maison de la recherche en santé
DRCI • CHU Nantes - CHD Vendée

PAAF Project

Analysis of the relationship between early post-operative anaemia and changes in independence at 6 months in patients aged 75 and over who have undergone surgery for a fracture of the upper end of the femur

Non-interventional research

PAAF protocol

Registration number: 2017-A03505-48
Ref: CHD 117-17

"Analysis of the relationship between early post-operative anaemia and changes in independence at 6 months in patients aged 75 and over who have undergone surgery for a fracture of the upper end of the **femur"**

Coordinating Investigator:
Dr Romain DECOURS
Geriatrician
Vendée Departmental Hospital Centre
85925 La Roche sur Yon Cedex 9
Romain.decours@chd-vendee.Fr

Methodologist:
Aurélie LE THUAUT
Nantes University Hospital Research Centre
53 chaussée de la Madeleine
44000 Nantes
Aurelie.le.thaut@chu-nantes.fr

Sponsor:
Vendée Departmental Hospital Clinical Research Unit Boulevard Stéphane MOREAU
85 925 La Roche sur Yon Cedex 09
Tel: 02 51 44 65 72
Fax: 02 51 08 05 91

SIGNATURE PAGE

SIGNATURE OF THE PROMOTER

The sponsor undertakes to conduct this study in accordance with all legislative and regulatory provisions applicable to the research and in accordance with the protocol.		
Name and position of the signing representative: Mr Francis SAINT-HUBERT Managing Director CHD Vendée	**Date:**	**Signature:**

SIGNATURE OF INVESTIGATORS

I have read all the pages of the clinical trial protocol sponsored by CHD Vendée. I confirm that it contains all the information necessary to conduct the trial. I undertake to conduct the trial in accordance with the protocol and the terms and conditions set out therein. I undertake to conduct the trial in accordance with:

- the principles of the "Helsinki Declaration",
- the rules and recommendations of international (ICH) and French (rules of good clinical practice for biomedical research relating to medicinal products for human use)
- European regulations and/or national legislation and regulations relating to clinical trials,

I also undertake to ensure that investigators and other qualified members of my team have access to this protocol and to the documents relating to the conduct of the trial, so that they can work in accordance with the provisions contained in these documents.

Coordinating Investigator	**Name:** Dr Romain DECOURS	**Date:**	**Signature:**
Principal Investigator	**Name and institution:**	**Date:**	**Signature:**

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
ANSM	French National Agency for Medicines and Health Products Safety
MA	Marketing Authorisation
ARC	Clinical Research Associate
ASA	American Society of Anaesthesiologists
GCP	Good Clinical Practice
CAM	Confusion Assessment Method
CHD	Departmental Hospital Centre
CIRS - G	Cumulative Illness Rating Scale - Geriatrics
CoDEx	Cognitive Disorder Examination
CSP	Public Health Code
CST	Transferrin Saturation Coefficient
CPP	Committee for the Protection of Individuals
CNIL	French Data Protection Authority
CRF	Case Report Form
CRP	C-reactive protein
EHPAD	Residential care homes for the Elderly for Elderly Dependent
EvIG	Serious Adverse Event
SAE	Serious Adverse Effect
EIGI	Unexpected Serious Adverse Effect
FESF	Fracture of the Upper End of the Femur
IADL	Instrumental Activities of Daily Living
ICH	International Conference on Harmonisation (International Conference on Harmonisation)
Nursing	State-registered nurse
INSERM	National Institute of Health and Medical Research
MiniGDS	Mini Geriatric Depression Scale
MR	Reference Methodology
NFS	Complete Blood Count
RCP	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SLD	Long-term care
SSR	Follow-up Care and Rehabilitation Service
TEC	Clinical Research Technician

TABLE OF CONTENTS

INTRODUCTION

Fractures of the upper femur (FUF) are a condition that becomes more common with age. It is a serious condition with multiple consequences, such as reduced life expectancy, quality of life and independence for patients.
In this non-interventional study, we aim to evaluate changes in the independence of very elderly patients who have undergone surgery for a fracture of the upper end of the femur (FESF) in relation to early post-operative anaemia.

1. JUSTIFICATION FOR THE STUDY

1.1. POSITIONING OF THE RESEARCH

With the increase in life expectancy among the French population, there has been a rise in the number of patients with fractures of the upper femur (FESF), particularly among the elderly. In France, the number of hospital stays for UEF has been increasing by 0.3% per year since 1998, and the incidence remains predominantly female. The crude incidence rate of UEF was 42.1/10,000 for people over 55 years of age in 2007. UEF mainly affects elderly and very elderly people. There has been a gradual increase in the average age of fracture patients. Again in 2007, patients over 80 years of age accounted for 60% of male patients operated on for FESF and 70% of female patients (1). This is a serious condition, with the risk of death increasing with age. It is 2% in women under 80 during hospitalisation, rising to 8.3% in those over 95. This mortality rate is higher in men, reaching 15% in men over 94 during hospitalisation (1). Longer-term mortality rates vary according to studies, from 14.7% at one year (2) to 46% at one year in patients over 90 years of age (3). However, there has been a gradual decrease in this mortality rate in France, probably due to improved surgical and perioperative care for patients (4).

Anaemia is common in the geriatric population. In a survey of a hospitalised geriatric population, 24% of patients had anaemia, the aetiology of which was iron deficiency in 15% of cases (5). It is also common in surgery, particularly in the perioperative period. In a study of 546 patients with fractures of the upper femur, 40.4% had anaemia on admission and 93.0% had anaemia postoperatively (6).
Postoperative anaemia has multiple causes. It is probably aggravated by rehydration upon admission of patients with fractures (7). There is blood loss associated with the fracture and the formation of a haematoma prior to surgery (8), but also some postoperative occult bleeding: in 546 patients with a fracture of the upper end of the femur, Foss et al. showed that post-operative occult bleeding ranged from 547 to 1473 mL, in addition to the blood loss observed during surgery. Finally, there is a degree of acute inflammatory anaemia secondary to surgery. This inflammatory component is caused by a decrease in progenitor proliferation, a reduced red blood cell half-life and iron retention by macrophages. This retention is mediated by ferritin, which is then increased, and by hepcidin, a recently discovered protein that regulates iron metabolism (9).

Loss of independence, defined as a decrease in the ability to care for oneself, is also significant after a fracture of the upper end of the femur. Of 390 patients over the age of 65 who underwent surgery for an FESF and were analysed by Vochteloo's team, nearly half did not regain their previous independence after one year. Only 25% of patients who were mobile without assistance regained their previous independence within three months of surgery. Nineteen percent of patients became bedridden. The most significant risk factors were a low level of previous independence and the occurrence of postoperative confusion (10).
The consequences of a loss of independence in elderly people are manifold (11). It leads to the intervention of outside help for activities of daily living, a change of living arrangements, a change in family relationships, and a risk of abuse by carers. The economic consequences are also significant:

health insurance expenditure for dependent elderly people was around €20.9 billion in 2011 (12).
A patient's independence can be analysed in various ways. In the studies cited above, functional independence (walking) was prioritised because it was related to the condition being treated. However, in frail patients, overall independence is a key factor to measure because it affects quality of life and institutionalisation. Two scales can be used to measure this independence: Kartz's Activities of Daily Living and Lawton's Instrumental Activities of Daily Living. They take into account the patient's independence in performing daily activities alone or with assistance (washing, dressing, continence, eating, financial management, medication management, etc.).

Anaemia appears to be associated with the independence of patients who have undergone FESF surgery, but few studies have analysed the relationship between post-operative anaemia and rehabilitation, especially in elderly subjects (13). However, it is known that anaemia in hospitalised medical patients is an independent factor in poor functional independence (14,15).
There are numerous studies analysing the superiority or otherwise of a strict transfusion protocol (following standard transfusion guidelines) compared to a broader transfusion protocol (transfusing patients below the 10 g/dL threshold). This topic was recently addressed in a Cochrane literature review (16) (6 studies, 2,722 patients), which found no difference in mortality, functional recovery, or post-operative morbidity.

This extensive research is based primarily on five studies attempting to establish a link between anaemia and functional autonomy, each of which used different assessments at different post-operative dates.

- **Lawrence (2003)** retrospectively analysed a cohort of 5,793 patients over the age of 60 from 1982 to 1993. It was shown that the average haemoglobin level during hospitalisation was associated with the walking distance covered upon discharge from hospital (p<0.001 adjusted for age, Activities of Daily Living (ADL), neurological diseases, diabetes, Charlson and ASA comorbidities, beta-blocker treatment) [*no reference to possible transfusions] (*17).
- **Foss's** work **(2008)** found a link between haemoglobin levels in the first three days post-operatively (487 patients, all ages combined) and patient mobility during those first three days (p<0.05, before any transfusion). Independent risk factors for inability to walk were age over 75, dementia, reduced pre-fracture mobility, the presence of post-operative complications, and haemoglobin below 10 g/dL. Patients were treated according to a specialised perioperative rehabilitation protocol [*surgery within 24 hours, spinal anaesthesia, epidural analgesia for 96 hours postoperatively, oral high-protein supplementation, daily 30-minute physiotherapy sessions from the first day] (*18).
- **Halm (2004)** conducted a prospective observational study of 550 patients over the age of 50. High pre- or post-operative haemoglobin levels were correlated with a reduction in length of hospital stay and readmission rates, but not with motor function scores (ability to walk and climb stairs, at day 60, assessed by telephone interview) [*adjusted for age, sex, pre-fracture functional status, dementia, institutionalisation, transfusion]* (19).
- **Gruson (2002)** showed that anaemia on admission in 395 patients over the age of 65 (from 1991 to 1997) with a femoral neck fracture was correlated with a longer hospital stay and higher mortality at 6 and 12 months. A telephone call at 3, 6 and 12 months allowed for the assessment of an ADL and Instrumental Activities of Daily Living (IADL) score and functional autonomy, which were no different between anaemic and non-anaemic patients [*patients who were previously autonomous, living at home and without cognitive impairment; based solely on anaemia on admission]* (20).

- **Maraldi (2006)** analysed 56,752 patients over the age of 65 hospitalised in geriatrics (medicine sector). The recovery of independence at the end of hospitalisation was less significant in anaemic patients than in non-anaemic patients (p<0.001).

However, to our knowledge, no study has examined the association between the recovery of overall functional autonomy, as measured by ADL, and the post-operative haemoglobin level in the very elderly. The aim of these analyses is to improve our understanding of the loss of autonomy observed post-operatively following FESF, especially in the longer term, in order to manage it as effectively as possible. For example, at the Centre Hospitalier Départemental (CHD) in La Roche sur Yon, it would be interesting to optimise the transfusion protocols adopted within the hospital. There are also patient profiles where functional autonomy, and the resulting quality of life, is more important than mortality alone (in very elderly patients, for example, or those with multiple comorbidities). Furthermore, in our department, anaemia is a factor that limits patient mobility (sitting in a chair, physiotherapy), which probably has consequences for their early and future autonomy. The database could be used to set up interventional studies seeking to limit this loss of autonomy.
In this study, we therefore propose to evaluate the impact of post-operative anaemia on the functional recovery of very elderly patients following surgery for a fracture of the upper end of the femur.

1.2. BENEFITS AND RISKS FOR THE PEOPLE PARTICIPATING IN RESEARCH

1.2.1. Benefits

It is hoped that this study will improve understanding of the factors influencing the loss of independence commonly observed following a femoral neck fracture.
The management of post-operative anaemia is not formalised, either in national recommendations or at institutional level. The aim of this study is to improve understanding of the repercussions of post-operative anaemia, but also to derive a standardised management protocol. This protocol must, in particular, determine the transfusion strategy for these fragile patients, in order to reserve blood transfusions for those who need them most, but above all to avoid less useful transfusions.

1.2.2. Risks

No risks related to the protocol are expected for the individuals participating in the research. The patient incurs the usual risks associated with the procedure and possible peri- and post-operative complications, including anaemia and its management, in the target population.

1.2.3. Benefit/risk balance

The research manager classifies this **research** as **non-interventional**, since:

✓ All procedures are performed in the usual manner (blood sampling, interventions, etc.).

The research does not involve innovative or obsolete techniques or strategies.

All patient care will be identical to standard practice. In particular, the discharge date will be decided by the physician in charge of the patient, independently of the study, but will be recorded in the patient's file and the research CRF.

Consequently, the specific implementation procedures in the research represent negligible constraints for the person participating in the research. (Article R 1121-3 of the Public Health Code (CSP), Decree No. 2006-477 of 26 April 2006)

The research manager shall therefore submit the study protocol to the South-East I Committee for the Protection of Persons (CPP) Sud-Est I for approval and confirmation of the research's eligibility, in accordance with Article L 1121-1 of the Public Health Code (CSP) as resulting from Laws No. 2004-806 of 9 August 2004 and No. 2006-450 of 18 April 2006 relating to public health policy.

BIBLIOGRAPHICAL REFERENCES

1. Oberlin Ph., Mouquet M.C. Femoral neck fractures in France between 1998 and 2007: what impact does ageing have? Studies Results. Apr 2010;(723).
2. Kim S-M, Moon Y-W, Lim S-J, Yoon B-K, Min Y-K, Lee D-Y, et al. Prediction of survival, second fracture, and functional recovery following the first hip fracture surgery in elderly patients. Bone. June 2012;50(6):1343-50.
3. Jennings AG, de Boer P. Should we operate on nonagenarians with hip fractures? Injury. Apr 1999;30(3):169-72.
4. Maravic M, Taupin P, Landais P, Roux C. Decrease in mortality among patients hospitalised for hip fractures in France. Rev Rhum. July 2011;78(4):368-72.
5. Joosten E, Pelemans W, Hiele M, Noyen J, Verhaeghe R, Boogaerts MA. Prevalence and causes of anaemia in a geriatric hospitalised population. Gerontology. 1992;38(1-2):111
-7.
6. Foss NB, Kehlet H. Hidden blood loss after surgery for hip fracture. J Bone Joint Surg Br. 8 Jan 2006;88-B(8):1053-9.
7. Odumala AO, Ayekoloye CI, Packer G. Predictors of excessive blood loss during operative treatment of hip fractures. J R Coll Surg Edinb. June 2002;47(3):552-6.
8. Smith GH, Tsang J, Molyneux SG, White TO. The hidden blood loss after hip fracture. Injury. 2011 Feb;42(2):133-5.
9. Beaumont C, Karim Z. Current developments in iron metabolism. Rev Médecine Interne. Jan 2013;34(1):17–25.
10. Vochteloo AJ, Moerman S, Tuinebreijer WE, Maier AB, de Vries MR, Bloem RM, et al. More than half of hip fracture patients do not regain mobility in the first postoperative year. Geriatr Gerontol Int. 2013;13(2):334–341.
11. National College of Geriatric Teachers. Module 5: Ageing (2nd edition). Masson. 2010. 272 p. (Abstracts).
12. High Council for the Future of Health Insurance. Health insurance and loss of autonomy: HCAAM contribution to the debate on dependency among the elderly. June 2011.
13. Potter LJ, Doleman B, Moppett IK. A systematic review of pre-operative anaemia and blood transfusion in patients with fractured hips. Anaesthesia. Apr 2015;70(4):483–500.
14. Maraldi C, Ble A, Zuliani G, Guralnik JM, Mussi C, Fellin R, et al. Association between anaemia and physical disability in older patients: role of comorbidity. Aging Clin Exp Res. 2006 Dec;18(6):485–92.
15. Bailey RA, Reardon G, Wasserman MR, McKenzie RS, Hord RS. Association of anemia with worsened activities of daily living and health-related quality of life scores derived from the Minimum Data Set in long-term care residents. Health Qual Life Outcomes. 19 Oct 2012;10:129.
16. Brunskill SJ, Millette SL, Shokoohi A, Pulford EC, Doree C, Murphy MF, et al. Red blood cell transfusion for people undergoing hip fracture surgery. Cochrane Database Syst Rev. 2015;4:CD009699.
17. Lawrence VA, Silverstein JH, Cornell JE, Pederson T, Noveck H, Carson JL. Higher Hb level is associated with better early functional recovery after hip fracture repair. Transfusion (Paris). 2003;43(12):1717–1722.
18. Foss NB, Kristensen MT, Kehlet H. Anaemia impedes functional mobility after hip fracture surgery. Age Ageing. 3 Jan 2008;37(2):173–8.
19. Halm EA, Wang JJ, Boockvar K, Penrod J, Silberzweig SB, Magaziner J, et al. The effect of perioperative anaemia on clinical and functional outcomes in patients with hip fracture. J Orthop Trauma. July 2004;18(6):369-74.

20. Gruson KI, Aharonoff GB, Egol KA, Zuckerman JD, Koval KJ. The relationship between admission haemoglobin level and outcome after hip fracture. J Orthop Trauma. Jan 2002;16(1):39-44.
21. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardised measure of biological and psychosocial function. JAMA J Am Med Assoc. 21 Sept 1963;185:914-9.
22. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. The Gerontologist. 1969;9(3):179–86.
23. Foss NB, Kristensen MT, Kehlet H. Prediction of postoperative morbidity, mortality and rehabilitation in hip fracture patients: the cumulated ambulation score. Clin Rehabil. 8 Jan 2006;20(8):701–8.
24. Hillman TE, Nunes QM, Hornby ST, Stanga Z, Neal KR, Rowlands BJ, et al. A practical posture for hand grip dynamometry in the clinical setting. Clin Nutr Edinb Scotl. Apr 2005;24(2):224–8.
25. Hoffer MM, Feiwell E, Perry R, Perry J, Bonnett C. Functional ambulation in patients with myelomeningocele. J Bone Joint Surg Am. Jan 1973;55(1):137–48.
26. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 15 Dec 1990;113(12):941-8.
27. Laplante J, Cole M, McCusker J, Singh S, Ouimet MA. Confusion Assessment Method validation of a French version. Perspectives infirmières. Oct 2005;12–22.
28. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. May 1968;16(5):622–6.
29. Salvi F, Miller MD, Grilli A, Giorgi R, Towers AL, Morichi V, et al. A manual of Guidelines for scoring the modified cumulative illness rating scale and its validation in acute hospitalised elderly patients. J Am Geriatr Soc. Oct 2008;56(10):1926–31.
30. Owens WD, Felts JA, Spitznagel EL. ASA physical status classifications: a study of consistency of ratings. Anesthesiology. Oct 1978;49(4):239–43.

2. OBJECTIVES AND EVALUATION CRITERIA

2.1. OBJECTIVE AND PRIMARY ENDPOINT

2.1.1. Primary objective

The primary objective is to analyse the relationship between the severity of early postoperative anaemia and functional independence at 6 months postoperatively in elderly patients who have undergone surgery for a fracture of the upper femur.

2.1.2. Primary evaluation criterion

- Haemoglobin level on day 5 post-operatively (considered the post-operative haemoglobin reference level in this study)
  - In the case of patients who received a transfusion postoperatively, the reference haemoglobin level will be the haemoglobin level at the end of hospitalisation
- Change in the Activities of Daily Living (ADL) score pre-fracture and 6 months post-operatively.
  A loss of independence will be defined as a decrease of one point or more in the ADL.

The reference value for haemoglobin levels was arbitrarily set at 5 days post-operatively. This is because haemoglobin levels recorded in A&E or on admission to the ward prior to surgery, or immediately post-operatively, may be influenced by factors other than isolated anaemia. Dehydration, present in the emergency department or on admission to the ward before the operation, corrected preoperatively, and postoperative haemodilution due to fluid replacement, cause the haemoglobin level to vary without there being any real deglobulation. We therefore postulate that the haemoglobin level on the 5th postoperative day can serve as a reference.

Confounding factors collected
All confounding factors related to loss of autonomy will be collected:
- Transfusion and number of red blood cell concentrates received

The indication for transfusion is at the discretion of the prescriber. However, it is generally accepted to transfuse patients with haemoglobin levels below 8 g/dL, or below 10 g/dL in cases of ischaemic heart disease or poor clinical tolerance.
- Age
- Gender
- Height, weight, Body Mass Index (BMI) calculation
- Screening for past or present higher brain function disorders
- Screening for major sensory disorders
- Screening for depressive symptoms: Mini Geriatric Depression Scale (MiniGDS)
- Comorbidities assessed using the Cumulative Illness Rating Scale - Geriatrics (CIRS-G)
- ASA score
- Number of medications (per class) taken by the patient (anticoagulants, antiplatelet agents, NSAIDs, anti-osteoporotic drugs, analgesics)

- Lifestyle and living environment
- Severe fractures before and after inclusion
- Other falls during the year
- Protein-energy malnutrition
- Iron deficiency (ferritin < 30 µg/L or CRP > 20 mg/L associated with a transferrin saturation coefficient < 15%)
- Recurrence of falls at 1, 3 and 6 months post-op

2.2. SECONDARY OBJECTIVES AND EVALUATION CRITERIA

2.2.1. Secondary objectives

The secondary objectives are to analyse:
- the influence of post-operative anaemia:
  - on independence in elderly patients who have undergone surgery for a fracture of the upper end of the femur upon discharge from hospital, at 1 month and 3 months post-operatively
  - on mortality 6 months after surgery
- the progression of post-operative anaemia

2.2.2. Secondary evaluation criteria

- Lowest postoperative haemoglobin level recorded on admission to the emergency department, on admission to the ward, on D0 (day of surgery), D1, D3, D5, D10 and D15 (postoperative days)
).
  The severity of anaemia will be defined as follows:
  - greater than 12 g/dL,
  - less than or equal to 12 g/L
  - less than or equal to 8 g/L
  - less than 8 g/dL (and therefore requiring a transfusion)
- Assessment of Activities of Daily Living (ADL): pre-fracture, on day 5 post-operative (or on discharge from hospital if discharged before day 5) at 1 month, 3 months and 6 months post-operative.
- Assessment of instrumental Activities of Daily Living (IADL): pre-fracture, at 1 month, 3 months and 6 months post-operative.
  Loss of independence will be defined as a decrease of one point or more in the ADL and/or IADL.
- Vital status at 6 months post-operatively

3. STUDY POPULATION

3.1. DESCRIPTION OF THE POPULATION

This study is intended for patients over the age of 75 who have undergone surgery for a fracture of the upper end of the femur.

3.2. INCLUSION CRITERIA

- Patients aged 75 years and older, regardless of gender.
- Patients who have undergone surgery for a fracture of the upper end of the femur.
- Patients, family members or trusted relatives who do not object to participation in the study
- Patients affiliated with a social security scheme
- Patients who can be monitored within the framework of the protocol

3.3. EXCLUSION CRITERIA

- Refusal to participate in the study (patient, family or trusted relative)
- Patient with weight-bearing on the operated limb not authorised by the surgeon
- Patient with an associated fracture (multiple trauma, concomitant trauma to the upper limb, etc.)
- Patient with a pathological fracture
- Patient included in a category 1 interventional study (involving a drug or medical device)
- Patient deprived of liberty
- Patients not affiliated with a social security scheme

4. STUDY DESIGN AND PROCEDURE

4.1. STUDY SCHEDULE

The inclusion period will be 42 months. Follow-up is 6 months post-operative.

Patients may be included up to 48 hours after their arrival in the orthopaedic/orthopaedic surgery department.

a. D0 - Arrival in the orthopaedic/orthopaedic surgery department (after surgery)

Provision of the information leaflet and collection of non-objection after a reflection period.
Completion of the ASA score *(investigator)*
Biological tests (complete blood count (CBC), CRP, ferritin, transferrin saturation coefficient, albumin, vitamins B12, folate and vitamin D) *(investigator – performed on arrival at A&E or on admission to the department before surgery)*
Record of severe fractures prior to inclusion: upper end of the femur or humerus, proximal tibia, distal femur, 3 simultaneous ribs, wrist, pelvis and spine (Grio 2011 recommendations) *(investigator)*
Screening for previous or current upper function disorders *(investigator)*
Screening for major sensory disorders *(investigator)*
Completion of ADL and IADL questionnaires: **information relating to the week preceding the intervention** *(investigator: interview with patient, family or staff of residential care homes for elderly dependents (EHPAD))*
Completion of the CIRS-G score *(investigator)*
Completion of the CAS questionnaire
Recording of lifestyle and living environment *(investigator)*
Number of medications (by class) taken by the patient on admission (anticoagulants, antiplatelet agents, NSAIDs, anti-osteoporotics, analgesics) *(investigator)* Completion of the MiniGDS score (investigator)
Collection of data on the procedure: time to surgery, type of fracture, surgical procedure, type of anaesthesia, weight-bearing authorisation, transfusion, number of red blood cell units received
Haemoglobin measurement (if different from that taken in the emergency department or on admission to the ward before the procedure)

b. During the hospital stay: *(trained orthopaedic nurses)*

CAS score performed on days 1 to 3 post-operative, as well as on day 5 (or on discharge if this occurs before day 5)
Daily screening for confusion (CAM) until D10 if the patient is still hospitalised Completion of ADL questionnaires *(patient, family or nursing home resident interview)* on D5 post-operative (or on discharge if this occurs before D5)
Measurement of grip strength – Hand Grip on day 5 (or upon discharge if this occurs before day 5)
Record of falls occurring during hospitalisation
Record transfusions and number of red blood cell concentrates Measure
haemoglobin levels on days 1, 3, 5, 10 and 15 after surgery
Recording of Venofer® administration on day 5 (or on discharge if this occurs before day 5)
Recording of post-operative complications: post-operative infection requiring antibiotic therapy (surgical site, pulmonary, urinary, skin, other), acute urinary retention requiring catheterisation, dislocation/loosening of prosthesis, iron deficiency (ferritin < 30 µg/L or CRP > 20 µg/L)

requiring urinary catheterisation, dislocation/loosening of prosthesis, iron deficiency (ferritin < 30 µg/L or CRP > 20 mg/L associated with a transferrin saturation coefficient < 15%) and/or vitamin deficiency (B12 < laboratory threshold, B9 (folate) < 3.5 ng/mL), cardiovascular/neurological complications, post-operative bleeding (including local and digestive), reoperation, haematomas.

Prescription for haemoglobin monitoring on days 5, 10 and 15 post-operatively if the patient has been discharged from hospital
Time allowed for completion: +/- 2 days

c. At the end of hospitalisation: *(investigator)*

Number of medications (by class) (anticoagulants, antiplatelet agents, NSAIDs, anti-osteoporotics, analgesics)
Screening for current higher brain function disorders Record of length of hospital stay
Record of discharge status
Record of vital status

d. Follow-up telephone call 1 month and 3 months post-operative *(supplemented if necessary by questioning the patient, family or nursing home staff)*

Record of living arrangements and location
Completion of ADL and IADL questionnaires Completion of CAS questionnaire
Investigation of late post-operative complications: infection requiring antibiotic treatment (surgical site, pulmonary, urinary, skin, other), acute urinary retention requiring urinary catheterisation, dislocation/loosening of prosthesis, cardiovascular/neurological complications, reoperation.
Record of recurrent falls or fractures New hospitalisation and reason for hospitalisation Record of vital status

e. Telephone follow-up 6 months post-operative *(supplemented if necessary by questioning the patient, family or nursing home staff)*

Record of lifestyle and living arrangements
Completion of ADL and IADL questionnaires
Completion of CAS questionnaire
Search for late post-operative complications: infection requiring antibiotic treatment (surgical site, pulmonary, urinary, skin, other), acute urinary retention requiring urinary catheterisation, dislocation/loosening of prosthesis, cardiovascular/neurological complications, reoperation.
Record of recurrent falls or fractures New hospitalisation and reason for hospitalisation
Number of medications (by class) taken by the patient (anti-osteoporotic, analgesic) Vital status record

STUDY TIMELINE

Actions	**D** Arrival in the orthopaedic surgery department (day of surgery)	**From D1 to D4 post-op.**	**Day 5** post-op**	End of hospitalisation	**M1, M3 and M6 post-op** *(+/- 15 days)* Telephone follow-up
Information for patient/family/trusted relative Collection of non-objection form	X *				
ADL	X[1]		X		X
IADL	X[1]				X
CAS	X [1]	X **(from D1 to D3)**	X		X
HandGrip Test			X		
ASA score/CIRS-G score/MiniGDS score	X				
Confusion screening (CAM)		X **(daily – *up to day 10 if patient is still hospitalised*)**			
Screening for previous or current higher brain function disorders	X			X	
Check for major sensory disorders	X				
Haemoglobin	X	X **(D1, D3, D5, D10, D15)**			
NFS, CRP, albumin, ferritin, transferrin saturation coefficient, vitamins B12, folates and vitamin D	X				
Information about the procedure[2]	X				
Post-operative complications		X **(daily)**[3]			X[4]
Fractures/falls	X (fractures)	X **(daily)**			X
Length of hospital stay/Discharge status				X	
Re-hospitalisation and reason					X
Concomitant treatments	X[5]	**X (End of hospitalisation)[5]**			**X(M6)[6]**
Vital status		X	X	X	X

* Can be performed up to 48 hours after arrival at the department

** Five days after surgery or upon discharge from hospital if this occurs before five days

[1]: Information relating to the week preceding the operation

[2] : Time of surgery, type of fracture, surgical procedure, type of anaesthesia, weight-bearing authorisation, transfusion, number of red blood cell units received

[3] : Post-operative infection requiring antibiotic treatment (surgical site/pulmonary/urinary/skin/other), acute urinary retention requiring urinary catheterisation, dislocation/loosening of prosthesis, iron and/or vitamin deficiencies, transfusion, number of packed red blood cell units received, cardiovascular/neurological complications, post-operative bleeding (including local and digestive), reoperation, haematomas,

[4] Infection requiring antibiotic therapy (surgical site/pulmonary/urinary/cutaneous/other), acute urinary retention requiring urinary catheterisation, dislocation/loosening of prosthesis, cardiovascular/neurological complications, repeat surgery,

[4][5] : anticoagulants, antiplatelet agents, NSAIDs, anti-osteoporotic agents, analgesics

[6]: anti-osteoporosis drugs, analgesics

4.2. GENERAL RESEARCH METHODOLOGY

The research has the following characteristics:

- **Multicentre** study
- **Prospective** study
- **Uncontrolled** study
- **Non-randomised** study

4.3. DESCRIPTION DETAILED OF THE EVALUATION AND THE DATA COLLECTED

a. On patient autonomy:
   - **Activities of Daily Living (ADL)** (21): Measured at inclusion (information relating to the week preceding the procedure) (*questioning of patient, family, nursing home staff),* on day 5 post-op (or on discharge from hospital if discharged before day 5) (*in hospital),* 1 month, 3 months and 6 months post-op (*telephone call).*

Validated scale for assessing independence in simple activities of daily living: hygiene, dressing, mobility, going to the toilet, continence, eating. Each item is coded as follows:
1: done independently
0.5: done partially or with assistance
0: not done
Scale ranging from 0 to 6, with a high score indicating a more independent patient.

   - Lawton's 4-item **Instrumental Activities of Daily Living (IADL)** (22): Measured at inclusion (information relating to the week preceding the intervention) *(questioning of patient, family, nursing home staff)*, at 1 month, 3 months and 6 months post-operatively *(telephone call).*

Validated scale for assessing patient autonomy in so-called "instrumental" activities of daily living: managing finances, preparing medication, using the telephone, using transport. Each item is coded as follows:
1 : done alone
0.5: does partially or with assistance
0: does not do
The score ranges from 0 to 8. A high score indicates that the patient is independent. This score can only be interpreted for subjects living at home.

- **Cumulative Ambulation Score** (23): Measured at inclusion (information relating to the week preceding the procedure), from D1 to D3 post-operative, on D5 post-operative (or on discharge if before D5) *(in-hospital)*, and at 1 month, 3 months and 6 months *(telephone call)*

Validated score predictive of mortality, morbidity and rehabilitation. Three areas (transfer from lying to sitting, transfer from sitting to standing, walking with appropriate aids) are assessed from 0 (unable despite the help of two people) to 2 (able to do independently). The scores are cumulative over the first 3 days post-operatively and give a score of 0 to 18. A cumulative score greater than 10 corresponds to a 99% probability that the patient will be alive at one month, 93% that they will have returned home, and 94% that they will not have had any major post-operative complications.

b. On the patient's physical performance:
   - Measurement of **grip strength** (Hand Grip) on day 5 post-operatively (or on discharge from hospital if this occurs before day 5) *(in-hospital).*

This is measured using a dynamometer. Patients, in a lying or sitting position, are encouraged to squeeze as hard as they can. The best value from three attempts with the dominant hand is used for analysis. The assessment of grip strength using a suitable dynamometer has shown good reproducibility and validity for elderly hospitalised subjects (24).

c. Regarding the surgical procedure:

- **Time to surgery** (time between admission to the emergency department or admission to the ward prior to surgery and the surgical procedure)
- **Types of fractures**:

* Intracapsular fracture (or true cervical fracture): Garden classification I to IV
* Extracapsular (or per-trochanteric) fracture: true trochanteric or trochanteric-diaphyseal

- **Surgical procedures**:

* total or intermediate hip replacement arthroplasty, with or without cement
* Osteosynthesis

-
- Spinal regional **anaesthesia** or general anaesthesia
- Need for intraoperative or immediate postoperative **transfusion** (recovery room)
- **Authorisation for weight-bearing** (surgical instructions)
- Record **of transfusions** and the number of red blood cell concentrates administered (intraoperative and perioperative – in the recovery room).

d. Regarding hospitalisation and complications:

- **Length of hospitalisation**
- Occurrence **of acute postoperative confusion** - daily and up to day 10 if the patient is still hospitalised (screened during hospitalisation using the Confusion Assessment Method CAM scale)(26,27).

This is a diagnostic aid, which can be carried out by a nurse, looking for the presence of sudden and fluctuating symptoms, inattention, disorganised thinking and/or disturbances of consciousness. The presence of the first two criteria and the third or fourth criterion leads to a diagnosis of acute confusional syndrome.

During hospitalisation:

- Occurrence of a **post-operative infection** (surgical site, pulmonary, urinary, skin, other) requiring antibiotic therapy.
- Occurrence of **acute urinary retention** requiring urinary catheterisation
- Occurrence of **dislocation/loosening of prosthesis**
- Screening for **iron deficiency** (ferritin < 30 µg/L, CRP > 20 mg/L associated with a transferrin saturation coefficient < 15%) or **vitamin deficiency** (vitamin B12 < laboratory threshold and B9 (folate) < 3.5 ng/mL)
- Record **of transfusions** and number of red blood cell concentrates administered.
- Occurrence of **cardiovascular complications**: deep vein thrombosis, pulmonary embolism, myocardial ischaemia (increased troponin).
- Occurrence of a **neurological complication**: stroke, cerebrovascular accident, etc.
- **Post-operative bleeding** (including localised bleeding and gastrointestinal bleeding)
- Need for **repeat surgery**
- Occurrence of **haematomas**
- Record of **falls**
- **Vital status**

Post-operative M1, M3 and M6:
- Occurrence of **infection** (surgical site, pulmonary, urinary, skin, other), requiring antibiotic therapy.
- Occurrence of **acute urinary retention** requiring urinary catheterisation
- Occurrence of **dislocation/loosening of prosthesis**
- Occurrence of a **cardiovascular complication**: deep vein thrombosis, pulmonary embolism, myocardial ischaemia (increased troponin)
- Occurrence of a **neurological complication**: stroke, etc.
- Need for **repeat surgery**
-
- Record of recurrent **falls or fractures**
- Record of **new hospitalisations** and reasons
- **Vital status**

e. <u>On geriatric assessment</u>

- **CIRS-G**(28) **scale** *(in-hospital - inclusion)*:

This is a comorbidity scale frequently used in studies because it provides a description of the health status of a population, describing chronic conditions and diseases that have an impact on autonomy, with good reliability and reproducibility
(29). For 14 major systems or groups of systems (cardiac, vascular, pulmonary pathologies, etc.), a score out of 4 is given: 1 being a mild pathology (chronic sinusitis or smoking less than 20 pack-years, for example), 4 is a severe condition causing disability or requiring immediate treatment (acute urinary retention or stroke with hemiparesis).

- **ASA score** (30) *(in-hospital - inclusion)*

Scale used in anaesthesiology Classifying patients into 6 categories: 1: healthy
patient,
2 : with moderate impairment of a major function,
3 : patient with severe impairment of a major function that does not result in disability,
4 : patient with severe impairment of a major function, which is disabling and life-threatening,
5 : moribund patient,
6 : patient declared brain dead whose organs are being harvested for transplantation.

- Screening for depressive symptoms: **MiniGDS** score *(intra-hospital – inclusion)*.
- Screening for previous and current **higher function disorders** by interviewing family and friends or consulting the patient's file *(in-hospital – inclusion and during hospitalisation)*.
- Screening for **major sensory disorders** *(in-hospital – inclusion)*.
- **Number of medications** (by class) taken by the patient at inclusion and at the end of hospitalisation, including anticoagulant therapy, antiplatelet therapy, NSAIDs, anti-osteoporotic therapy, analgesics, and at 6 months post-operatively, including anti-osteoporotic and analgesic therapy.
- Patient's **living arrangements** *(in hospital – inclusion and at 1, 3 and 6 months)*: alone, with family or partner, widowed, in a care home. Home help for shopping, cleaning and personal care.
- **Patient discharge arrangements** *(in-hospital – end of hospitalisation)*: return home, return to care facility, transfer to follow-up care unit.
- **Previous** osteoporotic **fractures** (*in-hospital – inclusion)*: low-energy fractures of the hip, wrist, vertebral body or humerus.
- **Albumin** level *(assessment upon admission, coupled with CRP)*: a level below 35g/L upon admission indicates protein-energy malnutrition.
- **Recurrence of falls or fractures** at 1 month, 3 months and 6 months post-operatively *(telephone call)*.

4.4. SPECIAL SITUATIONS

Dementia patients: the interview with dementia patients will be completed by their family or nursing home staff. Information about participation in the study will be provided to the family/trusted relative.

If surgery is postponed (due to the patient's general condition or the presence of antiplatelet or anticoagulant treatment, for example), D0 remains the date of the procedure and corresponds to the patient's return to the orthopaedic/orthopaedic surgery department (after the procedure).

If the patient is discharged early, a standardised prescription will allow haemoglobin to be monitored on D5, D10 and D15 (timeframe: +/- 2 days).

A patient may receive a transfusion,

- pre- or peri-operative transfusion in the recovery room
- post-operative transfusion
    - In hospital: during the orthopaedic stay
    - Post-hospital: new hospitalisation required for transfusion

4.5. REASON FOR THE TELEPHONE CALL

This study is aimed at elderly and often frail patients. The participating centres are referral centres that treat patients from all regions. For the most optimal and objective recovery possible, the 1-month, 3-month and 6-month assessments should have taken place during a geriatric consultation. Due to the likely frailty of the patients, the absence of systematic post-hospitalisation surgical consultations, and the sometimes significant distance from the patients' place of residence, we felt it was reasonable to limit this follow-up to a telephone follow-up, either with the patient, their family or the nursing staff at the nursing home. Thus, the telephone assessments are based on simple criteria that can be assessed over the phone.
It should be noted that follow-up, including autonomy, was also carried out by telephone during the study by Halm et al. (19).

4.6. IDENTIFICATION OF ALL SOURCE DATA NOT INCLUDED IN THE MEDICAL RECORD

- Lifestyle and living environment
- Previous fractures
- Screening for previous or current higher brain function disorders
- Screening for major sensory disorders
- Screening for depressive symptoms (mini GDS)
- Handgrip strength measurement
- ASA/CIRS-G/CAS/ADL/IADL score
- Screening for confusion (CAM)
- Discharge mode
- Late post-operative complications
- Recurrence of falls or fractures

4.7. RULES FOR DISCONTINUING A PERSON'S PARTICIPATION

4.7.1. Criteria for premature termination of a person's participation in the research

Any patient included in the protocol who no longer wishes to participate will be withdrawn from the study as soon as they express their request.

4.7.2. Procedures for of of participation participation of a person in the research

For the terms and conditions governing the use of data from individuals who have withdrawn prematurely from the study, please refer to the statistics section.

4.7.3. Criteria for discontinuing part or all of the research (excluding biostatistical considerations)

Part or all of the study may be terminated permanently or temporarily by decision of the French National Agency for Medicines and Health Products Safety (ANSM), the CPP, or the study sponsor.

In all cases:
- Written confirmation will be sent to the study's coordinating investigator (specifying the reasons for early termination).
-All patients in the study will be informed and will be required to attend their early exit visit.

To complete this section, refer to the "statistics" section, which presents the statistical criteria for stopping the research.

5. DATA MANAGEMENT AND STATISTICS

5.1. COLLECTION AND PROCESSING OF STUDY DATA

5.1.1. Data collection

An electronic case report form (eCRF) will be created for each patient. All information required by the protocol must be provided in the eCRF. It must include the data necessary to confirm compliance with the protocol and all data necessary for statistical analysis; it must allow for the detection of major deviations from the protocol.

The person(s) responsible for completing the eCRF (investigator, ARC, etc.) must
be defined and identified in the table of delegated responsibilities for each centre (kept in the investigator's binder).

5.1.2. Data coding

By signing this protocol, the principal investigator and all co-investigators undertake to keep the identities of the patients who participated in the study confidential.

Each patient included in the study will be assigned an incremental code consisting of the following three items: treatment centre number, serial number, initials (first letter of surname and first letter of first name).

This code will be the only information that will appear on the electronic case report form (eCRF) and will enable the eCRF to be linked to the patient at a later date.
The investigator is also required to code patient data on all documents in their possession (imaging reports, biology reports, etc.) that are attached to the eCRF.

5.1.3. Data processing

Clinical data collection will be based on the establishment of a database and the creation of data entry forms modelled on the observation log, in accordance with the protocol and regulations currently in force.

5.2. STATISTICS

Statistical analyses will be performed by Lucie PLANCHE, Statistical Engineer at the Vendée Departmental Hospital Centre.

Statistical analyses will be performed using R software version 3.5.3.

5.2.1. Description of methods planned planned, including the schedule for planned interim analyses

All variables collected will be described by minimum, maximum, quartiles, mean and standard deviation for quantitative variables and by number and percentage of each modality for qualitative variables.

Analysis of the primary endpoint:
The relationship between loss of independence at 6 months and post-operative anaemia will be analysed using a logistic model. If a link is found, a multivariate analysis will be performed to confirm the independence of the anaemia/independence relationship. To do this, all potential confounding factors will be tested in a univariate analysis. Factors associated with a p value <0.20 will be retained in the multivariate model.

Analysis of secondary criteria:
- The analysis of the relationship between loss of autonomy on day 5 (or on discharge from hospital if discharged before day 5), at 1 and 3 months, and post-operative anaemia will be performed using the same method as for the primary endpoint.

- The 6-month mortality rate will be estimated with its 95% confidence interval using the Kaplan-Meier method.
The association between anaemia and mortality at 6 months will be studied using a Cox proportional hazards model in order to take confounding factors into account.
- The progression of post-operative anaemia (D0 to D15) will be described graphically.

5.2.2. Statistical justification for the number of inclusions

According to data from the Medical Information Department (DIM) of the CHD in La Roche Sur Yon, over an inclusion period of 18 months, 320 patients aged over 75 underwent surgery on the upper end of the femur (210 patients per year, on average over the last 4 years of activity).
Assuming a mortality rate of 10% and a loss to follow-up rate of 10%, 255 patients could be analysed.
According to Gruson (20), 67.8% of patients regained their previous level of independence within 12 months, while 6.3% died within 6 months.
According to Halm (19), 65% of patients had post-operative anaemia of less than 10g/dL.
As the presence of at least 10 events (loss of independence) per criterion selected in the multivariate analysis is recommended, the inclusion of 255 patients appears to be consistent.

5.2.3. Expected degree of statistical significance

The significance threshold is set at 5%.

5.2.4. Method of into account of missing, unused or invalid data

No imputation will be performed on missing data. These will be described in terms of numbers and percentages.

5.2.5. Selection of individuals to be included in the analyses

All patients for whom preoperative and 6-month loss of autonomy is recorded will be included in the analysis.

6. MONITORING AND MANAGEMENT OF ADVERSE EVENTS

6.1. DEFINITIONS

Vigilance	This refers to the monitoring of medicines, medical devices and other health-related products It also consists of prevention of the risk of adverse effects resulting from their use, whether this risk is potential or proven,
Adverse events (AE)	Any harmful event occurring in a person participating in research involving human subjects, whether or not the event is related to the research or the product being researched.
Adverse effects (AE)	An adverse event occurring in a person participating in research involving human subjects, when this event is related to the research or the product being researched.
Serious Adverse Effects/Events (SAE)/(SAE)	Any adverse effect/event that: * results in death, * is life-threatening, * causes temporary or permanent incapacitation or disability, * requires or prolongs hospitalisation of the patient, * causes a congenital or neonatal abnormality, * is medically significant (the list of medically significant effects/events is defined by the EMA).
Unexpected adverse effects (UEAEs)	Any adverse effect whose nature, severity or progression is inconsistent with the information relating to the products, procedures and methods used during the research.
New information	Any new data that could lead to a reassessment of the benefits and risks of the research or the product being researched, to changes in the use of this product, in the conduct of the research, or in the documents relating to the research, or to the suspension, interruption or modification of the research protocol or similar research. For trials involving the first administration or use of a health product in people who do not have any medical conditions: any serious adverse effect.
Abuse	Intentional, persistent or sporadic excessive use of a drug that is accompanied by harmful physical or psychological reactions.
Overdose	Administration of a quantity of a drug, given in a single dose or cumulatively, that is above above the maximum recommended dose according to the rules of

	compliance or use of the product. Clinical judgement should always be applied. (actual overdose: due to an excessive gross quantity /relative overdose: due to predisposing factors in the patient such as renal failure, hypoalbuminaemia, etc.)
Misuse or off-label use	A situation where the product is intentionally used in a manner that does not comply with the product's specifications for use (e.g. route of administration/dosage or indication different from those listed in the reference document)
Medication error (ME)	Refers to any proven (or potential) omission or unintentional action that occurred during the care process, *in the chain (from manufacture to administration)* involving a product that may cause a risk or adverse event for the patient. The risk of error or potential error refers to situations where the error did not occur, was intercepted but could have have occurred

6.2. LIST OF EXPECTED ADVERSE EVENTS

No complications are expected from the protocol procedure, which consists of analysing the relationship between early post-operative anaemia and functional autonomy at 6 months post-operatively.
A malfunction in the information collection or data analysis system could have a detrimental impact on the results but would not be harmful to the patients included.
The expected adverse events related to the patient's condition, the procedure and its possible complications and their management, co-morbidities and ancillary treatments are no different from those observed in the population routinely treated for the same condition.

Post-operative AEs may be directly related to surgery, anaesthesia, associated treatments including analgesics, but may also be related to the patient's previous condition and comorbidities:
- haematomas and bleeding at the surgical site
- infection of the surgical site
- local or regional pain
- limited movement
- sciatic nerve paralysis

Related to anaesthesia: in addition to the risk of immediate hypersensitivity, delayed awakening, drowsiness, confusion, etc., the adverse effects of the various drugs used are listed in the respective drug summaries of product characteristics.

Related to pain relief treatment: confusion, drowsiness, dizziness, nausea, etc. The adverse effects of the various drugs used are listed in the respective summaries of product characteristics for each drug.

Other complications of the procedure:
- deterioration in general health
- decompensation of a chronic condition (diabetes, respiratory failure, etc.)
- cardiac decompensation
- acute confusion, disorientation

- anaemia
- phlebitis/thrombophlebitis
- pulmonary embolism
-neurological complications (stroke, etc.)
- post-operative infections
- osteoarthritis
- bedsores
- malnutrition

Evl of pathology under study:
- pain,
- loss of independence and immobilisation
- haematoma, blood loss-anaemia
- decompensation of general condition
- phlebitis
- pulmonary embolism and secondary cardiorespiratory or neurological complications

AEs relating to possible **ancillary treatments**: expected AEs are listed in the SPC for medicines used within the scope of the MA or in the instructions for use for MDs used in accordance with the CE marking, therapeutic procedures implemented in accordance with recommendations and good professional practice

6.3. MANAGEMENT OF ADVERSE EVENTS

6.3.1. Collection of ADRs/AEs

As part of this non-interventional research, the protocol does not involve any changes to the usual care of patients, so any adverse events or effects observed will be unrelated to the study.

Under the investigator's responsibility, as with care, the reporting of complications from surgery (post-operative events), treatments, associated procedures or examinations is subject to regulated systems: ADRs related to medicines and medical devices are reported to pharmacovigilance and medical device vigilance systems, while complications from procedures and examinations are integrated into the risk management system of the establishments.

As part of this study to assess the relationship between post-operative anaemia and independence, only complications that may have a potential impact on the study objective during hospitalisation and until the end of the study (i.e. 6 months post-operatively) will be collected and reported in the CRF:
- Occurrence of a **post-operative infection** (pulmonary, urinary, surgical site, other) requiring antibiotic therapy.
- Occurrence of **acute urinary retention** requiring urinary catheterisation
- Occurrence of **prosthesis dislocation/loosening**
- **Iron deficiency** (ferritin < 30 µg/L or CRP > 20 mg/L associated with a transferrin saturation coefficient < 15%) or **vitamin deficiency** (vitamin B12 < laboratory threshold and folate < 3.5 ng/mL)
- Record **of transfusions** and number of red blood cell concentrates administered.
- Occurrence of **cardiovascular complications**: deep vein thrombosis, pulmonary embolism, myocardial ischaemia (increased troponin)
- Occurrence of **neurological complications**: stroke, cerebrovascular accident, etc.

- **Post-operative bleeding** (including localised bleeding and gastrointestinal bleeding)
- Need for **repeat surgery**
- Occurrence of **haematomas**
- Recording of **falls**
- Records of **fracture recurrence**
- Need for **re-hospitalisation** (and reason)

6.3.2. Notification of serious adverse events/serious adverse events requiring investigation

SIs and AEs are reported to the appropriate vigilance channels (a copy will be kept in the patient's clinical file).

Under this protocol, complications necessary for the analysis of the objective (see section 6.3.1) will be recorded in the CRF and analysed according to the study schedule (end of study). When there is a severity criterion in the context of an RNI, it is not necessary to notify the sponsor.
Only new developments occurring during the research and any safety measures taken will be notified to the sponsor and reported to the competent authorities.

6.3.3. Promoter notification period

The investigator is responsible for collecting and reporting the various complications presented by patients to the appropriate vigilance system:
- from inclusion
- until the end of the study (M6)

6.4. TERMS AND DURATION OF FOLLOW-UP OF PERSONS FOLLOWING THE OCCURRENCE OF ADVERSE EVENTS

Any event, particularly a serious one, must be followed up until recovery, consolidation or death (closed event).

7. ADMINISTRATIVE AND REGULATORY ASPECTS

7.1. RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS

Each patient's medical data will only be disclosed to the sponsor or any person duly authorised by the sponsor and, where applicable, to the competent health authorities, under conditions that guarantee confidentiality.
The sponsor and the supervisory authorities may request direct access to the medical file to verify the procedures and/or data of the clinical trial, within the limits authorised by laws and regulations.

7.2. DATA CONFIDENTIALITY

Persons with direct access shall take all necessary precautions to ensure the confidentiality of information relating to the persons involved, in particular with regard to their identity and the results obtained.
These persons, like the investigators themselves, are subject to professional secrecy (under the conditions defined by Articles 226-13 and 226-14 of the Penal Code).
During or at the end of the research, the data collected on the individuals involved and transmitted by the participants shall be anonymised.
Under no circumstances shall the names or addresses of the persons concerned be disclosed.
Only the first two letters of the subject's surname and the first letter of their first name will be recorded, accompanied by a coded number specific to the study indicating the order of inclusion of the subjects.

7.3. COMPUTERISED DATA AND SUBMISSION TO THE CNIL

The data collected as part of this study is collected for scientific research purposes, in the public interest.

This study falls within the scope of the "Reference Methodology" MR-003 registered for the CHD Vendée under number 1995177 v 0 for the following reasons:
- Collection of health data for research purposes
- Obtaining the opinion of a CPP to commence research
- Use of pseudo-anonymised data
- Individual information for the persons concerned
- Access to data only by professionals (healthcare and sponsor) involved in the study.

The fact that this study falls within the scope of MR003 and the reasons for this will be noted in the sponsor's processing register.

7.4. MONITORING OF THE TRIAL

Monitoring will be carried out by the internal promotion unit of the Clinical Research Unit. A Clinical Research Associate (CRA) will visit each investigator site regularly to perform quality control checks on the data reported in the observation logs.

On-site monitoring visits will be organised after consultation with the investigator. CRAs must be able to consult the following at each site:
- the data collection notebooks for included patients,
- the patients' medical and nursing records,
- the investigator's file.
-

7.5. INSPECTION/AUDIT

An inspection or audit may be conducted as part of this study. The sponsor and/or participating centres must be able to provide inspectors or auditors with access to the data.

7.6. ETHICAL CONSIDERATIONS

7.6.1. Obtaining the patient's consent

The investigator undertakes to obtain the non-objection of the patient/trusted person after providing them with information about the protocol (information note in the appendix). They will give them a copy of the information note. The person may only be included in the study after having read the information note and given their non-objection to participating in the study, after having had time to reflect, if necessary.

The patient's information and consent to participate in the research must be noted in their medical records.

7.6.2. Human Protection Committee

The research manager undertakes to submit the study project for prior authorisation by a Human Protection Committee (CPP). The information provided covers

the methods and nature of the research and, secondly, the safeguards provided for patients participating in the trial.

7.7. INFORMATION TO THE COMPETENT AUTHORITIES

This protocol will be reported to the ANSM.

7.8. AMENDMENTS TO THE PROTOCOL

Requests for substantial amendments shall be submitted by the sponsor to the relevant CPP for its opinion in accordance with the law in force and its implementing decrees.

The amended protocol must be updated and dated.
The information form shall be amended if necessary.

7.9. FUNDING

The sponsor shall ensure the financing of the study.

7.10. RULES RELATING TO PUBLICATION

The study will be registered on a freely accessible website (Clinical Trial) before the first patient is included in the study.

Scientific communications and reports relating to this study will be produced under the responsibility of the study coordinator with the agreement of the principal investigators of the participating centres.
.

Publication rules will follow international recommendations (N Engl J Med, 1997; 336:309-315).

The first author must be a doctor from the Vendée Regional Hospital Centre: Romain DECOURS, geriatrician, Vendée Regional Hospital Centre.
The second and penultimate authors will be Marine GEGU, geriatrician, CHD Vendée, and Ronan FEVRIER, geriatrician, CHD Vendée, respectively.
The last author will be Laure de DECKER, geriatrician, Nantes University Hospital.
The co-authors of the report and publications will be the investigators and clinicians involved, in proportion to their contribution to the study, as well as the biostatistician and associated researchers.

A copy of the publication will be sent to the CHD Vendée, the study sponsor, which will necessarily be cited.

7.11. ARCHIVING OF SOURCE DATA

The investigator must keep all information relating to the study for at least 15 years after the end of the study.
At the end of the study, the investigator will receive a copy of the data for each patient from their centre, sent by the sponsor.

LIST OF APPENDICES