	Discharge 2 (± 3 days)	12 (± 4) weeks	12 (± 1) months
Patient information / consent	X					
Eligibility	X					
Demographics	X					
Charlson Comorbidity Index	X					
Screening assessments	X					
Pre-injury residential status	X*					
Clinic organization	X		X			
Timing of baseline activities	X	X				
Nutrition status evaluation			X	X	X	X
Cognitive status: MMSE			X	X		
Injury and surgical details		X				

Activities of daily living:						
Pre-injury Modified Barthel Index			X*			
Modified Barthel Index			X	X	X	X
EQ-5D					X	X
Pain			X	X	X	X
Readmission					X	X
Residential status			X	X	X	X
Mobility:						
Pre-injury Parker Mobility Score			X*			
Parker Mobility Score				X	X	X
TUG test				X	X	X
Falls			X	X	X	X
Contralateral hip fracture				X	X	X
Pre-injury analgesics			X*			
Medication details	X		X	X	X	X
Major adverse events		X	X	X	X	X
Other adverse events		X	X	X	X	X
Direct and indirect costs	X	X	X	X	X	X

§ Discharge 1 and 2 may occur on the same date

* Data are retrospectively assessed referring to the pre-injury status.

** All postoperative FU visits with the defined time windows are calculated from the day of surgery (i.e. day 0).

Outcome measures

Primary outcome measure

The major predefined AEs related to treatment / residential status / immobilization include and are limited to:

- Delirium (acute confusional state): acute, transient, fluctuating and usually reversible disturbance in attention, cognition or attention level. Upon suspicion of delirium, the Confusion Assessment Method (CAM) will be used to make the diagnosis. The Mini Mental State Examination (MMSE) will be used to assess the cognitive status of the patient.
- Congestive heart failure: clinical disorder that results in pulmonary vascular congestion and reduced cardiac output [19]. Congestive heart failure should be considered in the differential diagnosis of any adult patient who presents with dyspnea and/or respiratory failure. The diagnosis of heart failure is determined based on the Modified Framingham Criteria [20].
- Pneumonia: is an inflammation of the lung that is most often caused by infection with bacteria, viruses, or other organisms. Diagnosis of pneumonia is done according to the local standard of care through imaging or body fluid laboratory testing.
- Deep venous thrombosis is evaluated by the local investigator based on clinical examination and confirmed using any of the following techniques, as per local standard of care through ultrasound, phlebography or other techniques.
- Pulmonary embolism: is evaluated by the local investigator based on clinical examination and confirmed using any of the following techniques, as per local standard of care through CT scans, angiography, radionuclide examination.
- Pressure ulcers are defined as a localized injury of ≥ 2 cm diameter to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear.
- Myocardial infarction is defined as evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

Secondary outcome measures

- Any other AEs not mentioned under the predefined major AE. According to GCP guidelines an adverse event is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment" [21]. Of special interest are new fractures resulting from a fall, in particular contralateral hip fractures. This information will be retrieved from the medical record or by asking the patient or proxy.

- Mortality: will be assessed in 4 time frames: perioperative (from admission until 72 hours post-surgery), and within the first 14, 30 and 365 days after surgery.
- Activities of daily living measured using the modified Barthel Index.
- Quality of life using EuroQoL5 (EQ-5D).
- Pain using the numerical rating scale (NRS).
- Timing of baseline activities: defined as time elapsed to surgery, start of pain management, fluid management and acute care since admission.
- Hospital readmissions: is defined as any admission to a hospital (whether or not the study site) after the baseline visit up to the 12 month FU. As not all readmissions occur in the same initial hospital, the patient or proxy is asked at the FU time points whether any readmission has occurred.
- Residential status: will be defined within the next 4 categories: living alone at their own home (or with a roommate), living with a spouse/partner at their own home, living with children or sibling and living in a facility, defined as a non-family environment such as a nursing home or supervised residential setting. Details of care provided by family members and/or professional staff (physician, nurse, geriatrician) will be recorded as one of the following categories: 24 hour care, daily, irregular and no care.
- Mobility assessed with the Parker Mobility Score and TUG test
- Falls: at each FU visit after discharge occurrence of falls since last visit will be asked to the patient or caretaker.
- Secondary fracture prevention: are strategies to avoid secondary fractures, which include strength and balance training, home hazard assessment, vision assessment and medication review. The participation of the patient in such a program will be documented
- Medications: number and type of medications. Of particular interest are the use of analgesics, osteoporosis treatment, drugs that increase the risk of delirium (neuroleptics, benzodiazepines, morphine and derivates).
- Cost-effectiveness: costs and resources related to the treatment will be assessed for the in-hospital stay. After discharge, the patient will document all direct and indirect resources in a Cost Diary which can be filled in by the patient with help of a caretaker or the investigator during a FU visit (Supplementary 1). The Cost Diary documents the number and cost of appointments with doctors, physiotherapists or similar, imaging tests, laboratory tests, medications, walking aids,

assisted living facilities, assistance at home, additional expenses, number of days the patient is unable to perform usual activities and lost work productivity by family members taking care of the patient. The cost of the geriatric co-management will be collected from each participating clinic. Quality-adjusted life years (QALYs) will be derived from the EQ-5D.

Instruments

- Confusion assessment method (CAM): was originally developed in 1988-1990 to improve the identification and recognition of delirium. The CAM was intended to provide a new standardized method to enable non-psychiatrically trained clinicians to identify delirium quickly and accurately in both clinical and research settings. The CAM is usually rated by a clinical or trained lay interviewer on the basis of an interview with the patient that includes at least a brief cognitive assessment. It was originally validated for use based on observations made during a brief, structured interview that included the MMSE and Digit Span Test. It has four features: 1) acute onset or fluctuating course, 2) inattention, 3) disorganized thinking and 4) altered level of consciousness. The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4 [22].
- Mini Mental State Examination (MMSE): is a tool that can be used to systematically and thoroughly assess mental status. It is an 11-question measure that tests 5 areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. The MMSE is effective as a screening tool for cognitive impairment with older, community dwelling, hospitalized and institutionalized adults [23]. The cognitive status evaluated through MMSE at discharge may be predictive of the transfer to a rehabilitation center or nursing home.
- Barthel Index: is an ordinal scale and each performance item is rated with a given number of points assigned to each level or ranking. It uses 10 variables describing activities of daily living and mobility. A higher number is associated with a greater likelihood of being able to live at home with a degree of independence following discharge from hospital. The score is available in several languages and has been used extensively to monitor functional changes in individuals receiving in-patient rehabilitation, mainly in predicting the functional outcomes related to stroke. The modified Barthel Index [24, 25] has demonstrated high inter-rater reliability (0.95) and test-

retest reliability (0.89) as well as high correlation (0.74–0.8) with other measures of physical disability. An expert consensus [26] recommends the Barthel Index as the most applicable instrument to assess activities of daily life and suggests assessing the pre-injury status (which could be done by a caretaker).

- EQ-5D: standardized instrument that was designed for self-completion. It has 5 items (mobility, self-care, usual activities, pain/discomfort anxiety/depression) with a categorical response scale where health today is assessed. A good evidence for reliability, validity and responsiveness both for SF36 and EQ-5D has been shown [27, 28]. It will be documented if the questionnaire was self-completed or with help of someone.
- Numerical rating scale (NRS): self-reported score based on a numerical rating scale that ranges from 0 to 10 to evaluate the presence and intensity of pain. A higher value implies greater pain. If a patient is unable to answer this question, the reason for it will be captured and the question will remain unanswered.
- Parker Mobility Score: is a functional assessment with three walking ability questions that can each attain a maximum of 3 points. The final calculated score ranges from a minimum of 0 points to 3 or 9 points at maximum. The higher the score, the higher the function [29].
- Timed Up and Go test (TUG): is a commonly used screening tool to assist clinicians to identify patients at risk of falling. It measures the time (in seconds) that it takes for an individual to rise from an armchair (chair seat height = 45 cm / 1.5 feet), walk 3 meters (= 10 feet) to a line drawn on the floor, turn around and return to the chair. The total time taken for the patient to complete the entire task is the outcome measure. Those who complete the test in less than 10 seconds are freely mobile, patients completing the test between 10 and 19 seconds are independent for basic transfers, and those who need 20-29 seconds to complete the test often use a cane. Patients with 30 seconds and more are much more dependent on walking aids and typically they need help with chair or toilet transfer [30, 31]. Since TUG is a continuous endpoint assessed several times, mixed effects regression models will be used to enable all available outcome data to be included in the analysis. In case of missing values, imputation techniques could also be used.

All analysis will be performed according to a statistical analysis plan which will be ready before data collection ends.

Sample size estimation

The sample size calculation has been performed on the basis of difference in the risk of major AEs. Available literature reports a wide variation in complication rates on these patients ranging from 4-57% in the GFC group and from 61-71% in the UCC depending on the type of complications reported [4, 6, 9, 11, 32]. Based on the above data, the assumption was that one year following surgery, the risk of at least one predefined major adverse event was estimated at 35% for GFC group and at 55% for the UCC Group. With a significance level of 5%, a power of 80%, and equal treatment groups, a sample size of 212 patients (106 per group) was calculated. This total was adjusted for an expected loss of patients of about 20%, giving an estimated total sample size of 266 patients (133 per group).

Statistical analyses

The primary analysis will be conducted using firstly the full analysis population ("enrolled" patients), and subsequently the per-protocol population. The risk of major AEs related to the treatment, hospitalization and/or immobilization occurring from surgery to the 1 year FU and regardless of time point of data collection will be reported at the patient level along with the 95% confidence intervals according to each treatment group. In addition, univariable and multivariable Poisson regression models will be used whereby the outcome will be the actual number of major AEs related to the treatment, hospitalization and/or immobilization.

Secondary analyses will be conducted using the per-protocol population. Initially, univariable statistical tests (e.g. Chi-square test or Fisher's exact test for categorical variables; t-test or Wilcoxon rank-sum test for continuous variables) will be used to evaluate differences in clinical and administrative parameters between the two treatment groups. Subsequently, longitudinal data will be analyzed by means of mixed effects regression models to estimate differences in mean scores (e.g. EQ-5D, modified Barthel Index, TUG, Parker Mobility Score, pain NRS) between FU and the respective baseline assessment by treatment group. The proposed cost-utility analysis will use decision modelling and sensitivity analysis techniques to ensure the robustness of the study's conclusions. Cost-effectiveness will be assessed using the incremental cost-effectiveness ratio, which is determined by calculating the difference in costs divided by the difference in QALYs between the GFC and the UCC groups.

Enrolled patients who withdraw from study FU for any reason (withdrawal of consent, death, loss to FU, etc.) will be included in the analysis until the time at which they withdrew.

Data collection and management

Data handling and protection are conducted according to the ISO 14155 guidelines and ICH-GCP and applicable regulations. An electronic Case Report Form (eCRF) in REDCap [33] will be designed to accommodate the specific features of the study. Modifications of the eCRF will be made only if deemed necessary and in accordance with any amendment to the study protocol. Access to the eCRF is password protected and specific functions are assigned (e.g. study coordinator, investigator, monitor, etc.). The eCRF is to be completed in a timely manner after a patient's visit (i.e. 14 days after occurrence of a documentable event). During the site initiation visit and prior to recruiting the first patient, the research team at each site will undergo a defined training program that will include explanations on inclusion and exclusion criteria, study procedures, how to use the eCRF and general aspects of ISO 14155 and GCP. Monitoring visits will be performed as frequently as required to guarantee the completeness and accuracy of the information in the eCRF. At the end of the study, a site close out visit will be performed and all final clarifications will be done. Source data and any other essential documents have to be archived according to the legal requirements at the study site. Clinical study data (i.e. eCRF) and essential documents will be archived by the sponsor according to legal requirements.

Premature termination

Due to the nature and design of the study there are no stopping rules defined. All treatments are per standard of care and no investigational medical device or additional medication or intervention is applied during the study.

Reporting of adverse events

All AEs are collected. In case of a serious adverse event, the sponsor is immediately notified. AEs and serious adverse events need to be reported by the investigator to the EC/IRB according to their regulatory requirements.

ETHICAL CONSIDERATIONS AND DISSEMINATION

This is an observational study in which vulnerable patients who are in an emergency situation, mentally incompetent (temporarily or permanently) or able to give oral consent only might be included. In these cases, surrogate consent will be obtained according to the local regulation and the patient's informed consent will be obtained as soon as possible. This study has been registered in Clinical Trials.gov under registration number NCT02297581. Ethics approval for this study was granted from the local Ethics committees or Institutional Review Board from each of the 12 participating sites prior to patient enrollment commenced at each site. The results of this study will be published in peer-reviewed journals and presented at different conferences.

DISCUSSION

Fragility fractures and their care are an increasing challenge to health care systems and societies. Due to the great number of comorbidities present in elderly patients, geriatric fractures and their treatment present several complications. Different orthogeriatric concepts have been developed to improve patients' outcome but until now, the beneficial effect of these models could not be proven. The reason to choose an observational study design was to assess the actual effectiveness of current geriatric care all around the world. In contrast, a randomized study would not have provided real world data which was our objective. Collecting real world data is particularly important for our study, as one of the main secondary aims of the study is a detailed cost-effectiveness analysis. Moreover the feasibility to perform such a study in an international multicenter setting is challenging as it might require a huge investment to build the infrastructure needed and changing the organization of participating sites. All of the above could have a negative impact on patient care or data collection due to the learning curve and would bias our results. In our initial call, the applicants were not asked whether if they were a GFC or a UCC; instead the selection of centers was based on previously defined criteria and their allocation to either group was done according to the responses they gave on the site selection questionnaire. The site selection process has been detailed elsewhere (sent as a joint publication, currently under review).

The primary outcome measure based on the number of AE occurred during the time of the study is an objective and well defined parameter. However, our secondary outcome measures include tests or patient reported outcomes which require compliant patients. There is a risk of bias due to patients lost during FU or unable to complete the tests or questionnaires. In the latter case, caretakers might help complete the questionnaires and cost diaries if feasible. Important variables which may influence the outcome will be controlled during the analysis of results. Likewise, missing values will be handled using statistical methods performed according to a Statistical Analysis Plan which will be ready before data collection is finished.

The results of this study are expected to give important evidence on the impact of geriatric co-management for patients with fragility fractures regarding the quality of life, outcomes in the elderly and cost-effectiveness. As we increase our life expectancy and the demographic pyramid continues to shift, these problems will be an increasing economic and social burden in particular in industrialized countries.

CURRENT STUDY STATUS

The target sample was reached on October 2016; however recruitment was extended 3 months to allow the recruitment of at least 20 patients in each site. The number of patients recruited by site is as follows: Almelo 25, Bangkok 25 on each center, Innsbruck 25, Linz 20, Maastricht 25, Marbella 22, New York 20, Palma de Mallorca 24, Singapore 25 on each site and St Louis 21. Data collection will be completed (last patient last visit) on February 2018.

AUTHORS' CONTRIBUTIONS

AJ, DH, VK, MB: Conception and design of the study, development and approval of original study protocol, revision and approval of final manuscript.

AH-Ch: Data collection, manuscript drafting, revision and approval of final manuscript.

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COMPETING INTERESTS

AH-Ch, AJ, DH and VK are AOCID employees and receive salary from the AO Foundation.

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A prospective multicenter cohort study to evaluate the benefit of the geriatric fracture center (GFC) concept

Patient Diary

Thank you for participating in this study.
Your responses are very valuable to us!

As part of the clinical trial in which you are a participant, we are asking that you keep track of your hospital and doctor visits, physiotherapy appointments, medications and any other health services you may use during the 12 months after your hip fracture. We would also like you to record any personal expenses that you incur and the time that your caregiver missed from work because of your surgery and recovery. We are providing this diary to help you record all this information.

Please record only health care services that you believe have resulted from or are related to your hip fracture and recovery.

An example of how to fill out the diary is attached on the next page. The last pages are for you to record your information.

Please keep the diary in a place where you can easily find it whenever you need to write in it. Please bring your diary to your follow up visits. If required, your caregiver or family member can assist in filling out the diary. We will provide you with a new diary after each of your study follow-up visits.

If you have any questions about how to fill out this diary, please contact:

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EXAMPLE

Mr. Smith was discharged from the hospital on January 15, 2015. Over the next 12 weeks, he purchased and used a walker to get around and he was unable to complete his activities of daily living. His wife took care of him for these 12 weeks and a home care aid visited daily. His daughter took him to his medical appointments, which included 2 appointments with his orthopaedic surgeon and 3 appointments with his family physician. He had x-rays at each of the appointments with his orthopaedic surgeon. He also attended physiotherapy 2 times a week for 12 weeks, and had 1 in-home occupational therapy consult. He was prescribed Tylenol #3 by his surgeon for any pain and purchased some Advil. His only additional expense was a charge for parking at the hospital when he saw his surgeon for his post-surgery follow-up appointments.

This is how Mr. Smith would complete his Cost Diary, based on the information provided above:

1. VISITS TO SPECIALISTS

Have you visited a specialist physician (e.g. surgeon, emergency room physician) since your last study follow-up?
Yes ☐ *No* ☐
If "Yes", please fill in the details below. If "No", please continue to the next table.

Specialist Physician Name	***Date of Visit***	***Type of Specialist***	***Reason for Visit***	***Out of Pocket Cost***	***Total Cost***
	YYYY-MM-DD		*e.g. check-up, repeat prescription, increase in pain, etc.*	*Please indicate any amount you paid that will not be reimbursed by insurance*	*Please indicate the total cost of the visit, if known*
Dr. Jones	*2015-01-22*	*Orthopaedic surgeon*	*post-op follow-up*	*0*	*unknown*
Dr. Jones	*2015-03-05*	*Orthopaedic surgeon*	*post-op follow-up*	*0*	*unknown*

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2. VISITS TO GENERAL PRACTITIONER

Have you visited your family physician since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Physician Name	Date of Visit	Reason for Visit	Out of Pocket Cost	Total Cost
	YYYY-MM-DD	e.g. check-up, prescription refill, increase in pain, etc.	Please indicate any amount you paid that will **not** be reimbursed by insurance	Please indicate the total cost of the visit, if known
Dr. Peters	2015-01-22	post-op follow-up	0	unknown
Dr. Peters	2015-02-20	post-op follow-up	0	unknown
Dr. Peters	2015-03-10	post-op follow-up	0	unknown

3. VISITS TO PHYSIOTHERAPY/PHYSICAL THERAPY

Have you visited a physiotherapist since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Clinic Name	Date of Visit	Reason for Visit	Out of Pocket Cost	Total Cost
	YYYY-MM-DD		Please indicate any amount you paid, per visit, that will **not** be reimbursed by insurance	Please indicate the total cost per visit, if known
Someplace Physio	2015-01-20	rehab, pain control	10 *	50
Someplace Physio	2015-01-22	rehab, pain control	10 *	50
Someplace Physio	2015-01-27	rehab, pain control	10 *	50
Someplace Physio	2015-01-29	rehab, pain control	10 *	50
Someplace Physio	2015-02-03	rehab, pain control	10 *	50
Someplace Physio	2015-02-05	rehab, pain control	10 *	50
Someplace Physio	2015-02-12	rehab, pain control	10 *	50

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Someplace Physio	2015-02-17	rehab, pain control	10 *	50
Someplace Physio	2015-02-19	rehab, pain control	10 *	50
Someplace Physio	2015-02-24	rehab, pain control	10 *	50
Someplace Physio	2015-02-26	rehab, pain control	10 *	50
Someplace Physio	2015-03-03	rehab, pain control	10 *	50
Someplace Physio	2015-03-05	rehab, pain control	10 *	50
Someplace Physio	2015-03-10	rehab, pain control	10 *	50
Someplace Physio	2015-03-12	rehab, pain control	10 *	50
Someplace Physio	2015-03-17	rehab, pain control	10 *	50
Someplace Physio	2015-03-22	rehab, pain control	10 *	50
Someplace Physio	2015-03-24	rehab, pain control	10 *	50
Someplace Physio	2015-03-29	rehab, pain control	10 *	50
Someplace Physio	2015-03-31	rehab, pain control	10 *	50
Someplace Physio	2015-04-02	rehab, pain control	10 *	50
Someplace Physio	2015-04-07	rehab, pain control	10 *	50
Someplace Physio	2015-04-09	rehab, pain control	10 *	50

** Mr. Smith's extended health insurance pays 80% of the cost for physiotherapy treatment. As a result, he is responsible for paying on 20% (or $10) per treatment. He enters this amount into the "Out of Pocket Cost" column and the full treatment charge of $50 into the "Total Cost" column.*

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4. VISITS FROM OCCUPATIONAL THERAPY

Have you seen an occupational therapist since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Clinic Name /Therapist Name	***Date of Visit***	***Reason for Visit***	***Out of Pocket Cost***	***Total Cost***
	YYYY-MM-DD		*Please indicate any amount you paid, per visit, that will **not** be reimbursed by insurance*	*Please indicate the total cost per visit, if known*
Jane Doe	*2015-02-05*	*In-home consult*	*0*	*200*

5. VISITS TO COMPLEMENTARY AND ALTERNATIVE MEDICINE SPECIALISTS

Have you visited a complementary and alternative medicine specialist (e.g. chiropractor, acupuncturist) since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

***Clinic/Practitioner Name** Please indicate the name and type of practitioner (e.g. chiropractor, acupuncturist)*	***Date of Visit***	***Reason for Visit***	***Out of Pocket Cost***	***Total Cost***
	YYYY-MM-DD		*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the visit, if known*

6. MEDICAL IMAGING

Have you had any medical images taken (e.g. x-rays, CT, MRI) since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Type of Image *Please indicate the type of image you had taken (e.g. x-ray, CT, MRI)*	***Date of Image***	***Reason for Image***	***Out of Pocket Cost***	***Total Cost***
	YYYY-MM-DD		*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the imaging, if known*
x-ray	*2015-01-22*	*requested by surgeon*	*0*	*unknown*
x-ray	*2015-01-22*	*requested by surgeon*	*0*	*unknown*

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7. LABORATORY TESTS

Have you had any laboratory tests (e.g. blood tests etc.) since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Type of Laboratory Test	***Date of Test***	***Reason for Test***	***Out of Pocket Cost***	***Total Cost***
Please indicate the type of test you had taken (e.g. blood test)	*YYYY-MM-DD*		*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the imaging, if known*

8. PRESCRIPTION MEDICATIONS

Have you received any prescription medications since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Name	***Out of Pocket Cost***	***Total Cost***
e.g. Hydrocodone/acetaminophen	*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost, if known*
Tylenol 3	4.99	15.58

9. OVER-THE-COUNTER MEDICATIONS

Have you received any over-the-counter medications since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Name *e.g. Aleve, Feminax Ultra, Tylenol*	***Purchase Cost***
Advil	12.99

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10. Walking Aids

Have you received any walking aids since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Type of Aid	***Reason for Aid***	***Out of Pocket Cost***	***Total Cost***
Please indicate the type of walking aid you received (e.g. wheelchair, walker, crutches)		*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the aid, if known*
Walker	*walking aid suggested by physician for everyday activity*	*50*	*250*

11. ASSISTED LIVING FACILITIES

Have you stayed at an assisted living facility (e.g. rehabilitation facility, nursing home) since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Type of Facility	***Number of Days***	***Reason for Assisted Living Facility Stay***	***Out of Pocket Cost***	***Total Cost***
Please indicate the type of facility you stayed in (e.g. rehabilitation facility, nursing home)			*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the assistance, if known*

12. ASSISTANCE AT HOME

Have you received any assistance at home since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Type of Assistance	***Number of Hours***	***Duties Performed***	***Out of Pocket Cost***	***Total Cost***
Please indicate the type of assistance you received (i.e. in-home nursing care, assistance with activities of daily living by a paid caregiver, assistance from a family member or friend)		*e.g. assistance with bathing, dressing, housework, etc.*	*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the assistance, if known*
In-home nurse	*100*	*assistance with bathing and hygiene*	*500*	*2500*
daily activities	*300*	*assistance with dressing, hygiene and housework*	*N/A*	*N/A*

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13. ADDITIONAL EXPENSES			
Have you had incurred any expenses (e.g. parking costs, transportation) since your last study follow-up? Yes ☐ No ☐ *If "Yes", please fill in the details below. If "No", please continue to the next table.*			
Type of Expense	**Reason for Expense**	***Out of Pocket Cost***	***Total Cost***
Please list any additional expenses that you have not already listed above.		*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the expense, if known*
Parking	*Surgeon post-op follow-up*	*5*	*5*
Parking	*Surgeon post-op follow-up*	*5*	*5*
Transportation	*Daughter drove to appointments - fuel*	*80*	*80*

14. HOUSEHOLD AND LEISURE ACTIVITIES	Number of Days
Since your last visit, approximately how many days were you unable to perform usual household activities? (e.g. housework, cleaning)	
Since your last visit, approximately how many days were you unable to perform usual personal care activities on your own? (e.g. bathing, dressing)	
Since your last visit, approximately how many days were you unable to perform usual leisure activities (e.g. sports, social activities, etc.)?	

15. FAMILY MEMBER EMPLOYMENT (PAID WORK)			
Have any of your caregivers missed work due to your hip fracture? Yes ☐ No ☐ *If "Yes", please fill in the details below. If "No", you have completed the survey. Thank you for your time.*			
Family Member	***Occupation***	***# Of Work Days Missed***	***Reason***
Daughter	*Teacher*	*5*	*Transportation to appointments*

This is the end of the Example section.

Please start completing your diary on the next page.

Thank you very much!

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This box to be completed by attending physician or research coordinator.

Date of Visit (DD/MM/YY): _____ Subject ID Number: _____

Study Visit 12 week follow-up ☐

12 month follow-up ☐

1. VISITS TO SPECIALISTS

Have you visited a specialist physician (e.g. surgeon, emergency room physician) since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Specialist Physician Name	***Date of Visit***	***Type of Specialist***	***Reason for Visit***	***Out of Pocket Cost***	***Total Cost***
	YYYY-MM-DD		*e.g. check-up, repeat prescription, increase in pain, etc.*	*Please indicate any amount you paid that will not be reimbursed by insurance*	*Please indicate the total cost of the visit, if known*

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2. VISITS TO GENERAL PRACTITIONER

Have you visited your family physician since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Physician Name	***Date of Visit***	***Reason for Visit***	***Out of Pocket Cost***	***Total Cost***
	YYYY-MM-DD	*e.g. check-up, prescription refill, increase in pain, etc.*	*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the visit, if known*

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3. VISITS TO PHYSIOTHERAPY/PHYSICAL THERAPY

Have you visited a physiotherapist since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Clinic Name	***Date of Visit***	***Reason for Visit***	***Out of Pocket Cost***	***Total Cost***
	YYYY-MM-DD		*Please indicate any amount you paid, per visit, that will **not** be reimbursed by insurance*	*Please indicate the total cost per visit, if known*

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3. VISITS TO PHYSIOTHERAPY/PHYSICAL THERAPY (continued)				
Clinic Name	***Date of Visit***	***Reason for Visit***	***Out of Pocket Cost***	***Total Cost***
	YYYY-MM-DD		*Please indicate any amount you paid, per visit, that will **not** be reimbursed by insurance*	*Please indicate the total cost per visit, if known*

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4. VISITS FROM OCCUPATIONAL THERAPY

Have you seen an occupational therapist since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Clinic Name /Therapist Name	***Date of Visit***	***Reason for Visit***	***Out of Pocket Cost***	***Total Cost***
	YYYY-MM-DD		*Please indicate any amount you paid, per visit, that will **not** be reimbursed by insurance*	*Please indicate the total cost per visit, if known*

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5. VISITS TO COMPLEMENTARY AND ALTERNATIVE MEDICINE SPECIALISTS

Have you visited a complementary and alternative medicine specialist (e.g. chiropractor, acupuncturist) since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Clinic/Practitioner Name	***Date of Visit***	***Reason for Visit***	***Out of Pocket Cost***	***Total Cost***
Please indicate the name and type of practitioner (e.g. chiropractor, acupuncturist)	*YYYY-MM-DD*		*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the visit, if known*

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6. MEDICAL IMAGING

Have you had any medical images taken (e.g. x-rays, CT, MRI) since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Type of Image	***Date of Image***	***Reason for Image***	***Out of Pocket Cost***	***Total Cost***
Please indicate the type of image you had taken (e.g. x-ray, CT, MRI)	*YYYY-MM-DD*		*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the imaging, if known*

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7. LABORATORY TESTS

Have you had any laboratory tests (e.g. blood tests etc.) since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Type of Laboratory Test	***Date of Test***	***Reason for Test***	***Out of Pocket Cost***	***Total Cost***
Please indicate the type of test you had taken (e.g. blood test)	*YYYY-MM-DD*		*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the imaging, if known*

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8. PRESCRIPTION MEDICATIONS

Have you received any prescription medications since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Name	***Out of Pocket Cost***	***Total Cost***
e.g. Hydrocodone/acetaminophen	*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost, if known*

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9. OVER-THE-COUNTER MEDICATIONS

Have you received any over-the-counter medications since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Name *e.g. Aleve, Feminax Ultra, Tylenol*	***Purchase Cost***

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10. Walking Aids

Have you received any walking aids since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Type of Aid	***Reason for Aid***	***Out of Pocket Cost***	***Total Cost***
Please indicate the type of walking aid you received (e.g. wheelchair, walker, crutches)		*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the aid, if known*

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11. ASSISTED LIVING FACILITIES

Have you stayed at an assisted living facility (e.g. rehabilitation facility, nursing home) since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Type of Facility	***Number of Days***	***Reason for Assisted Living Facility Stay***	***Out of Pocket Cost***	***Total Cost***
Please indicate the type of facility you stayed in (e.g. rehabilitation facility, nursing home)			*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the assistance, if known*

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12. ASSISTANCE AT HOME

Have you received any assistance at home since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Type of Assistance	***Number of Hours***	***Duties Performed***	***Out of Pocket Cost***	***Total Cost***
Please indicate the type of assistance you received (i.e. in-home nursing care, assistance with activities of daily living by a paid caregiver, assistance from a family member or friend)		*e.g. assistance with bathing, dressing, housework, etc.*	*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the assistance, if known*

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13. ADDITIONAL EXPENSES

Have you had incurred any expenses (e.g. parking costs, transportation) since your last study follow-up?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", please continue to the next table.

Type of Expense	**Reason for Expense**	***Out of Pocket Cost***	***Total Cost***
Please list any additional expenses that you have not already listed above.		*Please indicate any amount you paid that will **not** be reimbursed by insurance*	*Please indicate the total cost of the expense, if known*

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14. HOUSEHOLD AND LEISURE ACTIVITIES	Number of Days
Since your last visit, approximately how many days were you unable to perform usual household activities? (e.g. housework, cleaning)	
Since your last visit, approximately how many days were you unable to perform usual personal care activities on your own? (e.g. bathing, dressing)	
Since your last visit, approximately how many days were you unable to perform usual leisure activities (e.g. sports, social activities, etc.)?	

15. FAMILY MEMBER EMPLOYMENT (PAID WORK)

Have any of your caregivers missed work due to your hip fracture?

Yes ☐ *No* ☐

If "Yes", please fill in the details below. If "No", you have completed the survey. Thank you for your time.

Family Member	*Occupation*	*# Of Work Days Missed*	*Reason*

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	☒
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	☒
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	☒
Objectives	3	State specific objectives, including any prespecified hypotheses	☒
Methods			
Study design	4	Present key elements of study design early in the paper	☒
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	☒
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	☒
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	☒
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	☒
Bias	9	Describe any efforts to address potential sources of bias	☒
Study size	10	Explain how the study size was arrived at	☒
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	☒
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	☒
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	☒
		(*e*) Describe any sensitivity analyses	☒

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	☒
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	☒

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.