FULL/LONG TITLE OF THE TRIAL

The Effect of Denosumab on Pain and Bone Marrow Lesions in Symptomatic Knee Osteo-arthritis: A Randomised Double Blind Placebo Controlled Clinical Trial

SHORT TRIAL TITLE: DISKO

This protocol has regard for the HRA guidance and order of content;

NB see TMF for all other trial contacts

Version 2.7, 16 May 2019

RESEARCH REFERENCE NUMBERS

Trial registry number and date	**:**	**ISRCTN96920058**
IRAS Number	**:**	**191262**
Sponsor Reference	**:**	**R118528**
EudraCT Number	**:**	**2016-000754-35**
Protocol version number and date	**:**	**Version 2.7 Dated 16 May 2019 (Reference R118528)**
SPONSOR	**:**	**University of Manchester**
Sponsor Trial reference ID	**:**	**DISKO-ARUK/Oct 2015/T O'NEIL**
UKCRC CLINICAL TRIALS UNIT	**:**	**Manchester-CTU (reference 15_CTU_026)**
AMGEN	**:**	**Prolia ISS 20149112VA 20829**
Versus Arthritis (funder)	**:**	

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

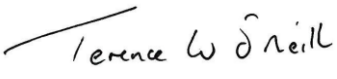
Signature: 

Date: 16 May 2019

Name (please print): Dr Mohammed Zubair

Position: Research Governance, Ethics and Integrity Officer

Chief Investigator:

Signature: 

Date: 16 May 2019

Name: (please print): Professor Terence O'Neill

Statistician:

Signature: 

Date: 16 May 2019

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Committees	TSC / DMC (see relevant Terms of Reference for current details)

LAY SUMMARY

The Effect of Denosumab on Pain and Bone Marrow Lesions in Symptomatic Knee Osteoarthritis: The DISKO study

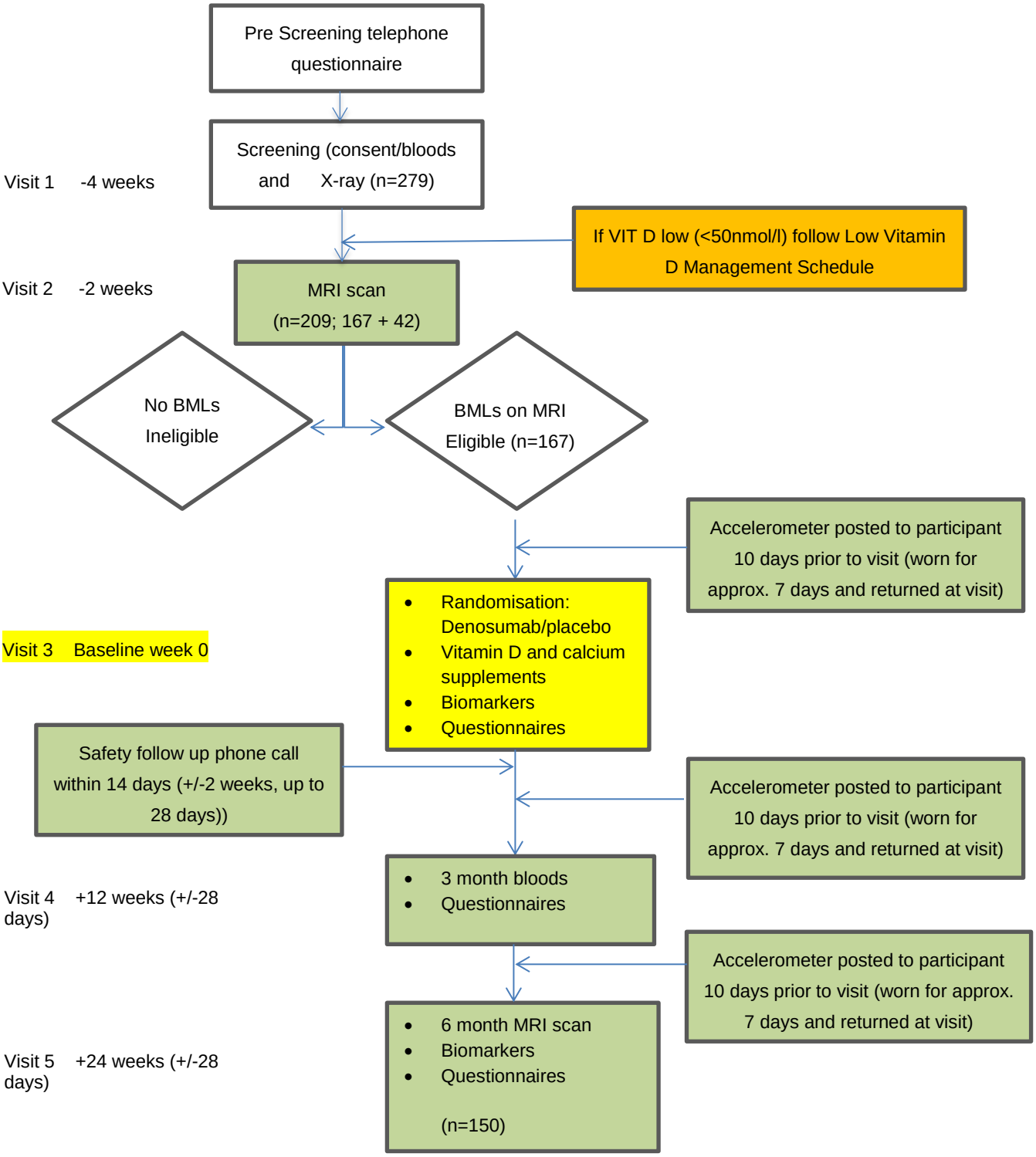
Knee osteoarthritis (OA) is the most common cause of chronic knee pain in older adults. Currently available therapies for OA may be difficult to take, linked with significant adverse events or ineffective. To date, there are no licensed treatments which reduce knee pain and also slow structural progression of disease. Cartilage loss is the most widely recognised structural change in OA, however, many patients with OA also have 'bone marrow lesions' on magnetic resonance imaging (MRI). These are discrete areas adjacent to the bone and appear as highlighted areas on MRI scans. In studies these lesions are associated with pain and they change as pain changes, suggesting they may be a cause of OA pain. The results of a recent small pilot study suggest that treatment which targets bone resorbing cells may reduce both knee pain and also the size of the ‘bone marrow lesions’. Larger studies are, however, needed to determine whether the approach, targeting those with ‘bone marrow lesions’, is effective at reducing pain and progression of OA.

Our aim is to determine whether a one off administration of a potent osteoporosis treatment which targets bone resorbing cells called ‘denosumab’, and given as an injection under the skin, is effective at relieving pain in people with painful knee OA and reducing the size of knee bone marrow lesions.

Two hundred and seventy nine men and women aged 40 and over with painful knee OA will be recruited from primary care, from outpatient clinics at local hospitals and from the community through advertisement in local newspapers. They will attend for a screening visit which will include questionnaires, clinical assessment and a blood test. If eligible following this visit they will attend for a magnetic resonance image of their knee. One hundred and sixty seven eligible participants with bone marrow lesions will attend usually within a couple of weeks of the scan for a baseline visit when they will be randomised to receive either a single injection (under the skin) of 60mg denosumab or a matched placebo. All participants will receive calcium and vitamin D supplements. Participants will be seen 3 and 6 months later for repeat questionnaires; and a repeat MRI scan will be obtained at the final visit in 6 months. The analysis will test whether, compared with placebo injection, treatment with denosumab reduces knee pain and shrinks bone marrow lesions.

If successful, this trial will offer real hope for development of a new approach to therapy in patients with painful knee OA. It will also establish whether a targeted approach to therapy, based on findings from MRI scans will improve treatment outcomes in patients with painful knee OA.

TRIAL FLOW CHART
Study visit schedule: The Effect of Denosumab on Pain and Bone Marrow Lesions in Symptomatic Knee OA



TRIAL SUMMARY

Trial Title	The Effect of Denosumab on Pain and Bone Marrow Lesions in Symptomatic Knee Osteoarthritis : A Randomised Double Blind Placebo Controlled Clinical Trial	
Internal ref. no. (or short title)	DISKO	
Trial Design	Randomised controlled clinical trial	
Trial Participants	Men and women aged 40 years and over with symptomatic knee osteoarthritis	
Planned Sample Size	167	
Treatment duration	6 months	
Planned Trial Period	3 years	
	Objectives	Outcome Measures
	1.To determine the effect of a single denosumab 60mg subcutaneous (SC) dose on the total bone marrow lesion (BML) area in participants with symptomatic knee osteoarthritis (OA)	Primary Outcome Total BML area, assessed on magnetic resonance imaging (MRI) at 6 months
	2. To determine the effect of a single denosumab 60mg subcutaneous (SC) dose on, i) the reduction in intensity of knee pain and knee symptoms after 3 and 6 months, ii) change in quality of life, iii) change in BML volume, in participants with symptomatic knee osteoarthritis (OA) 3. To determine whether there is any correlation between the reduction in knee pain and change in BMLs. 4. To determine safety of therapy with denosumab	Secondary Outcome: • knee pain using NRS $_{Last\ Week}$: Numerical Rating Scale – Last week (Participant perceived Pain/Discomfort overall in the last week), and • pain on nominated activity using NRS_{NA} : Numerical Rating Scale – Nominated Activity (participants nominated aggravating activity causing most pain) • KOOS, EuroQOL, SF12, at 3 and 6 months and maximal volume of BMLs at 6 months. • Adverse events
Investigational Medicinal Product(s)	Denosumab (Prolia®)	
Formulation, Dose, Route of Administration	Subcutaneous injection	

LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
ALT	Alanine aminotransferase
AR	Adverse Reaction
BMI	Body Mass Index
BML	Bone Marrow Lesion
Ca	Calcium
CA	Competent Authority
CI	Chief Investigator
cm	centimetres
CRF	Case Report Form
CRN	Clinical Research Network
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DAF	Data Access Form
DMC	Data Monitoring Committee
DMab	Denosumab
DSUR	Development Safety Update Report
EDTA	Ethylenediaminetetraacetic acid
EUROQOL	European Quality of life
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hep B	Hepatitis B
Hep C	Hepatitis C
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G

IMP	Investigational Medicinal Product
IPQ_Brief	Illness perception questionnaire brief.
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
JSN	Joint Space Narrowing
Kg	Kilograms
KOOS	Knee injury and Osteoarthritis Outcome Score
LH	Luteinising hormone
LLN	Lower Limit of Normal
LFTs	Liver Function Test
MA	Marketing Authorisation
MCTU	Manchester Clinical Trials Unit
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging Scan
MS	Member State
NHS R&D	National Health Service Research & Development
NICE	National Institute for Care and Clinical Excellence
NIMP	Non-Investigational Medicinal Product
nmol/l	nanomol per litre
NRS	Numerical Rating Scale
$NRS_{Last\ Week}$	Numerical Rating Scale – Last Week (Participants perceived Pain/Discomfort overall in the last week)
NRS_{NA}	Numerical Rating Scale – Nominated Activity (participants nominated aggravating activity causing most pain)
OA	Osteoarthritis
ONJ	Osteonecrosis of the Jaw
PAL	Physical activity levels
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RANK	Receptor Activated nuclear Factor

RANKL	Receptor Activated nuclear Factor Kappa-B Ligand
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SC	Subcutaneous
SDV	Source Data Verification
SF12	Short Form 12
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
ULN	Upper Limit of Normal
WOMAC	Western Ontario and McMaster Universities Arthritis Index

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
Versus Arthritis (Research funder) Peter Morley Research Programme Officer Copeman House St Mary's Court St Mary's Gate Chesterfield S41 7TD Tel : 0300790 0403 Email: enquiries@arthritisresearchuk.org	**Funding of the research costs for the study as detailed the AccoRD guidelines**
AMGEN 240 Cambridge Science Park Milton Road, Cambridge CB4 0WD	**Supply of active treatment and placebo free of charge**
Dayle Roberts Study Support Services Lead NIHR CRN: Greater Manchester Manchester University NHS Foundation Trust North Road Manchester M13 9WL Tel: 0161 276 8074 Email: Dayle.Roberts@mft.nhs.uk	**Service support and NIHR infrastructure funding at local trusts and CCG**
Salford Royal NHS Foundation Trust Stott Lane Salford M6 8HD	**NHS Support**
University of Manchester Mohammed Zubair Research Governance, Ethics and Integrity Officer Research Governance and Integrity Team Directorate of Research and Business Engagement Support Services Christie Building The University of Manchester Manchester, M13 9PL Tel: 0161 275 2725 Email: Mohammed.Zubair@manchester.ac.uk	**Support as Sponsors representative**

ROLE OF THE SPONSOR AND FUNDER

Role of Sponsor

The University of Manchester will be acting as sole Sponsor for the study. The sponsor will have oversight of the conduct of the study. The sponsor has delegated responsibilities for the management of the study to the Manchester Clinical Trials unit (MCTU) and the Research in Osteoarthritis Manchester Trial Chief Investigator and research team, who will manage the daily aspects of study management on behalf of the sponsor.

Role of the funder

Versus Arthritis (VA) is the funder for this research and requires that relevant regulatory approvals are in place prior to the research commencing.

The funder requires to be informed of any regulatory approvals and copy of the final protocol.

Updates to the protocol, which are the subject of a substantial amendment to ethics, will also be provided to VA.

External peer review of the study design and research questions was conducted by VA at the grant application stage. During this process the comments VA provided have been incorporated into the trial during protocol development.

A trial management group (TMG) will be established to co-ordinate the day to day management of the study and there will be a trial steering committee that will include an independent Chair that has been approved by VA.

A Data Monitoring Committee (DMC) will be formed in accordance with the sponsor requirements.

Versus Arthritis will be informed of the first patient first visits (FPFV) and last patient last visit (LPLV).

Progress reports will be completed as requested by VA, and submitted for consideration by the progress review committee to report to the VA clinical studies subcommittee to facilitate continued support of the project.

VA accepts no responsibilities or liabilities, financial or otherwise, arising from the work funded by this grant.

The sponsor and the funder will have no involvement in the data analysis, interpretation or reporting of the results from this study. This will be the responsibility of the Chief investigator and trial team.

Protocol contributors

The study has been designed by Terence O'Neill, Professor of Rheumatology and Clinical Epidemiology, with collaboration from the MCTU, Amgen, and independent feedback from patients with arthritis. The study was rigorously peer reviewed during the funding application.

The protocol has been written by the CI and Trial Manager incorporating input from members of the:

- Research in Osteoarthritis Manchester Research team
- MCTU
- Sponsor
- Amgen
- DMC/TSC
- Pharmacy

This incorporates individuals with specific expertise in set up, recruitment, trial management and analysis.

The funder, VA has requested that the study incorporates an interim analysis to assess trial futility.

Key Words

Osteoarthritis, denosumab, knee, randomised controlled trial, pain

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TRIAL PROTOCOL

The Effect of Denosumab on Pain and Bone Marrow Lesions in Symptomatic Knee Osteoarthritis : A Randomised Double Blind Placebo Controlled Clinical Trial

1 BACKGROUND

Osteoarthritis (OA) – Significance and health burden

OA is a significant and rapidly growing problem, impacting both at a personal level with pain and reduced quality of life and causing significant burden to health services and health economies. OA remains one of the few chronic diseases of ageing for which there is no effective strategy to prevent disease progression. The cost of OA in the UK is currently estimated at 1% of gross national product, reflecting the cumulative cost of absence from work (OA being the second most common cause of work absence), medical costs, community and social services (Arthritis Care Res, 2003). Radiographic knee OA is one of the most frequent sites of OA and affects about one in four middle age and older men and women (Peat et al, 2001). Symptomatic knee osteoarthritis (defined as frequent knee pain and an x-ray showing OA) affects about 12% of persons aged 60 years and over. Despite medical advances, symptomatic knee OA remains for the over half a million UK people affected a major source of pain and functional limitation (Arthritis Research Campaign, 2002; Arthritis and Musculoskeletal Alliance, 2004)

Developments in understanding OA pathology
It is now recognised that the pathology of osteoarthritis involves the whole joint in a disease process that includes focal and progressive hyaline articular cartilage loss with changes in the subchondral bone, development of marginal out-growths, osteophytes, and increased bony sclerosis. This is accompanied by synovial inflammation, lax ligaments and muscle weakness (Felson, 2000). Such advances in understanding have derived largely from magnetic resonance (MRI) imaging which has also helped in understanding the relationship between knee symptoms and structural changes in the knee. Pain is the most important presenting feature in OA. There are many potential sources of pain in OA, though bone marrow lesions and synovial inflammation (synovitis) are strong candidates.

Bone Marrow Lesions
Bone marrow lesions (BMLs) are seen as ill-defined sub-chondral regions of high signal intensity on fat suppressed MRI. Histologically BMLs show evidence of bone trauma with scarring and reversal lines that are signs of repair of micro-fractures. They are seen more frequently in painful knees with OA, than non-painful knees. For example, in an observational study of people with knee x-ray and pain, 37% had large BMLs in their knees on MRI compared with only 2% of OA knees that were not painful ($p<.001$) (Felson et al, 2001). To the extent that it is possible to assess cartilage loss, studies suggest that bone marrow lesions are strongly related to risk of cartilage loss, especially in the compartment overlying the BML (Hunter et al, 2006). A series of longitudinal studies from OA knee cohorts have noted that BMLs fluctuate in size with some lesions disappearing or shrinking (Phan et al, 2006; Garnero et al, 2005 ; Roemer et al, 2007). For example, Garnero et al obtained baseline and 3 month MRI's in persons with knee OA and noted that 10% of those with BML's had substantial and scorable regression of lesions without treatment (Garnero, 2005). Recently, it has been shown that the fluctuation in size of these lesions correlates with the fluctuation of knee pain, suggesting that these lesions are a cause of pain (Felson et al, 2007; Hill et al, 2007; Zhang et al, 2007). Specifically, in the Multicenter Osteoarthritis Study (MOST) (Felson et al,2007) where serial MRI's were obtained, the new onset of BMLs or their enlargement was strongly associated with new onset frequent knee pain in previously pain free knees. In a later report from the same study, Zhang et al (2011) reported that 37% of knees with BML's showed a decrease in lesion volume over a 30 month follow up, a decrease strongly related to diminution of Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scores. WOMAC is a widely used, proprietary set of standardized questionnaires used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. There is increasing evidence that BMLs change in response to intervention. In a small randomised trial of patients with symptomatic knee OA, intravenous zoledronate was associated with a reduction in the maximal area of bone marrow lesions after 6 months (Laslett, 2013). Recently, in an intervention study using a knee brace in participants with patellofemoral OA, we showed using gadolinium enhanced images, that BMLs vary in size over a short time (6- 12 weeks) and further that use of a patellar brace (compared with control), which alters

biomechanics at the knee, led to a reduction in BML volume in the patello-femoral joint (Felson, 2012; Felson 2013, Callaghan, 2014). Thus, there is strong evidence that bone marrow lesions are an important cause of pain in knee OA, that they fluctuate with the level of pain and that they are reversible in response to targeted therapy. BML's are therefore a potentially important treatment target in trials which target bone including bone active therapies and therapies which alter biomechanics (e.g. brace / orthotics) in knee OA. The evidence also suggests that treatments which target BMLs may be effective at reducing pain in OA.

What current treatments are used to treat knee OA?

Current National Institute for Health and Clinical Excellence (NICE) and European League against Rheumatism (EULAR) guidelines include topical treatments such as NSAID gel and capsaicin cream, oral analgesia (including paracetamol and oral NSAIDs) and non-pharmacological therapy (Conaghan, 2008). However, these treatments are restricted by their duration, degree of efficacy and considerable associated toxicities. NSAIDs are associated with significant morbidity and mortality, exacerbated by the co-morbidities that are frequent in a typical OA population, whilst analgesic medications, for example codeine, can cause nausea, constipation and drowsiness. Intra-articular steroid injections may be used for short-term pain relief, but are limited by feasibility in terms of clinician time, a lack of evidence for their effectiveness and to some extent concerns over the long term safety of therapy. It is evident therefore that none of the currently recommended therapies are desirable for long-term usage, and that for patients with severe pain and disability, surgery may be the only safe long-term treatment. The identification of alternative treatment options, which will give good analgesic effect with few or acceptable associated side-effects, is important in enabling optimal management of patients with knee OA. In particular it would be desirable to find further treatment options which may be used in the primary care setting.

Disease Modifying Osteoarthritis Drugs

An ideal treatment for osteoarthritis would not only reduce pain, but also reduce the progressive destruction of joint tissue and delay progression of the disease. Such treatments, which may potentially impact on the natural history of the disease by structural modification, have been termed disease modifying osteoarthritis drugs (DMOADs). None of the current licensed therapies for OA have an effect on disease progression. A number of candidates have been considered including compounds inhibiting matrix-metalloproteinases, cytokine blockers, bisphosphonates, calcitonin, inhibitors of inducible nitric oxide synthase (iNOS), strontium, glucosamine and diacereine, though the results to date have been largely disappointing (Qvist, et al,2008). This may be, in part, because of inappropriate targeting of therapy. Given the likely importance of BMLs in explaining pain in knee OA, targeting BMLs is an attractive approach to reducing knee pain and preventing progression. BML's have been shown to be related to malalignment across the knee (e.g. varus knees with medial BML's). Biomechanical interventions offer hope for reducing BMLs through redistribution of mechanical force across the knee. Another approach is reducing bone microdamage and traumatic injury for which anti-resorptive therapy would be appropriate. A number of previous studies have looked at oral bisphosphonate therapy, including alendronate and risedronate, though the rationale was not necessarily to target subchondral bone including BMLs and maintain structural integrity of the compartment. In a recent analysis from the NIH Osteoarthritis Initiative cohort, pain scores in people with knee OA were significantly reduced among those taking bisphosphonates compared to those not taking bisphosphonate therapy and there was a trend towards less joint space narrowing in bisphosphonate users over time (Laslett, 2014). There are data also from clinical trials; in a one year prospective, double-blinded, placebo-controlled study of risedronate for treatment of mild to moderate knee OA, 285 men and women were randomised to receive daily doses of 5 or 15mg of risedronate or placebo (Spector et al, 2005). After one year the 15mg group showed significant improvement in the WOMAC index of OA and patient global assessment, with a trend towards attenuation in joint space narrowing (JSN) a trend which did not reach statistical significance. In a larger multi-national study, (the knee OA structural arthritis (KOSTAR study)), there was no effect of risedronate on symptoms or radiographic progression of OA (Bingham, 2006). In both studies, a clear dose-dependent biochemical response to risedronate was observed in the urinary excretion of C-telopeptides of type II collagen, i.e. CTX-II suggesting an effect on cartilage. In a sub-analysis of 400 individuals from the KOSTAR study, among those with significant radiographic progression (JSN) the 15 mg/day and the 50mg/week dose of risedronate over 2 years retained trabecular structure and improved trabecular number, respectively, over the placebo group, thereby preserving the structural integrity of the subchondral bone (Buckland-Wright et al, 2007). Neither of the studies, however, included MRI imaging and so there was no information concerning bone marrow lesions. Recent data from a pilot study of the more potent bisphosphonate, zoledronic acid, has provided evidence to support the hypothesis that antiresorptive therapy reduces BMLs and

therefore that targeted therapy may be required (Laslett et al, 2012). In the study 59 men and women with BMLs were randomised to either zoledronic acid or placebo. At 6 months (though not 12 months) treatment was linked with a reduction in knee pain and the size of BMLs. Thus use of potent and targeted (BML) antiresorptive therapy may provide the key to therapeutic benefit. Studies of other osteoclast inhibitors such as calcitonin and strontium have also shown positive and promising findings as treatments for OA (Manicourt et al, 2006; Karsdal et al, 2010; Reginster et al, 2013).

Denosumab

a) Therapy

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts (Miller, 2011). Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby profoundly decreasing bone resorption in cortical and trabecular bone. RANKL is present on multiple non-skeletal tissues though relatively little is known about the physiological or pathological role for the RANKL-OPG-RANK pathway in these tissues. Denosumab is cleared by the reticulo-endothelial system and so, unlike bisphosphonates, does not accumulate in renal impairment. It has a biological effect at the registered dose of 60 mg by subcutaneous injection for 6 months at least as measured by prolonged effects on the bone resorption marker collagen-cross-link C-telopeptide (Miller, 2011).

b) Clinical studies of denosumab

There is a current EU marketing authorisation for denosumab which is manufactured by AMGEN and known as 'Prolia'. The therapeutic indications are, ''Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures'' (SPC, 2015). There has been an extensive clinical trial program underpinning the licensing of the therapy for use in osteoporosis including both phase 2 and 3 trials (Bone et al, 2008; Brown et al, 2009, Cummings et al, 2009; Kendler et al, 2010). The pivotal trial on which the licensing was approved comprised 7808 postmenopausal women with osteoporosis randomised to receive either 60mg subcutaneously densoumab or placebo (Cummings et al, 2009). Over 3 years treatment reduced the incidence of vertebral fractures by 68%, hip fractures by 40% and non-vertebral fractures by 20%. Treatment was linked also with reduction in bone turnover markers.

c) Safety profile

Based on data collected during the course of the comprehensive phase 2 and 3 clinical trials of osteoporosis, denosumab has been shown to be relatively safe (Diab, 2014). A clinical concern was the potential risk for infections because of the presence of RANKL on cells of the immune system. However in the pivotal licensing trial (FREEDOM) including 7,800 patients followed for three years, providing safety data on over 21,000 person years of follow up, there were no significant differences between participants who received denosumab and those who received placebo in the total incidence of adverse events, serious adverse events, or discontinuation of study treatment because of adverse events. There was, though, a very small increased risk of cellulitis requiring hospital admission (Cummings et al, 2009). Denosumab has also been studied in cancer patients with bone metastases or multiple myeloma, and no increased risk of infection was observed for a higher dose of denosumab (120mg every 4 weeks) compared with zoledronic acid in several large trials (Diab, 2014). To date though, no studies have looked at the impact on infections in patients who are immune-suppressed or on other biological drugs. All antiresorptive therapies may induce a small and transient hypocalcemic effect after administration though in the FREEDOM study clinically significant hypocalcemia was not observed in the 3,902 women who were taking denosumab (Cummings, 2009). Osteonecrosis of the jaw is a rare complication of long term bisphosphonate therapy. There were, no cases of ONJ in the FREEDOM trial though there have been case reports of ONJ in oncology studies in which much higher doses are used (Stopek, 2010). Atypical fractures have been reported in patients on long term bisphosphonates, however, in the FREEDOM trial there were no fractures of the femoral shaft in the denosumab group and three such fractures in the placebo group (Cummings, 2009). Additional precautions for use as outlined in the investigator brochure (located in the TMF) include; i) patients with severe renal impairment (creatinine clearance < 30ml/min) are at greater risk of developing hypocalcemia, ii) the needle cover of the pre-filled syringe contains dry natural rubber which may cause allergic reactions, iii) the product also contains sorbitol as an excipient and patients with hereditary problems of fructose intolerance

should not therefore use Prolia.(http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/001120/WC500093526.pdf)

Denosumab and OA
To our knowledge there are no clinical data concerning the effect of denosumab on OA. The main hypothesis underpinning our proposed clinical trial is that denosumab through its antiresorptive action will reduce the risk of microdamage and the occurrence of BMLs and thereby reduce knee pain. There is strong evidence for an antifracture effect of denosumab in women with postmenopausal osteoporosis – and so it is plausible that therapy may reduce also microfractures in knee OA (Cummings et al, 2009). Osteoarthritis is also associated with an increase in subchondral bone resorption and thinning of the subchondral plate (Burr & Gallant, 2012) in which pain molecules have been detected (Ogino, et al, 2009). Whether reducing subchondral bone loss impacts on pain, however, is unknown. As discussed above, however, two other therapies with anti-resorptive effects have now been shown to reduce pain in knee OA. There is rationale also from animal studies that targeting the RANK/RANKL system may have beneficial effects in OA. In research supported by Versus Arthritis, male sprague dawley rats were treated with modified osteoprotegrin (which binds RANKL) between 1 and 27 days before and after 21 and 27 days after injection of monosodium iodoacetate (MIA) which induces joint damage. Hindpaw withdrawal was used to assess pain behaviour and the joints were subsequently assessed for joint pathology. Pre-emptive treatment with modified osteoprotegrin inhibited formation of osteophytes and improved structural pathology while treatment reduced pain behaviour. The data support the hypothesis that early targeting of osteoclasts may reduce pain in OA (Sagar, et al, 2013). T cells carry receptors for RANK and function. Given the high levels of pro-inflammatory cytokines and the evidence of immune cell infiltration into OA joints coupled to the strong correlations observed between synovitis and pain, there is rationale for considering that denosumab may also help reduce symptoms in knee OA via a reduction in synovitis.

2 RATIONALE

Rationale for undertaking an experimental trial of denosumab in knee OA
Osteoarthritis of the knee is associated with substantial pain and disability. None of the currently recommended therapies are desirable for long-term usage, and currently for patients with severe pain and disability surgery may be the only safe long-term treatment. Accumulating evidence points to BMLs and also synovitis identified on MRI imaging as an important source of pain in knee OA. There is evidence that BMLs predict progressive loss of cartilage, which is to date the most widely accepted indicator of disease progression. Targeting therapies at BMLs provides therefore real hope for not just reducing pain but also structural progression. There is pilot evidence for an effect of potent antiresorptive therapy on reducing BMLs and pain. However, further data are needed to confirm this and to confirm also that the mechanism of pain reduction is through structural modification and specifically reduction in BMLs. Denosumab is an attractive candidate for use – it is one of the most potent anti-resorptive therapies available, it is relatively cheap, safe and easy to administer and could be delivered in the community.

Summary
Osteoarthritis of the knee affects one in eight men and women aged 60 years and over and causes significant joint pain and disability. Current treatments for knee OA have major limitations and safe, long-term analgesic treatments are needed. Furthermore to date, in contrast to other types of arthritis, there are no licensed structure-modifying therapies. Previous studies of anti-resorptive therapies in knee OA suggest a possible disease modifying effect though the results are somewhat inconsistent. Denosumab is a monoclonal antibody targeted at RANK Ligand (RANKL), with resulting significant reduction in bone resorption and used currently in patients with osteoporosis. It is plausible that treating patients with moderate to severe OA pain using denosumab will reduce the size and occurrence of BMLs and reduce their pain. This will potentially provide a new disease modifying treatment for OA which would be easy to administer and could be of use in the primary care setting.

2.1 Assessment and management of risk

Adverse effects related to denosumab injection based on the investigator brochure (located in the TMF) include lower limb cellulitis and hypocalcemia. To minimise these risks, we propose to exclude those with a history of cellulitis within the last 5 years and to screen also for hypocalcemia and hypovitaminosis D prior to intervention. We will advise participants to inform the trial team and to seek prompt medical attention if they develop signs or symptoms of cellulitis. We plan to exclude those with significant hypocalcemia (Calcium < lower limit of normal [LLN]) and with a vitamin D level of less than 25 nmol/l. Those with vitamin D between 37.5 and 50nmol/l will be given booster vitamin D therapy (120,000IU of colecalciferol). Those with vitamin D between 25 and 37.5nmol/l will receive 240,000IU of colecalciferol. Furthermore we propose to supplement all participants with calcium and vitamin D (at least 500mg of elemental calcium daily and 400IU vitamin D daily) unless they are already taking these levels. Because of the potential adverse effect on fetal development we will exclude women who are of child bearing potential who are, or are planning to become, pregnant during the course of the trial and for up to 5 months afterwards, and advise on importance of contraception measures for those who are not yet menopausal. Bisphosphonates have been associated with rare long term adverse events including osteonecrosis of the jaw and atypical fractures. These tend to occur in patients on long term therapy and in the case of Osteonecrosis of the Jaw (ONJ) in those taking higher doses of therapy. There are isolated reports of ONJ and atypical fracture with denosumab when used in osteoporosis, however, the relatively short term use in our proposed study makes the occurrence of these adverse effects very unlikely. Participants will be advised, however, to maintain good oral hygiene during the 6 months of the study, to continue with their routine dental checkups, to contact their doctor or dentist if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge. They will be advised also to avoid invasive dental procedures during the course of the study if possible. Participants will be advised also to report any new or unusual thigh, hip or groin pain which may be an early presenting feature of an atypical fracture.

This trial should be categorised as: Type A = No higher than the risk of standard medical care. Although the indication is not licensed, a different range of adverse events would not be expected in this population.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Objectives

1. To determine the effect of a single denosumab 60mg subcutaneous (SC) dose on the total area of bone marrow lesions (BMLs) in participants with symptomatic knee osteoarthritis (OA).

2. To determine the effect of a single denosumab 60mg subcutaneous (SC) dose on,
   i) the reduction in intensity of knee pain and knee symptoms after 3 and 6 months,
   ii) change in quality of life
   iii) change in BML volume, in participants with symptomatic knee osteoarthritis (OA)

3. To determine whether there is any correlation between the reduction in knee pain and change in BMLs.

4. To determine safety of therapy with denosumab

3.2 Primary endpoint

Total area of bone marrow lesions (assessed on MRI) at 6 months.

3.3 Secondary endpoints

1. Knee pain using an 11 point (0–10) numerical rating scale ($NRS_{Last\ week}$) of knee pain intensity, at 3 and 6 months. The change in knee pain using a NRS scale is the primary outcome recommended by IMMPACT (http://immpact.org/).

2. Knee pain on nominated activity using an 11 point (0-10) numerical rating scale (NRS_{NA}) at 3 and 6 months.

3. Knee symptoms assessed using KOOS (Roos,1998) at 3 and 6 months (Roos,1998).

4. Quality of life assessed using EuroQOL & SF12. We propose to assess the secondary outcomes at both 3 and 6 months.

5. Adverse events

6. BML volume measured on MRI.

3.4 Exploratory endpoints/outcomes

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure (if applicable)
To compare the effect of denosumab on synovitis-effusion in knee OA	Synovitis-effusion volume assessed using MRI	MRI image at baseline and at 6 months

3.5 End of Trial

For individual participants the trial will end on either completion of 6 months in the trial or withdrawal due to any reason. The overall end of the trial will be the time the last patient randomised has completed his / her final visit.

4.0 TRIAL DESIGN

Parallel group design

There will be an interim analysis after 75 participants have 6 month outcome data to assess futility (projected lack of benefit), see section 10.3.

5.0 TRIAL SETTING AND REIMBURSEMENT

This is a single centre trial, where the recruitment and trial management will be based at Manchester University and the trial visits will be undertaken at Salford Royal NHS Foundation Trust or The Wellcome Trust/NIHR Manchester Clinical Research Facility. We will recruit participants from primary, secondary care and the community.

5.1 Participant Reimbursement

Participants will be reimbursed up to £25 for travel per visit whilst participating in this research

6.0 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

1. Age 40 years and over.
2. Ambulatory (not wheel chair bound), and able and willing to comply with the intervention and follow up.
3. Significant knee pain (have at least a score of 3 out of 10 on the primary symptom outcome of the trial, knee pain on a numerical rating scale (NRS $_{\text{Last week}}$ ≥3)
4. Evidence of significant OA on, x-ray – Kellgren Lawrence grade 2 or 3. Participants can have Kellgren and Lawrence grade 2 or 3 in any knee compartment.
5. Evidence of BMLs in index knee on magnetic resonance scanning (MRI)
6. Written informed consent

For those with bilateral symptomatic knee OA, we will obtain pain scores and x-ray images for both knees provided both knees meet the pain eligibility criteria (NRS $_{\text{Last week}}$ ≥3). If only one knee meets the inclusion criteria on x-ray, we will select this knee for our primary outcome and will obtain the MRIs on this knee. If knees are equally symptomatic, we will study the one with the more severe radiographic changes (providing it is eligible) as it is more likely to have BMLs and if both symptoms and radiographic changes are equivalent, we will choose the dominant knee.

6.2 Exclusion criteria

1. History of septic arthritis affecting the index knee
2. History of inflammatory arthritis
3. Current treatment for gout and/or acute attack of gout within the previous 5 years
4. GFR < 35 ml/min
5. Vitamin D level of < 50 nmol/l
6. Abnormal liver function (ALT or AST > twice upper limit of normal) or elevated total bilirubin > 1.5 x ULN
7. Potential participants with a positive Hepatitis B surface antigen (HBsAg) or hepatitis C test result or a history of immune-deficiency diseases, including a positive HIV test result
8. History of malignancy in the past 5 years (other than basal cell carcinoma)
9. History of any solid organ or bone marrow transplant
10. History of alcohol abuse within previous 12 months[1]
11. Known hypersensitivity to Latex
12. Hereditary problems of fructose intolerance
13. Non-healed dental / oral surgery
14. History of cellulitis of the lower limb within the last 5 years, osteonecrosis of the jaw, osteonecrosis of the external auditory meatus or atypical femoral fracture
15. Unhealed open soft tissue lesions in the mouth
16. History of invasive dental surgery in previous 6 months and/or invasive dental work planned in the next 6 months
17. Current anorexia nervosa, suspected bulimia (by history or physical examination) or obvious malnutrition
18. Active inflammatory bowel disease or current or recent malabsorption syndrome.
19. Hypo or hyperparathyroidism
20. Hypocalcemia (Calcium < LLN) / hypercalcemia (Ca > Upper Limit of Normal [ULN])
21. Osteoporosis on bone active therapy
22. Current or recent Osteomalacia (within the last 5 years) or other bone diseases which may affect bone metabolism (osteopetrosis / osteogenesis imperfecta)
23. Suspected knee fracture
24. Intra-articular therapy in the knee within the previous 3 months
25. Prior antiresorptive therapy with bisphosphonates in the last year (oral therapy) or 3 years (IV therapy)

[1] As assessed by consenting physician

26. Prior treatment in the last year with strontium ranelate / HRT / raloxifene / testosterone
27. Previous knee surgery (including cartilage surgery) or arthroscopy within 6 months on the affected knee
28. Planned knee or hip surgery in the next 6 months
29. Currently having physiotherapy for knee OA
30. Women of childbearing potential currently pregnant or planning pregnancy or breast feeding
31. Women of childbearing potential and refusal to use at least one highly effective form of contraception (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) and to continue until 5 months following intervention.
32. Concurrent life threatening illness or any other condition that in the opinion of the investigator would compromise participants safety or data integrity
33. Contraindication to MRI such as implants which prohibit safe use of MRI scan including cochlear implants / metal objects in the body including certain joint prosthesis, cardiac or neural pacemakers, hydrocephalus shunts, or certain types of intrauterine-device. Also trial knee circumference must not be >55cm or weight >125kg as these exceed the maximum MRI limits
34. Currently enrolled in or has not yet completed at least 1 month since ending other investigational device or drug trial(s), or potential participant is receiving other investigational agent(s)
35. Pain from sites outside the knee that are significantly more troublesome to the potential participant than knee pain and which significantly interferes with the ability of the potential participant to assess their knee pain.
36. Unable to understand or retain the information provided regarding the trial procedures.
37. Known hypersensitivity to denosumab or any ingredients of Prolia

7 TRIAL PROCEDURES

7.1 Recruitment

Recruitment will be through a variety of sources

1. The community via:
   - Primary care clinical commissioning groups; we will utilise GP lists of potential participants age 40 years and over with a clinical / radiological diagnosis of knee OA.
   - Intermediate care (multi-professional) teams based in the community in Clinical Assessment and Treatment Services (CATS).
   - Advertisements using hard copy and electronic media.
2. Secondary care. This will utilise lists of patients referred to teaching hospitals for knee pain, including rheumatology, orthopaedic clinics and also the radiology department
3. From a register of potential participants who have previously taken part in studies of OA knee and who have consented to be approached to take part in further studies

7.1.1 Patient identification

1) The community via:-

a) Primary care. We will utilise GP lists of patients age 40 years and over with a clinical diagnosis of knee OA. Standard letters will be sent to potential participants from the relevant GP to invite them to participate in the trial and enclosing a patient information sheet (PIS). A tear off slip at the end of the letter enables the potential participant to provide the research team with their details using an enclosed prepaid envelope. The team will then contact them to discuss eligibility. Alternatively the patient can contact the team directly by phone to discuss their involvement.

b) Intermediate care (multi-professional) teams based in the community in Clinical Assessment and Treatment Services (CATS). These teams will identify potential participants attending these centres with OA knee. Patients will be provided with the PIS and asked for their agreement (using a signed data access form [DAF]) to be approached by the research team. The DAF also records their permission to access their medical records for the purpose of determining eligibility e.g. X-ray. All signed DAFs will be forwarded securely to the research team who will then contact the potential participant to discuss their involvement.

c) Advertisements will be used to generate interest via the local press, the ROAM website and other internet sources and e-media including Facebook and Twitter. Posters will be placed in various appropriate locations within and outside of the NHS. Radio interviews may also be performed. Potential participants would contact us directly and will be provided with a PIS via post if they are interested in taking part.

2) Secondary care. Participant identification centres will be set up in NHS trusts. This will utilise lists of patients referred to teaching hospitals for knee pain, including rheumatology and orthopaedic clinics. Patients may be informed about the trial at a clinic visit, in which case they will be given a PIS. Provided they give permission, their contact details will be forwarded to the research team via a DAF. Alternatively they may be contacted by post in the same manner as GP mailings. A member of the research team will contact the potential participant if they express interest in participation.

3) From registers of people who have either previously taken part in studies of OA knee and who have consented to be approached to take part in further OA studies, or were ineligible for other OA studies but had expressed interest in hearing about other research in Knee OA. People on the register will receive a study invite letter and a PIS through the post.

7.1.2 Screening

Telephone Screening
All potential participants who have expressed an interest in participating will be pre-screened by telephone interview regarding age, symptoms of knee pain, history of knee problems, other conditions and any treatment which may preclude their participation. The source of recruitment and DAFs will be recorded and stored in the individual's telephone screening notes.

During the telephone screening, potential participants will be also asked the date of their last knee X-ray. Verbal permission will be sought to review X-rays within the last 24 months for the purpose of determining eligibility. This permission will be recorded on the telephone questionnaire. Once X-ray eligibility has been assessed, a member of the research team will contact the potential participants to further discuss whether or not they are still eligible at this stage.

All potential participants who have no obvious exclusion criteria will be invited to attend for a screening visit and the PIS will be sent via post at least 24 hours prior to screening, if they have not already received one.

Consent
At the screening visit the nature and objectives of the trial will be explained and potential participants will be given the opportunity to ask questions. Once this is done and the potential participant is happy they have received all the required information and would like to take part, written consent must be obtained.

The participant's consent must be confirmed at the time of consent by the personally dated signature of the participant and by the personally dated signature of the Clinician conducting the informed consent discussion.

The original signed consent form will be retained in the ISF, a copy given to the patient and a copy filed in the patient's clinical notes.

Clinical Screening
Following consent potential participants will be assigned a screening ID and asked further questions about their personal and medical history. A knee examination will be performed and level of pain assessed using NRS Last

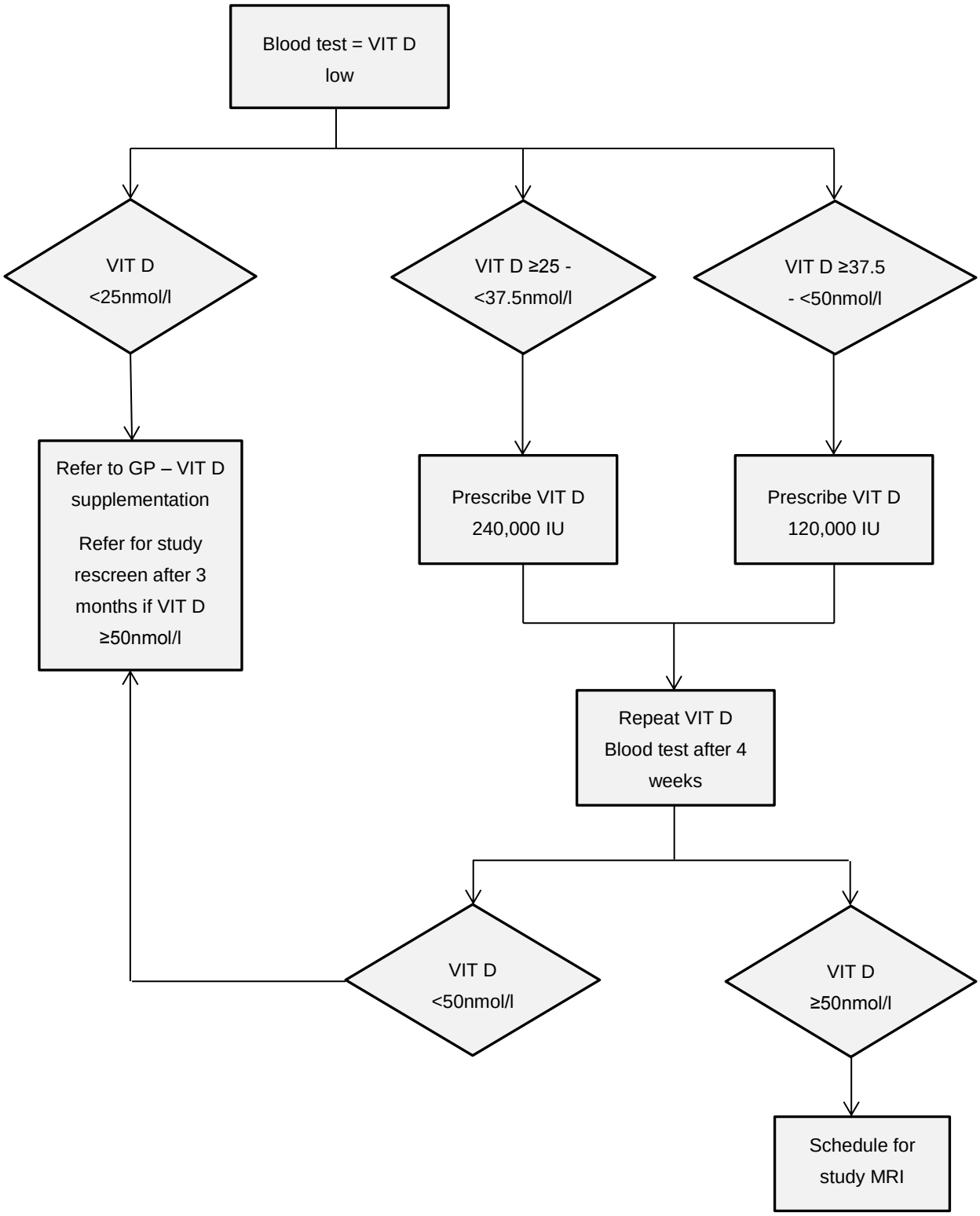
week. Potential participants who have not had an x-ray of their knee within the previous 24 months will then be sent for PA, skyline and lateral radiograph to confirm the presence and severity of OA. All potential participants will have blood taken for assessment of calcium and vitamin D, Renal and Liver function tests, Hepatitis BsAg, Hep C and HIV. Women < 55 years and amenorrhoeic, but have had menses in the last year, will have FSH/LH and estradiol levels performed. If the radiograph indicates they are unsuitable (Kellgren/Lawrence grade 1 or 4) the participants will be defined as 'screen failures' and will not continue in the trial.

If otherwise eligible and their vitamin D is less than 50 nmol/l but greater or equal to 37.5 nmol/l they will attend the hospital for a prescription of cholecalciferol 120,000IU and will have their blood checked for vitamin D again in 4 weeks. If otherwise eligible and their vitamin D is less than 37.5 nmol/l but greater or equal to 25 nmol/l they will attend the hospital for a prescription of cholecalciferol 240,000IU and will have their blood checked for vitamin D again in 4 weeks (See 'Low Vitamin D management schedule flow chart below) Those with vitamin D < 25nmol/l will not continue in the trial with recommendation to their GP to treat their deficiency. Further screening is possible though not before at least 3 months following therapy. Those with hypocalcemia (Ca < LLN) will not continue in the trial (screen failure).
If potential participants return for vitamin D checks, other aspects of eligibility may be rechecked where possible. For example, the participant may be asked if they have had any dental treatment, any newly developed symptoms, or, if they are a woman of child bearing potential, whether they could be pregnant. Any responses should be documented in the medical notes to evidence any screening rechecks. Calcium results, liver and kidney function will not be rechecked during this time. It is anticipated that calcium levels will increase after treatment with cholecalciferol, so there will be no additional risk of hypocalcemia at this time.

Provided the vitamin D is normal, potential participants will be sent for MRI imaging to assess for the presence of Bone Marrow Lesions. The MRI imaging appointments will take up to 90 minutes. If bone marrow lesions are present, they will be invited to attend for a baseline visit. If bone marrow lesions are absent, they will not continue in the trial.

Provided the patient consents, their GP will be informed of their participation.

DISKO: Low Vitamin D Management Schedule



Baseline & Follow up : Participants who meet the inclusion / exclusion criteria on the basis of the screening assessment will be invited to attend for baseline assessment usually within 2 weeks (though up to 6 weeks) of their MRI scan. At the baseline assessment participants will complete KOOS (Roos and Lohmander, 1998), and a numerical rating scale (NRS $_{\text{Last Week}}$) for overall knee pain, pain on a nominated activity (NRS $_{NA}$), Hospital Anxiety and Depression Scale, (HADS), EuroQol, SF12 and the illness perception questionnaire (IPQ-B). Following this the participants will be randomised to either denosumab or placebo which will be administered by a subcutaneous injection. At this visit participants will be given calcium and vitamin D supplements from site hospital stock as required (refer to section 8.11 for further details).

Participants will be contacted within 14 days (+/- 2 weeks) of the injection for the purpose of determining adverse effects and in particular whether there are any symptoms suggestive of hypocalcemia, in which case the participant will be recalled for a further blood test for calcium level. The participant will be seen again at 3 months (+/- 4 weeks) for the purpose of assessment of knee pain, knee symptoms, quality of life and assessment of calcium level. They will attend at 6 months (+/- 4 weeks) for a final visit at which time they will complete questions about knee pain and knee symptoms, SF12, HADS and EuroQOL and have a repeat MRI. Imaging appointments will take up to 90 minutes.

Participants will also be invited to provide a blood and urine sample at the baseline and 6 month visits to be stored for future analyses.

7.2 The randomisation scheme

Patients who have consented to take part in the research will be given a screening number. This number will be recorded on the study screening log which will be retained by the Research Nurse at Salford Royal NHS foundation Trust. Following eligibility screening for entry into the study, eligible patients will be randomised at baseline.

The patients will be randomised 1:1 to receive either a single injection of denosumab or matched placebo, using the method of permuted blocks within a single stratum. Adjacent block sizes will also vary randomly within pre-defined limits. Both the study team and randomisation process will be blinded.
From this randomisation process the study team will use the randomisation number to identify patients taking part in the study.

Each patient will be issued with a DISKO study emergency contact card that will provide details of the study title, individual randomisation study number and out of hours emergency contact information.
NB. Please see Randomisation Standard Operating Procedure for full details of the randomisation process.

7.2.1 Method of implementing the allocation sequence

See Randomisation Operating Procedure. Participants will be randomised to placebo or active intervention

7.3 Blinding

Blinding will be maintained by use of identically packaged and labelled placebo so that participants and all trial staff (including the research team and outcome assessors) are unaware of treatment allocation throughout the period of the trial.

The MCTU statistician is unblinded to the intervention groups.

See Randomisation Operating Procedure. All records will be kept confidential and data sets for each participant will be identified by the participant subject number and initials only.

7.4 Unblinding

Due to the low toxicity profile of denosumab, the likely need for unblinding has been classified as low risk. Details of the emergency unblinding procedure will be given in the Pharmacy Manual and will be available at all times in the Pharmacy Department at the recruiting site and in the investigator site file.

In the unlikely event that unblinding is deemed necessary by the investigator for medical or safety reasons (e.g. in the case of a severe adverse event where unblinding is necessary to determine the necessary treatment), this can be done (see Unblinding Operating Procedure). Subject always to clinical need, where possible, members of the research team will remain blinded. Provided consent is given, the unblinded participant will continue to contribute data to the trial for the purpose of obtaining outcome and safety data. The CI/PI will document the breaking of the blind and the reason in the CRF and participants notes. Reasons for unblinding include:

- Medical emergency where unblinding of the medication is necessary
- In the event of a SUSAR needing expedited reporting
- Request by Data Monitoring and Ethics

For 'out of hours' periods, participants will be provided with an emergency contact card detailing the number for the central switch board at SRFT who have contact details for the CI or nominated medical professional. This would allow relevant clinical teams to contact the CI to discuss the nature of the trial if required. However, in emergency situations, responsibility for breaking the treatment code resides solely with the investigator who may therefore unblind treatment allocation without any involvement from the CI or sponsor. Where an unblind is required, the investigator will follow the Unbinding Operating Procedure.

7.5 Assessments and procedures

The trial will be run in accordance with the principles of GCP and the current regulatory requirements as detailed in the Medicine for Human Use (Clinical Trials) Regulations 2004 and any subsequent amendments of the clinical trial regulations. This section describes the trial schedule and procedures for the trial and provides further information about the assessments which will be undertaken.

The trial will be carried out at Salford Royal NHS Foundation Trust.

Screening visit (1)

The following will be performed at this visit

- Consent. The participant will have received information, including the Participant Information Sheet, at least 24 hours before the screening visit. Their knowledge of the nature and objectives of the trial will be verified and his/her informed consent will be obtained. Participants will be encouraged to ask questions and clarify any concerns. The screening period will provide further opportunity for a participant to re-consider and consent will also be confirmed at the baseline visit.
- A screening ID number will be assigned
- Inclusion/exclusion criteria available at this time will be checked.
- NRS $_{\text{Last Week}}$
- Demographic variables describing the participant (age and sex).
- Personal and medical / surgical / drug history (relevant to inclusion / exclusion criteria), and alcohol history will be taken.
- Concomitant medications recorded.
- Physical examination, including measurement of body weight and height and measurement of trial knee circumference
- Knee examination
- Vital signs (blood pressure after a 5-minute rest, pulse rate).
- Blood monitoring –renal & liver function test (LFT), bone profile including calcium and 25OHD. Also bloods for prior infection (Hepatitis BsAG, Hep C and HIV) FSH / LH / Estradiol if < 55 years and currently amenorrhoeic though menses in the past year
- Serum pregnancy test in female participants with child-bearing potential (see section 8.9). Only those with a negative test will be enrolled

- Among those who have not had an X-ray in the past 2 years an X-ray will be performed to confirm evidence of significant OA in the affected knee.
- Those with 25OHD levels between 25 and 50 nmol/l will be prescribed vitamin D (cholecalciferol) to normalise their levels with levels re-assessed after 4 weeks. Those with levels < 25nmol/l deficiency will be recommended to their GP for treatment and withdrawn though may be rescreened after minimum of 3 months.

Screening (MRI) (visit 2)

Provided an individual satisfies the inclusion / exclusion criteria and their 25OHD is normal they will then have an MRI of their index knee scheduled. The MRI imaging appointments will take up to 90 minutes. If there are evidence of bone marrow lesions they will be invited to attend for a baseline assessment. If no BMLs are present on MRI they will be not continue in the trial (screen fail). Adverse events will be assessed and participants will also be shown how to use the accelerometer; this will be forwarded to them by post and they will be asked to wear for approximately 7 days once eligibility (presence of BMLs) has been confirmed.

Baseline (visit 3)

Those who satisfy all the inclusion and exclusion criteria and with normal levels of vitamin D and with evidence of BMLs on MRI will be seen at baseline for assessment. The following will be performed at this visit (and relevant information recorded in the case report form). Those not already on calcium and vitamin D supplements will receive supplements from site hospital stock (refer to section 8.11 for further details).

- Collect accelerometer
- Confirmation of eligibility, consent confirmed
- $NRS_{Last\ week}$, NRS_{NA}, KOOS, SF12, EuroQOL, HADS, IPQ-B
- Concomitant medication check
- Adverse events assessment
- Vital signs (blood pressure after a 5 minute rest, pulse rate)
- Randomisation
- Blood and urine (optional) will also be taken for storage (-70 degrees) as resource for future biomarker studies
- Dispense trial drugs according to treatment arm and according to the randomisation schedule
- Injection of subcutaneous placebo or denosumab
- Patients will be provided with emergency contact cards for use throughout the trial.
- Pregnancy test (Urine)

Telephone follow up:– within 14 days of baseline (telephone follow up).

Participants will be contacted by telephone within 14 days (up to 28 days) to assess for possible adverse effects including symptoms of hypocalcemia; in this case if such symptoms are present the participant will be invited to attend for a repeat blood test for calcium. They will also be asked about concomitant medication / rescue medication and note any adverse events. Information will be recorded in the case report form.

Visit 4 :– 3 months +/- 28 days

The following will be performed (and recorded in the case report form):

- Collect accelerometer (forwarded to patient prior to their visit)
- Concomitant medication check (Analgesia and drugs related to bone activity such as bisphosphonates)
- $NRS_{Last\ Week}$, NRS_{NA}, KOOS, SF-12, EuroQOL
- Adverse events assessment
- Blood for calcium level
- Pregnancy test (Urine)
- Compliance check with calcium and vitamin D supplements

Visit 5 : – 6 months+/- 28 days. Final visit

The following will be performed (and recorded in the case report form)

- Collect accelerometer (forwarded to patient prior to their visit)
- $NRS_{Last\ Week}$, NRS_{NA}
- KOOS / SF12 / EuroQOL / HADS
- Concomitant medication check (Analgesia and drugs related to bone activity such as bisphosphonates)
- Adverse events assessment
- MRI scan. The MRI imaging appointments will take up to 90 minutes.
- Weight and height assessment
- Vital signs
- Compliance check with calcium and vitamin D supplements
- Pregnancy test (urine)
- Blood and urine will also be taken for storage (-70 degrees) as resource for future biomarker studies.

If pain scores have reduced at follow up visits, this will not be classed as a protocol deviation as long as patients scored ≥3 on $NRS_{last\ week}$ at the screening visit.

Unscheduled visits

While participants will be encouraged to attend for the normal visit schedule, unscheduled visits will be undertaken if the participant is unwell or there are any concerns as to the patient's progress. Participants visits will still be considered active up to 21 days either side of the scheduled date, but will revert to the original schedule for the next visit.

Participant discontinuation and withdrawal of participants

All participants have the right to withdraw consent at any time without prejudice. At the time of withdrawal of consent, a full efficacy and safety evaluation will be performed if the participant consents. Participants who withdraw will be asked to complete the questionnaires as per the next planned trial visit.

Participants will be withdrawn if any of the following occur:

- Participant decision
- Principal investigator decision
- Sponsor decision

Participants who withdraw from the trial, are lost to follow up or who die, will not be replaced - this trial has been powered to allow for a ~10% drop-out.

The end of the trial

The end of the trial is defined as the last visit (month 6) of the last participants.

7.6 Trial assessments and procedures

For an overview of the clinical measurements, see trial visit schedule below (Table 1).

Table 1: Trial Schedule

	Screening			Trial visits			
		(-4weeks)	(-2weeks)	(week 0)	(week 1)	(3month)	(6 Months)
Visit procedures	**Tele-screening**	**Visit 1 - Screening**	**Visit 2 MRI**	**Visit 3 Baseline**	**Phone call (14-28 days)**	**Visit 4 (+/- 28 days)**	**Visit 5 (+/-28 days)**
Personal, Medical and Surgical history	X	X					
Concomitant meds check		X		X		X	X
Adverse event reporting			x	X	X	X	X
Knee examination		X					
Vital signs		X		X			X
Body weight	X	X					X
Height	X	X					X
Knee circumference		X					
X-ray		X					
Inclusion /Exclusion criteria		X					
Consent		X					
MRI acquisition			X				X
HADS				X			X
NRS last week	X	X		X		X	X
NRS NA				X		X	X
KOOS Full				X		X	X
SF12				X		X	X
EuroQUOL				X		X	X
IP-Q brief				X			
Liver function Test		X					
Renal Function		X					
Calcium		X			X A	X	
Vitamin D (250HD)		X					
HepBsAG		X					
Hep C		X					
HIV		X					
FSH		X B					
LH		X B					
Estradiol /Oestradiol		X B					
Pregnancy test (serum)		X					
Pregnancy test (urine)				X		X	X
Vitamin D/Calcium supplements administration				X		X	
Vitamin D/Calcium supplements compliance checks						X	X
Randomisation				X			
IMP/Placebo Administration				X			
Biomarker - Blood collection				X			X
Biomarker - Urine samples				X			X
Activity Monitor				X C		X C	X C

A - Schedule repeat blood test for calcium if signs of hypocalcemia
B - Applies only if participants <55 and currently amenorrhoeic through menses in past year
C – Issue week prior to visit

7.6.1 Physical Examination and Vital Signs

Vital signs (including pulse / BP) and assessment of height and weight will be performed at screening, and at the end of the trial. Examination of the index knee will be performed to determine presence or absence of effusion and or tenderness at the knee at screening.

7.6.2 Medical history/demographic data

Personal and Medical / Surgical history including current therapy will be assessed at screening. Relevant information will be documented in the trial CRF.

7.6.3 Imaging Assessments

a) Radiographs

Participants who agree to take part in the trial, and who have not had radiograph of their knee in the past 24 months will have a knee radiograph performed. Posterior- anterior, skyline and lateral views will be performed to confirm eligibility (Kellgren/ Lawrence grade of 2-3) in any compartment.

b) Magnetic Resonance Imaging

Those who are eligible for participation based on their personal and medical history and who have confirmed Kellgren-Lawrence radiographic grade 2-3 at their index knee and whose vitamin D levels are satisfactory will undergo MR imaging of their index knee joint. The scan will take approximately 45 minutes though up to 90 minutes to complete. The participants will lie in the scanner usually wearing shorts. A knee coil will be used to acquire the images. Imaging will include fat suppressed sagittal proton density (PD) weighted images. We will look for evidence of bone marrow lesions in the subarticular marrow. These are poorly demarcated areas of increased signal intensity in the normally hypo intense fatty marrow on the fat-suppressed spin-echo images. Knee joint synovitis will also be assessed on non-contrast enhanced images; because not possible to distinguish fluid from synovitis on MRI this will be referred to as 'synovitis- effusion'.

7.6.4 Clinical parameters

Response assessments (NRS $_{\text{Last Week}}$ and NRS $_{\text{NA}}$ and KOOS) will be performed at 0, 3 and 6 months, as will SF12 and EuroQOL. IPQ-B will be performed at baseline only. HADS will be performed at baseline and 6 months.

7.6.4a Numerical rating scales

Participants will be asked to assess their average overall knee pain severity over the past week (NRS $_{\text{Last Week}}$) and their knee pain on nominated activity (NRS $_{\text{NA}}$) over the past week. Participants will be asked to assess their average knee pain on a 0-10 11 point numerical rating scale. The scale ranges from 'No pain at all' to 'Worst pain imaginable'. Numerical scales have been found to be reliable and demonstrate good face and criterion validity.

7.6.4b Hospital Anxiety and Depression Score (HADS)

Participants will be asked to complete a hospital anxiety and depression score to assess depression and anxiety. The Hospital Anxiety and Depression Scale (HADS) is a 14-item scale designed to detect anxiety and depression, independent of somatic symptoms. It consists of two 7-item subscales measuring depression and anxiety. A 4-point response scale (from 0, representing absence of symptoms, to 3, representing maximum symptomatology) is used, with possible scores for each subscale ranging from 0 to 21. Higher scores indicate higher levels of disorder.

7.6.4c EuroQOL
A generic measure of self-reported health status that defines health status in terms of five dimensions – mobility; self-care; usual activity; pain or discomfort; and anxiety or depression. EuroQOL has been extensively validated and shown to be sensitive, internally consistent, and reliable in the general population and other patient groups, including for inflammatory arthritis.

7.6.4d SF-12
The SF-12 is a general health related quality of life instrument and composed of 12 questions from the SF-36 Health Survey, designed to measure generic health concepts from a patient's perspective. The questions include 2 questions concerning physical functioning; 2 questions on role limitations because of physical health problems; 1 question on bodily pain; 1 question on general health perceptions; 1 question on vitality (energy/fatigue); 1 question on social functioning; 2 questions on role limitations because of emotional problems; and 2 questions on general mental health (psychological distress and psychological well-being).

7.6.4e KOOS
The Knee injury and Osteoarthritis Outcome Score (KOOS) was developed as an extension of the WOMAC Osteoarthritis Index with the purpose of evaluating short-term and long-term symptoms and function in participants with knee injury and osteoarthritis. The KOOS holds five separately scored subscales: Pain, other Symptoms, Function in daily living (ADL), Function in Sport and Recreation (Sport/Rec), and knee-related Quality of Life (QOL). The KOOS has been validated for several orthopaedic interventions such as anterior cruciate ligament reconstruction, meniscectomy and total knee replacement. In addition the instrument has been used to evaluate physical therapy, nutritional supplementation and glucosamine supplementation. The effect size is generally largest for the subscale QOL followed by the subscale Pain. The KOOS is a valid, reliable and responsive self-administered instrument that can be used for short-term and long-term follow-up of several types of knee injury including osteoarthritis (Roos et al., 2003).

7.6.4f Illness Perception Questionnaire-Brief
The illness Perception Questionnaire – Brief (IPQ-B) was developed to provide a quantitative assessment of the five components of the illness representation – identity, consequences, timeline, control/cure and cause in Leventhal's Self-Regulatory Model. Since then it has been used in studies of illness adaptation in patients with a wide range of conditions, including heart disease, rheumatoid arthritis, cancer, chronic obstructive pulmonary disease and diabetes. A revised version stemmed from a need to deal with minor psychometric problems with two subscales, and to include additional subscales, assessing cyclical timeline perceptions, illness coherence, and emotional representations (Broadbent et al., 2006). While it is possible that the new subscales will vary in their applicability in different patient groups, the IPQ-B provides a more comprehensive and psychometrically acceptable assessment of the key components of patients' perceptions of illness.

7.6.5 Blood analysis for assessment of eligibility
The following bloods will be checked at screening: Calcium, albumin, 25OHD, and LFTs. FSH/LH and estradiol and serum pregnancy test for women < 55 who are amenorrhoeic though have had menses in the past 12 months. Also hepatitis surface antigen (HBsAg), hepatitis C and an HIV test

7.6.6 Blood analyses for safety monitoring
Calcium level to be checked at 3 months for all participants and after the telephone call usually within 2 weeks of the injection if symptoms suggestive of hypocalcemia.

7.6.7 Biomarker samples
If a participant agrees for samples to be taken for storage for future biomarker studies then urine (approximately 5 ml) and blood samples (up to 20ml) will be taken at baseline and at 6 months.

7.6.8 Accelerometers

It is generally assumed that the pain and impairment associated with knee OA limits physical activity levels (PAL), typical levels and patterns of PAL in knee OA patients are poorly described (Farr et al. 2008).If pain improves with Denosumab, participants may increase their weight bearing physical activity. Therefore we will monitor a change in PAL objectively using a motion monitoring device accelerometer rather than solely on participants' recall or diaries. The monitor captures both the pattern (sedentary / standing / stepping) and intensity of activities. The monitor will be posted to the patient following their first MRI scan if there is evidence of BMLs. They will be asked to wear it for approximately 7 days. They will be instructed how to do so at the MRI visit. They will be posted the accelerometer again prior to the 3 month and 6 month visits.

7.7 Long term follow-up assessments

There are no plans to monitor participant's long term after active participation is completed.

7.8 Qualitative assessments – Nested studies

There are no planned qualitative assessments.

8.0 TRIAL MEDICATION

8.1 Name and description of investigational medicinal product(s)

Denosumab 60mg (Prolia®) subcutaneous injection and matched placebo.

8.2 Legal status of the drug

The drug is currently licensed in the UK for the 'Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures'. (EU Marketing authorisations EU/1/10/618/001, EU/1/10/618/002, EU/1/10/618/003)

The trial is being carried out under a Clinical Trial Authorisation (CTA). The drug is therefore only to be used by the named investigators, for the participants specified in this protocol, and within the trial.

8.3 Investigator Brochure (IB)

The approved version of the Investigator Brochure (IB) will be used in the trial.

8.4 Drug storage and supply

The IMP will be supplied by AMGEN. The participating site should ensure the IMP is managed and dispensed in accordance with the DISKO Pharmacy Manual which contains detailed information on storage, handling and supply of IMP. The manual is stored at Salford Royal NHS Foundation Trust, Trials Pharmacy, located within in- patient pharmacy, Irving Building, Stott Lane, Salford M6 8HD. Trust Pharmacy operational SOP's are also located in this area.The participating site Pharmacy will be responsible for ensuring the accountability process by maintaining adequate records of the disposition of the IMP.

8.5 Dosage schedules

The injection will be a one off administration of subcutaneous injection. The recommended dose of denosumab is 60 mg administered as a single subcutaneous injection into the thigh, abdomen or upper arm.

8.6 Dosage modifications

Denosumab is given as a one off subcutaneous injection and the dose will not be modified. Stopping rules will be agreed with the DMC at the start of the trial. In cases where participants are not eligible then no dose will be given – there will be no provision to reduce dose based on the person's clinical circumstances. For participants with hypocalcemia treatment will not be prescribed.

8.7 Known drug reactions and interaction with other therapies

In an interaction study, denosumab did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4). This indicates that denosumab should not alter the pharmacokinetics of medicinal products metabolized by CYP3A4. There are no clinical data on the co-administration of denosumab and hormone replacement therapy (oestrogen), however the potential for a pharmacodynamic interaction is considered to be low. In postmenopausal women with osteoporosis the pharmacokinetics and pharmacodynamics of denosumab were not altered by previous alendronate therapy, based on data from a transition study (alendronate to denosumab).

8.8 Concomitant medication

Where possible, participants will be asked to avoid changes to their analgesic, anti-inflammatory medication, glucosamine and chondroitin for the duration of the trial. However, if a participant is experiencing increased pain and requires an increase in the dose of analgesics then the use of paracetamol, topical/oral NSAIDS and/or opioids will be permitted, but the reason for the dose increase, and the dose used, must be documented in the CRF. Chronic NSAID and opioid use (> 50% of days using at least one dose, in the last 3 months) will be included as a covariate in the analysis. Data on concomitant pain medications will be collected at each assessment by recording analgesia use in the previous week.

Steroids

Participants will be asked not to have intra-articular steroid injections either in the index or contralateral knee during the trial period. Any participants requiring intra-articular knee corticosteroids will be recorded as a protocol deviation. Other forms of steroid therapy (oral, rectal and inhaled) will be permitted during the trial period.

Chondroitin and glucosamine

Participants will be permitted to continue current use of chondroitin and glucosamine; however their use must be clearly documented in the CRF. Chondroitin or glucosamine therapy should not be commenced during the duration of the trial.

Drug usage will be documented in the CRF at each trial visit (baseline, 3 and 6 months) and by follow-up telephone call at 1-2 weeks. At baseline participants will fill in their current knee OA medications with the research nurse.

Participants will be asked not to start any new non-pharmacological therapies for the knee OA including physiotherapy and splinting.

8.9 Trial restrictions

Males

Men in whom the female partner could become pregnant (that is, she is not postmenopausal or has not had surgery to remove either her uterus, both ovaries and both fallopian tubes), will be advised to let her know about participation in this trial.

Women not of childbearing potential include

Any female who is postmenopausal (as defined below) and/or permanently sterilized (eg, hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy). Tubal occlusion or ligation is considered a highly effective

method of birth control, but does not exclude the possibility of pregnancy. Therefore women who have undergone tubal occlusion/ligation should be treated as a woman of child bearing potential.

Postmenopausal women are those who fit into one of the following categories:
− Age ≥ 55 years, with cessation of menses for 12 or more months
− Age < 55 years, but no spontaneous menses for at least 2 years
− Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or, secondary to hysterectomy), AND with documented postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.
− Underwent a bilateral oophorectomy

Women of childbearing potential must agree to use at least one highly effective form of contraception (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) and to continue until 5 months following intervention. Acceptable methods of contraception are surgical sterilisation (subject or partner), oral, implantable or injectable hormone methods associated with inhibition of ovulation, or intrauterine devices, or intrauterine hormone releasing systems or sexual abstinence.

Pregnancy avoidance measures and information will be included in the patient information sheet.

8.10 Assessment of compliance

Because the drug is given as a one off subcutaneous injection by the research team, we do not foresee any problems with compliance. Participants will be prescribed calcium and vitamin D supplements and these will be recorded at each visit

8.11 Name and description of each Non-Investigational Medicinal Product (NIMP)

All participants will be given calcium and vitamin D supplements (to include at least 500mg of elemental calcium and 400 IU of vitamin D per day) as part of the trial as required (may not be needed if they are already on supplements). These supplements are combined in the form of Adcal D3. Compliance will be assessed. For those who have a vitamin D between 37.5nmol/l and 50nmol/l a separate booster dose of cholecalciferol 120,000IU will be given. For those who have a vitamin D less than 37.5 but greater or equal to 25nmol/l a separate booster dose of cholecalciferol 240,000IU will be given.

9.0 PHARMACOVIGILANCE

9.1 Definitions

The trial will adhere to recognised definitions of adverse events.

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An adverse event can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation unless the hospitalization is for routine treatment or monitoring of the studied indication; • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' will also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability, a causal link between the event and the trial treatment cannot be ruled out.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the approved version of the investigator's brochure.

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

The following scale of severity definition will be used during the trial:

1 *Mild*	Aware of sign / symptom but easily tolerated
2 *Moderate*	Discomfort enough to cause interference with usual activity
3 *Severe*	Incapacitating, unable to work or perform usual tasks
4 *Life-threatening*	Risk of death at time of event
5 *Fatal*	Death ensues

9.2 Adverse Events (AEs)

All adverse events that occur from the time of consent until 6 months post cessation of trial treatment must be recorded in the participant notes and relevant events in the appropriate section of the trial CRF. Details on what information is required will be detailed in the CRF and CRF completion guidelines.

If the adverse event is still on-going at the time of the final AE check (6 months post injection), the participant may be followed up for a longer period of time until the event has resolved, stabilised or has been fully investigated to the satisfaction of the PI and the study Sponsor.

If an investigator becomes aware of any drug-related SARs that occur after the end of safety reporting period (6 months post injection) these must also be reported to the MCTU within the expedited timelines.

The PI or medical delegate at the recruiting centre will be responsible for assessing any AE on the following characteristics: seriousness, relationship to the study drug, and severity.

AEs meeting the definition of a Serious Adverse Event (SAE) must also be reported to the CTU trial manager using the trial specific SAE Report Form immediately but no later than 24 hours of observing or learning about the event.

9.3 SAEs

Medical judgement will be exercised in deciding whether an SAE is serious. Hospitalisation is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious; however, it is not in itself considered an SAE.

For the purposes of this trial, the following are not considered a SAE

- A hospitalization for a pre-existing condition that has not worsened.
- Hospitalization for routine treatment or monitoring of the studied indication not associated with any deterioration in condition
- Hospitalization for treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition e.g. pre-planned hip replacement operation which does not lead to further complications.
- Hospitalization for treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions. If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

9.4 Recording and reporting of SAEs AND SUSARs

All SAEs occurring from the time of consent until 6 months post cessation of trial treatment (Subcutaneous injection) must be recorded on the relevant form and reported to the CTU trial manager immediately, but no later than 24 hours of the research staff becoming aware of the event. The original will be stored in the ISF.

All SAEs must be reported by email immediately but no later than 24 hours of being aware to the M-CTU trial manager.

Email: SAEreport_MANCTU@manchester.ac.uk

For each SAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be emailed to the CTU trial manager immediately, but no later than 24 hours of the information becoming available. All serious adverse events will be followed up until the event has resolved, stabilise or a final outcome has been reached.

Initial assessment of seriousness, causality and expectedness will be made by the PI or delegated doctor at the recruiting centre. If an authorised doctor from the reporting site is unavailable, initial reports without causality will be submitted to the MCTU trial manager by a healthcare professional immediately but no later than 24 hours after becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

Assessment of seriousness, causality and expectedness will be reviewed by the CI against the current approved version of the Reference Safety Information (RSI) within the IB. If a difference of opinion exists between the investigator and CI regarding causality, the event cannot be downgraded by the CI as the investigator is more familiar with the participant's history, clinical signs and symptoms, lab findings and other investigations. The CI may, however, upgrade the investigator's assessment of causality.

All SAEs assigned by the CI or delegate (or following central review) as both **suspected** to be related to IMP-treatment **and unexpected** will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA). The MCTU senior trial manager will perform the unblinding (as detailed in the Unblinding procedure document) and, if appropriate, the MHRA, the REC and the Sponsor will be informed of SUSARs within the required expedited reporting timescales.

9.5 Notification of deaths

All deaths occurring from the time of consent until 6 months post cessation of trial treatment of the IMP will be reported as an SAE as detailed 9.4. All deaths, including deaths deemed unrelated to the IMP, if they occur earlier than expected will be reported via the SAE process.

9.6 Pregnancy reporting

The Investigator must ensure that all participants are fully aware at the start of a clinical trial of the importance of reporting all pregnancies that occur whilst being treated with the study drug and occurring up to 5 months post cessation of trial treatment. This should be done as part of the consent process by explaining clearly to the participants or the participant representative of the potential dangers of being or becoming pregnant.

Any pregnancy occurring in a participant during treatment or within 5 months post cessation of trial treatment must be reported to the DISKO trial manager ***by*** **email immediately but no later than 24 hours** of the site staff becoming aware of it using a Pregnancy Notification Form. It is the Investigator's responsibility to obtain consent for follow-up from the participant. The DISKO trial manager will follow-up all pregnancies for the pregnancy outcome via the Investigator, using a Pregnancy Outcome Form.

The DISKO trial manager will then inform the sponsor and AMGEN within one working day of receipt of all pregnancy notification and outcome forms. The DISKO trial manger will work with the investigator to ensure that all relevant information is provided to the sponsor and AMGEN.

Should a pregnancy occur during the trial, the Investigator should offer counselling to the participant, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the

participant and the baby should continue until the conclusion of the pregnancy. Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE and reported as per usual SAE process.

9.7 Overdose

Accidental overdose will be reported to the MCTU trial manager by the completion of the Overdose CRF page. The completed Overdose CRF page should be reported to the DISKO trial manger ***by*** **email immediately, but no later than 24 hours** of the investigator or site staff becoming aware. The MCTU will then inform the sponsor and manufacturer within one working day of receipt. The MCTU will work with the investigator to ensure that all relevant information is provided to the sponsor and manufacturer.
Given the nature of the trial which is a one off injection of either active treatment or control it seems unlikely that overdose will occur. Participants will continue study participation. No adverse effects are anticipated for an accidental overdose.

9.8 Reporting urgent safety measures

If any urgent safety measures are required the CI/MCTU Trial Manager will contact the MHRA by telephone to discuss the issue with a safety scientist, ideally immediately but no later than 3 days from the date the measures are taken. The CI/ CTU Trial Manager will send written notice to the MHRA, Sponsor and relevant REC of the measures taken and the circumstances giving rise to those measures. Written notification in the form of a substantial amendment will also be submitted within 7 days. The DISKO Trial manger will also notify the recruiting centres within 24 hours of the measures being imposed.

9.9 New Safety Findings

If a new safety finding emerges from sources such as study drug manufacturers, data analysis or DMC findings, the CI will review the finding for its impact on the subjects participating in the relevant trial(s). If there is a potential impact on trial participants' safety, the DISKO trial manager will take appropriate action in conjunction with the Sponsor, CI and research team. Appropriate reporting mechanisms are followed in the event of actions being taken.

9.10 The type and duration of the follow-up of participants after adverse events.

Participants who develop an adverse drug reaction will be followed up until resolved; reporting of adverse events and reactions will be recorded and reported from the time of consent up to 6 months post cessation of the trial treatment. Any SUSAR related to the IMP will be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

9.11 Development safety update reports

9.11.1 Development safety update reports (DSUR)

The CI/DISKO trial manager will submit a development safety update report (DSUR) to the MHRA and the REC within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended by the research team on behalf of the Sponsor.

9.11.2 Annual progress reports (APR)

The CI/DISKO Trial Manager will submit an annual progress report (APR) to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

9.12 Prolia Product Information

Any concerns or irregularities about packaging, appearance or usage of the IMP that is supplied by AMGEN will be reported by Pharmacy to AMGEN and the DISKO Trial manager. The following could be considered potential product complaints that need to be reported to Amgen:

• Packaging: for example, broken container or cracked container
• Devices: issues with delivery of Investigational Product by device
• Usage: for example, healthcare provider cannot appropriately use the product

• Labelling: for example, missing labels, illegible labels, incorrect labels, and/or suspect labels
• Change in Investigational Product appearance: for example colour change or presence of foreign material
• Unexpected quantity in bottle: for example number of tablets or amount of fluid
• Evidence of tampering or stolen material

The Investigator will report to Amgen if any product complaint is noted on the product complaint reporting form provided by Amgen. If there are any concerns or irregularities about the packaging, appearance or usage the product will not be used until AMGEN confirms that it is permissible to use.

NB Please refer to the DISKO pharmacy manual for the specific reporting process and associated documentation.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

Our primary end point is powered on a sample size of 150. We anticipate a dropout rate of 10% and plan therefore to randomise 167 participants and as we anticipate 80% of participants with symptomatic knee OA have bone marrow lesions we will need to screen around 209 participants with MRI scans to achieve our target. We anticipate that approximately one in four potential participants will not be eligible because of their vitamin D status and aim therefore to screen 279 participants in total. The primary structural hypothesis concerns the Total Bone Marrow Lesion Area (TBMLA). Pooling the baseline TBMLA estimates from a recent randomised trial of zoledronic acid in knee OA (Laslett, 2012) yields a mean (SD) of 467mm_2 (378mm_2). A mean reduction in value of 140mm_2 is felt to be clinically significant (Davies-Tuck et al, 2009; Dore D, et al 2010) and so we aim to have reasonable power if such a difference truly exists (this corresponds to a standardized effect size (SES) of 140/378 = 0.370). A t-test using just 6 month TBMLA values with a 1:1 randomisation, 2-tail significance level of 5% and power of 80% requires n=116 participants per arm. A more efficient analysis uses Analysis of Covariance (ANCOVA) with baseline TBMLA values as covariate. The sample size for such an analysis requires (1 - r2)*n participants per arm (Borm, 2007) where n is as above and r is the correlation coefficient between baseline and 6 month TBMLA values. We anticipate there will be a moderate positive correlation and with a value r=0.6, 75 participants are required per arm i.e. 150 participants in total. Unfortunately there is no direct information about the value of r given in the Laslett paper but a calculation using some indirect information given in the manuscript leads to an estimate of around 0.7 and so our sample size should be appropriately conservative.

10.2 Analysis of the primary / secondary outcomes

All baseline data will be summarised by treatment group. All outcomes will be described descriptively (mean, standard deviation, median, minimum and maximum for continuous data and counts and percentages for categorical data). No formal statistical comparisons of baseline data will be undertaken. For analysis of the primary outcome total BML area (TBMLA) we will use an analysis of covariance (ANCOVA) with 6 month values as response, baseline values as covariate and an indicator variable for trial arm. We anticipate that the TBMLA distribution may well exhibit positive skew and so transformations e.g. log may be required. We will be using an 11 point ordinal scale for the pain outcome at 6 months but anticipate that standard ANCOVA will provide an adequate approximate model for this outcome as well. If this turns out to not be the case then ordinal regression models e.g. proportional odds models will be used instead. A similar approach will be taken for the secondary

pain outcome at 3 months and the other secondary outcomes. We will explore if any changes in self reported pain levels are associated with changes in TBMLA.

For continuous outcomes the regression model assumptions will be checked and, if necessary, data will be transformed prior to analysis if this improves the model fit, or normalises the distribution of residuals.

For each outcome measure the number of people with missing data will be calculated for each treatment group and response rates compared. Appropriate sensitivity analyses will be used to examine the effects of missing data on outcomes. The numbers of participants withdrawing from treatment will be summarised by treatment group.

All analyses will be conducted on an intention to treat basis, including all randomised participants in the groups to which they were randomised. Analyses will be conducted in SAS 9.2 and Stata 11 (versions may change), using 2-sided significance tests at the 5% significance level.

10.3 Interim Analysis

We propose to undertake a futility (lack of benefit) analysis after 75 participants have 6 month outcome data (half of the 150 target). This analysis will be undertaken by an independent observer; it will be unblinded based on the total BML area data and the purpose is to determine whether the trial should stop because of lack of benefit (futility). An O'Brien & Fleming stopping boundary will be used in a setting of a one-tail superiority test (in the direction of Denosumab) at the 2.5% significance level. If the nominal p value is > 0.5 then the trial will be stopped for 'lack of benefit'. All analyses will be conducted on an intention to treat basis, including all randomised participants in the groups to which they were randomised.

10.4 Planned recruitment rate

The aim is to recruit 8 participants per month. This is about 2 per week.

10.5 Summary of baseline data and flow of participants

We will produce a consort flow diagram for the trial. The numbers of participants withdrawing from treatment will be summarised by treatment group.

11.0 DATA HANDLING

11.1 Data collection tools and source document identification

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at MCTU and the trial centre.

The Manchester Clinical Trials Unit and the trial centre will comply with all aspects of the General Data Protection Regulation (GDPR) and the Data Protection Act 2018. Operationally this will include: consent from participants to record personal details including name, date of birth, address and telephone number, NHS ID, hospital ID, GP name and address appropriate storage, restricted access and disposal arrangements for participants personal and clinical details, consent from participants for access to their medical records by responsible individuals from the research staff, the sponsor or from regulatory authorities, where it is relevant to trial participation, consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.

Source Data

ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

A case report form will be provided for each participant.
All protocol-required information collected during the trial will be recorded by the investigator, or designated representative, in the case report form. If the investigator authorizes other persons to make entries in the case report form, the names, positions, signatures, and initials of these persons will be supplied to the sponsor, and noted on the delegation of duties log at site.

The investigator, or designated representative, will complete the case report form pages as soon as possible after information is collected, preferably on the same day that a trial participant is seen for an examination, treatment, or any other trial procedure. Any outstanding entries will be completed immediately after the final examination. An explanation should be given for all missing data.

A source data location list will be prepared prior to the start of the trial. This list will be filed in both the trial master file and the investigator trial file and updated as necessary. All clinically relevant data will be recorded in the patient notes (source), in addition to a statement that all trial relevant data is recorded in the CRF for the appropriate Trial Visit.

The completed case report form will be reviewed and signed by the investigator named in the clinical trial protocol or by a designated sub-investigator.

Source Documents
ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

CRFs as Source Documents
Information will be entered onto a workbook and then transcribed into the CRF. If the CRF is sent to the sponsor, the trial site will retain a copy as well as the workbook to ensure that the principal investigator can provide access to the source documents to a monitor, auditor, or regulatory agency. Participant completed questionnaires will be classed as source data. Additional information can be found in ICH E6, section 6.4.9.

Participant Questionnaires as Source Data
Some source data will be collected using self-assessment questionnaires completed by the study participants themselves. Completed participant questionnaires will be classed as source documents containing source data, therefore the completed participant questionnaires will be stored and retained as source documents. If the completed participant questionnaires are sent to the sponsor, the trial site will retain a copy to ensure that the principal investigator can provide access to the source documents to a monitor, auditor, or regulatory agency. Additional information can be found in ICH E6, section 6.4.9.

Data processing
Data provided to the MCTU will be checked for errors, inconsistencies and omissions. If missing or questionable data are identified, the MCTU will request that the data be clarified. All aspects of data collection and handling throughout the life cycle of the trial will be described in trial specific documents.

11.2 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected.

The University of Manchester will be responsible for archiving trial documents for 25 years from the date of the final publication in a way that will facilitate any audit and inspection. Documents should archived in accordance with guidance provided by funding bodies, professional guidance and the Sponsor Records Management Policy. Documents will be securely stored with access restricted to authorised personnel. Destruction of essential documents will require authorisation from the Sponsor. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the minimum/maximum period of time permitted.

12. STUDY MONITORING

A detailed risk assessment will be completed by the Sponsor and the MCTU as part of the study set-up process to ascertain the frequency and intensity of monitoring visits required (although additional monitoring may be conducted if necessary). The sponsor & MCTU's risk assessments will be used to ensure that all risks pertinent to the study are incorporated into the associated project delivery plan. The project delivery plan will be agreed by the sponsor. A copy of the MCTU & sponsor's risk assessment and the project delivery plan will be stored in the TMF. On-site monitoring will be performed by the MCTU based on this detailed risk assessment.

Central Monitoring

Essential documents will be requested periodically and reviewed remotely by the Clinical Study Monitor. Details of the documents required and the frequency of the requests will be detailed in the Project Delivery Plan stored at the MCTU.

Site Monitoring

On-site monitoring will be defined using a risk-based strategy and a thorough risk assessment will be completed by the MCTU as part of the site set-up process to ascertain the frequency and intensity of monitoring visits required (although additional monitoring may be conducted if necessary). This risk assessment and associated plans to monitor will be stored at the MCTU.

The purpose of these visits is:

- To verify that the rights and well-being of participants are protected.
- To verify accuracy, completion and validity of reported trial data from the source documents.
- To evaluate the conduct of the trial within the institution with regard to compliance with the currently approved protocol, GCP and with the applicable regulatory requirements

Audit and Inspection

Authorised representatives of Sponsor, regulatory authority, or an Ethics Committee may perform audits or inspections at the recruiting centres, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) Review & Reports

Before the start of the trial, an application will be submitted to Health Research Authority (HRA) for approval. Approval will also be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters

Substantial amendments will be submitted with the oversight of the study Sponsor. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study, confirmation of No Objection is received from MHRA and local R&D department approval.
In addition:

- All correspondence with the REC will be retained in the Trial Master File/Investigator Site File

- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- The Chief Investigator, DISKO trial manager and Sponsor will notify the REC of the end of the study. If the study is ended prematurely or temporarily halted, the Chief Investigator, MCTU and Sponsor will notify the REC, including the reasons for the premature termination within 15 days of the decision.
- The Chief Investigator, DISKO trial manager and Sponsor will submit a final report with the results, including any publications/abstracts to the REC within 12 months of the declaration of end of the trial.

13.2 Regulatory Compliance

Before the trial commences a Clinical Trial Authorisation (CTA) will be obtained from the Medicine and Healthcare products Regulatory Agency (MHRA). The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.
In addition:

- All correspondence with the MHRA will be retained in the Trial Master File/Investigator Site File
- An annual development safety update report (DSUR) will be submitted to the MHRA within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.
- The Chief Investigator, DISKO trial manager and Sponsor will notify the MHRA of the end of the study. If the study is ended prematurely or temporarily halted, the Chief Investigator will notify the MHRA within 15 days of the decision, including the reasons for the premature termination or halt.
- The Chief Investigator, DISKO trial manager and Sponsor will submit a final report with the results, including any publications/abstracts to the MHRA within 12 months of the declaration of end of the trial.

13.2.1 Local capability and capacity review

Before any site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee will apply for confirmation of local capability and capacity from the site's Research & Development (R&D) department.
It is the Principal Investigator's responsibility to update participants (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the participant's willingness to continue in the trial. The Principal Investigator must ensure this is documented in the patient's medical notes and the participant is re-consented where applicable. It is the responsibility of the PI to ensure that the trial has local R&D approval and the sponsor and DISKO trial manager will verify this, plus the presence of all other essential documentation (and potentially an initiation meeting), before giving the "green light" to open the trial to recruitment. The PI is also responsible for ensuring that any subsequent amendments gain the necessary approvals.

13.3 Amendments

Any changes in research activity will be reviewed and approved by the Chief Investigator. With the oversight of the sponsor, the subsequent amendment will be categorised as substantial or non-substantial. Any required changes to the CTA or the documents that supported the original application for the CTA and/or ethical approval will be submitted as an amendment to the appropriate ethical and regulatory authorities by the DISKO Trial Manager. Substantial amendments will not be implemented until the HRA grants approval of the study and confirmation of 'No Objection' is received from MHRA is obtained. The DISKO Trial Manager will maintain an amendment history tracker to ensure the most recent version of the protocol and supporting documents are used at all times.
For any amendment that will potentially affect a site's local capability and capacity, the DISKO Trial Manager will confirm with each participating site's R&D department that local capability and capacity is ongoing.
The DISKO Trial Manager will ensure that all relevant stakeholders are informed of substantive changes in appropriate time.

13.4 Peer Review

The clinical study protocol will be reviewed and approved by the funder, the Sponsor and the independent chair(s) of the TSC prior to the submission to the ethical and regulatory committees.

13.5 Public and Patient Involvement (PPI)

The trial lay summary and patient information sheet have been reviewed by the PPI group affiliated with ARUK Centre of Excellence in Epidemiology at the University of Manchester.

13.6 Protocol Compliance

The UK Regulations on Clinical Trials state that no deviation must be made from an approved trial protocol, unless it is an urgent safety measure taken to protect a participant from immediate harm. Deviations from the protocol may be taken by an investigator without prior approval from the Sponsor or regulatory bodies to eliminate an immediate hazard to a participant. The rationale must be submitted to the DISKO trial manager and the appropriate regulatory bodies as soon as possible after the deviation for urgent safety measures.
Accidental protocol deviations can happen at any time. The participating sites are encouraged to contact the DISKO trial manager if a potential protocol deviation has occurred (or if an event has occurred and it is unclear whether it should be classified as a deviation). The DISKO trial manager will advise the site what information and actions are required. All notified protocol deviations will be compared to the protocol deviation assessment document by DISKO trial manager to assess their severity (Minor/Major/Serious breach) and whether immediate action is required. The DISKO trial manager will maintain a protocol deviation log to aid the monitoring of frequently recurring protocol deviations. Any participating sites with evidence of continuous non-compliance will be escalated to the sponsor for immediate action and could potentially be classified as a serious breach.

13.7 Notification of Serious Breaches to GCP and/or the protocol

For Clinical Trials of Investigational Medicinal Products (CTIMPs), there is a legal requirement to report serious breaches of GCP or the trial protocol to the MHRA and appropriate REC within a defined timeframe. If a major deviation on a CTIMP meets the criteria for a serious breach, it is notified immediately to the Sponsor and reported to the HRA and the MHRA within 7 days of confirmation by the DISKO trial manager.
Complete investigations of breaches will be fully documented, filed in the TMF and a copy sent to the sponsor.

13.8 Data Protection and Patient Confidentiality

Participants will be assigned a unique Trial ID that will be used throughout their participation in the trial. Any personal data recorded will be regarded as confidential, and any information that would allow individual participants to be identified will not be released into the public domain.
Investigators and trial site staff must not provide any participant- identifying data (e.g. name, address, hospital, reference number) to the DISKO trial manager during the course of the trial, unless with prior approval by the Research Ethics Committee. Any participant identifying data received by DISKO trial manager will be redacted or destroyed, and the sender notified.

Each participating centre should keep a separate Trial ID and screening log of all participants consented and screen status. The investigator must maintain this screening log and all other trial documents (including participant's written consent forms) which are to be held at the participating centre, in strictest confidence. The investigator must ensure the participants' confidentiality is maintained.

The DISKO trial manager and MCTU will maintain the confidentiality of all participants and will not reproduce or disclose any information by which participants could be identified. The Investigator and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial.

Representatives of the MCTU and the regulatory authorities will be required to have access to participants' notes for quality assurance purposes but participants should be assured that their confidentiality will be respected at all

times. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.
All Investigators and trial site staff involved with the trial must comply with the requirements of the Data Protection Act with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The sponsor will be the data custodian.
Participant notes and trial files at site must be kept in a secure storage area with limited access. Computers used to collate the data will have access restrictions via user names, passwords, and the use of encrypted digital files and storage media. Published results will not contain any personal data that could allow identification of individual participants.

13.9 Financial and Other Competing Interests

None of the research team, investigator teams, and the sponsor has any financial or other conflict of interest. All members of the oversight committees will declare any potential conflicts of interest as part of their membership agreement. If any financial or other completing interests come to light during the course of the trial, a declaration of these conflicts of interest will be sorted in the agreement & finance section of the TMF.

14.0 Indemnity

14.1. As the research governance sponsor for the CTIMP, the University of Manchester will arrange insurance for research involving human participants that provides cover for legal liabilities arising from its actions or those of its staff or supervised students, participant to policy terms and conditions.

14.2 For research where all recruitment and other trial procedures are conducted on NHS premises by substantive or honorary NHS staff, the NHS indemnity scheme will apply.

14.3 As the proposed CTIMP is being led by a University of Manchester Employee holding a substantive contract, the University of Manchester will arrange insurance for research involving human participants that provides compensation for non-negligent harm to research participants occasioned in circumstances that are under the control of the University of Manchester, participant to policy terms and conditions.

15.0 Publication Policy

Results from this trial will be written up and submitted to peer reviewed journals.

In accordance with the Versus Arthritis requirements, on acceptance for publication, a copy of the final manuscript of all peer reviewed research papers must be deposited in an open access archive such as PubMed Central (PMC) or UK PubMed Central (UKPMC), to be made freely available within six months of publication.

All publications, presentations, correspondence and advertisements arising or related to the grant must acknowledge Versus Arthritis as the trial's funding source.

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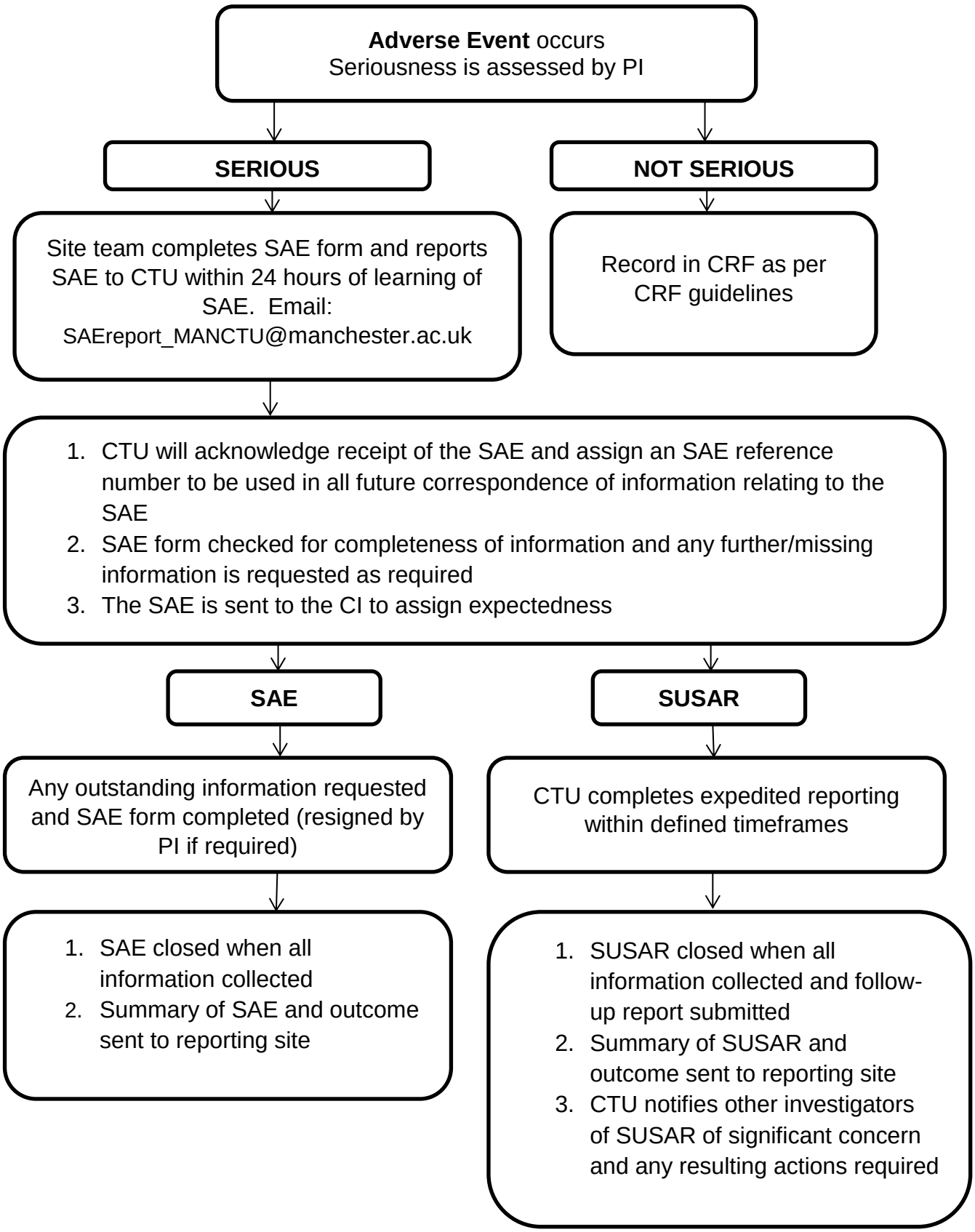
17.0 Appendices

Appendix A SAE Flow Chart



Further Trial Information

DISKO DMC Terms of Reference
Please see fully detailed DISKO DMC Terms of Reference in TMF

DISKO TSC Terms of Reference
Please see fully detailed DISKO TSC Terms of Reference in TMF

DISKO study risk assessment
Please see fully detailed DISKO risk assessment document in TMF

Protocol amendment history
See fully detailed 'Amendment Tracker' in the TMF