BMJ Open

Evaluation of the geriatric co-management for patients with fragility fractures of the proximal femur (Geriatric Fracture Centre (GFC) concept): protocol for a prospective multicentre cohort study

Alexander Joeris,1 Anahi Hurtado-Chong,1 Denise Hess,1 Vasiliki Kalampoki,1 Michael Blauth2

ABSTRACT

Introduction Treatment of fractures in the elderly population is a clinical challenge due partly to the presence of comorbidities. In a Geriatric Fracture Centre (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 centres (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 patients diagnosed with hip fracture and planned to be treated with osteosynthesis or endoprosthesis in either a GFC or UCC study site will be recruited, 133 per type of centre. 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 orthopaedic/trauma department, discharge to definite residential status, 12 weeks and 12 months postsurgery. 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 centre type; patient-reported outcomes will be analysed 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 enrolment. The results of this study will be published in peer-reviewed journals and presented at different conferences.

Trial registration number ClinicalTrials.gov: NCT02297581; pre-results.

Strengths and limitations of this study

- Observational cohort study design provides real-world data about geriatric care, combining objective, patient reported and health economic outcomes.
- International multicentre setting provides a better picture of the status of geriatric fractures around the world.
- Broad inclusion criteria are more representative of the population under study.
- Lack of randomisation might induce bias due to the influence of uncontrolled or unbalanced variables or due to differences in co-management among countries.
- Risk of bias due to death, loss of follow-up or uncompliant patients unable to complete tests or questionnaires.

INTRODUCTION

The number of patients with geriatric trauma 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 healthcare 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 review1 grouped the orthogeriatric care into four treatment models but could not identify the best one. The efficacy of orthogeriatric management is contradictory.3–10 A Cochrane


BMJ Open: first published as 10.1136/bmjopen-2016-014795 on 12 July 2017. Downloaded from http://bmjopen.bmj.com/ on July 13, 2023 by guest. Protected by copyright.
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. Kammerlander et al concluded that integrated care resulted in better outcomes regarding mortality and length of stay; however, a later systematic literature review and meta-analysis showed no significant improvement on these parameters. Three manuscripts published after the registration and start of this study found better mobility and a high probability of cost-effectiveness with comprehensive geriatric care; however, they found no difference on cognitive function, delirium, mortality or complications.

To improve clinical outcomes in the elderly, the following key principles have been suggested: prioritisation of the geriatric patient resulting in shorter time to surgery, early surgical stabilisation 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 mobilisation of the patient with weight bearing as tolerated, begin discharge planning at admission and use of standardised protocols. Overall, the main goals of an orthogeriatric co-management are reduction of complications, readmission and mortality, return to prefracture status, improvement of patient and family satisfaction, provision of best value of care to the health system and secondary fracture prevention. In 2013, an expert consensus 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 (EuroQoL (EQ-5D)), pain (Verbal Rating Scale), activities of daily living (Barthel Index), medication use (adverse drug reactions), place of residence and costs.

The Geriatric Fracture Centre (GFC) study was designed to evaluate the impact of standardised 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, immobilisation or residential status within the 12 months following a fracture fixation surgery compared with usual care centres (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, multicentre, 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 programme which is as follows: general geriatrician or orthogeriatrician available in trauma/orthopaedic 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 orthopaedic 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 orthopaedic/trauma department and daily visits to the patient by the following specialists: geriatrician, orthopaedic surgeon in combination with nurse, physiotherapists (except weekends) and social workers if required.

An UCC is defined as a centre in which no geriatrician is available in trauma/orthopaedic department, preoperative visit by a geriatrician is not a standard, there are no predefined medical guidelines for patients with geriatric fracture and daily visits to the patient from the postoperative phase until discharge from orthopaedic/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 worldwide open call was launched to invite interested sites to participate. In order to account for local differences in healthcare systems and to allow comparisons based on geographical 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. A total of 12 sites in six different countries are participating in this study: in Austria, the Medizinische Universitätsklinik (Innsbruck) and the Allgemeines Krankenhaus (Linz); in Thailand, Bangkok Hospital and Bhumibol Adulyadej Hospital (Bangkok); in Netherlands, Ziekenhuisgroep Twente (Almelo) and Academisch Ziekenhuis (Maastrich); in Spain Hospital Universitario Costa del Sol (Marbella) and Hospital Son Llatzer (Palma de Mallorca); in the USA, 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 Institutional Review Board (IRB)/ Ethics Committee (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 this 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 EC, a surrogate will be able to sign the informed consent on behalf of patients who are 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 who were screened for the inclusion and exclusion criteria are entered on the patient prescreen and enrolment 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, anaesthesia), comorbidities, nutritional status and 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 orthopaedic trauma/department (discharge 1), discharge to definite residential status (discharge 2), 12 weeks and 12 months postsurgery. Number of visits by a geriatrician, orthopaedic 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 summarised in table 1.

Outcome measures

Primary outcome measure
The major predefined AEs related to treatment/residential status/immobilisation include and are limited to:
1. Delirium (acute confusional state): acute, transient, fluctuating and usually reversible disturbance in attention, cognition or attention level. On 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.
2. Congestive heart failure: clinical disorder that results in pulmonary vascular congestion and reduced cardiac output. Congestive heart failure should be considered in the differential diagnosis of any adult patient who presents with dyspnoea and/or respiratory failure. The diagnosis of heart failure is determined based on the Modified Framingham Criteria.
3. 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.
4. 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.
5. 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 or radionuclide examination.
6. Pressure ulcers are defined as a localised 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.

7. Myocardial infarction is defined as evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia.

**Secondary outcome measures**

1. Any other AEs not mentioned under the predefined major AE. According to good clinical practice (GCP) guidelines, an AE 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’. 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.

2. Mortality will be assessed in four time frames: perioperative (from admission until 72 hours postsurgery), and within the first 14, 30 and 365 days after surgery.

3. Activities of daily living measured using the modified Barthel Index.

4. Quality of life using EQ-5D.

5. Pain using the Numerical Rating Scale (NRS).
6. Timing of baseline activities defined as time elapsed to surgery, start of pain management, fluid management and acute care since admission.

7. Hospital readmissions is defined as any admission to a hospital (whether or not the study site) after the baseline visit and 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.

8. Residential status will be defined within the next four 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 hours care, daily, irregular and no care.

9. Mobility assessed with the Parker Mobility Score and TUG test.

10. Falls: at each FU visit after discharge occurrence of falls since last visit will be asked to the patient or caretaker.

11. 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 programme will be documented.

12. 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 derivatives).

13. 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 (see online supplementary file 1) which can be filled in by the patient with help of a caretaker or the investigator during an FU visit. 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**

1. 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 standardised method to enable non-psychiactically 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) disorganised 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.

2. 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 25 or lower is indicative of cognitive impairment. The MMSE is effective as a screening tool for cognitive impairment with older, community dwelling, hospitalised and institutionalised adults. The cognitive status evaluated through MMSE at discharge may be predictive of the transfer to a rehabilitation centre or nursing home.

3. 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 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 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).

4. EQ-5D is a standardised 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 36-Item Short Form Health Survey (SF-36) and EQ-5D has been shown.

5. NRS is a self-reported score 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.

6. Parker Mobility Score is a functional assessment with three walking ability questions that can each attain a maximum of three points. The final calculated score ranges from a minimum of zero point to three or nine points at maximum. The higher the score, the higher the function. Since 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 m (=10 feet) to a line drawn on the floor, turnaround 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 <10 s are freely mobile, patients completing the test between 10 and 19 s are independent for basic transfers, and those who need 20–29 s to complete the test often use a cane. Patients who take 30 s or more are much more dependent on walking aids and typically they need help with chair or toilet transfer. 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 analyses 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 based on the difference in the risk of major AEs. Available literature reports a wide variation in complication rates on these patients ranging from 4% to 57% in the GFC group and from 61% to 71% in the UCC depending on the type of complications reported. Based on the above data, the assumption was that 1 year following surgery, the risk of at least one predefined major AE was estimated at 35% for the 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 first the full analysis population (‘enrolled’ patients), and subsequently the per-protocol population. The risk of major AEs related to the treatment, hospitalisation and/or immobilisation 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% CIs 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, hospitalisation and/or immobilisation.

Secondary analyses will be conducted using the per-protocol population. Initially, univariable statistical tests (eg, χ² 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 analysed by means of mixed effects regression models to estimate differences in mean scores (eg, 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 International Organization for Standardization (ISO) 14155 guidelines and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-GCP and applicable regulations. An electronic case report form (eCRF) in REDCap 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 (eg, study coordinator, investigator, monitor, etc). The eCRF is to be completed in a timely manner after a patient’s visit (ie, 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 programme 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 (ie, 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 AEs**

All AEs are collected. In case of a serious AE, the sponsor is immediately notified. AEs and serious AEs 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 healthcare 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 randomised 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 multicentre setting is challenging as it might require a huge investment to build the infrastructure needed and changing the organisation 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 centres 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.

The primary outcome measure based on the number of AEs 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 industrialised 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 centre, 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) in February 2018. The present manuscript has been prepared following the STROBE checklist (see online Supplementary file 2).

**Acknowledgements**  The authors thank AOCD staff who has contributed directly or indirectly to this study, in particular to Joffrey Baczkowski and Patrick Hillpold for providing relevant data for the development of this manuscript.

**Contributors**  AH-C: data collection, manuscript drafting and revision, approval of final manuscript.

**Funding**  The GFC study and the development of this manuscript were entirely funded by the AO Foundation via AOTrauma.

**Competing interests**  AH-C, AJ, DH and VK are AOCD employees and receive salary from the AO Foundation.

**Patient consent**  All patients participating in the study have signed the informed consent approved by the local EC/IRB. However, no patient data has been used or presented on this manuscript.

**Ethics approval**  Local ethics committee/IRB at each participating site.

**Provenance and peer review**  Not commissioned; externally peer reviewed.

**Open Access**  This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

**REFERENCES**


