

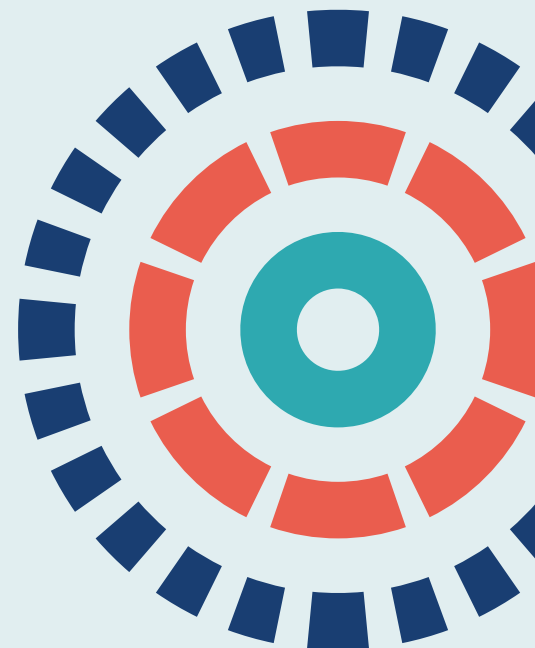
## Health Technology Assessment

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# Assessing a 12-month course of oral alendronate for adults with avascular necrosis of the hip: MANTIS RCT with internal pilot

*Sion Glyn-Jones, Muhammad K Javaid, David Beard, Julia Newton, Robert Kerlake, Callum McBryde, Tim Board, Susan J Dutton, Melina Dritsaki, Vikas Khanduja, Magbor Akanni, Shaun Sexton, John Skinner, Nicholas Peckham, Ruth Knight, Ines Rombach, Loretta Davies and Vicki Barber on behalf of the MANTIS study group*





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# Abstract

## Assessing a 12-month course of oral alendronate for adults with avascular necrosis of the hip: MANTIS RCT with internal pilot

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**Background:** People with avascular necrosis of the hip have very limited treatment options currently available to stop the progression of this disease; this often results in the need for a hip replacement. There is some weak evidence that a class of drugs called bisphosphonates may delay the course of the disease, and this trial was commissioned and set up to provide robust evidence regarding the use of bisphosphonates in adults aged  $\geq 18$  years with this condition.

**Objectives:** The aim of the Managing Avascular Necrosis Treatments: an Interventional Study (MANTIS) trial was to evaluate the clinical effectiveness and cost-effectiveness of a 12-month course of alendronate in the treatment of avascular necrosis.

**Design:** This was a 66-month, definitive, multisite, two-arm, parallel-group, placebo-controlled, double-blind, randomised controlled trial, with an internal pilot phase.

**Setting:** Eight secondary care NHS hospitals across the UK.

**Participants:** Planned trial size – 280 adult patients with avascular necrosis.

**Intervention:** Participants in the intervention group received 70 mg of alendronate (an oral bisphosphonate) weekly for 12 months.

**Main outcomes:** The main outcomes were Oxford Hip Score at 12 months (short-term outcome) and the time to decision that a hip replacement is required at 36 months (long-term outcome).

**Results:** Twenty-one patients were recruited and randomised to receive either the intervention drug, alendronate, or a placebo-matched tablet.

**Limitations:** This trial was principally limited by low disease prevalence. Other limitations included the late disease stage at which participants were identified and the rapid progression of the disease.

**Future work:** This trial was limited by a low recruitment rate. Avascular necrosis of the hip should be treated as a rare disease. Future trials would need to recruit many more sites and recruit over a longer time period, and, for this reason, a registry may provide a more effective means of collecting data pertaining to this disease.

**Conclusions:** The MANTIS trial was terminated at the end of the pilot phase, because it did not meet its go/no-go criteria. The main issue was a poor recruitment rate, owing to a lower than expected disease prevalence and difficulties in identifying the condition at a sufficiently early stage. Those patients who were identified and screened either were too advanced in their disease progression or were already taking medication. We would not recommend that a short-term interventional study is conducted on this condition until its prevalence, geographic foci and natural history are better understood. The difficulty of acquiring this understanding is likely to be a barrier in most health-care markets. One means of developing this understanding would be the introduction of a database/registry for patients suffering from avascular necrosis of the hip.

**Trial registration:** The trial is registered as ISRCTN14015902.

**Funding:** This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 43. See the NIHR Journals Library website for further project information.

# Contents

List of tables	xi
List of figures	xiii
List of abbreviations	xv
Plain English summary	xvii
Scientific summary	xix
<b>Chapter 1 Introduction</b>	<b>1</b>
Trial summary	1
Background and rationale	1
<i>Assessing avascular necrosis in the hip</i>	1
<i>Existing treatments for femoral head avascular necrosis</i>	2
<i>Bisphosphonates in the treatment of avascular necrosis</i>	2
<b>Chapter 2 Methods</b>	<b>5</b>
Trial design	5
Research governance	5
Management of the trial	6
Design and development of the protocol	7
Amendments to the trial protocol	7
Amendments to the trial	7
Support costs	7
Patient and public involvement	8
Site initiation	8
Investigator site file	9
Site management	9
<i>Site monitoring visits</i>	9
Inclusion criteria	9
Exclusion criteria	9
Screening and recruitment	10
Screening log	10
Informed consent	10
Randomisation and allocation procedure	11
Treatment groups	11
Dosing regimen	12
<i>Active substance</i>	12
<i>Placebo control</i>	12
Drug administration	12
Data collection	13
<i>Baseline</i>	13
<i>Subsequent follow-up</i>	13
Embedded pilot	13
<i>Evaluation criteria</i>	14
<i>Evaluation criteria outcomes</i>	15

## CONTENTS

Outcome measures	15
<i>Primary outcome measures</i>	15
<i>Secondary outcome measures</i>	15
Safety monitoring	16
Trial oversight	17
Data management	17
Sample size	18
<i>Power calculation</i>	18
Statistical analyses	18
<b>Chapter 3 Identified challenges</b>	<b>19</b>
Issues identified for the MANTIS trial	19
<i>Delayed set-up</i>	19
<i>Poorly defined patient pathway</i>	20
<i>Recruitment</i>	21
<i>Capacity at local sites</i>	22
Mitigation of issues identified	22
Further mitigation of issues identified	23
<b>Chapter 4 Results</b>	<b>25</b>
Explanatory statement	25
Sites open to recruitment	25
Study participants	25
Recruitment breakdown	26
Patient demographics	28
Treatment compliance	28
Follow-up of patients	28
Withdrawals and protocol deviations	36
Clinical outcome results	37
<i>Oxford Hip Scores</i>	37
<i>iHOT-33 scores</i>	37
<i>EuroQol-5 Dimensions, five-level version, scores</i>	37
<i>Hospital Anxiety and Depression Scale scores</i>	37
Safety reporting	37
<b>Chapter 5 Discussion and conclusions</b>	<b>43</b>
Limitations	43
Future work	43
Overall conclusion	44
<b>Acknowledgements</b>	<b>45</b>
<b>References</b>	<b>49</b>
<b>Appendix 1</b> List of participants' relevant medical history, taken at baseline	<b>53</b>
<b>Appendix 2</b> List of medications taken by participants at baseline	<b>55</b>

# List of tables

<b>TABLE 1</b> Schedule of procedures	14
<b>TABLE 2</b> Adverse events to be recorded	16
<b>TABLE 3</b> Screening and randomisation data for the MANTIS trial by site	26
<b>TABLE 4</b> Reasons for ineligibility of screened patients for the MANTIS trial by site	27
<b>TABLE 5</b> Reasons for declining participation in the MANTIS trial by site	28
<b>TABLE 6</b> Breakdown of recruitment by site	29
<b>TABLE 7</b> Average numbers of participants randomised and screened per site per month	30
<b>TABLE 8</b> Baseline categorical characteristics by trial arm	30
<b>TABLE 9</b> Continuous baseline factors by trial arm	32
<b>TABLE 10</b> Drug packs issued by trial arm	32
<b>TABLE 11</b> Treatment compliance from self-reported compliance questionnaires for the placebo arm	32
<b>TABLE 12</b> Treatment compliance from self-reported compliance questionnaires for the alendronate arm	34
<b>TABLE 13</b> Compliance with follow-up for the MANTIS trial	35
<b>TABLE 14</b> List of withdrawals from the trial with reasons and last data entered	36
<b>TABLE 15</b> List of protocol deviations from trial with action taken	36
<b>TABLE 16</b> Oxford Hip Score for the left hip by allocation	37
<b>TABLE 17</b> Oxford Hip Score for the right hip by allocation	37
<b>TABLE 18</b> iHOT-33 scores for the left hip by allocation	38
<b>TABLE 19</b> iHOT-33 scores for the right hip by allocation	39
<b>TABLE 20</b> The EQ-5D-5L utility and visual analogue scale scores by allocation	40
<b>TABLE 21</b> Hospital Anxiety and Depression Scale scores by allocation	41
<b>TABLE 22</b> Details of AEs and SAEs	41



# List of figures

<b>FIGURE 1</b> Trial Schema	<b>6</b>
<b>FIGURE 2</b> Delays experienced with sponsor approval for the MANTIS trial	<b>19</b>
<b>FIGURE 3</b> Delays attributable to the IMP supplier	<b>20</b>
<b>FIGURE 4</b> Month-by-month target number vs. actual number of sites open to recruitment for the MANTIS trial	<b>25</b>
<b>FIGURE 5</b> Participant flow diagram	<b>26</b>





## List of abbreviations

AE	adverse event	ITT	intention to treat
AP	anteroposterior	MANTIS	Managing Avascular Necrosis Treatments: an Interventional Study
AVN	avascular necrosis		
BMI	body mass index	MHRA	Medicines and Healthcare products Regulatory Agency
C&C	capability and capacity		
CI	chief investigator	MRI	magnetic resonance imaging
CRF	case report form	NIHR	National Institute for Health and Care Research
CRN	Clinical Research Network		
DSMC	Data Safety and Monitoring Committee	OCTRU	Oxford Clinical Trials Research Unit
EQ-5D-5L	EuroQol-5 Dimensions, five-level version	OHS	Oxford Hip Score
EudraCT	European Union Drug Regulating Authorities Clinical Trials	PI	principal investigator
GP	general practitioner	PIS	participant/patient information sheet
HADS	Hospital Anxiety and Depression Scale	PL	product licence number
HRG	health-care resource group	PLIS	patient-level informatics system
HTA	Health Technology Assessment	PPI	patient and public involvement
ICF	informed consent form	REC	Research Ethics Committee
iHOT-33	international Hip Outcome Tool-33	RRAMP	Registration/Randomisation And Management of Product
IMP	investigational medicinal product	SAE	serious adverse event
IMPD	investigational medicinal product dossier	SD	standard deviation
IQR	interquartile range	SFQ	site feasibility questionnaire
IRAS	Integrated Research Application System	SITU	Surgical Interventions Trials Unit
ISF	investigator site file	SIV	site initiation visit
		SmPC	summary of product characteristics
		THA	total hip arthroplasty
		TMG	Trial Management Group
		TSC	Trial Steering Committee



# Plain English summary

## What was the question?

The Managing Avascular Necrosis Treatments: an Interventional Study (MANTIS) trial was designed to compare ways of treating patients with avascular necrosis who are seeking to slow down the deterioration of their condition. Alendronate is a drug routinely available across the NHS in both tablet and injection form, and doctors and scientists believe that it might prevent ongoing hip deterioration and result in fewer patients requiring a total hip replacement.

## What did we do?

This trial attempted to compare alendronate taken as a tablet with an identical-looking tablet that did not contain any of the drug (a placebo) to find out if alendronate reduced the number of patients requiring a hip replacement and having pain (compared with patients who did not get alendronate).

## What did we find?

Patients were willing to participate in the trial but we were able to recruit only a small number to the study. The main reason for this was difficulty in identifying potentially suitable patients and approaching them at the right point in their medical care. This was more challenging than anticipated, particularly because the NHS sites and professionals that patients with this condition seek out are extremely variable in the UK. It was also difficult to locate and identify patients with the condition at an early enough stage, and before they had already started taking the drug.

## What does this mean?

More information on patients with this rare condition, such as NHS referral pathways, and an understanding of how the condition progresses may help to improve our understanding of this patient group. This information could also help us determine whether or not there is scope to carry out the study in a different way that might enable these patients to be more easily identified.



# Scientific summary

## Background

The Managing Avascular Necrosis Treatments: an Interventional Study (MANTIS) trial was a randomised placebo-controlled superiority trial designed to investigate a potential drug treatment to attenuate the progression of avascular necrosis (AVN) of the hip in adults aged  $\geq 18$  years. The primary purpose of the trial was to evaluate the clinical effectiveness and cost-effectiveness of an oral course of alendronate (70 mg, taken weekly for 12 months) compared with a placebo-matched course (one tablet, taken weekly for 12 months). The primary outcome was the Oxford Hip Score (OHS) at 12 months. A further long-term primary outcome was also included in the trial, namely, whether or not a total hip replacement operation was regarded as necessary within 3 years of randomisation.

## Objectives

### Primary objective

The aim of the MANTIS trial was to determine the clinical effectiveness and cost-effectiveness of a 12-month course of alendronate in the treatment of AVN, with the primary objective of answering the question, 'Does bisphosphonate treatment (alendronate) reduce the progression of AVN of the hip?'

The efficacy of alendronate in reducing the progression of AVN of the hip was to be measured using both the OHS at 12 months (short-term outcome) and the time to decision that a hip replacement is required at 36 months (long-term outcome).

### Secondary objectives

The secondary objectives of the MANTIS trial were to assess:

- pain and function using the OHS at 6, 24 and 36 months
- hip function using the international Hip Outcome Tool-33 (iHOT-33) questionnaire over the course of the trial at baseline and at 6, 12, 24 and 36 months
- anxiety and depression across the trial using the Hospital Anxiety and Depression Scale (HADS) questionnaire at baseline and at 6, 12, 24 and 36 months
- quality of life across the trial using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), at baseline and at 6, 12, 24 and 36 months
- radiological progression at 12 and 36 months using assessment of magnetic resonance imaging (MRI) scans and radiographs
- health-care resource use at 6, 12, 24 and 36 months.

## Methods

The MANTIS trial was funded to be a definitive, multisite, two-arm, placebo-controlled, double-blind, Phase IV randomised controlled superiority trial commissioned following a commissioning brief set by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme. Given the low prevalence of AVN of the hip and difficulty in detecting individuals with the condition at an early stage, the trial had an internal pilot phase with prespecified go/no-go criteria. It aimed to evaluate and compare the effectiveness of oral alendronate for attenuating the progression of AVN of the hip.

The trial was double blind. Active and placebo oral medication were produced and encapsulated identically and packaged into identical packaging. The trial aimed to randomise participants (1 : 1) into either the:

- intervention group – 12-month course of 70 mg of alendronate once per week
- control group – 12-month course of matched placebo once per week.

### Results

A total of 108 patients were screened, 86 of whom had completed the screening process at the time the trial was closed. Thirty-eight patients were found to be eligible and approached for consent, 21 of whom consented and were randomised; 22 patients had not completed the screening process when the trial closed and so their eligibility/ineligibility remained undetermined. Forty-eight (56% of those fully screened) were deemed ineligible. The most common reason for ineligibility was that the avascular necrosis was too advanced (Ficat and Arlet stages 3 and 4); the second most common reason was that the patients had already started bisphosphonate therapy. In addition, 17 patients (16%) declined to consent and 22 patients (20%) could not be randomised for other reasons.

A total of 21 patients were recruited and randomised into the MANTIS trial. All participants were recruited from secondary care by MANTIS trial researchers from six hospitals. Ten participants were randomised to the intervention group and 11 participants were randomised to the control group. Most participants (67%) had Ficat and Arlet stage 2 disease.

Of the participants randomised, 4 out of 10 (40%) in the intervention arm and 4 out of 11 (36%) in the control arm completed the full 12-month course.

Of the 21 participants randomised, two participants (both of whom were in the intervention group) withdrew from the trial.

### Conclusions for practice and research

The MANTIS trial was terminated at the end of the pilot phase, because it did not meet its go/no-go criteria. The main issues were a low recruitment rate owing to lower than expected disease prevalence, difficulties in identifying the condition at an early enough stage and more widespread use of the drug than expected.

### Implications for future research

We would not recommend that a short-term interventional study is conducted on this condition until its prevalence, geographic foci and natural history are better understood.

One means of developing this understanding would be the introduction of a database/registry for AVN of the hip that would include the clinical pathway to diagnosis. By analysing the current NHS pathway to diagnosis in terms of health-care setting by specialty and radiological modalities used, researchers could in turn design recruitment strategies that identify patients at an early stage of disease.

### Trial registration

The trial was registered as ISRCTN14015902.

## Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 43. See the NIHR Journals Library website for further project information.





# Chapter 1 Introduction

## Trial summary

The Managing Avascular Necrosis Treatments: an Interventional Study (MANTIS) trial was, to our knowledge, the first Phase IV UK trial designed to determine the clinical effectiveness and cost-effectiveness of a 12-month course of oral alendronate (70 mg weekly) compared with a matched placebo in reducing the progression of avascular necrosis (AVN) of the hip.

The trial was due to open in a minimum of 10 NHS hospitals, with 280 participants planned to be randomised to one of two treatments:

1. 70 mg of alendronate given as an oral tablet weekly for 12 months
2. placebo given as an oral tablet weekly for 12 months.

## Background and rationale

Avascular necrosis of the femoral head is an uncommon but devastating condition that affects around 0.001% of the population in developed countries<sup>1-3</sup> and occurs when the bone of the hip joint dies, resulting in significant disability in many cases. In the USA, an estimated 10,000–20,000 cases of AVN are diagnosed each year.<sup>3</sup> AVN typically affects younger people, with 45% of patients developing the condition before the age of 30 years.<sup>1</sup> 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 often cannot walk comfortably, cannot work and have sleep disturbances.<sup>3,4</sup>

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

### Assessing avascular necrosis in the hip

Several radiological and clinical classification systems were proposed. Feasibility work undertaken for the MANTIS trial indicated that standardising the imaging classification used to assess AVN as far as possible across different hospitals and practitioners would produce the best results. Ficat and Arlet, which is based on radiography, magnetic resonance imaging (MRI) changes and clinical symptoms, is the most widely used and clinically relevant classification.<sup>6,7</sup> The early stages (Ficat and Arlet stages 0 and 1) are not detectable on radiographs and rely on MRI scans 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 > 30% of the femoral head, particularly in the weight-bearing area, is correlated with poor outcome and subsequent joint replacement.<sup>5,8</sup> Among patients with untreated Ficat and Arlet stage 1 or 2 disease, 85% progress to femoral head collapse within 2 years and 76% undergo joint replacement within 3 years.<sup>4</sup>

Clinician- and patient-based scoring systems are typically used to assess patients with AVN.<sup>4,9-12</sup> 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,<sup>13,14</sup> as their pain

is significant and their resultant function very poor. The OHS, therefore, seems to be an acceptable and valid means of assessing AVN. As part of our preparation work, we explored the use of different patient-reported outcome measures [such as the International Hip Outcome Tool (iHOT-33)] with seven patients suffering from femoral head AVN.

Although the Harris Hip Score has been more commonly used in previous studies of AVN,<sup>15,16</sup> this is limited in that it is clinician reported and requires that patients be present for the examination.<sup>17</sup>

### ***Existing treatments for femoral head avascular necrosis***

The early phase of treatment usually involves asking the patient to use walking aids so that their hips are non-weight bearing for 3–7 months, with the aim of preventing hip collapse and controlling symptoms using simple analgesics. However, this is effective in only 15% of patients: most patients become so immobile that their pain can be alleviated only by joint-preserving operations and, eventually, hip replacement.

Joint-preserving operations for AVN have been practised for over 50 years. These either attempt to encourage revascularisation 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.<sup>4</sup>

Although total hip arthroplasty (THA) is an effective treatment, it is a large operation, with a revision rate of approximately 10 to 20 years.<sup>14,18</sup> In addition, patients who receive joint replacements for AVN are much more likely to require further surgery and be infected postoperatively than those who do not undergo surgery.<sup>18</sup>

Five hundred and seventy joint replacements were performed for AVN in England and Wales in 2012,<sup>12</sup> at a cost of over £5M. These procedures were predominantly performed in patients under 45 years old. AVN is the primary reason for 25% of hip replacements in patients under 30 years. The outcomes of hip arthroplasty are known to be worse in the English and Welsh population than in other populations in which the same procedure is common. They also present with significantly higher infection, dislocation and 10-year revision rates adding to the longer-term patient, health-care and economic burden of disease.<sup>14,18</sup>

Of more promise are pharmaceutical interventions, which provide a potentially cost-effective and lower risk option in comparison with the surgical interventions described above.<sup>9,15–17,19</sup> For example, the cost of oral bisphosphonate therapy is approximately £11 per year in osteoporosis treatment.<sup>20</sup> This is an order of magnitude less than surgical options and other pharmacological therapies. This treatment is also likely to be safer and more acceptable to patients than joint replacement or joint-preserving surgeries.

### ***Bisphosphonates in the treatment of avascular necrosis***

At present, there is little evidence for an effective drug treatment that prevents AVN, with very few publications relating to the efficacy of alendronate in the treatment of AVN.

The literature indicates that oral bisphosphonates may be of use in slowing or halting the progression of AVN.<sup>21</sup> Only two randomised controlled trials of bisphosphonates have been published. Chen *et al.*<sup>16</sup> demonstrated no difference in either clinical/structural appearance or symptoms with an oral bisphosphonate (alendronate) compared with a placebo control over 3 years when looking at the cumulative incidence of THA. By contrast, Lai *et al.*<sup>10</sup> found that alendronate is much more effective (65% vs. 3% structural progression;  $p < 0.001$ ) than a placebo control in preventing progression to THA at 2 years; however, this was an open-label trial with unclear randomisation. Agarwala *et al.*<sup>15</sup> demonstrated a sustained reduction in progression to THA at 10 years in a prospective cohort study of patients receiving alendronate. Despite the potential efficacy of oral alendronate shown in some studies, each trial was limited by critical design issues and the small number of patients included.

These trials also had differing inclusion criteria, with glucocorticoid-related AVN, a major cause of the condition, excluded in one trial.<sup>16</sup> Lai *et al.*<sup>10</sup> allowed surgical intervention in the treatment groups, meaning that the treatment effect of alendronate was difficult to estimate. Yuan *et al.*<sup>22</sup> performed a low-quality meta-analysis that included five papers of bisphosphonate therapy in femoral head AVN. 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 highlighted that a trial examining the efficacy of bisphosphonates in AVN was needed.

This trial, therefore, aimed to investigate the effect of alendronate plus standard care in the treatment of AVN of the hip.



# Chapter 2 Methods

## Trial design

The MANTIS trial was designed to be a 66-month project with an initial pilot phase leading into a definitive, multisite, two-arm, parallel-group, placebo-controlled, double-blind, Phase IV randomised controlled superiority trial. Its objective was to evaluate and compare the clinical effectiveness of oral alendronate with a placebo-matched control for participants with AVN. We planned to assess primary outcomes after 12 (short term) and 36 months (long term), and secondary outcomes at 6, 12, 24 and 36 months.

The trial was preceded by a feasibility study, which identified challenges in identifying patients with AVN of the hip, owing to a low prevalence rate and significant regional variations in at-risk groups and service delivery. To address this concern, the trial was designed with an internal pilot phase, with the intention of identifying hospitals/specialties that would be able to recruit adequate numbers of patients. According to the prespecified go/no-go criteria, the trial would be stopped if key recruitment targets could not be met.

The trial was designed as a placebo-controlled blinded trial with participants, clinicians, pharmacists and the research teams all blinded to the treatment allocation. The trial statistician who set up and monitored the randomisation schedules and prepared the unblinded data for review at independent data monitoring committee meetings was unblinded. Active and placebo oral medication were produced and encapsulated and packaged identically. The trial had two groups (*Figure 1*):

1. intervention group – active alendronate (70 mg taken as one tablet weekly for 12 months)
2. control group – matched placebo (taken as one tablet weekly for 12 months).

## Research governance

The trial was sponsored by the University of Oxford, with regulatory compliance oversight by Oxford Clinical Trials Research Unit (OCTRU) through the Surgical Interventional Trials Unit (SITU).

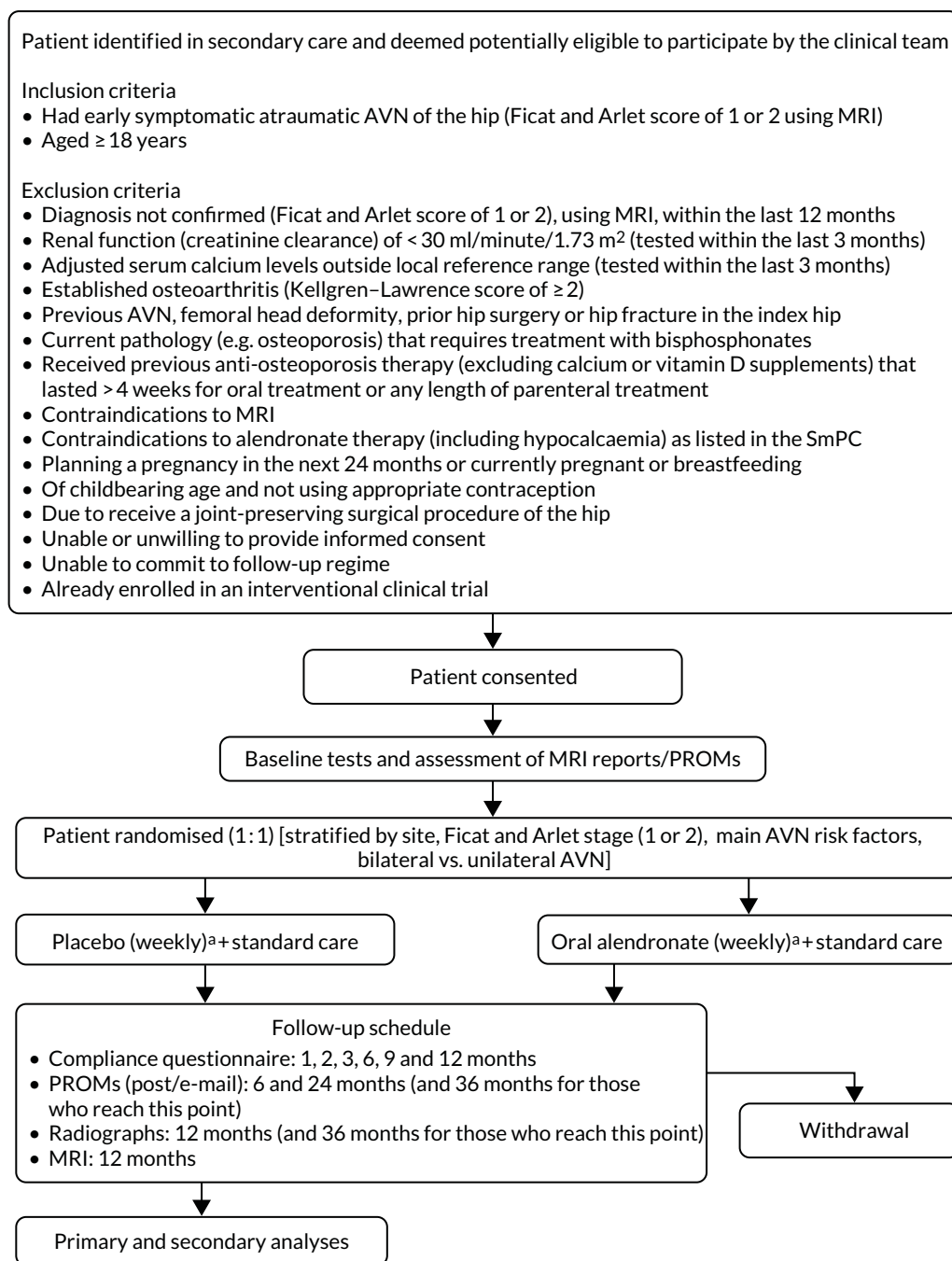
An ethics application under the Integrated Research Application System (IRAS) ID 230545 was submitted to the South Central – Oxford A Research Ethics Committee on 17 April 2018 and the MANTIS trial received a favourable Research Ethics Committee (REC) opinion on 29 May 2018 (reference number 18/SC/0247) and Health Technology Assessment (HTA) approval on 26 June 2018.

A clinical trial authorisation application under the European Union Drug Regulating Authorities Clinical Trials (EudraCT) number: 2017-002798-21 was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) on 23 April 2018, updated with further information on 8 June 2018 and the trial gained MHRA approval on 19 June 2018.

To ensure transparency, the trial was registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Registry on 11 June 2018 and was assigned ISRCTN14015902.<sup>23</sup>

The trial applied for National Institute for Health and Care Research (NIHR) Clinical Research Network (CRN) Portfolio status and was eligible for this support. The lead supporting network was the Thames Valley and South Midlands CRN.

Global NHS permissions were obtained through the IRAS and local NHS permissions were obtained from each participating NHS trust. A clinical trial site agreement based on the model non-commercial research agreement was signed by each participating NHS trust and the sponsor.



**FIGURE 1** Trial schema. PROM, patient-reported outcome measure; SmPC, summary of product characteristics. a, Treatment must be collected within 14 days of randomisation.

Following NIHR guidelines, a fully independent Data Safety and Monitoring Committee (DSMC) and a 66% independent Trial Steering Committee (TSC) were convened. Both committees met throughout the lifetime of the trial.

## Management of the trial

The trial manager (Gemma Greenall) was responsible for day-to-day management of the trial, with support from the data manager (Alistair Gray) and trial statistician (NP). The Trial Management Group (TMG) was responsible for overseeing day-to-day management of the trial and comprised the chief investigator (CI) (SGJ), the lead investigator (Kassim Javaid), the trial statisticians (IR, RK and NP), the trial manager (Gemma Greenall) and health economist (MD).

## Design and development of the protocol

Clinicians (including surgeons, rheumatologists and nurses), as well as patient representatives, were invited to discuss the trial protocol. Their feedback was utilised by the applicants when designing and developing the protocol.

## Amendments to the trial protocol

Following receipt of a favourable opinion of the trial protocol from the REC on 29 May 2018, no changes were made to the trial protocol – the trial started and ended on version 1.0, dated 10 April 2018.

## Amendments to the trial

Following the main REC approval, nine substantial amendments were submitted and received favourable opinion. As the trial was a clinical trial of an investigational medicinal product (IMP), any new sites had to be added as a substantial amendment. The nine substantial amendments were as follows:

1. Change to the investigational medicinal product dossier (IMPD) and updated summary of medicinal product characteristics (SmPC) to be used by the trial (24 August 2018).
2. Addition of one new trial site (Royal Orthopaedic Hospitals NHS Foundation Trust) (12 October 2018).
3. Addition of four new trial sites (Milton Keynes University Hospital NHS Foundation Trust, Taunton and Somerset NHS Foundation Trust, Royal National Orthopaedic Hospital NHS Foundation Trust and St George's University Hospitals NHS Foundation Trust) (23 January 2019).
4. Addition of two new trial sites (Ashford and St Peter's Hospitals NHS Foundation Trust and Royal Cornwall Hospitals NHS Trust) (19 March 2019).
5. Addition of two new trial sites (University Hospitals of North Midlands NHS Trust and Royal Free London NHS Foundation Trust) (6 June 2019).
6. Addition of one new trial site (Ayrshire & Arran Health Board) (23 July 2019).
7. Addition of six new trial sites (North Bristol NHS Trust, Maidstone and Tunbridge Wells NHS Trust, South Tyneside and Sunderland NHS Foundation Trust, Sandwell and West Birmingham Hospitals NHS Trust, Cambridge University Hospitals NHS Foundation Trust and Swansea Bay University Health Board) (13 November 2019).
8. Notification of temporary halt of the trial owing to recruitment being substantially below targets set in the original and revised recruitment timelines. Following discussions between the funder and TMG on how to proceed with the trial, it was decided that no further participants would be recruited (5 December 2019).
9. Confirmation that the trial would be closed after the temporary halt. Addition of patient-facing documentation to inform participants of what is happening to the trial, and addition of some patient-facing questionnaires to ask about their experience of the trial (7 February 2020).

## Support costs

NHS support and treatment costs were calculated in writing the protocol from health-care resource group (HRG) codes and the patient-level informatics system (PLIS) at the lead site. The PLIS allowed individual treatments, hospital bed occupancy, physiotherapy, outpatients costs and staff costs to be accurately calculated on a patient-level basis.

Routine NHS costs relating to the management of AVN typically consist of the cost of plain radiographs and a MRI scan (to make the diagnosis and stage the disease) and up to eight sessions of outpatient physiotherapy and three outpatient appointments with a clinician within the first year. Each session costs £50 plus £5 for equipment.

We estimated that NHS treatment costs for analgesia would be approximately £5–10 per week for 1 year in patients undergoing observation and investigations during the early stages of AVN (i.e. Ficat and Arlet stages 1 and 2).

NHS treatment costs for bisphosphonate therapy are not currently considered to be routine practice, so all drug costs were costed as a research cost and funded by the grant.

### Patient and public involvement

Patient and public involvement was present at all stages of the development and execution of the trial, including during the feasibility and pilot stages. A Research Design Service-appointed PPI representative was involved in the initial trial design and during the development of the patient information sheets.

The Young Adult Hip Group (Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford, UK. URL: [www.ndorms.ox.ac.uk/clinicaltrials/hipyoungadult](http://www.ndorms.ox.ac.uk/clinicaltrials/hipyoungadult)) was established in conjunction with the local CRN. This was an interest group for patients with conditions such as femoroacetabular impingement (FAI), hip dysplasia, osteoarthritis and AVN, based at the lead site. The trial was developed in conjunction with this group. A member of the group (Peter Lovell) is a co-applicant. In conjunction with advice from INVOLVE (URL: [https://involve.org.uk/resources/knowledge-base?gclid=CjwKCAjwu5yYBhAjEiwAKXk\\_eCs-6b8p7fHnnbTC04L8chUi43tz2KQLZLOBcr1sznSZHHIoub91HRoCLpYQAvD\\_BwE](https://involve.org.uk/resources/knowledge-base?gclid=CjwKCAjwu5yYBhAjEiwAKXk_eCs-6b8p7fHnnbTC04L8chUi43tz2KQLZLOBcr1sznSZHHIoub91HRoCLpYQAvD_BwE)) and the James Lind Alliance (Southampton, UK), the group advised on research design, developing patient information resources and monitoring screening in outpatient clinics. The co-applicant PPI member sat on the TSC. The Young Adult Hip Group were planning to help disseminate the trial findings through local (hospitals and PPI groups), regional (Thames Valley CRN) and national [National Musculoskeletal Clinical Research Network (Clinical Research Network Coordinating Centre, University of Leeds, Leeds, UK), Arthritis Research UK (Chesterfield, UK) and the James-Lind Alliance] entities at the end of the trial.

During the internal pilot we planned to conduct a focus group discussion with the help of the local NIHR Research Design Service to test the patient acceptability with the use of electronic patient-reported outcomes, the collection of drugs and compliance with drug therapy, and with follow-up and drug delivery method (blister or bottle). As the trial closed prematurely, the focus group discussion did not take place.

### Site initiation

At a minimum the trial manager (Gemma Greenall) attended all site initiation visits (SIVs). The CI (SGJ) also attended some of the SIVs. At the SIV a presentation was given that introduced the MANTIS trial – this included the team, the condition being studied and the trial premise and processes. In addition, the management of the MANTIS trial at sites including screening, recruitment, the taking of consent, case report form (CRF) completion, drug management and safety was presented, alongside trial responsibilities and the current status of the trial.

The principal investigator (PI) was always present at these visits and a register was taken of those who attended the visit.

To encourage surgical trainees to become involved in the trial, a MANTIS trial collaborator points scheme was introduced that resulted in certification and the potential to be cited in publications. An additional incentive was the MANTIS trial's inclusion in the NIHR Associate Principal Investigator Scheme in March 2019, a Royal College of Surgeons-endorsed scheme that aims to engage, recognise and promote trainees involved in NIHR portfolio research, and also to integrate clinical research into routine clinical training.



## Investigator site file

The investigator site files (ISFs) consisted of essential documents relating to trial conduct at a specific site (i.e. the location where participant-related trial activities were actually conducted), and were designed to enable both the conduct of the clinical trial and the quality of the data at that site to be evaluated. Among other essential documents, the ISF contained source documents, such as participant screening logs, consent forms, drug accountability records, delegation logs and CVs. Confirmation of receipt of the ISF was requested from sites and then filed centrally.

The ISF was then maintained by the PI at that site; the trial manager (Gemma Greenall) provided instructions on how to maintain the ISF, including the need for direct access to monitors, auditors and inspectors.

## Site management

### Site monitoring visits

We planned to monitor sites face to face at least once during each site's recruitment phase, and to undertake triggered monitoring visits if any of the below criteria were met:

- little or no recruitment for 3 months since site activation
- poor data quality (deemed appropriate and decided in conjunction with data manager)
- surgeon non-compliance with IMP administration technique (deemed appropriate and decided in conjunction with CI)
- persistent errors in the completion of the informed consent form (ICF)
- a serious breach identified at site
- any other situation deemed appropriate by the site, trial management team, sponsor and/or CI.

No monitoring visits had been undertaken when the trial closed prematurely.

## Inclusion criteria

Each participant in the trial had to meet both of the following criteria to be included in the trial:

- diagnosed with early symptomatic atraumatic AVN of the hip (Ficat and Arlet stage 1 or 2 using MRI)
- aged  $\geq 18$  years.

## Exclusion criteria

Otherwise eligible individuals who met any of the following criteria were excluded from the trial:

- diagnosis (Ficat and Arlet stage 1 or 2) had not been confirmed using MRI within the last 12 months
- renal function (creatinine clearance) of  $< 30$  ml/minute/1.73 m<sup>2</sup> (tested within the last 3 months)
- adjusted serum calcium levels outside local reference range (tested within the last 3 months)
- established osteoarthritis (Kellgren–Lawrence score of  $\geq 2$ )
- previous AVN, femoral head deformity, prior hip surgery or hip fracture in the index hip
- current pathology (e.g. osteoporosis) requiring treatment with bisphosphonates
- received previous anti-osteoporosis therapy (excluding calcium or vitamin D supplements) that lasted  $> 4$  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 currently pregnant or breastfeeding
- of childbearing age and not using appropriate contraception
- due to receive a 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.

### Screening and recruitment

Following attendance at a site initiation meeting, screening and recruitment were commenced at participating sites once the clinical trial site agreement had been signed and all necessary approvals were in place.

Potentially eligible patients were identified and approached by authorised members of staff about taking part in the trial. Patients interested in participating were referred to a research facilitator at recruiting sites, who then assessed whether or not they met the trial inclusion criteria. Information about the trial, which included its purpose, potential risks and benefits, the type of data, and when and how data would be collected during the trial, and who was funding and sponsoring it, was provided to the patient. This information was provided on a site-specific localised patient information sheet (PIS) that included the name and contact details of the local PI. All those approached to participate were able to keep the PIS.

Routinely MRI and radiography images and reports were then screened by the local care team to confirm the diagnosis and the Ficat and Arlet stage. For the diagnosis to be relevant to the trial, radiographs and MRIs had to have been taken no more than 12 months from the point of recruitment.

Before patients were officially recruited into the trial, they needed to have blood samples taken within the previous 3 months to confirm their renal function and adjusted serum calcium and 25(OH)-vitamin D levels. As such blood tests are routinely taken every 3 months in this patient population, all patients should have had these results available for consideration of eligibility.

Following consent, if pregnancy was suspected, participants of childbearing age were asked to take a pregnancy test to confirm their eligibility.

### Screening log

To enable full and transparent reporting for the trial, brief details of all patients screened for the trial were recorded at each site. Sites also recorded the date patients were considered for the trial and, for those that were ineligible, the reasons for ineligibility. Those who were considered eligible but declined to participate had their reasons for declining recorded.

### Informed consent

Participants had to personally sign and date the latest approved version of the ICF before any trial-specific procedures were performed.

Written and verbal versions of the PIS and ICF detailing the exact nature of the trial, what it involved for the participant, the implications and constraints of the protocol; the known side effects and any risks

involved in taking part were presented to participants. Both documents clearly stated that the participant was free to withdraw from the trial at any time and for any reason without prejudice to future care, without affecting their legal rights and with no obligation to provide a reason for withdrawal.

The participant was allowed as much time as needed to consider the information and had the opportunity to question the investigator, their general practitioner (GP) or other independent parties when deciding whether or not they wished to participate in the trial. Written informed consent was obtained by means of a participant-dated signature and dated signature of the person who presented and obtained the informed consent. It was expected that some of the patient population may be difficult to follow up and may not have a fixed address. Therefore, the consent form also asked the participant to consent to their clinical care team contacting their GP for information, which may have helped the clinical care team query missing data. The participant was also made aware of the fact that screening tests and previous tests and scans may need to be reviewed to confirm eligibility, and that images and reports of scans may need to be accessed from their routine appointments by the clinical care team to aid follow-up.

The person who obtained the consent had to be suitably qualified and experienced, and have been authorised to do so by the CI or relevant PI. A copy of the signed ICF was given to the participant, and the original signed ICF was retained at the trial site.

## Randomisation and allocation procedure

Randomisation to the interventions was undertaken via the centralised secure web-based randomisation service Registration/Randomisation And Management of Product [RRAMP (OCTRU, Oxford, UK)], run through OCTRU. In the event that sites were unable to randomise patients using RRAMP, they had to contact the central research office, and a member of the trial team was then able to randomise the patient via RRAMP. An emergency backup randomisation system was in place if the central research office was also unable to use RRAMP.

Participants were randomised on a 1 : 1 basis to receive either alendronate or the placebo-matched control. Randomisation was performed using a minimisation algorithm including a random element ( $p = 0.8$ ) to ensure balanced allocation of participants across the two arms stratified by:

- randomising site
- Ficat and Arlet stage (1 or 2)
- main AVN risk factors (steroid/alcohol/other) obtained from clinical notes
- bilateral vs. unilateral AVN.

However, the first 28 participants (10% of the expected sample size) were to be randomised using simple randomisation to seed the minimisation algorithm. Owing to the small numbers recruited, the trial did not move out of this seeding stage and so the stratification factors were not taken into account.

The intervention was expected to start within 4 weeks of randomisation.

## Treatment groups

A total of 280 participants with AVN of the hip as per the trial inclusion and exclusion criteria were to be randomised to one of two arms to receive one of the following:

1. alendronate
2. placebo-matched control.

## Dosing regimen

Both the active substance and the placebo control were manufactured and Qualified Person released for use in the trial by the holder of the Manufacturing and Import Authorisation (IMP) licence. Thereafter, bottles containing 13 weeks' supply of both the active substance and the control were sent to recruiting sites. All IMPs were overencapsulated and the bottles labelled with a MHRA-approved clinical trial label in accordance with Annex 13 (Investigational Medicinal Products) of the European Union Guidelines on Good Manufacturing Practice.<sup>24</sup> Both the active substance and the placebo control were administered alongside standard care for patients with AVN.

### Active substance

Alendronate was used as the active substance in the MANTIS trial. It is an off-white, oval, biconvex, 70-mg tablet, currently used to treat post-menopausal osteoporosis, and to reduce the risk of vertebral and hip fractures.<sup>25</sup>

Alendronate is marketed by Accord Healthcare Limited UK [product licence number (PL) 20075/0071] and was given to participants in accordance with the SmPC at the recommended dosage of 70 mg once weekly for the treatment period of the trial (52 weeks).

The effects of alendronate on pregnant and breastfeeding women are not known, as no data are available. However, studies in animals have shown reproductive toxicity; therefore, pregnant and breastfeeding women were not included in the trial and contraception was required for all participants of childbearing age.

Patients also received supplemental calcium and vitamin D if their estimated dietary calcium intake was < 700 mg per day. This was assessed at the point of eligibility screening. Those not requiring calcium supplements were advised to take at least 800 IU of vitamin D<sub>3</sub> or D<sub>2</sub> per day. Those with a 25(OH)-vitamin D level < 30 nmol/l were recommended treatment as per local vitamin D guidelines. Where no local guidelines existed, we recommended that the Oxfordshire Metabolic Bone Disease Vitamin D guidelines<sup>26</sup> be used at participating sites.

### Placebo control

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

## Drug administration

The active substance and the placebo control were both oral tablets to be taken once per week for 52 weeks. Patients received their supply of tablets in bottle form and received a patient card and automated weekly text reminders to take their tablet. The dispensing pharmacy was blinded to the treatment allocation. The tablets were provided to the patient in bottles containing 13 weeks' worth of treatment, which they needed to collect from the pharmacy within 14 days of randomisation. The patients received the next 13 weeks' supply at 3-monthly intervals.

To ensure sufficient absorption, the SmPC suggested that alendronate be taken at least 30 minutes before the first food, beverage or medicinal product of the day with plain water only. Therefore, we advised participants that it was preferable to take the tablet first thing in the morning, and take it whole without crushing or chewing it, as doing so could potentially cause oropharyngeal ulcers. Once the alendronate had been taken, patients were advised not to lie down or have the first food of the day for at least 30 minutes.

## Data collection

### Baseline

Data were collected only once a patient's eligibility and willingness to participate in the trial had been confirmed and they had given their informed consent. General patient demographics and participant contact details were collected to help enable follow-up assessments. Additional data on the intention for ongoing corticosteroid use, other AVN risk factors [e.g. smoking, drinking, body mass index (BMI) and relevant medical history], whether the participant had unilateral or bilateral involvement, and the current radiographic evidence for the AVN, were collected. The baseline assessment included a questionnaire to be completed by the patient which included the following measures:

- OHS
- iHOT-33
- EuroQol-5 Dimensions, five-level version (EQ-5D-5L)
- Hospital Anxiety and Depression Scale (HADS).

### Subsequent follow-up

Following entry into the trial, participants were to return to hospital, as part of routine clinical care, to undergo radiography (at 1 and 3 years from trial entry) and MRI (at 3 years from trial entry). Images and reports from these routine appointments were to be collected as part of assessing radiological progression. All other assessments were to involve patient-reported outcome questionnaires being sent directly to the participants by the central trial office team in Oxford. Participants could choose whether to complete these electronically (via a link sent in an e-mail) or on paper forms sent out via post with freepost return envelopes.

The follow-up questionnaires were to be sent at 6, 12, 24 and 36 months after entry into the trial.

Compliance with the IMP was planned to be monitored at 1, 2, 3, 6, 9 and 12 months during the 12-month treatment duration for both groups. This was to be conducted via a secure online platform or via post and involved participants completing a short compliance questionnaire.

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

An assessment table detailing the timing of assessments and visits is provided in *Table 1*.

## Embedded pilot

An internal pilot was planned that would progress to the definitive trial if predefined evaluation criteria regarding recruitment, patient characteristics, equipoise and compliance were met. The pilot trial was to mirror the procedures and logistics to be undertaken in the main definitive trial. We planned for the data that were collected in the pilot trial to contribute to the final analysis.

The pilot aimed to randomise 50 patients or more over a 12-month period from at least 10 sites, with a target recruitment rate of one patient per site per month. If any issues were identified, it was proposed that they be discussed with the TSC; any changes required for the definitive trial were to be discussed with the funder and submitted as amendments for approval.

TABLE 1 Schedule of procedures

Assessment	Timing of assessments									
	Pre randomisation		Post randomisation (months)							
	Screening	Baseline	1	2	3	6	9	12	24	36
Eligibility check	x									
Demographics	x									
Review screening blood samples (vitamin D levels, calcium levels, renal functioning)	x <sup>a</sup>									
Informed consent		x								
Pregnancy test		x								
OHS		x				x	x	x	x	x
Time to placement on surgical waiting list										x
iHOT-33		x				x	x	x	x	x
QoL		x				x	x	x	x	x
Resource use						x	x	x	x	x
MRI reports and images		x <sup>a</sup>								x <sup>a</sup>
Radiography reports and images		x <sup>a</sup>						x <sup>a</sup>		x <sup>a</sup>
Compliance with IMP (both active treatment or placebo)			x	x	x	x	x	x		
Compliance with prescribed standard care					x	x	x	x		

QoL, quality of life.  
a Routine care.

**Note**  
Assessments highlighted in green are those conducted via postal or electronic questionnaires.

## Evaluation criteria

### Recruitment

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

### Patient characteristics

The internal pilot aimed to further refine the inclusion criteria for the trial and identify if any groups (e.g. those with alcohol dependency) were likely to represent barriers to recruitment. The feasibility of including participants with ongoing steroid use in the trial, given that many of these patients would be undergoing treatment for inflammatory joint conditions or undergoing chemo/radiotherapy, was also to be assessed. It was also hoped that monitoring reasons for non-participation would determine if a non-randomised cohort could be appropriately developed alongside the main trial.

### Compliance

A weekly bisphosphonate treatment regime was to be used in the trial. Although it was thought that this would be acceptable to most patients, some groups (e.g. those with alcoholism or undergoing chemotherapy) may have faced issues with compliance. The trial team aimed to keep detailed compliance logs along with barriers to compliance as part of the pilot trial. If non-compliance was found to be an issue, then other methods of administration could have been explored.

### **Evaluation criteria outcomes**

The internal pilot trial was set up to consider the following outcomes for the evaluation criteria:

- recruitment rates
- number of eligible patients identified and conversion to randomisation
- feasibility of collecting OHS data
- quality of data collection for the end points of the main trial.

It was anticipated that the primary and secondary end points for the main trial would not have been analysed separately in the pilot trial.

## **Outcome measures**

### **Primary outcome measures**

The first primary outcome measure, the OHS,<sup>27</sup> is a 12-item validated patient-reported outcome measure assessing pain and functional outcomes in the hip. Each item is scored from 0 to 4; total scores are calculated as a sum across the 12 items and range from 0 (severe problems) to 48 (no problems).

We planned to measure the OHS at baseline and at 6, 12, 24 and 36 months; the short-term primary outcome time point was at 12 months post randomisation.

The second primary outcome measure was the decision to have a total hip replacement operation within 3 years. This was to be recorded as the date the participant was placed on the surgical waiting list by their surgeon. The decision to have surgery is reached after a series of discussions between the clinical care team and the patient.

### **Secondary outcome measures**

#### **Pain**

The OHS at 6, 24 and 36 months would record pain and function throughout the trial.

#### **Hip function**

To measure hip function the iHOT-33 questionnaire<sup>28</sup> was to be completed at baseline and at 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. The iHOT-33 consists of 33 items and total scores range from 0 (severe problems) to 100 (no problems).

#### **Anxiety and depression**

The HADS<sup>31</sup> detects states of depression and anxiety in the setting of a hospital medical outpatient clinic. The HADS was to provide an important insight into the overall disease perception and we planned to administer it at baseline and at 6, 12, 24 and 36 months. The HADS consists of two subscales, one for anxiety and one for depression, each scored from 0 (no problems) to 21 (significant problems).

#### **Quality of life**

To measure quality of life, the EQ-5D-5L<sup>32</sup> was to be administered at baseline and at 6, 12, 24 and 36 months. The EQ-5D-5L is a validated, generalised, health-related quality-of-life questionnaire consisting of five domains related to daily activities with a five-level answer possibility, which is converted into multiattributed utility scores using established algorithms. Utility scores range from -0.594 to 1, with better scores indicating better quality of life and a score of 0 representing a quality of life equivalent to death.

### Radiological progression at 1 and 3 years

Both MRI and radiography are 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 three-dimensional volumetric hip sequences at 1.5 or 3T were to be obtained at the 3-year assessment for each participant. Images and reports were also to be obtained from routine radiographic examinations of the index hip at 1 and 3 years. During these examinations, anteroposterior (AP) and lateral views of the index hip were to be acquired, and the lateral joint space width of the index hip was to be measured.

Radiological progression was to 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 was to be assessed using the Kellgren–Lawrence scoring system.

### Health-care resource use

Health-care use was to be monitored for the economic analysis at 6, 12, 24 and 36 months. This was to include micro-costing, HRG-based approaches, and detail on costing of components/consumables, health care, rehabilitation, productivity losses and informal care. We had aimed to use the microcosting obtained during the NIHR HTA Clinical Outcomes of Arthroplasty Surgery Trial (COAST) to accurately cost the interventions in any participants who underwent total hip replacement. We had also planned to include the underlying causes of AVN and employment status within the health economic analysis.

As part of the economic evaluation, we had planned to combine within-trial data on resource use, costs and outcomes with an extrapolation model to estimate long-term cost-effectiveness.

### Safety monitoring

Alendronate is a licensed medication, with a comprehensive safety profile. Only the adverse events (AEs) detailed in *Table 2* were to be recorded on the trial AE form.

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 was to help us assess reasons for non-compliance or withdrawals in this patient population. All AEs were to be recorded on the AE form as soon as the site or central trial office team became aware of them.

The following information was to be recorded on the AE form: description, date of onset, end date and action taken. Follow-up information was to be provided as necessary.

TABLE 2 Adverse events to be recorded

Adverse event	Definition
Upper gastrointestinal	Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, abdominal distension, acid regurgitation, peptic ulcer, nausea, vomiting, gastritis, oesophagitis, oesophageal erosions, melaena, oesophageal ulcer, dysphagia, odynophagia, oesophagitis, oesophageal stricture, oropharyngeal ulceration, upper gastrointestinal perforation, ulcers, bleeding
Osteonecrosis of the jaw	8 weeks of exposed bone in the oral cavity despite usual oral therapy
Atypical femoral fracture	Fulfils ASBMR 2013 criteria <sup>29</sup>
Musculoskeletal pain	Bone, muscle or joint pain unrelated to AVN
Hypocalcaemia	Symptoms of cramps and paraesthesiae and a concurrent serum calcium level below the local laboratory reference range

ASBMR, American Society for Bone and Mineral Research.



The investigator was to use their clinical judgement to decide whether or not an AE was of sufficient severity to necessitate the participant's removal from treatment. A participant was able to voluntarily withdraw from treatment because of what he or she perceived as an intolerable AE. In either of these scenarios, the participant was to undergo an end-of-trial assessment and receive appropriate care under medical supervision, until either the symptoms ceased or their condition became stable.

## Trial oversight

A DSMC (comprising two medically qualified clinicians and a statistician, all independent) was appointed to safeguard the interests of the trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the trial, protecting its validity and credibility. The DSMC was independent of the trial investigators and sponsor and adopted a Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES)-based charter<sup>30</sup> that defined its terms of reference and operation in relation to the oversight of the trial. We planned for this group to meet at least every 12 months over the duration of the trial.

The DSMC also monitored and reviewed accruing data from the internal pilot trial to determine if they would recommend to the TSC that the trial should continue and, if so, whether or not any amendments to the sample size or trial design were required. The DSMC fulfilled this role and, alongside the TSC, concluded that the trial should be closed prematurely.

Throughout the definitive trial, the DSMC would have continued to review accruing data and summaries of those data presented by the alendronate therapy group, and to assess the screening algorithm against the eligibility criteria. It would also have considered emerging evidence from other related trials or research and reviewed any related serious adverse events (SAEs) that were reported.

In addition to a DSMC, a TSC, whose primary function was to act as an oversight body for the trial on behalf of the sponsor and funding body, was appointed. The TSC was chaired by an independent member and considered and acted, as appropriate, upon the recommendations of the DSMC. The TSC also adopted a charter that defined its terms of reference and operation in relation to the oversight of the trial and agreed to meet at least every 12 months over the duration of the trial.

## Data management

A Data Management and Sharing Plan was produced for the trial and included reference to confidentiality, access and security arrangements. All data received were processed in accordance with data protection rules. The trial was set up for direct access to be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections; however, this was not invoked during the pilot phase of the trial.

All trial data were collected on trial-specific documents, such as questionnaires and CRFs. All trial-specific documents, except for the signed consent form and follow-up contact details, referred to the participant by a unique trial participant number/code and not by name. Participant-identifiable data were stored separately from trial data and in accordance with OCTRU standard operating procedures. All trial data were stored securely in offices accessible only by swipe card by the central co-ordinating team staff in Oxford and authorised personnel.

All data were entered into the trial's instance of OpenClinica (OpenClinica, LLC, Waltham, MA, USA), which was set up specifically for the trial.

## Sample size

### *Power calculation*

The trial required 140 participants per arm (280 in total). This sample size was to provide sufficient power for both co-primary end points of the MANTIS trial.

### **Short-term end point: the Oxford Hip Score at 12 months**

The minimum clinically important difference (MCID) in the OHS is estimated to be 5 points on the scale of 0–48 points.<sup>33</sup> Assuming a common standard deviation (SD) of 10 for the OHS at 12 months, using 90% power and a 5% two-sided significance level, and allowing for a loss to follow-up of 20%, 114 participants were required per arm (228 in total).

### **Long-term end point: the time to decision that hip replacement is required**

The time to the decision that a hip replacement was required was to be measured from randomisation to the date that the participant was placed on the surgical waiting list by their surgeon. This would have allowed us to account for such factors as delays to surgery, or participants not being fit for surgery. It was anticipated that 60% of participants in the control group would require a hip replacement at 36 months post randomisation. This trial was 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 participants requiring a hip replacement in this trial arm), translating to a hazard ratio of 0.5575.

Using 80% power and 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 were required per trial arm (280 in total). The sample size calculation assumed a three-quarters ratio between accrual time and total trial duration.

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

## Statistical analyses

Owing to the early halt in trial recruitment, only 21 participants were randomised. Therefore, no formal statistical analyses were planned, as the sample size was too small to provide adequate power for hypothesis testing.

The primary statistical analysis was carried out on the basis of intention to treat (ITT), with all participants being analysed according to their allocated treatment group, irrespective of which treatment they actually received. The analysis was descriptive in nature, and the principal analysis compared results between the intervention and control arms. Numbers and percentages were provided by treatment arm for categorical variables, and numbers, medians and interquartile ranges (IQRs) were provided by treatment arm for continuous variables. For clinical outcomes, means and SDs, and medians and IQRs were provided for both treatment arms.

## Chapter 3 Identified challenges

### Issues identified for the MANTIS trial

#### Delayed set-up

The set-up of the trial was subject to significant delays, which in turn delayed the start of recruitment. These delays have been summarised in *Figures 2 and 3*.

Overall, set-up resulted in a 14-month delay, with recruitment to the pilot beginning in month 17 rather than month 3. Consequently, the recruitment period was reduced from 36 months to 22 months and the recruitment predictions were remodelled based on estimates from sites. A major contributor to the delay in set-up was our sponsor office's, which was delayed owing to high local demand and staff shortage; therefore, although it was thought that this review would require only 1 month for completion, it took over 4 months (from 29 November 2018–11 April 2018). In addition, the original submission to the MHRA was not accepted, owing to its operating under the incorrect IMP Product Licence and insufficient details being provided regarding the testing of the over-encapsulated drug product.

We then encountered delays during the manufacture of the trial IMP; these are specified and detailed in *Figure 3*.

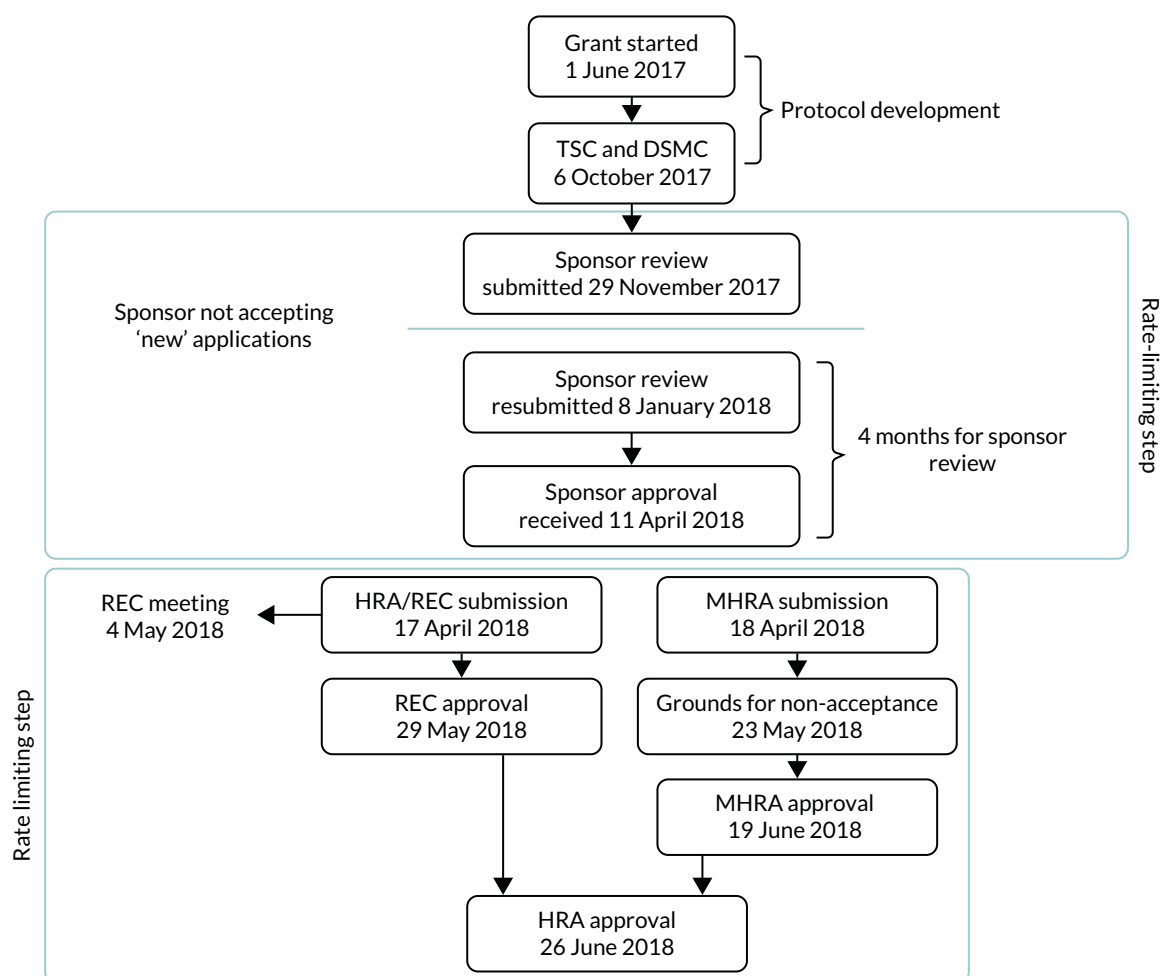


FIGURE 2 Delays experienced with sponsor approval for the MANTIS trial.

## IDENTIFIED CHALLENGES

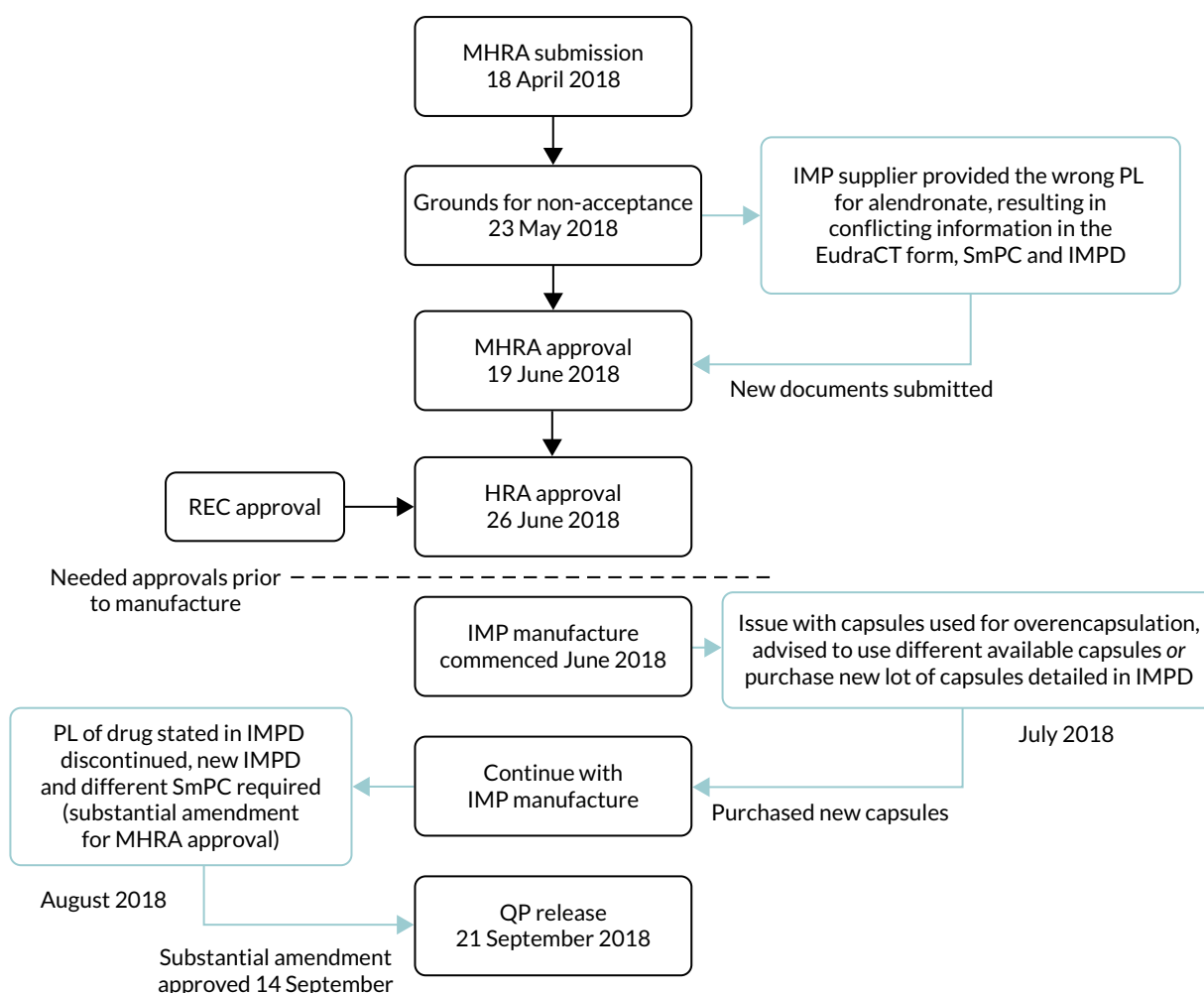


FIGURE 3 Delays attributable to the IMP supplier. QP, qualified person.

### Poorly defined patient pathway

The patient pathway for the MANTIS trial was complex, with patients identified across multiple specialties including, but not limited to, orthopaedics, haematology, sports medicine, metabolic bone disease, physiotherapy, rheumatology, physiotherapy and oncology. Recruitment predictions for each site were ascertained from hospital databases, a national NIHR CRN feasibility call and business intelligence reports, which may have led to an overestimation, given that these data are usually reflective of the site as a whole, not just one specialty.

In the UK, the patient pathway for AVN is highly variable, both geographically and with respect to the referring specialty. This is a particular challenge given the low disease prevalence. The only means of reliably identifying patients would be the development of a database/registry of hip AVN to detail the current diagnostic pathway, and identify potential solutions for the recruitment of individuals with early-onset disease as well as improvements in clinical care.

When sites were approached regarding the MANTIS trial, site feasibility questionnaires (SFQs) were provided so that the trial team could review predicted recruitment figures and assess the feasibility of local sites. The SFQs encouraged trial teams to think carefully about the number of potentially eligible

patients and where they could be identified from (the full patient pathway). The SFQ included the following five questions:

1. How many adult patients with AVN of the hip are seen by your site every year?
2. What information was used to determine this figure?
3. What is your expected recruitment rate for this trial based on the numbers above and the protocol selection criteria (AVN Ficat and Arlet stage 1 or 2)?
4. Which site/department are you associated with?
  - i. orthopaedic
  - ii. trauma
  - iii. surgical
  - iv. rheumatology
  - v. oncology
  - vi. transplant
  - vii. renal
  - viii. haematology
  - ix. other (please list).
5. How could patients be identified and recruited at your site/department?

On review of the answers provided in the SFQs and information obtained during the pilot phase of the trial, it became apparent that the patient pathway and disease prevalence of the relevant patient population was poorly understood nationally/defined locally. Identifying key patient clinics at recruiting sites was challenging owing to the delay in engaging the relevant clinicians across specialties. Permission to screen other clinics and refer patients to a trial clinician was sought from treating clinicians (who specialised in fields different to those of site PIs) across all sites; however, this was not granted.

The trial team initially recruited only via orthopaedic clinics, but recruitment via this route was slow, and reaching out to clinics for other specialties, including haematology and physiotherapy, resulted in our acquiring new sites and, consequently, improved recruitment rates. Specifically, Milton Keynes University Hospitals NHS Trust was led by a PI who was a haematologist and achieved the highest recruitment rate of all the open MANTIS trial sites.

In addition to this, NIHR National Specialty Groups (musculoskeletal, haematology) were engaged to help identify sites. National Clinical Specialty Groups in haematology and rheumatology were also engaged along with the British Hip Society (London, UK). At the outset of the trial there were no patient/public groups with a specialist interest in AVN of the hip.

### Recruitment

In addition to the complex patient pathway, there was a delay between identifying a potential participant and randomisation. This was partly because collaboration was required from the treating clinicians, but also because we required updated imaging and/or blood tests to comply with the eligibility criteria. This was not anticipated at the beginning of the trial, as blood tests and imaging are routinely and regularly conducted in this patient population. However, there are no agreed NHS minimal standards of care for diagnosis and early staging of AVN of the hip. Some sites identified a pool of potential participants who fell outside the inclusion window of 3 months for blood tests and 12 months for imaging and, therefore, had to request updated tests and scans to comply with the eligibility criteria.

At the beginning of the research project, we estimated that AVN had a disease prevalence of approximately 0.001% of the population. As the MANTIS trial was specifically looking at a subset of these patients (i.e. those with early-stage, atraumatic AVN), the number of eligible patients was found to be even lower.

## IDENTIFIED CHALLENGES

The TMG and TSC also met and discussed the main criteria for ineligibility to determine if it was possible to adjust these. However, they concluded that the ineligibility criteria could not be changed for the following reasons:

- Patients with advanced disease would not be suitable for this preventative treatment, as advanced disease is usually diagnosed once the hip joint has collapsed. The only suitable treatment for this level of disease is total hip replacement.
- Bisphosphonates have a long half-life and can metabolise in the bone for over 10 years; therefore, it would be unclear if the treatment effect had been caused by previous treatment or the trial medication.

### **Capacity at local sites**

Various sites that the trial team engaged with early on highlighted capacity issues with pharmacy, radiology and/or the local CRN teams. This remained an ongoing problem with sites already open to recruitment, sites in set-up and sites that expressed an initial interest in taking part in the trial.

Unless we had confirmation of capacity and capability (C&C) across pharmacy, radiology and the local CRN, the MANTIS trial was not feasible at local sites. Sites were slow to set up, primarily owing to a delay in receiving confirmation of C&C within one or more of these departments.

The MANTIS trial was designed to be as pragmatic as possible, with trial tasks coinciding with routine care wherever possible, as in the following examples:

- In the case of pharmacy, most of the drug management was to be dealt with centrally by the core trial team in Oxford; site departments were required only to dispense the IMP.
- Radiology had the option to send reports and images to the core trial team for scoring as opposed to completing the CRF locally.
- All patient follow-up was managed by the core trial team rather than the local CRN (e.g. co-ordination of follow-up questionnaires).

Capacity issues across departments were escalated to a higher level where possible, especially those present within local CRN teams. It is also worth noting that some sites that expressed an initial interest in the trial failed to progress with trial set-up; this was partly due to the discovery that the trial required considerable screening to identify only a small number of patients, and therefore participation in it was regarded as less worthwhile compared with trials that had higher recruitment rates per patient screened (and so could offer greater reimbursement).

### **Mitigation of issues identified**

The trial team mitigated the issues identified in the following ways:

- Exploring the use of primary care – ‘GP champions’ in two regions across the UK ran searches for patients with AVN to explore whether these patients may be identified in primary care. Unfortunately, both GP champions confirmed that musculoskeletal conditions are poorly coded in primary care, and both regions identified only two potential patients over a 3-year period. It was agreed with the GPs that this would not be a cost-effective way to improve recruitment.
- Engaging the surgical trainee networks – trainees were engaged through the NIHR Associate PI Scheme and via trainee research collaboratives across the UK. This helped to raise awareness of the trial, encouraged trainees to get involved in research, and resulted in an increased number of patients being screened at sites where trainees were involved.
- Attending relevant conferences – this again helped us to raise awareness of the trial and engage with potentially interested clinicians. The trial team attended the British Hip Society annual congress in 2018 and 2019, and the British Orthopaedic Association annual congress in 2019, where we engaged with approximately 50 clinicians, some of whom went on to join the trial as members of a recruiting site.

- Circulating potential patient pathways – as more potential pathways were identified, this information was circulated to existing sites as well as being fed back to potential sites early on in feasibility discussions. Encouraging the engagement between specialties enabled sites to review their recruitment predictions more thoroughly and addressed some capacity issues, as some sites were able to engage more than just the orthopaedic teams.

### Further mitigation of issues identified

The trial team researched some additional avenues to be explored at the review with the funder, which took place when recruitment was behind target. These included the following:

- Advertising the trial through primary care – this would have been in addition to existing posters used in clinic rooms and waiting rooms at recruiting sites. It was thought that this method may have increased recruitment, as patients with early-stage AVN may be unaware of their condition and will sometimes present to the GP only with generalised hip pain. If more patients had been aware of the trial, they may have asked their GP if they could self-refer to a recruiting site for more information.
- Re-engaging with sites that had been contacted previously – capacity issues may have been resolved since contact was last made and sites may have been more willing to take part in the MANTIS trial owing to the connections that were available through the trainee networks and a better understanding of the patient pathway.
- Reviewing the per patient payment fee – sites often queried whether or not more money was available to them (to allow them, for example, to cover archiving fees and pay for the time required by research nurses at visits). Although we believed the offered per-patient fee of £100 sufficiently covered the cost to sites (especially when taking into account that the IMP was provided to sites free of charge), the addition of a 'screening' fee may have encouraged more sites to take part in the trial. This practice is commonly seen in commercial trials, which often then provide funding for rare disease trials. The trial team could have explored ways that the 'screening' fee could be incorporated into the MANTIS trial budget: for example, the extra cost could have been offset by savings made on imaging costs.

However, owing to the early closure of the trial, the trial team did not have the chance to pursue these issues further.





# Chapter 4 Results

## Explanatory statement

Following the HTA meeting held on 21 November 2019, at which the difficulties in recruiting patients were discussed, it was decided that the MANTIS trial should be closed with immediate effect. Participants were unblinded by the trial team and those in the intervention arm were contacted, and the question of whether they wished to continue to receive alendronate was discussed.

A brief final report is presented in this chapter. No formal statistical tests were performed owing to the small number of participants recruited into the trial.

## Sites open to recruitment

The trial aimed to open 20 sites. By December 2019, when the trial was shut prematurely, only eight sites had opened to recruitment.

Figure 4 shows the target number of sites compared with the actual number of sites open to recruitment month by month.

Of the eight open sites, only six recruited at least one participant before the trial was closed to recruitment.

## Study participants

The flow of participants through the trial from screening through randomisation to follow-up is presented in a CONSORT (Consolidated Standards of Reporting Trials) flow diagram (Figure 5). Most randomised participants had not yet reached the primary outcome time point for conversion to hip replacement when the trial was stopped.

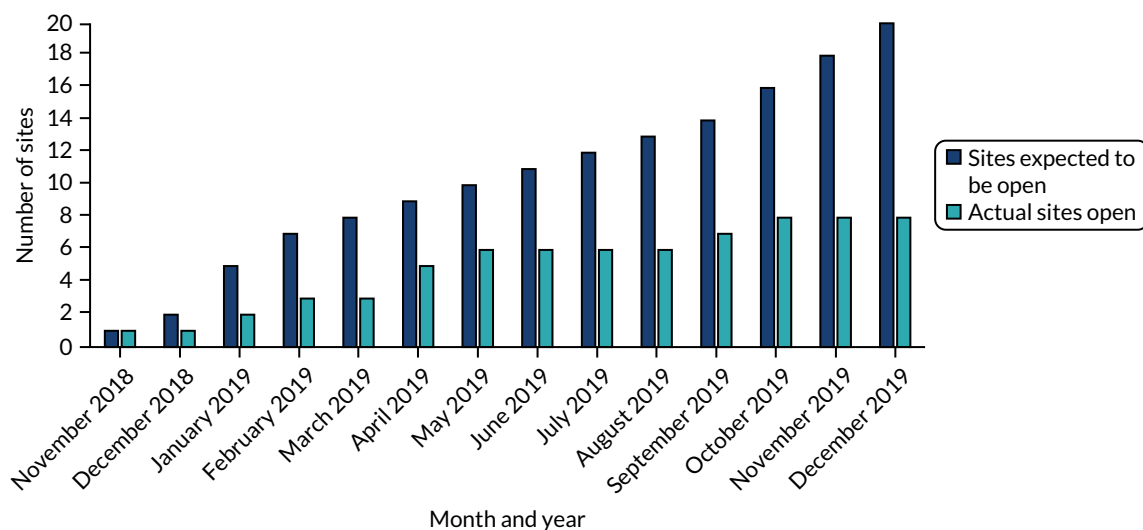


FIGURE 4 Month-by-month target number vs. actual number of sites open to recruitment for the MANTIS trial.

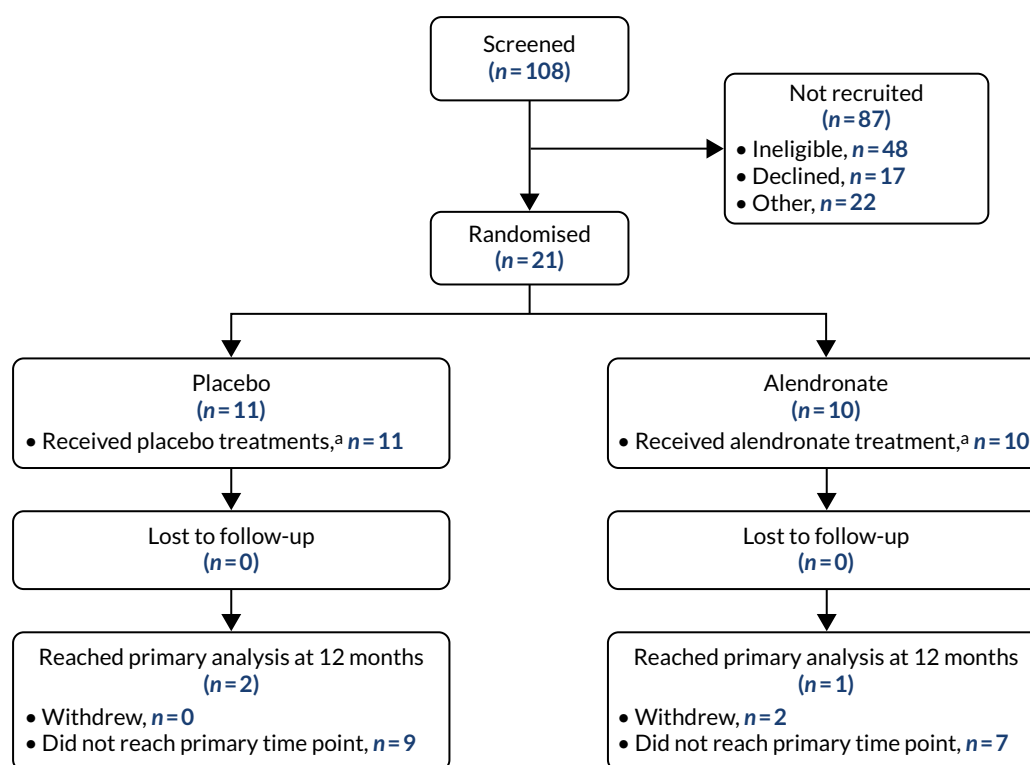


FIGURE 5 Participant flow diagram. a, Patients who received at least one course of treatment.

## Recruitment breakdown

Screening and randomisation data, including conversion rates, are summarised by recruitment site in *Table 3*. Out of 108 patients screened for the MANTIS trial, 48 patients (44%) were deemed ineligible for reasons detailed in *Table 4*. The most common reason was advanced disease, defined as either a Ficat and Arlet score of  $> 2$  or a Kellgren–Lawrence score of  $\geq 2$  (indicating osteoarthritis).

TABLE 3 Screening and randomisation data for the MANTIS trial by site

Site	Total screened	Total ineligible	Total declined	Total not randomised with no further information <sup>a</sup>	Total randomised	Conversion rate (%) <sup>b</sup>
Ashford	1	1	0	0	0	0
Cornwall	2	0	0	1	1	50
Milton Keynes	15	7	2	0	6	75
North Midlands <sup>c</sup>	0	0	0	0	0	0
Oxford	32	16	4	5	7	44
Birmingham	10	2	5	0	3	38
Stanmore	27	13	2	11	1	7
Wrightington	21	9	4	5	3	25
Total	108	48	17	22	21	35

a A number of screened patients were awaiting follow-up or MRIs before they could go further through the randomisation process when the trial was stopped.

b The conversion rate is given as the percentage of patients randomised out of the number of patients eligible.

c The North Midlands site did not screen or recruit any participants.

TABLE 4 Reasons for ineligibility of screened patients for the MANTIS trial by site

Site	No evidence of AVN of hip on imaging	Advanced disease	Already on treatment/previous treatment	Contraindication/unable to take treatment	Listed for surgery	Previous fracture	Other	Total
Ashford	0	0	0	0	1	0	0	1
Cornwall	0	0	0	0	0	0	0	0
Milton Keynes	1	5	0	0	1	0	0	7
Oxford	0	2	5	1	0	0	8 <sup>a</sup>	16
Birmingham	0	1	0	0	0	0	1 <sup>b</sup>	2
Stanmore	4	3	0	1	1	0	4 <sup>c</sup>	13
Wrightington	1	1	2	0	2	3	0	9
Total	6	12	7	2	5	3	13	48

a Other reasons for ineligibility at the Oxford site were awaiting decision, did not attend clinic ( $n = 3$ ), declined, reflux, duodenal ulcer and dysphagia.

b There was one patient at the Birmingham site with missing information.

c Other reasons at the Stanmore site were bilateral advances, renal disease and two patients with missing information.

#### Note

The North Midlands site has been omitted from this table as it did not screen or recruit any participants.

## RESULTS

Out of 108 patients screened for the MANTIS trial, 17 declined to take part (17.6%) for reasons detailed in *Table 5*. *Table 6* shows a breakdown of patient recruitment by site, including the numbers recruited at each site for the months in which the trial was open. *Table 7* provides more information about the average number of recruits per site per month.

### Patient demographics

*Tables 8* and *9* show information on the baseline characteristic comparability by allocated treatment arm.

### Treatment compliance

Of the 21 participants randomised, eight (38.1%) completed the full course of treatment as shown in *Table 10*; four were allocated to the placebo treatment arm and four were allocated to the alendronate treatment arm. *Tables 11* and *12* show the information from the self-completed compliance CRF for each treatment arm, where compliance with taking the allocated treatment once per week was high (> 80%), as measured from those responding to the CRF.

### Follow-up of patients

The number of follow-up questionnaires containing patient-reported treatment compliance and outcome measures, both expected and received, at 1 and 12 months post randomisation is summarised in *Table 13*. The compliance rate has been calculated as a percentage of those received out of the total expected. Please see *Appendices 1* and *2* for more details on treatment allocation and individual participant details.

Owing to the early closure of the trial, no participants reached the 24 or 36 months post-randomisation time point.

TABLE 5 Reasons for declining participation in the MANTIS trial by site

Site	Language barrier	Treatment preference	Did not respond	Concern over side effects	No reason given	Other reasons	Total
Ashford	0	0	0	0	0	0	0
Cornwall	0	0	0	0	0	0	0
Milton Keynes	0	0	0	1	1	0	2
Oxford	0	0	4	0	0	0	4
Birmingham	2	0	0	0	2	1 <sup>a</sup>	5
Stanmore	0	0	0	1	0	1 <sup>b</sup>	2
Wrightington	0	2	0	0	0	2 <sup>c</sup>	4
Total	2	2	4	2	3	4	17

a Other reasons for declining at the Birmingham site: patient wanted surgery.

b Other reasons for declining at the Stanmore site: patient does not want more medications.

c Other reasons for declining at the Wrightington site: health issues, randomisation issues.

#### Note

The North Midlands site has been omitted from this table as it did not screen or recruit any participants.

TABLE 6 Breakdown of recruitment by site

Site	Date opened	2018		2019											Total
		November	December	January	February	March	April	May	June	July	August	September	October	November	
Oxford	1 November 2018	0	2	1	0	0	2	0	0	0	1	0	1	0	7
Birmingham	10 January 2019	-	-	0	0	1	2	0	0	0	0	0	0	0	3
Wrightington	7 February 2019	-	-	-	0	1	0	0	1	0	0	1	0	0	3
Stanmore	15 April 2019	-	-	-	-	-	0	1	0	0	0	0	0	0	1
Milton Keynes	16 April 2019	-	-	-	-	-	0	0	0	1	4	0	0	1	6
Cornwall	10 May 2019	-	-	-	-	-	-	0	0	0	0	0	1	0	1
Ashford <sup>a</sup>	24 September 2019	-	-	-	-	-	-	-	-	-	-	0	0	0	0
North Midlands <sup>b</sup>	10 October 2019	-	-	-	-	-	-	-	-	-	-	-	0	0	0
<b>Total</b>		<b>0</b>	<b>2</b>	<b>1</b>	<b>0</b>	<b>2</b>	<b>4</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>5</b>	<b>1</b>	<b>2</b>	<b>1</b>	<b>21</b>

a The Ashford site screened only one patient and did not recruit any participants.

b The North Midlands site did not screen or recruit any patients.

## RESULTS

TABLE 7 Average numbers of participants randomised and screened per site per month

Site	Date opened	Months open <sup>a</sup>	Screened	Average screened per month	Randomised	Average randomisations per month
Oxford	1 November 2018	12.9	32	2.48	7	0.54
Birmingham	10 January 2019	10.6	10	0.94	3	0.28
Wrightington	7 February 2019	9.7	21	2.16	3	0.31
Stanmore	15 April 2019	7.5	27	3.60	1	0.13
Milton Keynes	16 April 2019	7.4	15	2.03	6	0.81
Cornwall	10 May 2019	6.7	2	0.30	1	0.15
Ashford	24 September 2019	2.2	1	0.45	0	0
North Midlands	10 October 2019	1.6	0	0	0	0
Total	-	58.6 <sup>b</sup>	108	1.84	21	0.36 <sup>c</sup>

a Months open was calculated using the total number of days between the site opening and recruitment being suspended, divided by 30.5 for the average month length in days. Recruitment was suspended for all sites on 28 November 2019.

b Total cumulative number of months open for all sites.

c Average number of randomisations per site per month open.

TABLE 8 Baseline categorical characteristics by trial arm

Characteristic	Placebo, n (%)	Alendronate, n (%)	Total, n (%)
<b>Minimisation factors<sup>a</sup></b>			
Affected hips			
Bilateral	3 (27.3)	5 (50.0)	8 (38.1)
Unilateral	8 (72.7)	5 (50.0)	13 (61.9)
AVN risk factor			
Alcohol	1 (9.1)	2 (20.0)	3 (14.3)
Other	9 (81.8)	7 (70.0)	16 (76.2)
Steroid	1 (9.1)	1 (10.0)	2 (9.5)
Ficat and Arlet stage <sup>b</sup>			
1	3 (27.3)	2 (20.0)	5 (23.8)
2	8 (72.7)	8 (80.0)	16 (76.2)
Site			
Milton Keynes	3 (27.3)	3 (30.0)	6 (28.6)
Oxford	4 (36.4)	3 (30.0)	7 (33.3)
Cornwall	0 (0.0)	1 (10.0)	1 (4.8)
Stanmore	1 (9.1)	0 (0.0)	1 (4.8)
Birmingham	1 (9.1)	2 (20.0)	3 (14.3)
Wrightington	2 (18.2)	1 (10.0)	3 (14.3)
<b>Baseline characteristics</b>			
Gender			
Female	4 (36.4)	1 (10.0)	5 (23.8)
Male	7 (63.6)	9 (90.0)	16 (76.2)

TABLE 8 Baseline categorical characteristics by trial arm (continued)

Characteristic	Placebo, n (%)	Alendronate, n (%)	Total, n (%)
Study hip			
Left	6 (54.5)	4 (40.0)	10 (47.6)
Right	3 (27.3)	4 (40.0)	7 (33.3)
Missing	2 (18.2)	2 (20.0)	4 (19.0)
Ethnicity			
Black or black British	4 (36.4)	1 (10.0)	5 (23.8)
Indian	1 (9.1)	0 (0.0)	1 (4.8)
White British	5 (45.5)	8 (80.0)	13 (61.9)
White other	1 (9.1)	1 (10.0)	2 (9.5)
Smoking status			
Current smoker	1 (9.1)	5 (50.0)	6 (28.6)
Former smoker	4 (36.4)	2 (20.0)	6 (28.6)
Never smoked	6 (54.5)	3 (30.0)	9 (42.9)
Alcohol frequency			
Two or three times per week	2 (18.2)	4 (40.0)	6 (28.6)
Two to four times per month	1 (9.1)	0 (0.0)	1 (4.8)
Four or more times per week	2 (18.2)	2 (20.0)	4 (19.0)
Monthly or less	2 (18.2)	1 (10.0)	3 (14.3)
Never	4 (36.4)	3 (30.0)	7 (33.3)
Alcoholic units (week)			
0–2	7 (63.6)	3 (30.0)	10 (47.6)
3 or 4	3 (27.3)	3 (30.0)	6 (28.6)
5 or 6	0 (0.0)	1 (10.0)	1 (4.8)
7–9	0 (0.0)	1 (10.0)	1 (4.8)
10 or more	0 (0.0)	1 (10.0)	1 (4.8)
Missing	1 (9.1)	1 (10.0)	2 (9.5)
Relevant medical history			
No	8 (72.7)	3 (30.0)	11 (52.4)
Yes <sup>c</sup>	3 (27.3)	7 (70.0)	10 (47.6)
Concomitant medications (last 6 months)			
No	1 (9.1)	1 (10.0)	2 (9.5)
Yes <sup>d</sup>	10 (90.9)	9 (90.0)	19 (90.5)
Kellgren–Lawrence grade <sup>b</sup>			
Grade 0	4 (36.4)	3 (30.0)	7 (33.3)
Grade 1	5 (45.5)	3 (30.0)	8 (38.1)
Grade 2	1 (9.1)	1 (10.0)	2 (9.5)
Missing	1 (9.1)	3 (30.0)	4 (19.0)

a Minimisation algorithm not reached, simple randomisation system was used to seed the first 28 participants.

b From the radiological assessment at baseline.

c Full details of relevant medical history can be found in *Appendix 1*.

d Full details of concomitant medications can be found in *Appendix 2*.

## RESULTS

TABLE 9 Continuous baseline factors by trial arm

Characteristic	Placebo			Alendronate			Total		
	n	Median	IQR	n	median	IQR	n	Median	IQR
BMI (kg/m <sup>2</sup> )	10	20.8	17.5–26.8	9	20.6	17.5–26.8	19	25.4	23.7–32.1
Height (m)	10	1.79	1.65–1.87	9	1.80	1.78–1.82	19	1.79	1.72–1.83
Weight (kg)	10	80.4	72.0–89.6	10	94.8	87.2–114.0	20	87.6	74.5–98.4
JSW (mm) <sup>a</sup>	7	4.0	3.0–5.0	6	5.0	4.0–6.0	13	4.0	3.5–6.0

JSW, joint space width.  
a Part of radiological assessment at baseline.

TABLE 10 Drug packs issued by trial arm

Drug packs issued	Placebo, n (%)	Alendronate, n (%)	Total, n (%)
First	11 (100.0)	10 (100.0)	21 (100.0)
Second	11 (100.0)	8 (80.0)	19 (90.5)
Third	8 (72.7)	7 (70.0)	15 (71.4)
Fourth (full 12-month course)	4 (36.4)	4 (40.0)	8 (38.1)

TABLE 11 Treatment compliance from self-reported compliance questionnaires for the placebo arm

CRF item	Month (n)					
	1	2	3	6	9	12
Forms returned	7	6	5	3	2	1
Tablet once per week						
Always (> 80%)	7	6	5	2	2	1
Usually (50–80%)	0	0	0	0	0	0
Sometimes (< 50%)	0	0	0	1	0	0
Never	0	0	0	0	0	0
First thing in morning						
Always (> 80%)	6	6	5	1	1	
Usually (50–80%)	0	0	0	1	1	1
Sometimes (< 50%)	1	0	0	1	0	0
Never	0	0	0	0	0	0
With water						
Always (> 80%)	6	4	4	3	2	1
Usually (50–80%)	0	1	0	0	0	0
Sometimes (< 50%)	0	0	0	0	0	0
Never	1	1	1	0	0	0



TABLE 11 Treatment compliance from self-reported compliance questionnaires for the placebo arm (continued)

CRF item	Month (n)					
	1	2	3	6	9	12
Swallowed whole						
Always (> 80%)	6	5	5	2	1	1
Usually (50–80%)	1	1	0	1	1	0
Sometimes (< 50%)	0	0	0	0	0	0
Never	0	0	0	0	0	0
No food or drink						
Always (> 80%)	6	5	4	3	1	1
Usually (50–80%)	0	0	0	0	1	0
Sometimes (< 50%)	0	0	0	0	0	0
Never	1	1	1	0	0	0
Remained sitting						
Always (> 80%)	3	3	2	2	1	0
Usually (50–80%)	2	0	1	0	1	1
Sometimes (< 50%)	1	3	2	0	0	0
Never	1	0	0	1	0	0
Worsened heartburn or indigestion						
Always (> 80%)	0	1	1	0	0	0
Usually (50–80%)	0	0	0	0	0	0
Sometimes (< 50%)	1	0	0	0	0	0
Never	6	5	4	3	2	1
Difficulty swallowing						
Always (> 80%)	1	1	1	0	0	0
Usually (50–80%)	0	0	1	0	0	0
Sometimes (< 50%)	0	0	0	0	0	0
Never	6	5	3	3	2	1
Chewable calcium supplements						
Always (> 80%)	0	1	1	1	0	0
Usually (50–80%)	1	0	1	0	0	0
Sometimes (< 50%)	0	0	0	0	0	0
Never	6	5	3	2	1	1
Missing	0	0	0	0	1	0
Side effects						
No	4	3	1	1	1	0
Yes	1 <sup>a</sup>	1 <sup>b</sup>	2 <sup>c</sup>	1 <sup>d</sup>	0	0
Missing	2	2	2	1	1	2

a Side effects at month 1: knee pain.

b Side effects at month 2: knee pain.

c Side effects at month 3: leg cramps and pain in knee and ankle.

d Side effects at month 6: bone pain.

## RESULTS

TABLE 12 Treatment compliance from self-reported compliance questionnaires for the alendronate arm

CRF item	Month (n)					
	1	2	3	6	9	12
Forms returned	7	8	7	5	1	1
Tablet once per week						
Always (> 80%)	7	8	7	5	1	1
Usually (50–80%)	0	0	0	0	0	0
Sometimes (< 50%)	0	0	0	0	0	0
Never	0	0	0	0	0	0
First thing in morning						
Always (> 80%)	6	6	5	3	0	1
Usually (50–80%)	0	0	1	1	1	0
Sometimes (< 50%)	1	1	1	1	0	0
Never	0	1	0	0	0	0
With water						
Always (> 80%)	4	6	4	2	1	1
Usually (50–80%)	1	0	1	1	0	0
Sometimes (< 50%)	2	2	2	2	0	0
Never	0	0	0	0	0	0
Swallowed whole						
Always (> 80%)	7	8	7	4	1	1
Usually (50–80%)	0	0	0	1	0	0
Sometimes (< 50%)	0	0	0	0	0	0
Never	0	0	0	0	0	0
No food or drink						
Always (> 80%)	5	7	5	3	1	1
Usually (50–80%)	1	1	2	1	0	0
Sometimes (< 50%)	1	0	0	1	0	0
Never	0	0	0	0	0	0
Remained sitting						
Always (> 80%)	6	7	6	4	1	1
Usually (50–80%)	0	1	0	0	0	0
Sometimes (< 50%)	1	0	1	1	0	0
Never	0	0	0	0	0	0
Worsened heartburn or indigestion						
Always (> 80%)	0	0	0	0	0	0
Usually (50–80%)	0	0	0	0	0	0
Sometimes (< 50%)	1	2	2	3	1	0
Never	6	6	5	2	0	1

TABLE 12 Treatment compliance from self-reported compliance questionnaires for the alendronate arm (continued)

CRF item	Month (n)					
	1	2	3	6	9	12
Difficulty swallowing						
Always (> 80%)	0	0	0	0	0	0
Usually (50–80%)	0	0	0	1	0	0
Sometimes (< 50%)	0	0	0	0	0	0
Never	7	8	7	4	1	1
Chewable calcium supplements						
Always (> 80%)	2	2	2	1	0	1
Usually (50–80%)	0	0	0	0	0	0
Sometimes (< 50%)	0	1	0	0	0	0
Never	5	5	5	4	1	0
Missing	3	1	2	0	0	1
Side effects						
No	1	1	1	1	0	0
Yes	4 <sup>a</sup>	6 <sup>b</sup>	4 <sup>c</sup>	4 <sup>d</sup>	1	0
Missing	5	8	5	5	2	1

a Side effects at month 1: stiffness of joints, tiredness, muscle pain and increased need to defecate.

b Side effects at month 2: stiff joint and muscle pain.

c Side effects at month 3: stiff hip joint.

d Side effects at month 6: stiff joints.

TABLE 13 Compliance with follow-up for the MANTIS trial

Questionnaire	Placebo		Alendronate		Total expected <sup>a</sup>	Total received, n (%)
	Expected <sup>a</sup>	Received, n (%)	Expected <sup>a</sup>	Received, n (%)		
Baseline <sup>b</sup>	11	11 (100.0)	10	10 (100.0)	21	21 (100.0)
1-month compliance	11	7 (63.6)	10	7 (70.0)	21	14 (66.7)
2-month compliance	11	6 (54.5)	10	8 (80.0)	21	14 (66.7)
3-month compliance	11	5 (45.5)	9	7 (77.8)	19	12 (63.2)
6-month compliance	9	3 (33.3)	6	5 (83.3)	15	8 (53.3)
6-month follow-up <sup>c</sup>	9	4 (44.4)	6	7 (116.6)	15	11 (73.3)
OHS	9	3 (33.3)	6	6 (100.0)	15	9 (60.0)
iHot-33	9	3 (33.3)	6	7 (116.6)	15	10 (66.7)
EQ-5D-5L utility	9	4 (44.4)	6	7 (116.6)	15	11 (73.3)
EQ-5D-5L VAS	9	4 (44.4)	6	7 (116.6)	15	11 (73.3)
HADS	9	4 (44.4)	6	7 (116.6)	15	11 (73.3)
Health resource	9	4 (44.4)	6	7 (116.6)	15	11 (73.3)

continued

## RESULTS

TABLE 13 Compliance with follow-up for the MANTIS trial (continued)

Questionnaire	Placebo		Alendronate		Total expected <sup>a</sup>	Total received, n (%)
	Expected <sup>a</sup>	Received, n (%)	Expected <sup>a</sup>	Received, n (%)		
9-month compliance	6	2 (33.3)	3	1 (33.3)	9	3 (33.3)
12-month compliance	2	1 (50.0)	1	1 (100.0)	3	2 (66.7)
12-month follow-up	2	2 (100.0)	1	1 (100.0)	3	3 (100.0)
OHS	2	2 (100.0)	1	1 (100.0)	3	3 (100.0)
iHOT-33	2	2 (100.0)	1	1 (100.0)	3	3 (100.0)
EQ-5D-5L utility	2	2 (100.0)	1	1 (100.0)	3	3 (100.0)
EQ-5D-5L VAS	2	2 (100.0)	1	1 (100.0)	3	3 (100.0)
HADS	2	2 (100.0)	1	1 (100.0)	3	3 (100.0)
Health resource	2	2 (100.0)	1	1 (100.0)	3	3 (100.0)

VAS, visual analogue scale.

a Expected: total number of participants who reached time point (excluding withdrawals). Follow-up ceased on 13 March 2020, and only follow-ups that were reached prior to this were sent.

b All questionnaires returned at baseline.

c Follow-up was sent and returned early for one patient at the 6-month follow-up and, therefore, the number received is higher than the number expected.

## Withdrawals and protocol deviations

Out of the 21 patients randomised, two withdrew from the trial. The details of both withdrawals are summarised in *Table 14*. In addition, *Table 15* shows information about the two protocol deviations that occurred during the trial and the actions taken to address these.

TABLE 14 List of withdrawals from the trial with reasons and last data entered

Allocation	Reason	Site	Time from randomisation to withdrawal (days)	Last CRF
Alendronate	Patient had osteoarthritis (not judged to have AVN)	Birmingham	70	Compliance (month 2)
Alendronate	Participant withdrew consent	Milton Keynes	93	Baseline

TABLE 15 List of protocol deviations from trial with action taken

Allocation	Information	Action taken	Site	Date
Placebo	Medication was not collected (second drug pack)	Patient was withdrawn from allocated treatment but continued follow-up	Milton Keynes	20 November 2019
Placebo	No response to the 1-month follow-up; a call was scheduled but was missed owing to staff annual leave	Trial cover plan was implemented	Milton Keynes	25 December 2019

## Clinical outcome results

### Oxford Hip Scores

Tables 16 and 17 show the OHS for the left and right hip, respectively, summarised by treatment arm at each time point using means and SDs, as well as medians and IQRs.

### iHOT-33 scores

Tables 18 and 19 show the iHOT-33 scores for the left and right hip, respectively, summarised by treatment arm at each time point using means and SDs, as well as medians and IQRs. Both the subscale scores and the total scores are summarised.

### EuroQol-5 Dimensions, five-level version, scores

Table 20 shows the EQ-5D-5L utility and visual analogue scale (VAS) scores summarised by treatment arm at each time point using means and SDs, as well as medians and IQRs.

### Hospital Anxiety and Depression Scale scores

Table 21 shows the HADS scores summarised by treatment arm at each time point using means and SDs, as well as medians and IQRs.

## Safety reporting

Details of AEs and SAEs are summarised in Table 22. Among 21 patients, two SAEs were recorded, both of which were considered to be unrelated to the treatment.

TABLE 16 Oxford Hip Score for the left hip by allocation

Time point	Placebo			Alendronate			Total		
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
Baseline	11	29.3 (12.5)	26.0 (19.0–37.0)	10	38.7 (13.3)	42.0 (31.0–48.0)	21	33.8 (13.4)	35.0 (24.0–47.0)
6 months	3	31.5 (17.9)	24.0 (18.5–52.0)	6	39.3 (12.6)	42.0 (28.0–49.0)	9	36.7 (14.0)	41.0 (24.0–49.0)
12 months	2	24.5 (0.7)	24.5 (24.0–25.0)	1	37.0 (–)	37.0 (–)	3	28.7 (7.2)	25.0 (24.0–37.0)

**Note**  
Oxford Hip Scores range from 0 to 48, with higher scores indicating better function.

TABLE 17 Oxford Hip Score for the right hip by allocation

Time point	Placebo			Alendronate			Total		
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
Baseline	11	31.2 (14.0)	30.0 (22.0–43.0)	10	36.0 (13.0)	36.5 (28.0–45.0)	21	33.5 (13.4)	35.0 (22.0–43.0)
6 months	4	26.4 (13.1)	20.0 (19.8–33.0)	6	35.5 (16.4)	33.5 (23.0–53.0)	10	31.9 (15.1)	24.0 (20.0–46.0)
12 months	2	13.0 (1.4)	13.0 (12.0–14.0)	1	13.0 (–)	13.0 (–)	3	13.0 (1.0)	13.0 (12.0–14.0)

**Note**  
Oxford Hip Scores range from 0 to 48, with higher scores indicating better function.

TABLE 18 iHOT-33 scores for the left hip by allocation

Time point	Placebo			Alendronate			Total		
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
<b>Section 1: symptoms and functional limitations</b>									
Baseline	11	60.3 (30.1)	54.0 (27.5–93.9)	10	37.3 (35.9)	28.3 (3.5–68.9)	21	49.3 (34.2)	51.6 (19.6–77.4)
6 months	3	55.6 (39.7)	72.3 (10.3–84.2)	7	37.8 (34.1)	23.6 (2.6–70.5)	10	43.2 (34.6)	40.9 (10.3–72.3)
12 months	2	68.5 (22.6)	68.5 (52.5–84.5)	1	26.1 (-)	26.1 (-)	3	54.4 (29.3)	52.5 (26.1–84.5)
<b>Section 2: sports and recreational activities</b>									
Baseline	11	50.4 (35.4)	43.5 (16.7–86)	10	22.3 (34.3)	8.4 (0.2–21.0)	21	37.0 (36.9)	21.0 (6.2–68.2)
6 months	3	34.6 (36.8)	15.4 (11.4–77.0)	7	29.6 (38.4)	9.0 (0.0–84.2)	10	31.1 (35.9)	13.4 (6.3–77.0)
12 months	2	43.5 (47.9)	43.5 (9.6–77.4)	1	5.4 (-)	5.4 (-)	3	30.8 (40.4)	9.6 (5.4–77.4)
<b>Section 3: job-related concerns<sup>a</sup></b>									
Baseline	8	59.1 (34.6)	72.7 (28.8–83.2)	5	36.4 (38.3)	21.3 (11.5–43.3)	13	50.4 (36.3)	43.3 (18.0–82.0)
6 months	2	82.2 (7.8)	82.2 (76.7–87.8)	3	45.2 (44.8)	46 (0.0–89.5)	5	60.0 (37.8)	76.7 (46.0–87.8)
12 months	2	78.3 (14.1)	78.3 (68.3–88.3)	1	18.0 (-)	18.0 (-)	3	58.2 (36.2)	68.3 (18.0–88.3)
<b>Section 4: social, emotional and lifestyle concerns</b>									
Baseline	11	47.6 (38.2)	46.3 (9.2–99.5)	10	26.0 (33.9)	15.5 (0.0–30.7)	21	37.2 (37.1)	26.3 (4.8–54.6)
6 months	3	38.6 (48.7)	11.9 (9.0–94.8)	7	23.4 (34.9)	6.8 (0.4–48.7)	10	28.0 (37.3)	9.1 (6.2–48.7)
12 months	2	55.1 (44.3)	55.1 (23.7–86.4)	1	23.5 (-)	23.5 (-)	3	44.5 (35.3)	23.7 (23.5–86.4)
<b>Overall score</b>									
Baseline	11	55.7 (30.3)	50.2 (36.5–94.5)	10	31.3 (33.6)	24.8 (2.1–44.7)	21	44.1 (33.5)	37.9 (16.2–64.5)
6 months	3	48.5 (37.1)	49.2 (11.0–85.2)	7	32.6 (33.2)	19.7 (1.5–65.4)	10	37.4 (33.2)	27.9 (11.0–65.4)
12 months	2	62.3 (30.7)	62.3 (40.6–84.0)	1	21.2 (-)	21.2 (-)	3	48.6 (32.2)	40.6 (21.2–84.0)

a Section 3 was completed by participants only if they were in work at the time; therefore, the n value for this subsection is lower for this subsection than for the other subsections.

#### Note

iHOT-33 total and subscale scores range from 0 to 100, with higher scores indicating better function.

TABLE 19 iHOT-33 scores for the right hip by allocation

Time point	Placebo			Alendronate			Total		
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
<b>Section 1: symptoms and functional limitations</b>									
Baseline	11	51.6 (34.1)	47.3 (18.8–86.9)	10	38.9 (35.0)	30.6 (6.3–61.6)	21	45.5 (34.2)	42.6 (17.2–72.3)
6 months	4	63.3 (26.9)	71.2 (45.2–81.5)	7	40.4 (41.6)	24.6 (41.0–91.2)	11	48.7 (37.3)	65.1 (5.1–86.0)
12 months	2	98.4 (1.1)	98.4 (97.6–99.3)	1	97.9 (–)	97.9 (–)	3	98.3 (0.9)	97.9 (97.6–99.3)
<b>Section 2: sports and recreational activities</b>									
Baseline	11	47.4 (35.0)	42.3 (17.5–79.5)	10	26.1 (32.6)	14.6 (1.5–32.6)	21	37.2 (34.8)	28.6 (8.0–62.5)
6 months	4	43.7 (27.1)	38.1 (22.8–64.6)	7	31.5 (34.1)	23.0 (0.0–73.7)	11	36.0 (30.9)	26.2 (5.0–73.7)
12 months	2	98.1 (2.7)	98.1 (96.2–100.0)	1	66.2 (–)	66.2 (–)	3	87.5 (18.5)	96.2 (66.2–100.0)
<b>Section 3: job-related concerns<sup>a</sup></b>									
Baseline	8	57.1 (40.4)	70.8 (14–91.6)	6	43.5 (39.2)	38.4 (8.7–75.7)	14	51.3 (39.0)	57.5 (8.7–83.8)
6 months	4	61.8 (39.8)	76.7 (39–84.5)	3	37.7 (37.6)	37.8 (0.0–75.3)	7	51.4 (37.8)	75.0 (3.0–78.3)
12 months	2	98.3 (1.9)	98.3 (97.0–99.7)	1	99.0 (–)	99.0 (–)	3	98.6 (1.4)	99.0 (97.0–99.7)
<b>Section 4: social, emotional and lifestyle concerns</b>									
Baseline	11	48.9 (37.8)	47.7 (9.2–81.2)	10	34.8 (35.2)	21.5 (11.0–46.4)	21	42.2 (36.4)	46.1 (11.0–76.7)
6 months	4	58.9 (44.3)	57.6 (20.6–97.2)	7	27.6 (31.8)	25.2 (0.0–39.1)	11	39.0 (38.0)	25.2 (6.0–90.1)
12 months	2	96.1 (5.5)	96.1 (92.2–100.0)	1	99.3 (–)	99.3 (–)	3	97.2 (4.3)	99.3 (92.2–100.0)
<b>Overall scores</b>									
Baseline	11	49.8 (34.7)	52.8 (15.7–79.9)	10	35.5 (33.7)	23.9 (7.2–54.9)	21	43.0 (34.2)	39.6 (14.8–71.9)
6 months	4	58.9 (28.8)	63.2 (36.3–81.5)	7	34.9 (35.8)	23.5 (2.9–68.4)	11	43.6 (34.1)	50.3 (4.6–76.0)
12 months	2	98.0 (2.2)	98.0 (96.4–99.6)	1	93.0 (–)	93.0 (–)	3	96.3 (3.3)	96.4 (93.0–99.6)
a Section 3 was completed by participants only if they were in work at the time; therefore, the n value is lower for this subsection than for the other subsections.									
<b>Note</b> iHOT-33 total and subscale scores range from 0 to 100 with higher scores indicating better function.									

TABLE 20 The EQ-5D-5L utility and visual analogue scale scores by allocation

Time point	Placebo			Alendronate			Total		
	<i>n</i>	Mean (SD)	Median (IQR)	<i>n</i>	Mean (SD)	Median (IQR)	<i>n</i>	Mean (SD)	Median (IQR)
<b>EQ-5D-5L utility score</b>									
Baseline	10	0.47 (0.39)	0.59 (0.41–0.74)	10	0.23 (0.32)	0.25 (0.0–0.59)	20	0.36 (0.37)	0.48 (0.16–0.61)
6 months	4	0.68 (0.12)	0.73 (0.60–0.75)	7	0.37 (0.36)	0.53 (0.04–0.60)	11	0.48 (0.33)	0.56 (0.17–0.74)
12 months	2	0.73 (0.15)	0.73 (0.62–0.84)	1	0.34 (-)	0.34 (-)	3	0.60 (0.25)	0.62 (0.34–0.84)
<b>EQ-5D-5L VAS</b>									
Baseline	11	57.8 (32.4)	60.0 (30.0–95.0)	10	45.5 (26.3)	47.5 (40.0–50.0)	21	52.0 (29.6)	50.0 (30.0–75.0)
6 months	4	75.0 (24.8)	82.5 (57.5–92.5)	7	47.9 (28.6)	40.0 (15.0–75.0)	11	57.7 (29.4)	75.0 (35.0–80.0)
12 months	2	87.5 (10.6)	87.5 (80.0–94.0)	1	40.0 (-)	40.0 (-)	3	71.7 (28.4)	80.0 (40.0–95.0)

VAS, visual analogue scale.

**Note**

EQ-5D-5L utility scores range from -0.594 to 1, with higher scores indicating better quality of life. A score of 0 is equivalent to death, and scores below this are possible. EQ-5D-5L VAS scores range from 0 to 100, with higher scores indicating better quality of life.



TABLE 21 Hospital Anxiety and Depression Scale scores by allocation

Time point	Placebo			Alendronate			Total		
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
<b>Anxiety</b>									
Baseline	11	8.2 (5.4)	7.0 (3.0–13.0)	9	9.7 (6.1)	10.0 (4.0–15.0)	20	8.9 (5.6)	8.5 (3.5–13.0)
6 months	4	5.5 (5.2)	5.5 (1.0–10.0)	7	10.4 (6.6)	11.0 (3.0–17.0)	11	8.6 (6.4)	10.0 (1.0–12.0)
12 months	2	5.5 (7.8)	5.5 (0.0–11.0)	1	11.0 (-)	11.0 (-)	3	7.3 (6.4)	11.0 (0.0–11.0)
<b>Depression</b>									
Baseline	11	5.6 (4.2)	4.0 (2.0–10.0)	9	7.2 (3.4)	6.0 (5.0–9.0)	20	6.4 (3.9)	5.0 (3.0–10.0)
6 months	4	5.3 (4.0)	5.0 (2.0–8.5)	7	9.9 (4.9)	12.0 (5.0–14.0)	11	8.2 (5.0)	10.0 (3.0–12.0)
12 months	2	3.5 (4.9)	3.5 (0.0–7.0)	1	7.0 (-)	7.0 (-)	3	4.7 (4.0)	7.0 (0.0–7.0)
<b>Note</b>									
HADS scores range from 0 to 21, with higher scores indicating higher levels of anxiety and depression (scores of 0–7 are categorised as normal, 8–10 as borderline and 11–21 as abnormal levels of anxiety and depression).									

TABLE 22 Details of AEs and SAEs

Site	Allocation	Information	Action taken	Relatedness	Time from randomisation to onset (days)
<b>Adverse events</b>					
Stanmore	Placebo	Numbness, light euphoric feeling all over. Flatulence. Nausea	Patient advised to eat before taking normal medications	-	11
<b>Serious adverse events</b>					
Milton Keynes	Alendronate	Infection of left total hip replacement	Admitted as inpatient for two stage revision of left total hip replacement	Unrelated	15
Birmingham	Alendronate	Patient complained of bad headaches	Admitted with referral to a neurologist and patient to have eye test. Update: referral came through; appointment due April 2020	Unlikely to be related	241



## Chapter 5 Discussion and conclusions

The MANTIS Trial was designed to determine whether or not a bisphosphonate could modify disease progression in AVN of the hip. Some of the challenges of delivering an interventional trial in a rare condition, such as AVN of the hip, were evident from the pre-trial feasibility work. The trial team therefore sought to introduce a phased study with an initial pilot leading to a main trial, subject to prespecified go/no-go criteria. From the outset, concerns regarding the prevalence of the condition, referral patterns and the variability in geographic distribution meant that identifying high-volume sites was difficult. Recruitment figures were lower than predicted, principally owing to a lower than expected disease prevalence. The CI, in discussion with the funder and trial committees, decided to terminate the study at the end of the internal pilot phase owing to the low recruitment rate, as low recruitment meant that the trial could not be delivered within the funding window of 5 years. Based on recruitment rate data, it is likely that recruitment for the trial would have taken 10 years or more.

### Limitations

The small recruitment figures, and the fact that the pilot phase closed prior to the primary outcome being recorded for most participants, makes it very difficult to interpret findings.

Although it is impossible to draw meaningful conclusions from the trial, several observations can be made.

First, we found that the later stages of AVN were those predominantly identified, meaning that many patients classed as Ficat and Arlet stage 3 or above were excluded from the trial. In addition, two-thirds of those included in the trial were classed as having Ficat and Arlet stage 2. This mirrors clinical observations of the condition, which is usually identified at a late stage, when joint-preserving treatments are of no value. These observations are supported by the Non-Arthroplasty Hip Register, which records very few joint-preserving surgical procedures (< 80) per year in early-stage patients. This contrasts starkly with the National Arthroplasty Register, which identifies several hundred joint replacements for late-stage AVN every year. The main barriers to targeting early disease is the fact that symptoms in the early stages of the condition are non-existent or mild. Consequently, even clinicians with a high awareness of the risks may miss early disease, and the few identified cases of early-stage AVN (Ficat and Arlet stage 0 or 1) are often diagnosed during routine screening of the contralateral hip.

Second, we observed that patient-reported outcomes worsen quickly over time in all patients. This further supports the clinical observation that only a small window of opportunity for intervention with joint-preserving treatments in early-stage AVN patients exists, beyond which joint replacement becomes inevitable. Ultimately, this may be the rate-limiting step to treatment.

Last, it seems that the intervention, alendronate, was well tolerated by most participants. The trial team deliberated between different formulations of bisphosphonate while designing the study. Concern was raised regarding the side effects and frequency of dosing in alendronate, but this does not seem to have adversely affected compliance, which was over 80%. However, given the longer rate of onset for oral medication, it remains to be tested whether or not a parenteral therapy would be more effective.

### Future work

By the end of the pilot phase, this trial was recruiting small but steady numbers in most sites. Recruitment projections performed at this stage demonstrated that it would take over 10 years to reach the full sample size. In its current form the trial is achievable; however, the cost may be prohibitive. It is likely that many

more sites would be required to recruit adequate numbers over a conventional NIHR funding cycle. Our pilot study therefore demonstrates that such a trial is unachievable without a better understanding of the referral pathways and geographic foci of the disease. Such a trial may be feasible in a health-care environment where AVN is more prevalent (e.g. South East Asia).

Early AVN of the hip should be treated as a rare disease in the UK. Although uncommon, the earlier stages of the condition are extremely hard to identify, further reducing its reported prevalence. This makes trials difficult and expensive to conduct, but more importantly, provides a very small window for treatment even if the condition is detected in time. An improved understanding of the condition's natural history is required, along with an understanding of the geographic locations where the condition is located. During the pilot study, we found it very difficult to identify areas of high disease prevalence. Despite identifying target demographics, we were unable to identify sites with large patient populations who met these criteria. Clinical Specialty Groups and specialist societies engaged extensively in this process; however, they were often unable to provide any useful advice.

This demonstrates the need for a registry or rare disease database for osteonecrosis of the hip. Several databases of rare diseases exist and have been shown to be effective. Many are patient-reported, such as the Rudy Study,<sup>34</sup> which provide a repository for patients with rare, long-term conditions. Such a database for osteonecrosis of the hip would help define the population and help clinicians better understand the natural history.

### **Overall conclusion**

The MANTIS trial was terminated at the end of the pilot phase, as it did not meet its go/no-go criteria. The main issues were a low recruitment rate, owing to lower than expected disease prevalence, and difficulties in identifying the condition at an early enough stage.

We would not recommend that a short-term interventional study is conducted on this condition until its prevalence, geographic foci and natural history are better understood. This is likely to be a barrier in most health-care markets.

One means of developing this understanding would be the introduction of a database/registry for AVN of the hip.

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## Trial Steering Committee

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## Data Monitoring Committee

Bo Abrahamsen (chairperson) (Holbæk Hospital), John Belcher (Keele University) and Nicola Peel (Sheffield Teaching Hospitals NHS Foundation Trust).

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## Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

## Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make

better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.





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## Appendix 1 List of participants' relevant medical history, taken at baseline

Repeat instance	Site	Medical history	Condition ongoing	Allocation
1	Milton Keynes	Arthritis	Yes	Alendronate
1	Oxford	Asthma (since childhood)	Yes	Alendronate
2	Oxford	AVN (2017)	Yes	Alendronate
3	Oxford	Brain tumour (6 years old)	No	Alendronate
4	Oxford	Right ankle fracture 2013 – cast	No	Alendronate
1	Oxford	SS (since birth)	Yes	Placebo
1	Oxford	Degenerative disease of spine	Yes	Alendronate
2	Oxford	SS (congenital)	Yes	Alendronate
3	Oxford	T4 # (injections in the past)	No	Alendronate
1	Oxford	RTHR (AVN)	No	Placebo
2	Oxford	Sickle cell anaemia	Yes	Placebo
1	Cornwall	COPD	Yes	Alendronate
2	Cornwall	Diverticulitis	Yes	Alendronate
3	Cornwall	Perianal abscesses	No	Alendronate
4	Cornwall	Sciatica	Yes	Alendronate
1	ROH	Fractured right ankle, ORIF (2016)	No	Alendronate
2	ROH	Psoriatic arthritis right knee	Yes	Alendronate
1	ROH	Eczema	Yes	Alendronate
1	Wrightington	Asthma	Yes	Placebo
1	Wrightington	Hodgkin lymphoma	No	Alendronate
2	Wrightington	Kidney stones	Yes	Alendronate
3	Wrightington	Non-Hodgkin lymphoma	No	Alendronate
4	Wrightington	Road traffic accident	No	Alendronate
5	Wrightington	Spinal decompression	No	Alendronate
6	Wrightington	Stem cell transplant	No	Alendronate

COPD, chronic obstructive pulmonary disease; ORIF, open reduction and internal fixation surgery; ROH, Royal Orthopaedic Hospital; RTHR, right total hip replacement; SS, sickle cell anaemia; T4 #, thoracic spine T4 fracture.



## Appendix 2 List of medications taken by participants at baseline

Repeat instance	Site	Medication	Dose	Frequency	Ongoing	Allocation
1	Milton Keynes	Chlordiazepoxide	20 mg	One tablet every 6 hours	No	Alendronate
2	Milton Keynes	Thiamine	100 mg	One tablet thrice daily	Yes	Alendronate
3	Milton Keynes	Spironolactone	50 mg	One tablet twice daily	Yes	Alendronate
4	Milton Keynes	Temazepam	10 mg	As required	Yes	Alendronate
5	Milton Keynes	Omeprazole	20 mg	One tablet once per day	Yes	Alendronate
6	Milton Keynes	Gabapentin	100 mg	As required	Yes	Alendronate
1	Milton Keynes	Naproxen	500 mg	Two tablets twice per day	Yes	Placebo
1	Milton Keynes	Ramipril	20 mg	One tablet once per day	Yes	Alendronate
2	Milton Keynes	Simvastatin	20 mg	One tablet once per day	Yes	Alendronate
3	Milton Keynes	Aspirin	75 mg	One tablet once per day	Yes	Alendronate
1	Milton Keynes	Aspirin	NR	NR	NR	Placebo
1	Milton Keynes	Lansoprazole	15 mg	One tablet once per day	Yes	Placebo
2	Milton Keynes	Ramipril	10 mg	One tablet once per day	Yes	Placebo
3	Milton Keynes	Atorvastatin, co-codamol	40/30/ 500 mg	One tablet once per day when required	Yes	Placebo
4	Milton Keynes	Metformin	500 mg	One tablet twice per day	Yes	Placebo
5	Milton Keynes	Amitriptyline	25 mg	One tablet per day	Yes	Placebo
6	Milton Keynes	Naproxen	500 mg	One tablet once per day	Yes	Placebo
1	Oxford	MSM, flax seed, omega 3 and collagen	NR	One of each	NR	Alendronate
2	Oxford	Wheat grass (drink)	NR	One drink and one tablet	NR	Alendronate
3	Oxford	Inhaler	Two puffs	TT AM, TT night	NR	Alendronate
4	Oxford	Turmeric, garlic and vitamins B, C, D and K	NR	One of each	NR	Alendronate
5	Oxford	Calcium, magnesium rosehip and glucosamine	NR	One of each	NR	Alendronate
6	Oxford	Ventolin	Two puffs	As required	NR	Alendronate
1	Oxford	Folic acid	5 mg	One inhalation/puff	Yes	Placebo
2	Oxford	Paracetamol	1 g	Up to four times per day	Yes	Placebo
3	Oxford	Tramadol	50 mg	As required (up to four times per day)	Yes	Placebo
1	Oxford	Glucosamine	500 mg	BD	No	Placebo
2	Oxford	Floradix	10 ml	BD	Yes	Placebo
3	Oxford	Flux D3	20,000 IU	Once per week	Yes	Placebo
1	Oxford	Folic acid	5 mg	One tablet once per day	NR	Alendronate
2	Oxford	Steroid injection	NR	NR	NR	Alendronate

## APPENDIX 2

Repeat instance	Site	Medication	Dose	Frequency	Ongoing	Allocation
3	Oxford	Penicillin	250 mg	BD	NR	Alendronate
4	Oxford	Morphine – Zomorph	30 mg	BD	NR	Alendronate
5	Oxford	Vitamin D	NR	Once per day	NR	Alendronate
6	Oxford	Oramorph	5 ml	As required	NR	Alendronate
1	Oxford	Codeine	30 mg	Twice per day	Yes	Placebo
2	Oxford	Ramipril	NR	NR	NR	Placebo
3	Oxford	Bisprolol	NR	NR	NR	Placebo
4	Oxford	Aspirin	NR	NR	NR	Placebo
1	Oxford	Ibuprofen	200 mg	As required	NR	Alendronate
2	Oxford	Pregablin	150 mg	BD	Yes	Alendronate
3	Oxford	Paracetamol	1 g	1ds	NR	Alendronate
1	Oxford	Folic acid	20 mg	Once per day	Yes	Placebo
2	Oxford	Penicillin	25 mg	Once per day	Yes	Placebo
1	Stanmore	Naproxen	500 mg	One tablet twice per day	Yes	Placebo
2	Stanmore	Mirtazapine	45 mg	One tablet at night	Yes	Placebo
3	Stanmore	Tramadol	50 mg	One to two tablets four times per day	Yes	Placebo
4	Stanmore	Amitriptyline	25 mg	One to three tablets per night	Yes	Placebo
5	Stanmore	Codeine	60 mg	One tablet four times per day	Yes	Placebo
6	Stanmore	Cetirizine	10 mg	Once per day	Yes	Placebo
1	Cornwall	Trimbow	Two ports	BD	Yes	Alendronate
2	Cornwall	Thiamine	100 mg	Three times per day	Yes	Alendronate
3	Cornwall	Morphine sulfate	30 mg/mlR	BD	Yes	Alendronate
4	Cornwall	Vitamin B strong	Tablets	Once per day	Yes	Alendronate
5	Cornwall	Lorazepam	1 mg	Four times per day	Yes	Alendronate
6	Cornwall	Lansoprazole	15 mg	Once per day	Yes	Alendronate
1	Birmingham	Naproxen	250 mh	One tablet when required	Yes	Alendronate
2	Birmingham	Dovonex	30 mg	Once per day	Yes	Alendronate
3	Birmingham	Paracetamol	1 g	Two tablets when required	Yes	Alendronate
4	Birmingham	Vitamin D + K <sub>2</sub>	3000 iu	Once per day	Yes	Alendronate
5	Birmingham	Dovobet	60 mg	Once per day	Yes	Alendronate
6	Birmingham	Flucidin cream	10 mg	Once per day	Yes	Alendronate
1	Birmingham	Dupilumab	300 mg	Fortnightly	Yes	Alendronate
2	Birmingham	Presnisolone	10 mg	Once per day	No	Alendronate
1	Wrightington	Paracetamol	1 g	As required	Yes	Placebo
2	Wrightington	Nytol (diphenhydramine hydrochloride)	25 mg	NOCTE	Yes	Placebo
1	Wrightington	Omeprazole	20 mg	Once per day	Yes	Placebo



Repeat instance	Site	Medication	Dose	Frequency	Ongoing	Allocation
2	Wrightington	Movicol	NR	Two sachets	NR	Placebo
3	Wrightington	Montelukast	10 mg	Twice per day	Yes	Placebo
4	Wrightington	Salbutamol inhaler	100 µg	Two puffs as required	Yes	Placebo
5	Wrightington	Fostair inhaler	100 mcg	Two puffs twice per day	Yes	Placebo
6	Wrightington	Tramadol	NR	As required	Yes	Placebo
1	Wrightington	Paracetamol	100 mg	As required	Yes	Alendronate

BD, twice daily; MSM, methylsulfonylmethane; NOCTE, at night; NR, not reported; T, inhalation; TDS, three times a day; TT, two inhalations; TT AM, two inhalations in the morning; TT night, two inhalations at night.





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