Trial Title: A multi-centre, blinded, randomised, placebo-controlled trial assessing the clinical and cost effectiveness of a 12 month course of oral alendronate (70mg weekly) in patients presenting with avascular necrosis of the hip - Managing Avascular Necrosis Treatments: an Interventional Study (MANTIS)

Internal Reference Number / Short title: MANTIS

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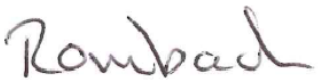
Statistician Signature: 

Conflict of interest declaration

There are no conflicts of interest to declare

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1 ABBREVIATIONS

AE	Adverse event
AP	Anterior-posterior
AR	Adverse reaction
ASBMR	American Society for Bone and Mineral Research
AVN	Avascular necrosis
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMC/DSMC	Data Monitoring Committee / Data Safety and Monitoring Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Score
HRA	Health Research Authority
HRG	Healthcare resource group
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
iHOT-33	international Hip Outcome Tool-33
ITT	Intention to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
OHS	Oxford Hip Score
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PPI	Patient and Public Involvement
PROM	Patient Reported Outcome Measure

QoL	Quality of Life
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SITU	Surgical Interventions Trials Unit
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
THA	Total Hip Arthroplasty
TMF	Trial Master File

2 KEY TRIAL CONTACTS

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Committees	**Project Management Group** Trial Manager Chief Investigator Trial Statistician Data Manager (SITU)

	Trial Steering Committee Professor Roger Francis (Newcastle University) Dr Sally Hope (Oxford University Hospitals NHS Trust) Professor Nicholas Harvey (University of Southampton) Dr Mark Edwards (Queen Alexandra Hospital) Miss Caroline Fairhurst (University of York) Mr Michael Sheperia (PPI member) **Data Monitoring Committee** Professor Bo Abrahamsen (Holbæk Hospital) Dr Nicola Peel (Sheffield Teaching Hospitals NHS Foundation Trust) Dr John Belcher (Keele University) **Patient advisory group** We will offer to participants the opportunity to join the patient advisory group of up to 10 participants. The group will include the trial manager and either the CI or a co-applicant. They will be offered the opportunity to meet in person, by Skype or a similar online platform to discuss issues around trial recruitment, retention, analyses and reporting.

3 SYNOPSIS

Trial Title	Managing Avascular Necrosis Treatments: An Interventional Study	
Internal ref. no. or short title	MANTIS	
Clinical Phase	Phase IV	
Trial Design	Multi-centre, parallel, two-arm, blinded, randomised placebo controlled trial	
Trial Participants	Participants of 18 years and older with symptomatic early AVN of the hip, who seek treatment in secondary hospital care	
Planned Sample Size	280	
Treatment duration	12 months	
Follow up duration	3 years	
Planned Trial Period	5.5 years	
	Objectives	Outcome Measures
Primary	To assess the effect of Bisphosphonate treatment (Alendronate) on AVN of the hip	OHS assessed at 12 months and time to decision that hip replacement is required assessed at 36 months
Secondary	1. To measure hip function, quality of life, radiological progression, complications and compliance 2. To assess the cost implications of treatment arms and compare cost-effectiveness at one year of oral alendronate versus placebo	1. iHOT-33 (Hip PROM for younger patients); EQ-5D; HADS and complication rates assessed at baseline, 6, 12, 24 and 36 months, X-ray and MRI reports and images at baseline; X-ray reports and images at 12 and 36 months and MRI reports and images at 36 months; compliance questionnaires for investigational treatment and standard care assessed at 1, 2, 3, 6, 9 and 12 months 2. Micro-costing; HRG-based approaches; level of detail on costing of components/consumables, health care, rehabilitation, productivity losses and informal care.
Investigational Medicinal Product(s)	Alendronate	
Formulation, Dose, Route of Administration	70mg; oral tablet weekly	

Abbreviations: AVN, avascular necrosis; HADS, hospital anxiety and depression score; HRG, healthcare resource group; OHS, Oxford Hip Score; PROM, patient reported outcome measure

4 BACKGROUND AND RATIONALE

Avascular Necrosis (AVN) of the femoral head is an uncommon but devastating condition that affects around 0.001% of the population in developed countries [1-3] and occurs when the bone of the hip joint dies, resulting in significant disability in many cases. In the US, an estimated 10-20,000 cases of AVN are diagnosed each year [3]. AVN typically affects younger people, with 45% of patients developing the condition before the age of 30 years [1].In the early stages of AVN people often feel pain, followed by a rapid collapse of the joint, which leads to severe immobility and suffering in over 60% of patients. This means that patients can often not walk comfortably, have sleep disturbances and cannot work [3, 4].

The natural history of AVN is well documented however the exact pathophysiology is poorly understood. There have been several postulated mechanisms based on whether AVN is classified as post-traumatic or atraumatic [5]. There are several established risk factors for AVN; glucocorticoid (steroid) therapy and alcoholism are two of the most common associations. Less common associated risk factors include sickle cell disease, radiotherapy, cocaine, methadone and heroin use and Caissons disease [3].

Assessing AVN in the hip

Several radiological and clinical classification systems have been proposed and previous feasibility work for the MANTIS trial suggests that current imaging used is standardised across most hospitals for AVN. The most widely used and the most clinically relevant is the classification of Ficat and Arlet, which is based on X-ray and MRI changes and clinical symptoms [6, 7]. The early stages (Ficat 0/1) are not detectable on X-ray and rely on MRI imaging and clinical assessment. The percentage involvement of the femoral head and the anatomical location of the lesion have been shown to be closely related to progression. Involvement of more than 30% of the femoral head, particularly in the weight bearing area, is correlated with poor outcome and subsequent joint replacement [5, 8]. In patients with untreated Ficat stage 1 or 2 disease, 85% progress to femoral head collapse within two years and 76% of these undergo joint replacement within three years [4].

Clinician and patient-based scoring systems have been used to assess patients with AVN [4, 11-14]. Given that many patients require surgery, including total joint replacement, the most appropriate scores are those that are used in these situations. The Oxford Hip Score (OHS) is usually used to assess patients in need of a total hip replacement but has been used previously in patients with AVN and does not seem to be limited by a ceiling effect in this younger patient population [9, 15]. As part of our preparation work, we have explored the use of different PROMS, such as the International Hip Outcome Tool (iHOT-33), with seven patients suffering from femoral head AVN. The OHS seems acceptable and valid. It does not seem to have a ceiling effect in these individuals, as their pain is significant and their resultant function very poor.

Whilst the Harris Hip Score has been more commonly used in previous studies of AVN [16, 17] this is limited in that it is clinician reported and requires that patients be present for the examination [18].

Existing treatments for Femoral Head AVN

The early phase of treatment usually involves asking the patient to use walking aids, to be non-weight bearing for 3 to 6 months, with the aim to prevent hip collapse and control symptoms using simple analgesics. This is only effective in 15% of patients and most patients will become so immobile that the only treatment for their pain will be joint preserving operations, eventually leading to hip replacement.

Joint preserving operations for AVN have been practiced for over 50 years. These either attempt to encourage revascularization and healing (core decompression or stem cell transplantation), or limit the impact of collapse (osteotomy and bone grafting techniques). Reported success rates vary from 30 to 90% in preventing radiographic progression and relieving pain [4].

Although total hip arthroplasty (THA) is an effective treatment, it is a large operation, with a revision rate of approximately 10 to 20 years [9, 10]. In addition, patients who receive joint replacements for AVN are at a much higher risk of needing further surgery and of postoperative infection than those who do not undergo surgery [10].

Five hundred and seventy joint replacements were performed for AVN in England and Wales in 2012 [13], at a cost of over £5 million. These procedures were predominantly performed in patients under 45 years old. AVN is the primary reason for 25% of the hip replacements performed in patients under 30 year olds. The outcomes of hip arthroplasty are known to be worse in this population compared to those in other populations commonly receiving the same procedure. They also present with significantly higher infection, dislocation and 10-year revision rate adding to the burden of disease [9, 10].

Of more promise are pharmaceutical interventions, as they provide a potentially cost-effective and lower risk option than surgery [11, 16-19]. The cost of oral bisphosphonate therapy is approximately £11 per year in osteoporosis treatment [20]. This is an order of magnitude less than surgical options and other pharmacological therapies. This treatment is likely to be safer and more acceptable to patients than joint replacement or joint preserving surgeries.

Bisphosphonates in the treatment of AVN

At present, there is little evidence for an effective drug treatment for preventing AVN, with very few publications relating to the efficacy of pharmaceutical treatment for AVN.

The literature indicates that oral bisphosphonates may be of use in slowing, or halting the progression of AVN. There are only two randomised controlled trials published on bisphosphonates in the literature. Chen et al (2012) demonstrated no difference in either clinical/structural appearance or symptoms with an oral bisphosphonate (alendronate) compared to a placebo control over three years when looking at the cumulative incidence of THA [17]. Conversely, Lai et al (2005) demonstrated that Alendronate is highly effective (65 vs 3% structural progression, $p<0.001$) compared to a placebo control in preventing progression to THA at 2 years, however this was an open label study with unclear randomisation [12]. Agarwala et al (2011) have demonstrated a sustained reduction in progression to THA at 10 years in a prospective cohort study of patients receiving Alendronate [16]. Despite the potential efficacy of oral Alendronate that some studies show, each study was limited with critical design issues and by the small number of patients included. They also have differing inclusion criteria, with glucocorticoid related AVN, a major cause of the condition, excluded in one study (Chen et al, 2012) [17]. Lai et al (2005) allowed surgical intervention in the treatment groups, making the treatment effect of Alendronate difficult to estimate [12]. Yuan et al (2016) performed a low-quality meta-analysis (including five papers) of bisphosphonate therapy in femoral head AVN [22]. They did not demonstrate any treatment efficacy and commented that the complications of bisphosphonate use (jaw osteonecrosis and atypical fractures) may outweigh the benefits.

These early results demonstrate that oral bisphosphonates (particularly Alendronate) may be of value in the treatment of AVN. Previous feasibility work using Patient and Public Involvement (PPI) groups has

highlighted that a trial looking at the use of bisphosphonates in AVN is needed. This trial is therefore looking at the effect of alendronate plus standard care for the treatment of AVN of the hip.

5 OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure (if applicable)
Primary Objective To assess the effect of Bisphosphonate treatment (Alendronate) on AVN of the hip	1. Short-term Outcome: OHS - PROMs to assess patient's pain and function. 2. Long-term Outcome: Time to decision that hip replacement is required	1. Baseline and 12 months for short-term outcome 2. 36 months for longer-term outcome
Secondary Objectives 1. To measure hip function, QoL, Radiological progression, Complications, compliance 2. To assess the cost implications of treatment arms.	1. OHS, iHOT-33 (Hip PROM for younger patients), HADS, EQ-5D 5L, X-ray and MRI reports and images, Complication rates, compliance questionnaire 2. Micro-costing; HRG-based approaches; level of detail on costing of components/consumables, health care, rehabilitation, productivity losses and informal care.	1. Baseline, 6, 12, 24 and 36 months; X-ray and MRI reports and images at Baseline; X-ray reports and images at 12 and 36 months and MRI reports and images at 36 months; Compliance questionnaire at 1, 2, 3, 6, 9 and 12 months 2. 6, 12, 24 and 36 months

Abbreviations: AVN, avascular necrosis; HADS, hospital anxiety and depression score; HRG, healthcare resource group; OHS, Oxford Hip Score; PROM, patient reported outcome measure; QoL, Quality of Life

5.1 Primary Outcome Measures

Oxford Hip Score (OHS). This is a 12-item validated patient reported outcome measure assessing pain and functional outcomes in the hip. The OHS is measured at baseline, 6, 12, 24 and 36 months, with the short-term primary outcome at 12 months post randomisation.

The long-term primary endpoint is the decision to have a total hip replacement operation within 3 years. This will be recorded as the date the participant is placed on the surgical waiting list by their surgeon. The decision to have surgery is a process of discussions between the clinical care team and the patient.

5.2 Secondary Outcome Measures

5.2.1 Pain

Oxford Hip Score at 6 months, 24 and 36 months. This will allow to show pain and function throughout the trial.

5.2.2 Hip Function

To measure hip function the iHOT-33 questionnaire will be completed at baseline, 6, 12, 24 and 36 months. This is a validated patient reported outcome used to measure symptom progression in younger patients who exhibit some ceiling effect with the OHS [23].

5.2.3 Anxiety and Depression

Hospital Anxiety and Depression Score (HADS) detects states of depression and anxiety in the setting of a hospital medical outpatient clinic [24]. The HADS score will provide an important insight into the overall disease perception and will be completed at baseline, 6, 12, 24 and 36 months.

5.2.4 Quality of Life

To measure quality of life the EQ-5D-5L will be collected at baseline, 6, 12, 24 and 36 months. The EQ-5D-5L is a validated, generalised, health related quality of life questionnaire consisting of 5 domains related to daily activities with a 5-level answer possibility [26, 27], which will be converted into multi-attributed utility scores using established algorithms [28].

5.2.5 Radiological Progression at 1 and 3 years

Both MRI scans and X-rays will be conducted as part of routine care for patients with AVN. In addition to the baseline reports and images, the images and reports from routine MRI scans of the index hip using 3D volumetric hip sequences at 1.5 or 3 Tesla will be obtained at the 3 year assessment for each participant. Images and reports will also be obtained from routine X-ray examinations of the index hip measured at 1 year and 3 years. Both anterior-posterior (AP) and lateral views of the index hip shall be acquired and the lateral joint space width of the index hip will be measured.

Radiological progression will be measured using the Ficat and Arlet scoring system by comparing the scans obtained during the routine patient assessments with those screened at baseline. The grade of chondral damage will be assessed using the Kellgren-Lawrence scoring system.

5.2.6 Healthcare resource use

Health care utilisation will be monitored for the economic analysis at 6, 12, 24 and 36 months. This includes micro-costing; HRG-based approaches; level of detail on costing of components/consumables, health care, rehabilitation, productivity losses and informal care. We will use the micro-costing obtained during the NIHR HTA COAST study to accurately cost the interventions in any patients who undergo total hip replacement [29]. We will include the underlying causes of AVN and possible employment status within the health economic analysis.

As part of the economic evaluation, we plan to combine within-trial data on resource use, costs and outcomes with an extrapolation model to estimate long-term cost-effectiveness. This will be done within the resources already agreed for the economic evaluation.

5.2.7 Compliance with investigational treatment regime

Compliance with the investigational treatment regime will be monitored closely throughout the pilot phase and then into the required full 12 months. A bespoke questionnaire has been developed to capture compliance data. This is based on a questionnaire routinely administered in general rheumatology clinics to capture patient compliance with bisphosphonates. The questionnaires will be sent to participants via post or using a secure online platform accessed through a link sent via email. Data will be collected at 1, 2, 3, 6, 9 and 12 months after randomisation. This questionnaire will also serve to assess if side effects have led to any SAEs that may not have been reported.

5.2.8 Compliance with standard care

Compliance with prescribed standard care will also be assessed. Questions will relate to any physical therapy prescribed, completed or discontinued. Other treatments such as injections or alternative health regimes will also be considered. This data will feed into resource use exploration. The questionnaire will be administered with the treatment compliance questionnaire via post or using a secure online platforms at 3, 6, 9 and 12 months post randomisation.

5.2.9 Day of Surgery Oxford Hip Score

If a participant was to undergo a surgical procedure for their index hip prior to the primary outcome time point (12 months) an OHS questionnaire will be administered. Where possible, this will be completed on the day of the prescribed intervention.

6 TRIAL DESIGN

MANTIS is a randomised, blinded, placebo controlled trial using a superiority two-arm parallel group design. Patients will be randomised on a 1:1 ratio. We will compare standard care plus a 12 month course of oral alendronate (70mg taken weekly) to a matched placebo taken weekly with short term and long term primary outcomes. Patients, clinicians and pharmacists will be blinded as to the treatment allocation of patients. The trial also includes a pilot study to review site feasibility, patient recruitment and follow up regime.

Patients will receive treatment for 12 months and will be followed for up to 3 years. Follow up data will be collected via post or an electronic data collection system whereby patients can complete their patient reported outcome measures (PROMs) directly into a secure on-line portal. An electronic data capture is planned to improve completion rates of this younger and more geographically mobile population. Follow up radiological data from patient reports and images will be collected from routine appointments at 1 year (X-ray), followed by a MRI and X-ray at 3 years, for those who have not had any surgery. Any additional imaging conducted prior to surgical intervention will also be recorded and images collated centrally.

Please see flowchart in Appendix A.

6.1 Pilot Study

A pilot is planned that will progress to the definitive trial if predefined evaluation criteria regarding recruitment, patient characteristics, equipoise and compliance are reached. The pilot trial will mirror the procedures and logistics undertaken in the main definitive trial. Data from the pilot trial will contribute to the final analysis.

The pilot will randomise 50 patients or more over a 12-month period from at least ten sites, with a target recruitment rate of between 1 to 2 patients per site, per month. Femoral head AVN is an uncommon condition, the pilot study is therefore designed to maximize recruitment and ensure that outcomes can be collected reliably and remotely in all patients. If the pilot identifies any issues these will be discussed with the trial steering committee and any changes required for the definitive trial will be discussed with the funder and submitted as amendments for approval.

6.1.1 Evaluation Criteria

The principal evaluation criteria of the pilot will be:

Recruitment

- To determine recruitment rates and referral patterns within different clinical services at each centre.
- To identify and recruit more centres and estimate recruitment rates at each centre.
- To work with the staff at recruiting centres to optimise identify potential barriers to recruitment (e.g. treatment equipoise)

Patient Characteristics

To further refine the inclusion criteria for the study and identify if any groups (e.g. those with alcohol dependency) are likely to represent barriers to recruitment. We will also assess the feasibility of including participants with ongoing steroid use in the trial, given that many of these patients will be treated for either inflammatory joint conditions or will be undergoing chemo/radiotherapy. Monitoring the reasons for non-participation will also help determine if a non-randomised cohort can be appropriately developed alongside the main trial.

Compliance

We have elected to use a weekly bisphosphonate treatment regime. Whilst this is likely to be acceptable to most patients, some groups (e.g. those with alcoholism or undergoing chemotherapy) may find compliance an issue. We will keep detailed compliance logs along with reasons/barriers to compliance, as part of the pilot study. If non-compliance is an issue, we may explore the possibility of exploring other methods of administration.

6.1.2 Evaluation Criteria Outcomes

The pilot study will consider the following outcomes for the evaluation criteria:

- Recruitment rates
- Number of eligible patients identified and conversion to randomisation
- Feasibility of collecting OHS data on the day of intervention (i.e. when a participant is listed for surgery)
- Quality of data collection for the endpoints of the main trial

The primary and secondary endpoints for the main trial will not be analysed separately in the pilot study.

6.2 Development of Imaging Protocol

All radiological examinations (X-ray and MRI) obtained for the MANTIS trial will be collected from routine appointments for the diagnosis and assessment of AVN, monitoring of disease progression and evaluation of treatment effect and will therefore be considered as standard care.

A radiology 'package' has been developed to ensure MRI sequence optimisation for the purposes of diagnosis and staging across sites. Sites will be expected to perform a test scan to ensure sites are using the correct scanning sequences and reporting the Ficat and Arlet classification within their routine algorithm.

The feasibility study for the MANTIS trial suggested that the current sequences used in most hospitals for imaging/staging AVN are already standardised. Where sequences are inadequate, a senior radiologist, who is a Co-applicant, will help modify the scanner settings with the local clinical team.

All radiological reports and associated images (both MRI and X-ray) will be sent to the central study office, in Oxford, via a secure data transferring system. A sample of the radiological examinations will be used to evaluate the processes conducted at participating sites to:

- Ensure baseline assessments are standardised (as patients will be recruited on the basis of the individual sites assessments)
- To confirm disease progression
- To confirm the need for surgery

6.3 The Use of Hospital Episode Statistics (HES)

The pilot will investigate using NHS Digital (including the HES database) and the NHS Central Register, to capture unreported hospital admissions, surgical procedures and missing data from patient questionnaires and CRFs. Patient consent to do this will be obtained. If the use of HES data is a feasible method for following up on missing data, we will continue to use it during the definitive trial.

7 PARTICIPANT IDENTIFICATION

7.1 Trial Participants

The study population will include adult patients (≥18 years) with early, symptomatic atraumatic AVN (hip pain with Ficat Stages 1or 2 and no head collapse, on MRI) seeking treatment in the secondary care hospital setting. We will not include patients under the age of 18 years, as there is little experience in this age group with bisphosphonate therapy in AVN.

All causes of atraumatic AVN will be considered, including idiopathic AVN, and AVN secondary to steroid use, cocaine, methadone or heroin addiction, alcoholism, sickle cell anaemia, HIV, radiotherapy, chemotherapy and autoimmune diseases.

Ongoing corticosteroid use may present a continuing risk for AVN, which in turn may reduce the efficacy of bisphosphonate therapy. Patients who have corticosteroid therapy induced AVN can have stopped treatment, or will still be undergoing drug therapy. We will therefore stratify for planned ongoing steroid use at baseline, which may be clinically necessary in some patients, such as those undergoing chemotherapy for leukaemia, where steroids are used to control side effects.

7.2 Inclusion Criteria

Patients will be eligible for inclusion into the trial if:

- They have early symptomatic atraumatic AVN of the hip (Ficat Score 1 or 2 using MRI)
- They are aged greater than or equal to 18 years

7.3 Exclusion Criteria

Patients will be excluded from this trial if they have/are:

- Not confirmed their diagnosis (Ficat 1 or 2), using MRI, within the last 12 months
- Renal function (creatinine clearance) of <30ml/min (tested within the last 3 months)
- Adjusted serum calcium levels outside local reference range (tested within the last 3 months)
- Established osteoarthritis (Kellgren-Lawrence ≥2)
- Previous AVN, femoral head deformity, prior hip surgery or hip fracture in the index hip
- Current pathology (e.g. osteoporosis) that requires treatment with bisphosphonates
- Received previous anti-osteoporosis therapy (excluding calcium or vitamin D supplements) that lasted more than 4 weeks for oral treatment or any length of parenteral treatment
- Contraindications to MRI
- Contraindications to alendronate therapy (including hypocalcaemia) as listed in the SmPC
- Planning a pregnancy in the next 24 months or are currently pregnant or breastfeeding
- Not using appropriate contraception and of child bearing age
- A planned joint preserving surgical procedure of the hip
- Unable or unwilling to provide informed consent
- Unable to commit to follow-up regime
- Already enrolled in an interventional clinical trial

8 TRIAL PROCEDURES

A table detailing all trial assessments and procedures is provided in Appendix B.

8.1 Recruitment

Patients presenting to outpatient, inpatient services or allied health services at participating sites will be screened for eligibility. Members of the clinical team will review clinic lists to identify any potential patients. Recruitment will proceed depending on site resources and set-up processes. Posters

encouraging participants to talk to their clinician about the MANTIS trial will be provided to sites to display around clinics.

If clinicians are able to confirm eligibility prior to an appointment, an invitation letter and a Patient Information Sheet (PIS) will be sent to the patient ahead of their appointment. The clinician will re-confirm eligibility and willingness to participate with the patient at the appointment and then refer them to the local clinical research team (for example the local research nurse) for recruitment and arrangement of screening and baseline assessments. Diagnosis must be confirmed, by the treating clinician, using the patient's available X-ray and MRI reports and images. If these are not available prior to the outpatient appointment, diagnosis and therefore eligibility cannot be confirmed.

If a patient's eligibility cannot be identified before an appointment, patients will be identified at the time of the appointment by the clinician and referred to the delegated, local clinical research team for recruitment and screening and to arrange baseline assessments. These appointments will take approximately 30 minutes in addition to the regular appointment.

Participants who do not meet the inclusion criteria or who do not wish to participate will receive the standard NHS treatment for AVN.

General information about the number of patients approached who are eligible but decline to participate will be recorded on screening logs at each site. Reasons for decline will be sought, but patients are not obliged to provide these. Information on any patient who meets the inclusion criteria but is then deemed ineligible (meets an exclusion criteria) will also be recorded on the screening log.

8.2 Screening and Eligibility Assessment

Patients interested in participating will be referred to a research facilitator at recruiting sites, who will assess whether they meet the trial inclusion criteria.

Routinely completed MRI and X-ray images and reports will be screened by the local care team, to confirm the diagnosis and the Ficat and Arlet staging. For the diagnosis to be relevant to the trial, the X-rays and MRIs need to have been completed within the previous 12 months from the point of recruitment. Before patients are officially recruited into the study, they will need to have blood tests completed to confirm their renal function, adjusted serum calcium and 25OH vitamin D levels. These will need to have been conducted within the previous 3 months from the point of recruitment. The blood tests are undertaken as part of routine care in this patient population every three months and so all patients should have these results available for consideration of eligibility. Following consent, if pregnancy is suspected, participants of child bearing age may be asked to take a pregnancy test to confirm their eligibility.

8.3 Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the PIS and Informed Consent form will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as needed to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written informed consent will then be obtained by means of a participant-dated signature and dated signature of the person who presented and obtained the informed consent. It is expected that some of the patient population may be difficult to follow up and may not have a fixed address. Therefore, the consent form will also ask the participant to consent for their clinical care team to contact their GP for information which may help the clinical care team query missing data. The participant will also be made aware that screening tests may be needed and previous tests and scans will need to be reviewed to confirm eligibility and the images and reports of scans will need to be accessed from their routine appointments by the clinical care team to aid follow up.

The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed informed consent will be given to the participant. The original signed form will be retained at the trial site.

8.4 Randomisation, blinding and unblinding

Randomisation to the interventions will be undertaken via a centralised web-based randomisation service (RRAMP) run through the Oxford Clinical Trials Research Unit (OCTRU). In the event that sites are unable to randomise patients using RRAMP, sites will need to contact the central research office and a member of the trial team will randomise the patient via RRAMP. If the central research office are also unable to use RRAMP, an emergency backup randomisation will take place.

Participants will be randomised on a 1:1 basis to either alendronate or placebo. Randomisation will be performed using a minimisation algorithm including random element to ensure balanced allocation of participants across the three treatment groups stratified by:

- Randomising site
- FICAT stage (1 or 2)
- Main AVN risk factors (steroid/alcohol/other) obtained from clinical notes
- Bilateral vs. unilateral AVN

The first 28 participants (10% of the expected sample size) will be randomised using simple randomisation to seed the minimisation algorithm.

The intervention will start within 4 weeks of randomisation.

8.4.1 Blinding

Both the active IMP and placebo will be over encapsulated to be identical in appearance. Each bottle of IMP will be allocated a random bottle number that links to the RRAMP system, ensuring

the blinding of the treatment. Patients, the local PIs, the local pharmacists and outcome assessors will be blinded to the treatment allocation. Any report of accidental unblinding will be investigated by the trial management team.

8.4.2 Unblinding

Patients will be requested to carry a patient card with them at all times, outlining that they are participating in the MANTIS trial and may be taking bisphosphonates. Patients should be assumed to be taking the active treatment and blinding should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the participant is receiving before the participant can be treated. Participants and their GPs will also not be unblinded at the end of the trial unless considered medically necessary to do so.

There are no known drug interactions that occur with alendronate, therefore 24-hour unblinding is unnecessary. If a treating clinician deems it necessary to unblind the patient or if the patient becomes pregnant, or suspects pregnancy, the attending clinician should request the patient to stop taking the trial medication immediately, and the PI or delegate should inform the MANTIS trial office using the secure SITU e-mail address (situ.oxford@nhs.net) as soon as possible.

Where possible, members of the research team should remain blinded.

Unblinding is completed via the OCTRU RRAMP system and the MANTIS trial office can unblind the patient during normal working hours. The participant should be requested to remain in the trial, and be followed up as per protocol. A 'Change of Status' form should also be completed.

PIs and sites will be trained on when emergency unblinding may be required and how to request to unblind using the RRAMP system.

8.5 Baseline Assessments

The baseline assessment will be completed once the patient's eligibility and willingness to participate has been confirmed and the patient has given informed consent.

The baseline assessment includes a questionnaire to be completed by the patient which will take approximately 20 minutes. These include:

- The Oxford Hip Score (OHS)
- iHot-33
- EQ-5D-5L
- HADS

In addition, the intention for ongoing corticosteroid use, other AVN risk factors, whether the patient has unilateral or bilateral involvement and the radiological involvement, based on the local radiological reported Ficat score from the most recent MRI, will be recorded on the randomisation form.

General patient demographics and patient contact details will also be collected to help co-ordinate the follow up assessments.

8.6 Subsequent Assessments

Following entry into the study, participants will return to hospital, as part of routine clinical care, to undergo X-rays at 1 and 3 years from study entry, in addition to a MRI scan at 3 years. Images and reports from these routine appointments will be collected as part of assessing radiological progression. All other assessments will involve patient reported outcome questionnaires sent directly to the patients by the central study office in Oxford. Participants will have a choice whether they would like to complete these electronically (via a link sent in an email) or completed on paper form sent out via post and the questionnaires will take between 10 and 30 minutes to complete.

The follow up questionnaires will be sent at 6, 12, 24 and 36 months after entry into the study.

Compliance with the investigational medicinal product (IMP) will be monitored at 1, 2, 3, 6, 9 and 12 months during the 12 month treatment duration and compliance with standard care will be monitored at 3, 6, 9 and 12 months during the 12 month treatment duration. This will be conducted via a secure online platform or via post and will involve participants completing a short compliance questionnaire.

Reminders to participants with uncompleted/unreturned questionnaires will be sent three days after the initial due date for the 1 and 2 month questionnaires and two weeks following the 3, 6, 9 and 12, 24 and 36 month questionnaires. One further reminder will be sent one week later. Following this, non-responders will be telephoned by a member of the central study team in Oxford to collect a minimum of the primary outcomes (OHS). Participants will then be scheduled for their next questionnaires.

At the end of the trial, participants will be sent a newsletter thanking them for taking part in the trial, outlining the trial conduct to date and an estimated timeline for the main analysis and publication.

An assessment table detailing timings of assessments and visits is provided in Appendix B.

8.7 Radiological Protocol

8.7.1 MRI examinations

MRI examinations will be screened at baseline (prior to randomisation) and images and reports will be collected from routine examinations conducted at 36 months from study entry. In the event that a participant has not had a MRI examination within 12 months prior to being screened for the study, eligibility will not be able to be confirmed. Patients may be referred for a MRI and re-screened prior to the examination at baseline. Reports and images will be accepted if conducted ±2 weeks of the 36 month follow up. Only the symptomatic hip (index hip) will be imaged per participant during the MRI examinations. Where possible, the same MRI scanner should be used at both time points for each participant and only 1.5T and 3T MRI scanners will be deemed acceptable for this trial.

The MANTIS MRI protocol is comprised of six MRI sequences:

- Multiplanar T1 weighted Gradient Echo;
- Coronal STIR Weighted Spin Echo;
- Coronal T1 Weighted Spin Echo;
- Sagittal 3D T1Weighted Gradient Echo with full Water Excitation;

- Axial T1 Weighted Spin Echo;
- Axial T2 Weight Spin Echo with fat saturation.

Total image acquisition duration will be around 22 minutes. Total scan duration is expected to be at maximum, 30 minutes.

Depending on the manufacturer and model of MRI scanner at each participating site, the central study office may be able to provide the MRI protocol in a digital format, which can be easily imported into the MRI scanner. For cases where this cannot be done, further technical details of the MRI imaging protocol and scanning technique can be provided.

8.7.2 X-Ray examinations

X-ray examinations will be screened at baseline (prior to randomisation) and reports and images will be collected from routine examinations conducted at 12 months and 36 months from study entry. In the event that a participant has not had an X-ray examination within 12 months prior to being screened for the study, eligibility will not be able to be confirmed. Patients may be referred for an X-ray and re-screened prior to the examination at baseline. Reports and images will be accepted if conducted ±2 weeks of the 12 month and 36 month follow up. Both anterior-posterior (AP) and lateral views of the index hip shall be acquired at all time points. Only the symptomatic hip (index hip) will be imaged per participant during the X-ray examinations. Where possible the same X-ray equipment should be used at all time points for each participant.

If imaging of the contralateral hip is also clinically required, during any of the trial visits, it is recommended that, in order to minimise dose exposure, a single AP view of the pelvis/both hips is performed instead of two AP X-rays for each hip. The same applies for the lateral view, providing the participant has sufficient hip rotation to allow for the acquisition of a correct 'Frog Legs' view.

Exposure values and other technical details should follow each site's specific departmental rules. Nonetheless, each X-ray image must display high bone detail and overall good image quality. Use of digital X-ray detectors and high resolution image plates is highly preferred.

8.7.3 Image Transfer methodology

It is anticipated that all participating sites will be NHS Trusts. For this reason, and in order to comply with both NHS policy and UK law regarding secure handling and storage of confidential information, all examinations shall be transferred to the central study office, in Oxford, via the nationwide data transfer network that connects all Trusts within the NHS.

All images (MRI and X-rays) must be transferred in DICOM format and without any form of pre-transfer image manipulation/processing. Image anonymisation will be conducted at the central study office by competent staff, which will not be involved in any aspect of data analysis or image review.

In the event of a non-NHS site also participating in the MANTIS trial, the transfer of images shall be done using other methods and further details will be provided to sites. The same applies in the event that a NHS Trust is not connected to the nationwide data transfer network.

8.7.4 Imaging reports

All radiological examinations performed shall be reported at the participating site where the images were acquired, by a competent element (e.g. Radiologist or Reporting Radiographer). All reports must be sent to the central study office, in Oxford, along with, and using the same data transfer method, as the respective images and completed radiology CRF.

8.8 Discontinuation/Withdrawal of Participants from Trial Treatment

In consenting to participate in the trial, participants are consenting to trial treatment, assessments, follow up and data collection. Randomisation will be undertaken only once the patient has been informed of all the trial obligations and of the importance of data collection and when the patient has given consent. Each participant has the right to withdraw from any aspect of the trial at any time. In addition to participant self-withdrawal, an investigator may decide to withdraw a participant if considered necessary for any reason including ineligibility either arising during the study or retrospectively, having been overlooked at screening. A withdrawal form will need to be completed.

8.8.1 Withdrawal or Change of Treatment

If patients have been randomised into the study and then do not continue with the treatment regime, either due to self-withdrawal or on the recommendation of their clinician, the reasons for withdrawal or change in treatment will be recorded if available and sites should explain the importance of patients remaining on the trial follow up. If participants are willing, they will be followed up accordingly.

8.8.2 Withdrawal from Follow Up

Participants may withdraw from the follow-up regime or from the trial altogether. If so, their decision should be recorded in the CRF and medical notes and only data up to the point of withdrawal will be collated and analysed accordingly. The patients will be encouraged to discuss treatment options with their clinician.

In the event of discontinuation or withdrawal from the trial the reason will be recorded on the Case Report Form (CRF). Withdrawn participants will not be replaced as withdrawals and loss to follow-up has been accounted for in the estimated sample size. Analysis will be performed on an intention-to-treat (ITT) basis.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

8.9 Definition of End of Trial

The end of trial is defined as 45 days after the final participant questionnaire has been delivered, and all the data has been entered and queries resolved.

9 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1 IMP Description

Both the active substance and placebo control will be manufactured and QP released for use in the study by the holder of the MIA(IMP) licence and supplied to recruiting sites in bottles containing 13 weeks supply of treatment. All IMPs will be over encapsulated and the bottles will be labelled with a MHRA approved clinical trial label in accordance with Annexe 13 (Investigational Medicinal Products) of the EU Guidelines to Good Manufacturing Practice. Both the active substance and placebo control will be administered alongside standard care for patients with AVN.

9.1.1 Active Substance

Alendronate will be used as the active substance in the MANTIS trial and is an off-white, oval, biconvex, oral 70mg tablet, currently used for the treatment of post-menopausal osteoporosis, and to reduce the risk of vertebral and hip fractures [30].

Alendronate is marketed by Accord Healthcare Limited UK (PL 20075/0071) and will be given to participants according to the Summary of Product Characteristics (SmPC) at the recommended dosage of 70mg once weekly for the treatment period of the trial (52 weeks).

The effects on pregnancies and breastfeeding women are not known, as there is no existing data available. Studies in animals have shown reproductive toxicity, therefore alendronate is not recommended. For the purposes of this study, pregnancy and breastfeeding women will not be included in the study and contraception is required for all participants of childbearing age (see section 10.9).

Patients will receive supplemental calcium and vitamin D if the estimated dietary calcium intake is less than 700mg/day. This will be assessed at the point of eligibility screening. For those not requiring calcium supplements, they will be advised to take at least 800 IU of vitamin D3 or D2 per day. For those with a 25OHD vitamin D level less than 30nmol/L, they will be recommended treatment as per local vitamin D guidelines. Where no local guidelines exist, the Oxfordshire Metabolic Bone Disease vitamin D guidelines will be recommended.

9.1.2 Placebo Control

A matched placebo control tablet will be manufactured using capsules backfilled with microcrystalline cellulose and will be identical in appearance to the active tablets. Participants will be asked to take the treatment in the same way as the active treatment (once weekly for the treatment period of the trial (52 weeks)).

9.1.3 Standard Treatment for Avascular Necrosis

Standard therapy is defined as non-weight bearing on the affected limb for 3 months, then full weight bearing as pain allows. Standard care may include up to 8 physiotherapy sessions over 12 months, the use of walking aids will be permitted and Vitamin D and Calcium supplements as per clinical requirements.

All of the trial participants will be advised to take over-the-counter analgesia (such as paracetamol with or without codeine, an oral nonsteroidal anti-inflammatory drug or similar) as required. In addition, all of the participants will be provided with advice on modifying activities that exacerbate symptoms and on sleeping positions.

Participants may seek other forms of treatment during the follow-up period of the trial. Additional treatments, including contact with their GP or other health professional, changes in medication including

analgesics, use of physical treatment and alternative therapies, will be recorded as part of treatment compliance through patient questionnaires at 3, 6, 9 and 12months post-randomisation and health resource use through patient questionnaires at 6, 12, 24 and 36 months post-randomisation.

9.2 Drug Administration

The active substance and the placebo control are both oral tablets to be taken once a week for 52 weeks. Patients will receive their supply of tablets in bottle form and will receive a patient card and weekly text reminders to take their tablet. Pharmacy dispensary will be blinded to the treatment allocation. The tablets will be provided to the patient in bottles containing 13 weeks' worth of treatment, which they will need to attend pharmacy to collect within 14 days of randomisation.

Alendronate must be taken preferably first thing in the morning. Summary of Products guidelines suggest it should be taken at least 30 minutes before the first food, beverage or medicinal product of the day with plain water only. This will ensure the most sufficient absorption. The tablet should also be taken whole and not crushed or chewed as this can cause potential oropharyngeal ulcers. Once the Alendronate has been taken, patients should not lie down or have the first food of the day for at least 30 minutes.

9.3 Storage of IMP

The active substance and placebo control will be stored in pharmacy at each site. Alendronate has a shelf life of 3 years and should be stored between 15 and 25 degrees Celsius [32].

9.4 Compliance with Trial Treatment

Compliance with the IMP (both active substance and placebo control) will be assessed at 1, 2, 3, 6, 9 and 12 months after randomisation and compliance with standard care in both arms will be assessed at 3,6, 9 and 12 months after randomisation. This will be conducted via an online platform or via post and will involve participants completing a short compliance questionnaire based on the Oxfordshire Fracture Prevention Service Questionnaire, used routinely in Osteoporosis and Fracture Prevention Clinics.

The three month compliance data will be reviewed within the pilot analysis. The team will consider this data in line with other pilot analyses and continue with or modify the main trial as necessary.

9.5 Accountability of the Trial Treatment

Both the IMP supplier and local pharmacy department will maintain accountability logs for the IMPs in the MANTIS trial. Site pharmacy will be responsible for logging receipt of the IMPs on the site accountability log within the site pharmacy file in addition to forwarding a copy of the shipping form to the central research office. Site pharmacy will be responsible for storing the IMP and all IMP dispensed by pharmacy will be logged on the site accountability log.

Each bottle of the trial drug will be numbered and records will be kept of the allocation of each bottle using the RRAMP system.

All unused IMPs will be returned to site pharmacy, to be then updated in the drug accountability log in the pharmacy site file. Unused IMP will be collected by the drug supplier and destruction will be conducted, once authorised by the sponsor, in accordance with the drug supplier's standard operating procedures.

9.6 Contraindications to the Trial Treatment

According to the SmPC; the following are listed as contraindications to Alendronate medication and must be considered when recruiting a patient into the study:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC
- Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypocalcaemia.

9.7 Concomitant Medication

All of the trial participants will be advised to take over-the-counter analgesia (such as paracetamol with or without codeine, or an oral nonsteroidal anti-inflammatory drug or similar) as required. These are NICE approved medications for patients with AVN. Summary of Products guidelines suggest Alendronate should be taken at least 30 minutes before the first medicinal product of the day with plain water only.

9.8 Post-trial Treatment

The alendronate will not be provided to patients outside of the study and beyond the 12 months of the treatment period.

9.9 Appropriate Contraception

The Summary of Medicinal Characteristics (SmPC) for Alendronate recommends that it should not be used during pregnancy. There is limited information available to indicate effects to pregnancy, foetal development and postnatal development. Therefore, both male and female participants in this study are required to use highly effective contraceptive methods for the duration of the trial treatment (52 weeks) and for a year after completing the trial treatment. Consent will also be obtained to ask for a pregnancy test to be conducted where necessary to confirm eligibility on the study. Highly effective contraceptive methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation - oral, intravaginal, transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation - oral, injectable, implantable
- intrauterine device (IUD)

- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments)

10 SAFETY REPORTING

10.1 Definitions

Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	All untoward and unintended responses to an investigational medicinal product (IMP) related to any dose administered.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure (IB) for an unauthorised investigational product or summary of product characteristics (SmPC) for an authorised product) and which also meets the definition of serious.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”.

10.2 Procedures for Recording and Reporting Adverse Events

Alendronate is a licensed medication, with a comprehensive safety profile. Only AEs detailed in the following table will be recorded on the AE form:

Adverse Event	Definition
Upper gastrointestinal	abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, abdominal distension, acid regurgitation, peptic ulcer, nausea, vomiting, gastritis, oesophagitis, oesophageal erosions, melena, oesophageal ulcer, dysphagia, odynophagia, oesophagitis, oesophageal stricture, oropharyngeal ulceration, upper gastro-intestinal perforation, ulcers, bleeding
Osteonecrosis of the jaw	Eight weeks of exposed bone despite usual oral therapy
Atypical femoral fracture	Fulfils ASBMR 2013 criteria
Musculoskeletal pain	Bone, muscle or joint pain unrelated to AVN
Hypocalcaemia	Symptoms of cramps, paraesthesia with a concurrent serum calcium level below the local laboratory reference range

Abbreviations: ASBMR, American Society for Bone and Mineral Research; AVN, avascular necrosis

The listed AEs are known to be expected and related to the trial drug and are detailed in the SmPC. The recording of the listed AEs will help to assess reasons for non-compliance or withdrawals in this patient population. These will be recorded on the Adverse Event form as soon as the site or central study office become aware of them.

The following information will be recorded: description, date of onset, end date and action taken. Follow-up information should be provided as necessary.

It will be left to the Investigator’s clinical judgment to decide whether or not an AE is of sufficient severity to require the participant’s removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

10.3 Procedures for Recording and Reporting Serious Adverse Events

If an adverse event is deemed to be serious (i.e. meets the SAE criteria), then this will be reported on the SAE form. The sites must notify the study office in Oxford of these events within 24 hours following knowledge of the event. The completed form will be sent to the Oxford study office via secure nhs.net email (situ.oxford@nhs.net). SAEs will also be reviewed at the next Data Safety and Monitoring Committee (DSMC) meeting.

Centres must routinely monitor patient records for any events that may have been missed.

The study office in Oxford will perform an initial check of SAE reports, request any additional information, and ensure it is reviewed by the trial's nominated person in a timely manner and according to the relevant SOP on safety reporting.

SAEs considered related to the trial medication will be followed either until resolution, or when the event is considered stable.

Each SAE will be assessed for causality and expectedness as described below.

10.3.1 Causality

The relationship of each SAE to the trial medication must be determined by a medically qualified individual according to the following Cancer Therapy Evaluation Program (CTEP) definitions:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related to investigational agent/intervention	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

Assessment of causality (i.e. relatedness) will be recorded in the SAE form as either 'related' or 'unrelated' by the site PI or a delegate (medically qualified doctor). In addition, this will be reviewed centrally by the Nominated Person for the trial, according to OCTRU's SOPs on safety reporting.

10.3.2 Expectedness

Section 4.8 of The Summary of Product Characteristics (SmPC) will be used as the Reference Safety Information (RSI) for the IMP for all safety assessments and reporting, including SUSARs. If the RSI is updated throughout the lifetime of the trial this will be sent to the MHRA for approval.

Assessment of expectedness will be performed against what is documented in the approved RSI and will be done centrally and independent of the site's PI by the Nominated Person for the trial. SARs that are more severe or described with more specificity than what is documented in the RSI section of the SmPC will be assessed as unexpected and hence will be reported as SUSARs.

In addition, all SARs that are classified as fatal or life-threatening will also be classified as unexpected and hence reported as SUSARs.

10.4 SUSAR Reporting

All SUSARs will be reported by the Clinical Trials Unit (CTU) to the eSUSAR tool and a copy sent to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than seven calendar days after the CTU is first aware of the reaction. Any additional relevant information will be reported within eight calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Treatment codes will be un-blinded for specific participants.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

10.5 Safety Monitoring Committee

A Data Safety and Monitoring Committee (DSMC) will be appointed to safeguard the interests of the trial participants, to assess the safety and efficacy of the interventions during the trial, and to monitor the overall conduct of the trial, protecting its validity and credibility. The DSMC will be independent of the trial investigators and sponsor and will adopt a DAMOCLES charter that defines its terms of reference and operation in relation to oversight of the trial. It will meet at least every 12 months over the duration of the trial.

The DSMC will monitor and review the pilot data to determine if the study will continue, and if so if any amendments need to be made to the sample size and trial design.

Throughout the definitive trial, the DSMC will continue to review accruing data and summaries of that data presented by the treatment group and will assess the screening algorithm against the eligibility criteria. It will also consider emerging evidence from other related trials or research and review any related SAEs that have been reported.

The DSMC will comprise of at least two independent medically qualified clinicians and a statistician.

In addition to a DSMC, a trial steering committee (TSC) will be appointed whose primary function is to act as an oversight body for the trial on behalf of the Sponsor and funding body. The TSC will be chaired by an independent member and will consider and act, as appropriate, upon the recommendations of the DSMC and ultimately carries the responsibility of deciding whether or not the trial needs to be stopped on the grounds of safety. The TSC will adopt a charter that defines its terms of reference and operation in relation to the oversight of the trial and will meet at least every 12 months over the duration of the study.

The DSMC may advise the chair of the TSC at any time if, in its view, the trial should be stopped for ethical reasons, including concerns about participant safety or clear evidence of the effectiveness of one of the treatments.

10.6 Development Safety Update Reports

The CTU will submit the annual Development Safety Update Reports (DSURs) within 60 days of the anniversary date of the MHRA trial approval. These will be submitted once a year throughout the clinical trial, or on request, to the Competent Authority (Medicines and Healthcare products Regulatory Agency (MHRA) in the UK), Ethics Committee and Sponsor.

10.7 Notification of Pregnancy

Following consent, pregnancy will be tested to confirm the eligibility of patients for recruitment. During follow up, participants will also be asked to declare that they are maintaining effective contraceptive methods in their follow up questionnaires. If participants indicate effective contraceptive methods have lapsed, they will be asked to take a pregnancy test. If the test shows a positive pregnancy, the related site must complete a Pregnancy Notification Form and submit this to the central study office in Oxford as soon as possible.

11 STATISTICS

11.1 The Number of Participants

The study requires 140 participants per arm, 280 in total. This sample size provides sufficient power for both co-primary endpoints of the MANTIS trial.

Short-term endpoint – The Oxford Hip Score at 12 months:
The minimum clinically important difference (MCID) of the OHS is estimated to be 5 points on the 0-48 point scale [33]. Assuming a common standard deviation of 10 for the OHS at one year, using 90% power, a 5% two-sided significance level, and allowing for a loss to follow-up of 20%, 114 participants are required per arm (228 in total).

Long-term endpoint– The time to decision that hip replacement is required measured from randomisation to the date the participant is placed on the surgical waiting list by their surgeon:
This allows for delays to surgery or participants not being fit for surgery. The criteria for this decision will be defined in the protocol. It is anticipated that 60% of participants in the control group will require a hip replacement by three years. This trial is powered to be able to detect an absolute reduction of 20% in the rate of participants requiring a hip replacement in the intervention group (i.e. a reduction to 40% of participant requiring a hip replacement in this trial arm), translating to a hazard ratio of 0.5575. Using 80% power, a 5% two-sided significance level, and allowing for 20% loss to follow-up assuming that recruitment takes 3 years with an additional 1 year follow-up, 140 participants are required per trial arm (280 in total). The sample size calculation assumed a ¾ ratio between accrual time and total trial duration.

Sample size calculations were performed in PASS (PASS 11 Power Analysis and Sample Size Software (2011). NCSS, LLC. Kaysville, Utah, USA).

11.2 Description of Statistical Methods

Full details of the statistical analysis will be provided in a separate statistical analysis plan (SAP) which will be drafted early in the trial and finalised prior to the data lock for the primary analysis of the short-term outcomes. Stata (StataCorp LP) or other appropriate, validated statistical software will be used for analysis. A summary of the planned statistical analysis is included here.

For the main analyses, participants will be grouped by the intervention allocated; irrespective of the intervention actually received (ITT principle).

11.3 Frequency of Analysis

Two formal statistical analyses are planned for the MANTIS study to coincide with the co-primary endpoints. The first analysis will take place after the completion of the one year follow-up to assess the short-term outcomes of the study; the long-term outcomes will be assessed at the end of the trial.

A Data Safety and Monitoring Committee will review descriptive summaries of the accumulating data at regular intervals throughout the trial recruitment and follow-up.

11.3.1 Primary Outcome Analysis

This two-arm trial comprises of a short term and long term primary outcome. The primary short-term outcome will be the Oxford Hip Score (OHS) at 12 months. This is a validated patient-reported measure for measuring reductions in pain and disability in patients with hip symptoms.

The primary long-term outcome will be the time to decision that hip replacement is required over 3 years. This is considered of particular importance to this young patient population.

The primary Null Hypothesis for the short term and long term primary outcomes is that there is no difference between the treatment arms; the statistical tests will be performed at the 5% significance level.

The primary analysis of the OHS will be performed using multilevel mixed-effects linear regression models, taking into account repeated OHS measurements per participant over time. The model will be adjusted for baseline OHS and randomisation factors. Supplementary analyses will include the additional adjustment for important pre-specified prognostic factors and the per protocol population.

The primary analysis of the time to decision that hip replacement is required will be evaluated via a Cox proportional hazards model. The model will be adjusted for randomisation factors and baseline OHS scores.

11.3.2 Secondary Outcome Analysis

Continuous secondary outcomes will be analysed using multilevel mixed-effects linear regression models to take into account repeated measures over time, adjusting for stratification factors and other relevant baseline measures.

Binary and categorical will be tabulated to show frequencies and percentages of participants falling into the relevant categories per arm. Chi-squared tests will be used to explore statistical significance.

Baseline data will be presented overall and by trial arm.

Reporting of the MANTIS trial will be in line with the CONSORT guidelines.

Safety data will be presented by trial arm.

11.4 Criteria for the Termination of the Trial

During the pilot phase, the independent DSMC will review accrual against the target of 50 patients randomised within 12 months. They will also review the sample size assumptions and make recommendations as to whether it is feasible to complete the trial within the proposed time frame.

During the definitive trial, the DSMC will review the safety and efficacy data and provide recommendations to the TSC. Both the DSMC and TSC will evaluate the risk of the trial continuing and take appropriate action where necessary.

11.5 Procedure for Accounting for Missing, Unused, and Spurious Data

Throughout the trial, missing data occurrence will be minimised through careful study design and data management, training of recruiters and site staff, as well as interaction with participants.

Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented by treatment arm. All data collected on data collection forms will be used, since only essential data items will be collected. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis.

The nature and mechanism for missing variables and outcomes will be investigated, and if appropriate multiple imputation will be used. Sensitivity analyses will be undertaken assessing the underlying missing data assumptions. Any imputation techniques will be fully described in the Statistical Analysis Plan.

11.6 Inclusion in Analysis

OHS analysis: Multiple imputation vs. available cases analysis using multilevel mixed-effects models

Either: The primary analysis of the OHS will include all participants with any available OHS follow-up data to one year.

OR: The primary analysis of the OHS will include all randomised participants according to the ITT principle. Missing data in the OHS will be imputed such that all randomised participants can be included in this analysis.

The time-to-event analysis for the time to hip replacement will include all randomised participants, with participants being censored at time of loss to follow-up, death or end of the study if event-free.

11.7 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

A detailed statistical analysis plan will be drawn up prior to patient recruitment or early in the trial with review and appropriate sign-off following OCTRU SOPs. Any changes to the statistical analysis plan during the trial will be subject to the same review and sign-off procedure with details of changes being included in the new version. Any changes/deviations from the original SAP will be described and justified in protocol and/or in the final report, as appropriate.

11.8 Economic Analysis

We have integrated an economic evaluation within the trial design. The economic evaluation will be conducted with reference to clinical NHS services and Personal Social Services perspective [34]. Data will be collected on health and social service resources used in the treatment of each participant at 6, 12, 24 and 36 months post-randomisation. We will estimate the costs of delivering bisphosphonate therapy including patient's education and pharmaceutical costs. We will also measure the costs of routine care (including physiotherapy, joint and other injections, occupational therapy) in patients with AVN. Permission will be requested from the study participants during the initial consent process for long-term follow-up and use of routine data (HES records) beyond the timeframe of the outcomes assessed in the trial. The effect of AVN and bisphosphonates on employment will be assessed given that the majority of trial participants will be of working age. We will measure factors such as time off work and loss of earnings as well as increased travel and living costs due to disability. We will also measure the cost of any complications of drug therapy (e.g. upper gastro-intestinal events).

12 DATA MANAGEMENT & SHARING PLAN

A Data Management and Sharing Plan will be produced for the trial and will include reference to confidentiality, access and security arrangements. All data will be processed in accordance with data protection rules. Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

All trial data will be collected on trial specific documents for example questionnaires and case report forms (CRFs). All trial-specific documents, except for the signed consent form and follow-up contact details, will refer to the participant with a unique study participant number/code and not by name. Participant identifiable data will be stored separately from study data and in accordance with OCTRU SOPs. All trial data will be stored securely in offices only accessible by swipe card by the central coordinating team staff in Oxford and authorised personnel.

On completion of the study, and with appropriate participant consent, fully anonymised data may be shared with other organisations at the behest of the funder. All requests for the use of the data from the MANTIS study will be approved by the CI, TMG and where necessary the TSC. A data request form should be completed detailing the decision as to whether the request is accepted. In cases where individual site data is requested, only summary data would be provided with caveats for dissemination, to emphasise that trial data should be interpreted as a whole.

13 QUALITY ASSURANCE PROCEDURES

The clinical trials unit (CTU) conducted a risk assessment prior to the study starting. Issues raised have been addressed within the final protocol and procedures have been planned to monitor the ongoing risks of the trial. A risk proportionate approach will be utilised within this trial and the trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. Central monitoring of trial procedures will be imbedded into the trial conduct and management. The trial will be subject to audit by the trial manager, according to OCTRU's Audit Programme. The trial will also undergo a process of review before it is granted the green light to begin recruiting patients.

14 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days. A detailed outline of this procedure will be available as a Trial Specific Instruction in the TMF.

15 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Patients and the public have already been involved in providing input on the design of the trial and will be actively involved in several stages of the trial going forward including:

- The management of the research
- Developing participant information resources
- Contributing to the reporting of the research
- Dissemination of research findings

PPI members will sit on the Trial Steering Committee (TSC), and be involved in acting as an oversight body for the trial as well as providing input into this protocol. We also aim to set up a patient advisory group, made up of 5-10 members of the public who may have already experienced treatment for AVN, to provide insight and comments on the patient facing material, to ensure the information we provide is relevant.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

16.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with the principles of Good Clinical Practice.

16.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC and Sponsor.

The funder, NIHR HTA Programme, also require submission of progress reports every 6 months. Monthly recruitment figures are also provided to the funding body.

16.5 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the data protection rules, which requires data to be anonymised as soon as it is practical to do so.

Consent will be obtained from patients for personal information to be sent to the central study team in Oxford (i.e.: name, address, email, telephone number, radiological reports). This information is required to coordinate the postal and electronic follow up.

16.6 Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

16.7 Other Ethical Considerations

The study is assessing the effectiveness of Alendronate in a new patient population. The study will undergo review by the Medicines and Healthcare products Regulatory Agency (MHRA) and an NHS Research Ethics Committee to ensure the medication is safe for use by these patients. Major concerns are not anticipated.

Alendronate will be compared to a placebo medication. Patients will be fully informed as to what receiving the placebo may involve. No standard treatment will be withheld. Patients will still receive standard care for their condition. The Alendronate/Placebo are extra to routine care.

Whilst the patient population are not considered vulnerable, if the trial team are made aware of any concerning statements in response to the patient questionnaires, the information will be referred to the local clinical team. Only where deemed clinically necessary will the patient be unblinded to their treatment allocation.

17 FINANCE AND INSURANCE

17.1 Funding

The study is funded by the National Institute of Health Research, Health Technology Assessment Programme (Ref 15/39/06). The Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences at the University of Oxford will manage the finances and budget.

17.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

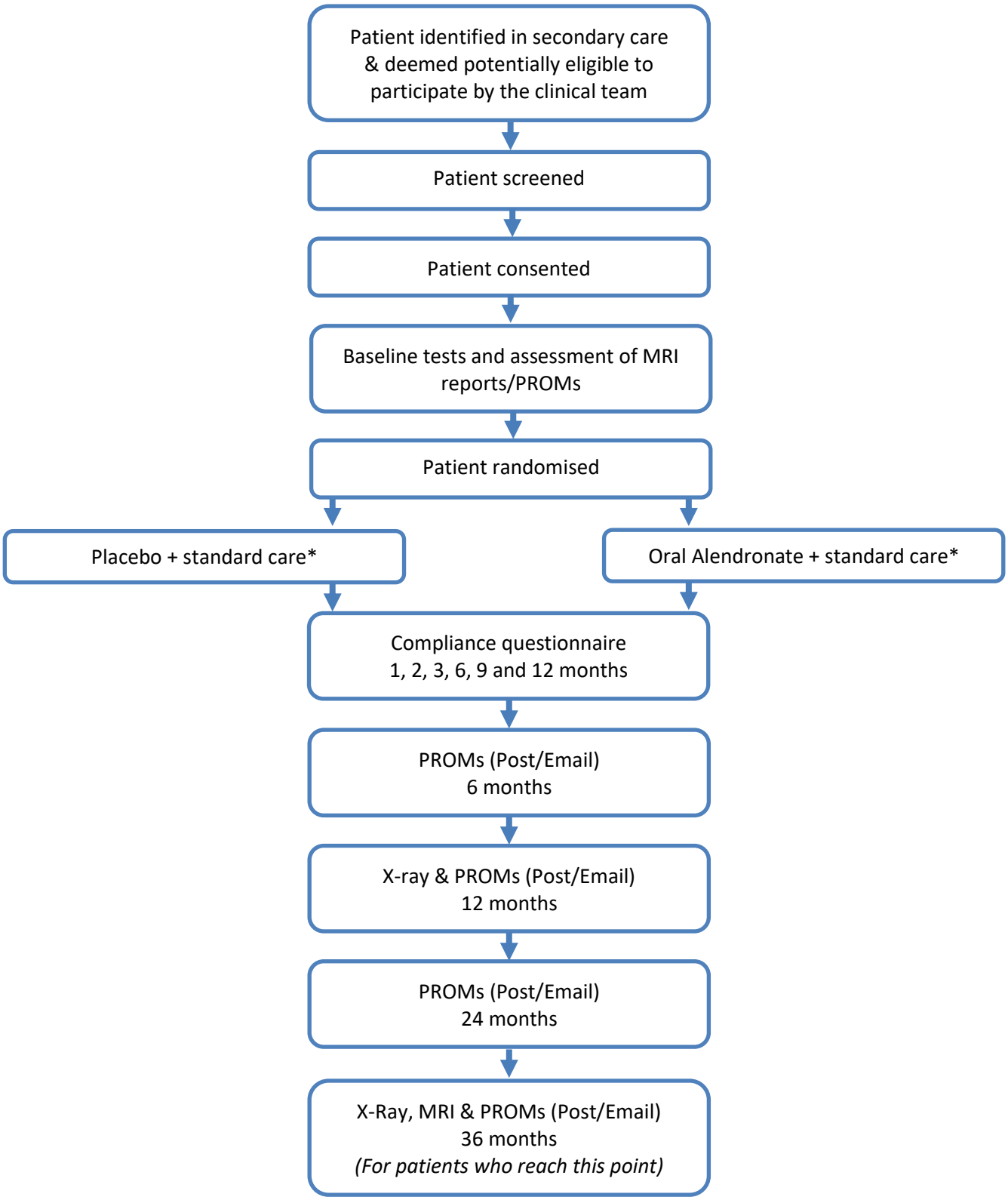
18 PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the National Institute of Health Research, Health Technology Assessment Programme (Ref 15/39/06). Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

All investigators and co-ordinators who take part in the study will be members of the MANTIS Study Group and will be publicly listed on the trial website. All MANTIS publications will be published on behalf of the MANTIS Study Group, which means all trial group members can list these in their curriculum vitae. All members of the MANTIS Study Group will be submitted to be listed and citable in PubMed.

We will also produce a newsletter to engage with trial participants at 1, 2 and 3 years after the study has begun recruitment and after publication of the main study findings. The content of the newsletter will be made available in a format suitable to be presented on the patient section of the study website.

19 APPENDIX A: TRIAL FLOW CHART



*Treatment must be collected within 14 days of randomisation

20 APPENDIX B: SCHEDULE OF PROCEDURES

Assessments	Timing of assessments										
	Pre-randomisation		Post-randomisation								
	Screening	Baseline	1 month	2 months	3 months	6 months	9 months	12 months	24 months	36 months	Day of intervention prior to primary outcome
Eligibility check	X										
Demographics	X										
Review screening blood samples (Vit D, Ca, Renal)	X*										
Informed Consent		X									
Pregnancy test		X									
Oxford Hip Score (OHS)		X				X		X	X	X	X
Time to placement on surgical waiting list										X	
iHot-33		X				X		X	X	X	
Quality of Life (QoL)		X				X		X	X	X	
Resource Use						X		X	X	X	
MRI reports and images		X*								X*	
X-ray reports and images		X*						X*		X*	
Compliance with IMP (both active treatment or placebo)			X	X	X	X	X	X			
Compliance with prescribed standard care					X	X	X	X			

Assessments highlighted in orange are those that will be conducted via postal or electronic questionnaires

*Routine care

21 APPENDIX D: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.

22 APPENDIX E: REFERENCES

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