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Division of Musculoskeletal Disease

University of Leeds

Research Protocol

Version 2.0, 10th July 2012

Hydroxychloroquine **E**ffectiveness in **R**educing symptoms of hand **O**steoarthritis: a randomised, double-blind, placebo-controlled trial (HERO)

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Signatures Page

Version 2.0 10th July 2012
Written and approved by the following:

_____ _____

Prof Philip G Conaghan Date
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Abbreviations

ACR: American College of Rheumatology
ASR: annual safety report
AE: adverse event
AUSCAN: Australian Canadian osteoarthritis hand index
BMI: body mass index
BMQ: Brief medication questionnaire
CMC: carpometacarpal
CRF: case report form
CPPD: Calcium pyrophosphate deposition disease
EULAR: European League against Rheumatism
FBC: full blood count
FIHOA: functional index of hand osteoarthritis
GCP: good clinical practice
GI: gastro-intestinal
HADS: Hospital Anxiety and Depression Score
HAQ: health assessment questionnaire
IA: intra-articular
IL: interleukin
IM: intra-muscular
IV: intravenous
IRB/EC: Institutional review board/ethics committee
LFT: liver function test
MDGA: physician global assessment
MHRA: Medicines and Healthcare products Regulatory Agency
MREC: Main Research Ethics Committee
MRI: magnetic resonance imaging
MTX: methotrexate
NICE: National Institute for Health and Clinical Excellence
NSAID: non-steroidal anti-inflammatory drug
OA: osteoarthritis
OA QoL: osteoarthritis quality of life scale
PA: posteroanterior
PGA: patient global assessment
PIL: patient information leaflet
RA: rheumatoid arthritis
RCT: randomised controlled trial
REC: research ethics committee
RHOA: radiographic hand osteoarthritis
SAARD: Slow-acting anti-rheumatic drug
SAE: serious adverse event
SD: standard deviation

SmPC: summary of product characteristics
SUSAR: serious unexpected adverse event
TMF: trial master file
U&E: urea & electrolytes
VAS: visual analogue scale
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Protocol Summary:

Title:
Hydroxychloroquine **E**ffectiveness in **R**educing symptoms of hand **O**steoarthritis: a randomised, double-blind, placebo-controlled trial (HERO)

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Main Study

Rationale

Recent studies indicate that synovitis (inflammation in the joints) is prevalent in osteoarthritis (OA) and is associated with pain in knee and hand OA. Hydroxychloroquine is used in routine practice at treating synovitis in inflammatory arthritides such as rheumatoid arthritis, is widely used anecdotally as a treatment for OA and has been shown to be effective at reducing pain. Hydroxychloroquine has an excellent safety profile, with toxicity generally associated with sustained periods of use that due to the natural history of hand OA are unlikely to be an issue. We propose that treating patients with moderate to severe OA hand symptoms with hydroxychloroquine will be a practical and safe treatment to reduce synovitis and therefore reduce pain. This will potentially introduce a new treatment into the OA armamentarium which could be of particular use in the primary care setting.

Aim

The main aim of the study is to determine the effectiveness of hydroxychloroquine as a treatment for hand OA.

Study overview

A phase III multi-centre, double-blind, placebo-controlled, 12 month, 252 patient randomised trial of hydroxychloroquine for the treatment of hand OA.

Study duration

The study will last approximately 30 months, the treatment period is 12 months and an 18 month period has been allocated for recruitment.

Study design
Subjects will be randomised 1:1 to either the treatment group (hydroxychloroquine 200-400mg daily) or the placebo group. Subjects will take study medication for 12 months.

Concomitant medications
Subjects will be allowed to remain on any medications they are taking for their hand OA prior to enrolment (including NSAIDs, paracetamol, opioids, chondroitin, glucosamine). A single steroid injection to non-hand joints will be allowed after the primary outcome at 6 months. No oral corticosteroids will be allowed for the duration of the trial.

Primary outcome
Average overall hand pain severity over the past 2 weeks (0-10 numerical rating scale) at 6 months.

Ultrasound Substudy

Baseline ultrasound imaging will be performed for the dominant hand of all patients enrolled at the 7 centres participating in the substudy (Leeds, Kings College London, Nottingham, Keele, Newcastle and Oxford).

Aim
To determine whether baseline synovitis is a predictor of therapeutic response.

1.0 Introduction

1.1 Background

The importance of osteoarthritis

Osteoarthritis (OA) is the most prevalent form of arthritis and an increasingly common problem in our aging society. In the UK an estimated 8.5 million people are affected by OA, causing an enormous burden to health authorities, as well as considerable pain and disability to these individuals[1,2]. The OA Nation survey in 2003 (a survey of almost 2000 people with OA) reported that 81% of people with OA experience constant pain and 72% have important related conditions, such as hypertension or depression.

How prevalent is symptomatic hand OA?

Unlike studies of knee and hip OA, there is a notable paucity of published clinical research examining the clinical impact, epidemiology and therapy of hand OA, especially symptomatic hand OA. Although radiographic hand OA (RHOA) is recognised as being highly prevalent in the older population, with 60-70% of people over the age of 55 estimated to have RHOA[3], there is a common misconception that symptomatic hand OA is not a prevalent disease. This can be mainly attributed to patients with symptomatic hand OA failing to seek medical care. A recent population-based study found that despite the prevalence of symptomatic hand OA being greater than that of symptomatic knee OA[4], care-seeking for symptomatic hand OA was substantially less than for symptomatic knee OA[5]. It is estimated that approximately 8% of people aged 60 or over are affected by symptomatic hand OA[6], with this number raising to 26% of women and 13% of men aged 70 or over reporting symptomatic OA in a least one hand joint[7]. The most commonly involved joints in symptomatic hand OA are the distal interphalangeal and proximal interphalangeal joints, followed by the base of the thumb[7]. Notably, the presence of symptomatic hand OA is associated with significant difficulty with day to day tasks, with activities such as gripping, writing, carrying heaving items and picking up small objects considerably impeded[7]. In a study of female patients between 50 and 70 years of age with hand OA, 50% reported problems in wringing out washcloths and opening jars, whilst grip strength was found to be reduced to less than 60% of normal strength[8]. Moreover, the onset of hand OA significantly impacts on the deterioration of global physical functioning, irrespective of concurrent lower limb joint pain[9]. Symptomatic hand OA therefore represents a considerable economic, clinical and social burden. Moreover, since the majority of data guiding treatment for OA is derived from studies on knee, symptomatic hand OA is also an important target for future research.

What are the current treatment options for hand 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. 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, and a lack of evidence for their effectiveness. A study looking at OA of the 1st CMC joint (thumb base) demonstrated no benefit of intra-articular steroid over placebo[10], whilst accuracy of needle placement for intra-articular injections in hand OA has been suggested to be as low as 58%[11]. Moreover, injection of multiple small joints in the hands would be both painful and impractical for routine clinical use. 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 critical in enabling optimal management of patients with hand OA. In particular it would be desirable to find further treatment options which may be used in the primary care setting.

Why are OA joints painful?

Synovitis in OA – a potential drug target?

Although traditionally considered a disease of articular cartilage, recent arthroscopic and imaging studies have vastly improved our understanding of the other tissues involved in the pathophysiology of OA and clearly demonstrate OA as a disease of the whole joint, involving subchondral bone changes, osteophyte formation and synovial inflammation[12,13]. Moreover, there is compelling evidence that synovitis may occur even in early OA, with localized proliferative and inflammatory changes of the synovium present in up to 50% of OA patients[14-16]. This synovitis is thought to be critical to the pathological process, with the production of inflammatory mediators and pro-inflammatory cytokines within the OA joint playing a central role in joint deterioration[14,17-19]. Since cartilage is relatively aneural, this inflammation is also likely to be a potential source of pain in OA, and therefore may represent an important target in the search for improved analgesic therapies for OA. In imaging studies of the knee, imaging-detected synovitis was demonstrated in 98% of painful OA knees using sensitive contrast-enhanced MRI (Conaghan, manuscript in preparation) whilst in a separate study a significant correlation between MRI-detected synovitis and knee pain and between change in synovitis score and change in pain score ($p<0.001$, $r=0.21$) was identified[20,21]. Similarly, in studies of hand OA 82% of painful OA hand joints were shown to display imaging-detected synovitis using ultrasonography, with painful hand joints more likely to have synovitis than non-painful hand joints ($p<0.001$)[22]. 86% of patients with ACR hand OA and erosive changes on X-ray displayed ultrasound-detected synovial thickening and 82% an increased power Doppler signal[23]. Studies in painful hand OA have also found that patients with higher levels of ultrasound-detected synovitis at baseline have a better response to intramuscular steroids, which are thought to work by reducing synovitis[24]. Taken together, these studies suggest that treatments to target synovitis may be effective in reducing pain in OA.

Hydroxychloroquine as an anti-synovial agent

Hydroxychloroquine has been successfully used for many years in the treatment of inflammatory arthritides such as rheumatoid arthritis (RA) and systemic lupus erythematosus, and less commonly in the seronegative spondyloarthropathies[25,26]. Placebo-controlled trials in RA have demonstrated significant efficacy of hydroxychloroquine, both as a monotherapy and in

combination with other RA drugs, and due to its excellent safety profile it remains a popular therapy for RA. Although hydroxychloroquine's mechanism of action in RA is poorly understood, it is presumed to be associated with an anti-synovial activity.

Hydroxychloroquine is a 4-aminoquinoline anti-malarial drug that, due to its weak diprotic base properties, is able to pass through lipid cell membranes and preferentially accumulate in acidic cytoplasmic vesicles within macrophages and antigen-presenting cells. In vitro studies demonstrate that by increasing vesicle pH hydroxychloroquine is able to modulate the antigen-processing activity of these cells resulting in down-regulation of the immune response[27]. Moreover, hydroxychloroquine is able to block T-cell activation[28], reduce the release of various cytokines, including interleukin (IL)-1, IL-6, tumour necrosis factor and IL-1β-induced nitric oxide that have all been shown to be involved in inflammation and cartilage degeneration in OA[29-31] and to significantly reduce matrix metalloprotease levels in a rat CPPD model[32]. Inhibition of cytokine production and reduction of T-cell activity is the likely mechanism underlying hydroxychloroquine's efficacy in RA. The relevance of these inflammatory pathways to OA pathology, coupled to the evidence that synovitis is closely correlated with pain in the OA joint, suggests that hydroxychloroquine may also be an efficacious analgesic agent for the treatment of OA.

Evidence for the efficacy of hydroxychloroquine as a treatment for OA

As a result of its efficacy in RA, hydroxychloroquine has become widely used anecdotally for the treatment of OA. However there have been few studies to determine the efficacy of hydroxychloroquine in OA and these studies have contained only small patient numbers. In a small study of 8 patients with erosive hand OA that was unresponsive to NSAIDs, treatment with 200 mg hydroxychloroquine bi-daily resulted in a 75% reported reduction in pain and a 100% documented reduction in synovitis, with no adverse effects noted[33]. In a 15-patient randomised, placebo-controlled trial, improvement in clinical symptoms was noted at 12 months[34], whilst 7 patients with erosive hand OA reported improvement with 200-400 mg hydroxychloroquine[35]. The use of other slow-acting anti-rheumatic drugs (SAARDs) in hand OA has also been investigated, with two studies demonstrating the effects of methotrexate (MTX) in erosive or painful hand OA. In the first, 21 patients with painful hand OA treated with 10 mg MTX for 2 months reported significant reduction in pain and stiffness ($p<0.01$)[36] whilst a study of 17 patients treated with 10 mg MTX for 6 months demonstrated significant reduction in pain, swollen and tender joint counts ($p<0.01$), although 17% of patients did withdraw from the study due to GI side-effects[37]. Two further studies have investigated the effects of SAARDs in painful knee OA; a 58-patient placebo controlled study using 7.5 mg MTX[38] and a 29-patient placebo controlled study using 400 mg hydroxychloroquine[39]. Although no pain reduction was observed at 4 months in either study, the small dose used in the MTX study may have contributed to the negative outcome data whilst the increased biomechanical influence in the pathophysiology of knee OA compared to hand OA may also have had a role in the lack of response in these two studies. It is important to note that owing to differences in anatomy, function, risk factors and outcome measures, OA at different sites may show very different responses to the same treatment. It is therefore critical that OA interventions are examined in a site-specific fashion. A pilot study examining low dose MTX as a treatment for

patients with calcium pyrophosphate deposition disease (CPPD) who fail to respond to standard therapy, demonstrated a significant decrease in pain intensity ($p<0.0001$), swollen and tender joint counts ($p<0.0001$), frequency of attacks and inflammatory biomarker expression in all patients with a mean response time of 7.4 weeks[40]. Although the numbers in these studies are small, and the different recruitment criteria and outcome measures used in each study allow limited conclusions to be drawn regarding drug efficacy, they do suggest that slow-acting anti-rheumatic drugs such as hydroxychloroquine may provide effective pain relief for hand OA. Notably, these preliminary data strongly support the need for a well-designed, large patient number, randomised placebo-controlled trial to fully examine the potential use of hydroxychloroquine as a treatment for OA.

Summary

OA is the most common type of arthritis and causes significant joint pain and disability. Its incidence will increase with the ageing population and is already a major cause of health care expenditure. Current treatments for OA have major limitations and other analgesic treatments are needed. Synovitis is prevalent in OA and previous studies have shown it to be associated with pain in knee and hand OA. Hydroxychloroquine is used in routine practice at treating synovitis in inflammatory arthritides such as rheumatoid arthritis, is widely used anecdotally as a treatment for OA and has been shown to be effective at reducing pain. Hydroxychloroquine has an excellent safety profile, with toxicity generally associated with sustained periods of use that due to the natural history of hand OA are unlikely to be an issue.

We propose that treating patients with moderate to severe OA hand symptoms with hydroxychloroquine will be a practical and safe treatment to reduce synovitis and therefore reduce pain. This will potentially introduce a new treatment into the OA armamentarium which could be of particular use in the primary care setting.

2.0 Study objectives

2.1 Main aim of study

This is a multi-centre, randomised, double-blind, placebo controlled trial to compare the analgesic efficacy of hydroxychloroquine in painful hand OA.

2.2 Primary outcome

Average overall hand pain severity over the past 2 weeks (0-10 numerical rating scale) at 6 months.

2.3 Secondary outcome

1. Structural assessment at baseline and 12 months
   Bilateral hand X-ray

2. Self-reported questionnaires at baseline, 3, 6 and 12 months
   - AUSCAN (pain, stiffness and function)[41] – 5 point likert scale
   - 11-point Numerical Rating Scales (NRS) and VAS scales for
     - Average overall hand pain severity / pain in the most painful joint over the past 2 weeks / 2 days *
   - NRS scales for
     - Global disease activity / average thumb pain / average pain in other joints over the past 2days
     - Severity rating of participant nominated main functional problem over the past 2 days[42]
     - Satisfaction with hand function over the past 2 days
     - Hand pain/aching/stiffness over the last month (no days-all days

   Self-reported questionnaires at baseline, 6 and 12 months
   - Quality of life using SF12v2[43] and OAQoL
   - EuroQol EQ-5D[44,45]
   - HADS

   Self-report measures at 3, 6 and 12 months
   - Global* improvement in hand problem
   - Global* improvement in hand pain
   - Global* improvement in ability to use hands
     *A 6-point likert scale: completely better, much better, better, no change, worse, much worse

Other measures

Baseline measures

- Pain elsewhere (pain manikin)
- Duration of hand pain over the past 12 months (<7 days, 1-4 wks, >1 month, <3 months, >3 months)
- Onset of hand pain (last 12 months, 1-5 years, 5-10 years, 10 years or more)
- Ultrasound synovitis score

Clinical measures (baseline, 6 and 12 months)

- Grip strength (JAMAR)[46]
- Joint count

Adherence to the protocol

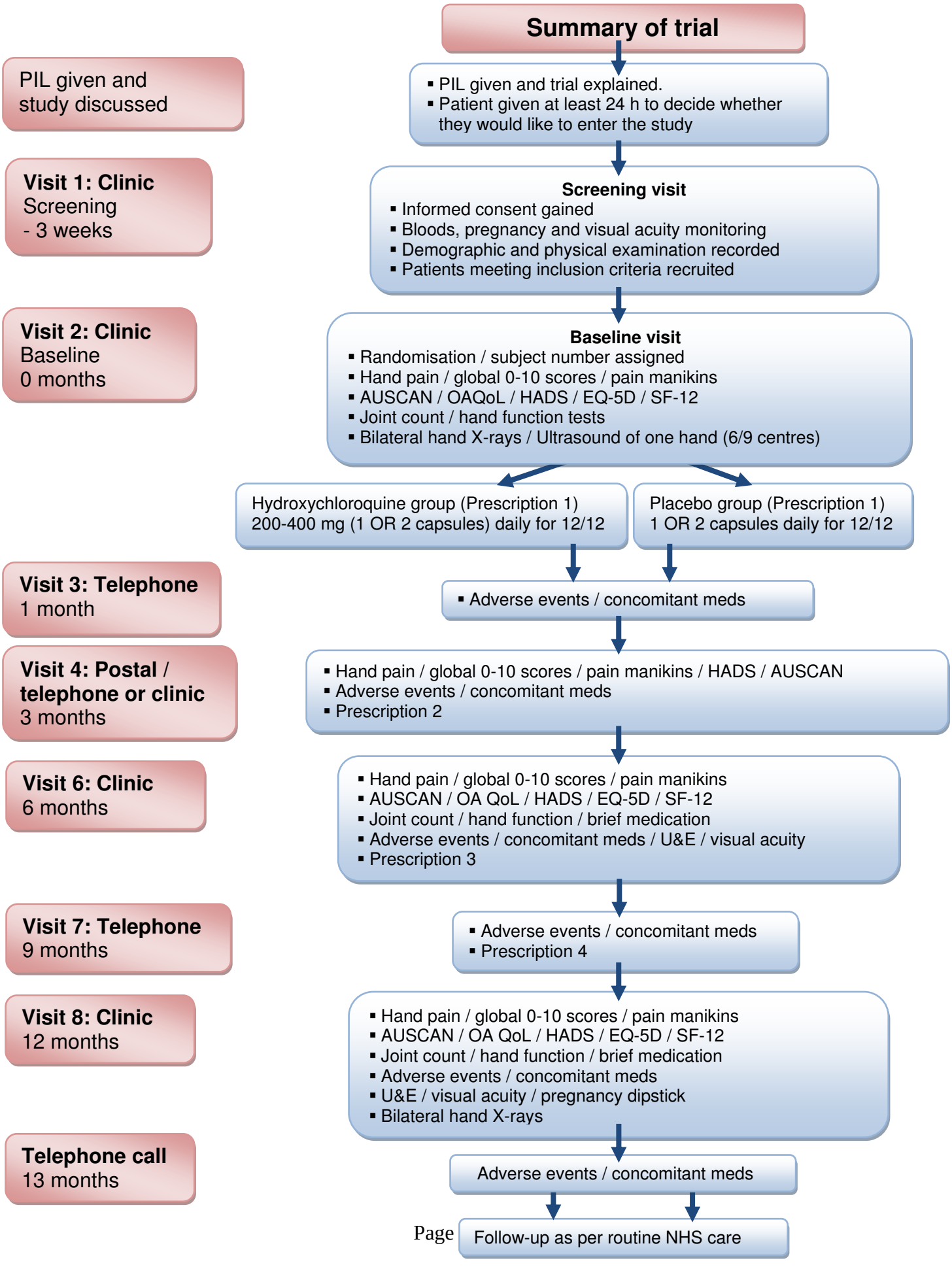
Self-report measure of adherence will be included at the 6 and 12 month follow-up visits. Adherence will be monitored using the Brief Medication Questionnaire[47]. In addition, pharmacy will keep a record of all returned medication to provide an estimate of compliance.

2.4 End point

The end points are defined as:

- Completion of 12 months of the study
- Withdrawal due to any reason

At the end of the study, follow-up of patients will be as per usual routine care, which may include the use of hydroxychloroquine. All patients who withdraw will be asked to have a withdrawal visit to allow clinical data to be collected.


Summary of trial
PIL given and study discussed
▪ PIL given and trial explained.
▪ Patient given at least 24 h to decide whether they would like to enter the study
Visit 1: Clinic
Screening
- 3 weeks
Screening visit
▪ Informed consent gained
▪ Bloods, pregnancy and visual acuity monitoring
▪ Demographic and physical examination recorded
▪ Patients meeting inclusion criteria recruited
Visit 2: Clinic
Baseline
0 months
Baseline visit
▪ Randomisation / subject number assigned
▪ Hand pain / global 0-10 scores / pain manikins
▪ AUSCAN / OAQoL / HADS / EQ-5D / SF-12
▪ Joint count / hand function tests
▪ Bilateral hand X-rays / Ultrasound of one hand (6/9 centres)
Hydroxychloroquine group (Prescription 1)
200-400 mg (1 OR 2 capsules) daily for 12/12
Placebo group (Prescription 1)
1 OR 2 capsules daily for 12/12
Visit 3: Telephone
1 month
▪ Adverse events / concomitant meds
Visit 4: Postal / telephone or clinic
3 months
▪ Hand pain / global 0-10 scores / pain manikins / HADS / AUSCAN
▪ Adverse events / concomitant meds
▪ Prescription 2
Visit 6: Clinic
6 months
▪ Hand pain / global 0-10 scores / pain manikins
▪ AUSCAN / OA QoL / HADS / EQ-5D / SF-12
▪ Joint count / hand function / brief medication
▪ Adverse events / concomitant meds / U&E / visual acuity
▪ Prescription 3
Visit 7: Telephone
9 months
▪ Adverse events / concomitant meds
▪ Prescription 4
Visit 8: Clinic
12 months
▪ Hand pain / global 0-10 scores / pain manikins
▪ AUSCAN / OA QoL / HADS / EQ-5D / SF-12
▪ Joint count / hand function / brief medication
▪ Adverse events / concomitant meds
▪ U&E / visual acuity / pregnancy dipstick
▪ Bilateral hand X-rays
Telephone call
13 months
Adverse events / concomitant meds
Follow-up as per routine NHS care

3.0 Study overview

3.1 Study Sites

The study will be managed by York CTU and the study sponsor, University of Leeds.

Recruitment will take place over 18 months and will be distributed over the following sites:

North and West Yorkshire – led by Professor Philip Conaghan

- Chapel Allerton Hospital, Leeds led by Professor Philip Conaghan
- Harrogate District Hospital, Harrogate led by Dr Mike Green
- York Teaching Hospitals NHS Trust, York led by Dr Mike Green

Keele - led by Professor Krysia Dziedzic

- Haywood Hospital (with University Hospital of North Staffordshire as a Patient Identification Centre (PIC)), led by Dr Peter Dawes, Dr Edward Roddy and Dr Jon Packham
- Derby Hospital, led by Dr Chris Deighton
- Cannock Hospital (with Stafford Hospital as a PIC) led by Dr Tom Sheeran

Manchester – led by Dr Terry O'Neill

- Greater Manchester Clinical Assessment & Treatment Service (CATS)
- Salford Royal Hospital

Oxford - led by Professor Nigel Arden

- Nuffield Orthopaedic Centre NHS Trust

Kings' Healthcare Partnership - led by Professor David Scott

- Kings' College Hospital
- Guys' and St Thomas' Hospital
- Lewisham Hospital

Imperial College London –led by Dr Fiona Watt and Dr Tonia Vincent,

- Charing Cross Hospital

Nottingham – led by Professor Mike Doherty

- City Hospital

Newcastle - led by Dr Fraser Birrell

- Northumbria and Newcastle NHS foundation trusts

Middlesbrough – led by Dr John Dickson

- Guisborough, Redcar and East Cleveland Primary Care Hospitals
- Belmont Surgery

- Sherburn Medical Centre
- James Cook University Hospital

All centres will also coordinate with their local PCRN and established links with GP surgeries for recruitment through primary care.

Recruitment will be split between the 9 sites, with Kings College London recruiting 20 patients, Imperial College London recruiting 24 patients and the remaining sites recruiting 30 patients each, equating to 1-2 patients per month. Given recruitment rates in recently completed and ongoing trials and the number of eligible patients seen at these centres, we are confident that recruitment can be comfortable achieved within the planned recruitment period. A media campaign will be run at all sites to aid recruitment.

Please see section 4.3 for further details on recruitment strategy.

Data to support the proposed recruitment rate:

- At Leeds a study investigating treatment of painful hand osteoarthritis using low dose oral prednisolone (POLO) with similar inclusion criteria and drug toxicity profile to those for HERO recruited an average at 7-8 per month with 5-6 meeting the inclusion criteria and agreeing to take part in the trial
- The recent SAMBA (Staffordshire Arthritis, Musculoskeletal and Back Assessment study) study led at Keele recruited 24 patients with nodal OA and 25 with generalised OA over a 12 month recruitment phase
- Manchester sees in the region of 150 patients with primarily non-inflammatory musculoskeletal conditions per week. Approximately 10 of these would have fulfilled the entry criteria over the last 6 months
- The specialist hand OA clinic at Imperial College London has around 70 patients with symptomatic hand OA under active follow-up, of which 40 are estimated to fulfil criteria for entry to the study
- Oxford sees approximately 25 patients that would have fulfilled the entry criteria every 6 months.
- According to patient records, the rheumatology clinics at King's College Hospital have treated 10 patients eligible for inclusion in HERO in the past 6 months
- Guisborough PCH saw more than 10 patients in the last 6 months that would have met the entry criteria for inclusion in HERO

3.2 Therapy during the trial period

This is a multi-centre, randomised, double-blind, placebo controlled trial of hydroxychloroquine in patients with painful OA of the hand. After informed consent has been obtained, each subject's potential eligibility will be assessed during a Screening Visit. Patients will be treated in the trial for a total of 12 months. Patients will be followed-up as per usual NHS care within the musculoskeletal or rheumatology clinics.

Patients will be randomised in a 1 to 1 ratio to one of two groups:

- Hydroxychloroquine used in combination with drugs licensed for use in pain management of OA; with choice of drugs and doses determined by clinicians for individual participants.

- Placebo group used in combination with drugs licensed for use in pain management of OA; with choice of drugs and doses determined by clinicians for individual participants.

Participants in either arm may not be prescribed hydroxychloroquine.

Patients who are eligible and agree to continue with the trial will return for a baseline visit within 21 days of screening.

3.2.1 Investigational medicinal product (hydroxychloroquine)
The Summary of Product Characteristics (SmPC) for hydroxychloroquine tablets provided by Sanofi-Aventis will be used. This will act as a reference for suspected side-effects and will give information on interactions and cautions of use for hydroxychloroquine. All patients enrolled will commence on either oral hydroxychloroquine 200-400 mg daily (1-2 capsules), or matching placebo (1-2 capsules) daily, as described in 3.2.2.

3.2.2 Frequency, duration and dose of hydroxychloroquine
Treatment will be for 12 months as follows:

- Participants with an ideal body weight of 30 - 45 kg will be prescribed one capsule with 200 mg hydroxychloroquine as a daily single dose (mean daily dose of 200 mg)
- Participants with an ideal body weight of 46 - 61 kg will be prescribed one capsule with 200 mg HCQ as a single dose on day 1 and two capsules with 200 mg HCQ as single dose on day 2 (mean daily dose of 300 mg)
- Participants with an ideal body weight of ≥ 62 kg will be prescribed two capsules with 200 mg HCQ as a single dose (mean daily dose of 400 mg)

Capsule/s should be taken as a single dose each day, with or just after food.

Ideal body weight (IBW) is calculated as follows:

Female IBW (Kg) = 45.5 + [(2.3 x height in cm above 152.4)/2.54]

Male IBW (Kg) = 50 + [(2.3 x height in cm above 152.4)/2.54]

Therefore, patient height will be measured and the correct dosage determined according to Table 1.

Table 1: Dosing schedule

		Male		Female		
Height		**Calculated Ideal body weight**	**Dosage**	**Height**	**Calculated ideal body weight**	**Dosage**
cm	**ft**					
< 148 cm	< 4'10''	< 46 kg	200 mg daily	<153 cm	<46 kg	200 mg daily
148-166 cm	4'10'' - 5'5''	46 - 62 kg	Alternating doses of 200 mg and 400 mg	153 - 170cm	46 - 62 kg	Alternating doses of 200 mg and 400 mg
≥166 cm	≥ 5'5''	≥ 62 kg	400 mg daily	≥ 170 cm	≥ 62 kg	400 mg daily

3.2.3 Dose modifications

If renal impairment is noted at 6/12 and felt to be clinically significant and requiring dose modification then dose will be reduced at the physician's discretion. If any unexplained visual changes are reported by the patient, or noted by the clinician at 6/12 and felt to be clinically significant study medication will be stopped.

3.2.4 Drug supply

Hydroxychloroquine 200 mg capsules will be supplied by Bilcare GCS (Europe) Ltd. Bilcare will purchase hydroxychloroquine sulphate 200 mg tablets (manufactured by Sanofi-Aventis) in commercial blister packs of one batch and in one consignment, will de-blister and then over-encapsulate 1 hydroxychloroquine 200 mg tablets into a size 0 capsule with added lactose and magnesium stearate to produce hydroxychloroquine 200 mg capsules. Bilcare will distribute randomly labelled bottles to each site in two dispatches, the first at the start of the study and the second at approximately 9 months into the study.

These capsules will be dispensed to patients according to the randomisation schedule provided by Bilcare as bottles containing 186 capsules. Patients will be provided with 3 months supply and will be asked to return bottles, including any untaken pills, when they return to collect their next prescription and at the end of the study. Patients will be advised that they may have excess capsules in their bottle due to the variations in dose according to ideal body weight. Pharmacy will maintain a record of returned pills to monitor compliance.

At the end of the study or on withdrawal from the study, patients will be asked to return any unused drugs to the pharmacy, who will keep a log of medications dispensed and returned. Unused or returned drugs will be checked by the trial monitoring team and destroyed as per usual Trust policy.

3.2.5 Placebo

Matching placebo capsules will be supplied by Bilcare. Bilcare will fill size 0 capsules with lactose and magnesium stearate blend to produce placebo capsules. These capsules will be dispensed to patients according to the randomisation schedule provided by Bilcare as bottles containing 186 capsules.

At the end of the study or on withdrawal from the study, patients will be asked to return any unused drugs to the pharmacy, who will keep a log of medications dispensed and returned. Unused or returned drugs will be checked by the trial monitoring team and destroyed as per usual Trust policy.

3.2.6 Withdrawal of treatment

(Please see also section 6.6) In the event that a patient is unable to tolerate the treatment they must be withdrawn from the treatment. The patient will continue to be followed up in the trial. A patient can choose to withdraw from the trial at any time and without giving a reason. This will in no way affect the care that they will receive and they will return to standard NHS care within the rheumatology/musculoskeletal clinics. All data will be used up to the point of withdrawal unless the patient withdraws consent for use of their data.

3.3 Clinical Evaluations

All patients will be asked to complete a series of questionnaires at baseline, 3, 6 and 12 months. A joint count of tender, swollen and painful joints of the hands will be performed at baseline, 6 and 12 months. A CRF will be produced for each visit design to prompt all study specific evaluations and to ensure a complete dataset is collected for each patient at each visit.

Imaging assessments:

Patients who agree to the study will have a hand radiograph of both hands at the baseline visit and again at 12 months. Plain radiographs of each hand will be taken (1 hand per film), as recommended by the OARSI taskforce for the design and conduct of clinical trials in patients with hand OA[48]. An x-ray protocol will be provided to each site. Briefly, a posteroanterior (PA) view will be taken, where the palmar aspect of the hand will be placed on the film with the fingers extended, separated slightly and spaced evenly and with the entire forearm placed flat against the X-ray table. A hand map will be provided to each trial site to aid reproducibility of positioning[48] and to ensure consistency of hand positioning between centres. An X-ray protocol will also be provided to each site to ensure reproducibility of image capturing between centres. In brief, the X-ray beam should be centered between the 2nd and 3rd MCPs with the central ray at 90° to the plane of the film. A consistent film-focal-distance of 115 cm should be maintained. Radiographs will be scored

using the Kallman scale, which showed the highest sensitivity to change and high intra-reader reproducibility and inter-reader reliability in a study comparing four scoring methods for the radiological assessment of hand OA[48]. The Kallman scale scores 24 joints (all but the metacarpophalangeal joints) for 6 radiological features according to a semi-numerical scale: osteophytes (0-3), joint space narrowing (0-3), subchondral bone sclerosis (0-1), subchondral bone cysts (0-1), lateral bony deviation (>15°; 0-1) and bone erosion (0-1), with total scores ranging from 0-208[49]. Radiographs will be scored by two readers and the mean score for each feature and the mean total score calculated for analysis.

Imaging Substudy Assessments:
Baseline ultrasound imaging will be performed for one hand of all patients enrolled at the centres participating in the substudy. 6 centres (Leeds, Kings College London, Nottingham, Keele, Newcastle and Oxford) will participate in the ultrasound imaging substudy. All patients recruited at these sites will have baseline ultrasound imaging of the most painful (or dominant if both equally painful) hand. An ultrasound atlas and manual will be produced during study set-up to provide a comprehensive guide for acquisition of ultrasound images. In addition the Leeds site will run a training day for all ultrasonographers that will be involved in the study. Imaging results will not affect randomisation of patients into the trial. The IP joint and the 4 DIP, 4 PIP and 4 MCP joints of the dominant hand will be imaged globally in multiple planes. Domains scored will be greyscale synovitis, power Doppler signal and osteophytosis. Greyscale synovitis and power Doppler will be scored using a semi-quantitive scoring system and osteophytosis will be scored as being absent or present, in line with DICHOA (Disease Characteristics in Hand OA). Scoring will occur during the acquisition process however stills will be taken of all joints for 10 subjects. These will be re-read by the same reader at the end of the study to provide intra-reader reliability for each centre. In addition a single reader at the lead centre (Leeds) will re-read the 10 sets of stills from each site to provide inter-site reliability. It is estimated that this protocol will take approximately 45 minutes per subject.

3.4 Rescue medications

Where possible, patients will be asked to avoid changes to their analgesic or anti-inflammatory medication for the duration of the trial. However, if a patient 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 (most days in the last 3 months) will be included as a covariate in the analysis.

Steroids
Patients will be asked not to use any form of steroids (oral, intravenous, intra-articular or intra-muscular) during the trial period. Any patient requiring oral corticosteroids for any problem will be recorded as a protocol violator. A single articular injection of corticosteroid will be allowed in non-hand joints after the first 6 month phase of the study and will be recorded in the CRF.

Chondroitin and glucosamine

Patients 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 will not be commenced during the duration of the trial.

Use of concomitant medication and any non-pharmacological interventions will be documented at each visit.

Drug usage will be documented in the CRF at each study visit (baseline, 6 and 12 months) and by follow-up telephone call at 1, 3 and 9 months. In addition patients will be provided with a hand OA medication diary at the start of the study (Appendix H). At baseline participants will fill in their current hand OA medications with the research nurse. During the study they will be asked to record any changes in their medication, for example a reduced or increased dose and will be asked to bring the diary with them to their study visits.

Good Clinical Practice (GCP) and Regulatory Compliance

This clinical trial, which involves the use of an investigational medicinal product has been designed and will be run in accordance with the Principles of GCP and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004 / 1031) and any subsequent amendments of the clinical trial regulations.

4.0 Study population

At least 252 patients will be enrolled (see Section 10.3 for power calculation). Informed consent will be taken by a clinician in the research team qualified by training and experience and delegated to do so.

4.1 Inclusion criteria

Patients to be included must meet the following criteria:

- Patient-reported inadequate response/toxicity to their existing medication (to include paracetamol, oral NSAID or opioid).
- Moderately severe symptoms (≥4/10 on a 0-10 visual analogue scale) at screening.
- Symptoms for more than half of days in the last 3 months.
- Fulfil the American College of Rheumatology criteria for OA (see Appendix 2).
- Radiograph of the hands in the past 5 years with changes consistent with OA.
- No change in the average weekly dose of analgesics (including NSAIDs) for at least 4 weeks.
- Has used chondroitin or glucosamine for at least 4 months with no change to the average weekly dose, is not using or is willing to stop using if recently started.
- Be able to adhere to the study visit schedule and other protocol requirements.
- Capable of giving informed consent and the consent must be obtained prior to any screening procedures.

4.2 Exclusion criteria

Patients will be excluded from this study for any of the following reasons:

- Presence of inflammatory arthritis (e.g. gout, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, seronegative spondylarthropathy, Lyme disease)
- Evidence of plaque psoriasis
- OA of the 1st CMC joint and no symptomatic OA in other hand joints.
- Oral, IM, IA, or IV steroids during the last 2 months.
- Any new hand OA treatment in the previous 2 months, including physiotherapy and provision of new hand splint.
- Planned hand surgery in the next 6 months.
- Sensitivity, anaphylaxis or allergy to hydroxychloroquine or any other 4-aminoquinoline compound.
- Unexplained visual impairment that is not corrected by glasses or presence of any eye problems.
- Pregnant or lactating
- Use of any investigational (unlicensed) drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer.
- Evidence of serious uncontrolled concomitant medical condition, including cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine, GI disease or epilepsy, which in the opinion of the investigator makes them unsuitable for the study

- Uncontrolled disease states, such as moderate/severe asthma or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids
- Melanoma or non-skin cancer in the past 3 years
- IA hyaluronans to the hand joints within the last 6/12
- Intolerance to lactose
- Significant haematological or biochemical abnormality
    - Haemoglobin ≤ 8.5 g/dL
    - WCC ≤ 3.5 x 10^9/L
    - Neutrophils ≤ 1.5 x 10^9/L
    - Platelets ≤ 100 x 10^9/L
    - ALT > 2 times ULN for the laboratory conducting the test.
    - Creatinine > 1.5 times ULN for the laboratory conducting the test

Potential participants who are deemed ineligible at screening will be allowed a second screening visit if ineligibility status is a temporary status which is likely to change (for example, recent steroid injection).

4.3 Recruitment strategy

Following information provision, patients will have at least 24 hours to consider participation and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial. This process will be clearly documented into the patient's medical notes.

Identification of potential participants

One or more of the methods below will be implemented at the study sites, in line with local practice:

1. Potential participants will be identified in arthritis clinics at the relevant hospitals/clinics as people suffering from osteoarthritis of the hand.
2. Potential participants who have consulted their GP with hand/finger pain (OA), and therefore might be eligible, will be identified by staff at GP surgeries, from the GP records or when they attend for a visit.
3. Potential participants will be identified through databases of previous research participants who have given their consent to be contacted regarding future research projects relating to hand OA.
4. A media campaign will be run at all sites to aid recruitment. A telephone number will be provided for potential participants to ring if they would like to request further information about the study.

Approaching potential participants

One or more of the methods below will be implemented at the study sites, in line with local practice:

1. Potential participants identified in rheumatology clinics as diagnosed with hand OA will be approached by the assigned study nurse or doctor. The study will be briefly outlined, and if interested, a patient information sheet (PIS) and consent form will be given to be considered for at least 24 hours. Potential participants will be encouraged to discuss the study with whoever they wish, including their GP, family and friends. The potential participant will be invited back to a further visit if they wish to ask any further questions or discuss joining the study.
2. Participants identified as having experienced hand/finger pain/OA through their GP records will be sent a letter from their GP, together with a letter from the PI outlining the study and will be asked to return a reply slip if they think they might be eligible to participate and would like to receive more information about the study. When they reply they will also be asked to answer 4 questions regarding their hand pain. Individuals who respond positively to this initial contact will again be sent the patient information sheet and a further reply slip so that they can confirm, having read the PIS, whether they wish to be seen for the study. Positive responders will again be contacted by the Research Team at the relevant trial site to arrange an appointment.
3. Participants recruited from previous research projects will be sent a letter of invitation from the PI. Individuals will be asked to return a reply slip indicating whether they are still experiencing pain in their finger joints and wish to be considered for participation in the study. Positive responders will be sent the patient information sheet and a further reply slip so that they can confirm whether they wish to be seen for the study. Individuals who confirm that they wish to be considered for participation in the study will then be contacted by the research team to arrange an appointment.
4. Participants telephoning in response to advertising will be asked a series of questions to define eligibility. If participants are potentially eligible for the study they will be sent the patient information sheet and a further reply slip so that they can confirm whether they wish to be seen for the study. Individuals who confirm that they wish to be considered for participation in the study will then be contacted by the research team to arrange an appointment.

4.4 Consent

The right of the patient to refuse consent without giving reasons will be respected. Further, the patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment. The written consent will be taken by an appropriately delegated clinician who is, by education and experience qualified to do so, who has signed/dated the staff authorisation/delegation log. The process of obtaining written consent will be clearly documented in the patient's medical notes.

The original signed consent document will be retained in the Investigator Site File (ISF). Other copies of the consent form are required:

- One copy of the informed consent document will be faxed to YTU and filed in the TMF
- One copy of the informed consent document will be kept in the patient's clinical notes where applicable. If a patient does not have clinical notes at the trial site the informed consent document will be filed in a separate folder.
- One copy will be given to the patient.

Consent forms to be faxed to:

01904 321 387

4.5 Randomisation and subject identification

Each subject will be assigned a unique subject number by sequential coding. A number must never be reassigned or reused for any reason. The investigator must maintain a subject master log linking the subject number to the subject's name. A screening log will also be maintained. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality. Information that could identify a subject will be masked on material received by the sponsor

Bilcare will prepare a randomisation schedule for each site using the random permuted block method and random number tables. Treatment allocation will be concealed from the investigator, patients and the blinded assessor for the full duration of the trial. Study drugs will be supplied to the hospital pharmacy unit in the order of the randomisation schedule prepared by Bilcare.

When a patient consents to participate in the trial, a prescription for the study drug will be given to the patient. The pharmacy at the trial site will issue bottles of the study drug in the order that it was provided to them. The trial site pharmacy will fax their updated Study Drug Log to the YTU every time a bottle of the study drug is issued to a participant.

Study drug log to be faxed to:

01904 321 387

4.6 Blinding/unblinding procedures

All records will be kept confidential and data sets for each subject will be identified by the patient's subject number and initials only. The master list detailing which patients are taking hydroxychloroquine or placebo will be held by Leeds General Infirmary Trials Pharmacy, who will provide an in-hours emergency unblinding service, Monday-Friday 9am-5pm. Site-specific codebreak envelopes will also be held at each site pharmacy. Due to the low toxicity profile of hydroxychloroquine, likely need for unblinding has been classified as low risk.

In the unlikely event that unblinding is deemed necessary for medical reasons, this can be done in the first instance by contacting the local site pharmacy (details provided in the ISF). As a back-up, the Leeds General Infirmary Trials Pharmacy may be contacted for unblinding. The unblinded patient must then be withdrawn from the trial. This will be documented in the CRF and patient's 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 Committee

Emergency Unblinding: Contact local pharmacy.

If unavailable contact Leeds General Infirmary Trials Pharmacy:

0113 392 2459

5.0 Concomitant Medications

5.1 Interaction with other medications

Concomitant use of the following should be avoided:

- Anti-arrythmics (amiodarone)
- Anti-bacterials (moxifloxicam)
- Antiepileptics
- Antimalarials
- Cardiac glycosides (digoxin)
- Ciclosporin
- Parasympathiomimetics (neostigmine, pyridostigmine)
- Cimetidine

As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

Hydroxychloroquine absorption is reduced by antacids and kaolin:

- Patients should be advised to leave a gap of at least 4 hours between use of antacids and taking study medication.

5.2 Use of other medications for hand OA

Where possible, patients will be asked to avoid changes to their analgesic or anti-inflammatory medication for the duration of the trial. However, if a patient 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 (most days in the last 3 months) will be included as a covariate in the analysis.

<u>Steroids</u>

Patients will be asked not to use any form of steroids (oral, intravenous, intra-articular or intra-muscular) during the trial period. Any patient requiring oral corticosteroids for any problem will be recorded as a protocol violator. A single articular injection of corticosteroid will be allowed in non-hand joints after the first 6 month phase of the study and will be recorded in the CRF.

<u>Chondroitin and glucosamine</u>

Patients 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 will not be commenced during the duration of the trial.

Non-pharmacological therapy

Patients will be asked not to start any new non-pharmacological therapies for their hand OA, including physiotherapy and hand splinting.

Use of concomitant medication and any non-pharmacological interventions will be documented at each visit.

Drug usage will be documented in the CRF at each study visit (baseline, 6 and 12 months) and by follow-up telephone call at 1, 3 and 9 months. In addition patients will be provided with a hand OA medication diary at the start of the study (Appendix H). At baseline participants will fill in their current hand OA medications with the research nurse. During the study they will be asked to record any changes in their medication, for example a reduced or increased dose and will be asked to bring the diary with them to their study visits.

6.0 Study visit schedule

This clinical trial, which involves the use of an investigational medicinal product has been designed and 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.

6.1 Recruitment

Recruitment will take place according to one of the following, as appropriate:

1. Patients consulting their rheumatologist, musculoskeletal physician, general practitioner or physiotherapist with hand OA will be invited to consent to further contact by the research team. The patient information leaflet will be provided and the study will be discussed. Any questions from the patient will be answered. The patient will then have at least 24 hours to discuss the information with whomever they choose, and will then be invited back for a screening visit if they wish to join the study.

2. Potential participants from previous research studies, who have given their consent to be contacted regarding future research projects, will be identified by the research team. Only participants will be approached. Potential participants will be sent a letter of invitation from the PI. Individuals will be asked to return a reply slip indicating whether they are still experiencing pain in their finger joints and wish to be considered for participation in the study. Positive responders will be sent the patient information sheet and a further reply slip so that they can confirm whether they wish to be seen for the study. Individuals who confirm that they wish to be considered for participation in the study will then be contacted by the research team to arrange an appointment.

3. People who have consulted their GPs with hand/finger pain (OA), and therefore might be eligible, will be identified by staff at GP surgeries, from the GPs records or when they attend for a visit. Participants identified as having experienced hand/finger pain/OA through their GP records will be sent a letter from their GP, together with a letter from the PI outlining the study and will be asked to return a reply slip if they think they might be eligible to participate and would like to receive more information about the study. When they reply they will also be asked to answer 4 questions regarding their hand pain. Individuals who respond positively to this initial contact will again be sent the patient information sheet and a further reply slip so that they can confirm, having read the PIS, whether they wish to be seen for the study. Positive responders will again be contacted by the Research Team at the relevant trial site to arrange an appointment.

4. Participants telephoning in response to advertising will be asked a series of questions to define eligibility. If participants are potentially eligible for the study they will be sent the patient information sheet and a further reply slip so that they can confirm whether they wish to be seen for the study. Individuals who confirm that they wish to be considered for

participation in the study will then be contacted by the research team to arrange an appointment.

6.2 Screening visit (visit 1)

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

- Consent. The patient will have received information, including the Patient Information leaflet, at least 24 hours before the screening visit. Their knowledge of the nature and objectives of the study will be verified and his/her informed consent will be obtained. The screening period will provide further opportunity for a patient to re-consider and consent will be confirmed at the baseline visit.
- A subject number will be assigned (see section 4.5)
- Inclusion/exclusion criteria available at this time will be recorded.
- Demographic variables describing the patient (age, sex and ethnic group).
- Medical and surgical history, family history and alcohol and smoking history will be taken.
- Concomitant medications.
- Physical examination, including measurement of body weight and height
- Patients will be asked about visual impairment (not corrected by glasses) and near visual acuity of each eye (with glasses where appropriate) will be recorded using a standard reading chart*
- Vital signs (blood pressure after a 5-minute rest, pulse rate and body temperature).
- Blood monitoring - full blood count (FBC), urea and electrolytes (U&E) and liver function test (LFT)
- Urinary dipstick pregnancy test in female patients with child-bearing potential (see Appendix 1)
- Patient VAS assessment
- Complete participant log and fax to YTU
- Photocopy completed CRFs and send originals by post to YTU

Participant drug log to be faxed to:
01904 321 387

Completed CRFs to be posted to:
HERO Trials Team, York Trials Unit, Lower Ground Floor, ARRC Building, University of York, Heslington, YO10 5DD

* According to BSR guidelines

Note: Whenever possible, rheumatological evaluations should be performed by the same investigator during all visits throughout the time course of the study for each patient to reduce potential investigator bias.

6.3 Baseline visit (visit 2)

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

- Check consent has been obtained, and fax a copy of the consent form to the YTU.
- Inclusion/exclusion criteria reviewed and recorded
- Randomisation to treatment arm (see section 4.5)
- Concomitant medication
- Joint examination for swollen, tender and painful joints
- Patient VAS assessments and patient reported questionnaires: OAQoL, AUSCAN, EQ-5D, SF12, HADS,
- Hand function test
- Complete record of hand OA medication in hand OA medication diary with patient – patient to take away copy to record changes during study
- Imaging assessments (to be performed prior to first administration of study treatments):
    - X-ray of both hands - according to the provided HERO x-ray protocol
    - Ultrasound substudy centres only: High resolution ultrasound of one hand (dominant hand or alternative hand if greater evidence of inflammation clinically). The dominant hand will be scanned unless the alternative hand has greater clinical evidence of synovitis at baseline. Ultrasound to be performed according to the provided HERO ultrasound protocol
- Dispense the next set of study drugs according to randomisation sequence provided by Bilcare (see section 3.2).
- Fax study drug log to YTU (see section 4.5)
- Complete participant log and fax to YTU
- Photocopy completed CRFs and send originals by post to YTU

6.4 Follow-up visits

Patients will be followed for 12 months as per Study Visit Schedule (Table 1). Study visits for clinical assessment will occur at months 0, 6 and 12, ± 21 days. Questionnaires will be completed at months 0, 3, 6 and 12. Questionnaire data will be collected by post at 3 months. Patients will receive a follow-up telephone call for safety at 1, 3 and 9 months. U&E screening, for all subjects over 60 or at risk of renal impairment, and visual acuity monitoring will be repeated at 6 and 12 months to ensure continued safety of therapy. Dipstick pregnancy testing will be repeated for all female participants of child-bearing potential at 12 months. All patients will have a second X-ray of both hands at the 12 month visit.

Visit 3 – 1 month. Telephone follow-up

The following will be performed during the telephone follow-up (and recorded in the case report form):

- Concomitant medication
- Adverse events
- Photocopy completed CRFs and send originals by post to YTU
- Complete participant log and fax to YTU

Visit 4 – 3 months. Postal questionnaire & Telephone follow-up
The following will be performed during the telephone follow-up (and recorded in the case report form):

- Concomitant medication
- Adverse events

The following will be recorded on the postal questionnaire:

- Patient VAS assessments and patient reported questionnaires: OAQoL, AUSCAN, HADS
- Concomitant medication
- Brief medication questionnaire

- Photocopy completed CRFs and send originals by post to YTU

- Complete participant log and fax to YTU

Study drug Prescription 2 should be dispensed at 3 months.

Visit 4 may be completed in clinic if preferred by individual sites.

Visit 6 – 6 months. Clinic visit
The following will be performed at this visit (and recorded in the case report form):

- Patient VAS assessments and patient reported questionnaires: OAQoL, AUSCAN, HADS
- Concomitant medication
- Brief medication questionnaire
- Review hand OA medication diary
- Joint examination for swollen, tender and painful joints
- Hand function test
- Blood monitoring – U&E
- Visual acuity
- Vitals
- Photocopy completed CRFs and send originals by post to YTU.
- Complete participant log and fax to YTU

Study drug Prescription 3 should be dispensed at 6 months

Visit 7 – 9 months. Telephone follow-up
The following will be performed during the telephone follow-up (and recorded in the case report form):

- Concomitant medication
- Adverse events
- Photocopy completed CRFs and send originals by post to YTU
- Complete participant log and fax to YTU

Study drug Prescription 4 should be dispensed at 9 months.

Visit 8 – 12 months. Clinic visit
The following will be performed at this visit (and recorded in the case report form):

- Patient VAS assessments and patient reported questionnaires: OAQoL, AUSCAN, HADS
- Concomitant medication
- Brief medication questionnaire
- Review hand OA medication diary
- Joint examination for swollen, tender and painful joints
- Hand function test
- Blood monitoring – U&E
- Urine dipstick pregnancy test for female patients with child-bearing potential (see Appendix 1)
- Visual acuity
- Vitals
- Imaging assessments
    - X-ray of both hands - according to the provided HERO x-ray protocol
- Photocopy completed CRFs and send originals by post to YTU
- Complete participant log and fax to YTU

6.5 Unscheduled visits

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

6.6 Subject discontinuation and withdrawal of patients

All patients 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 patient consents. Patients who withdraw will be asked to complete the questionnaires as per the next planned study visit. At a patient's request, their data collected up to the point of withdrawal can also be withdrawn from the trial and will not be used in the final analysis.

Subjects must be withdrawn from the study treatment if any of the following occur:

- Pregnancy
- Withdrawal of consent
- Principle investigator decision

- Sponsor decision

In order to perform an ITT analysis, all patients who discontinue their randomised medication will be asked to still complete their follow-up visits as outlined in the study schedule.
Patients who withdraw from the trial will not be replaced - this study has been powered to allow for a ~20% drop-out.

6.7 The end of the trial

The end of the trial is defined as the last visit (month 12) of the last patient (number 252).

Table 1: Study Visit Schedule

STUDY VISIT	**1** Screening	**2** Baseline	**3** Telephone	**4** Postal / telephone	**6** Clinic	**7** Telephone	**8** Clinic
DATE	**-3 weeks**	**0**	**1 month**	**3 months**	**6 months**	**9 months**	**12 months**
Informed Consent (Patient information will be provided at least 24 hours prior to screening)	X	X					
Inclusion / Exclusion	X	X					
Demographics / Medical History	X						
Vitals	X				X		X
U&E blood screening	X				X		X
FBC & LFT blood screening / research bloods	X						
Pregnancy test	X						X
Visual acuity checked	X				X		X
Randomisation		X					

STUDY VISIT	**1** Screening	**2** Baseline	**3** Telephone	**4** Postal / telephone	**6** Clinic	**7** Telephone	**8** Clinic
DATE	**-3 weeks**	**0**	**1 month**	**3 months**	**6 months**	**9 months**	**12 months**
Joint count		X			X		X
Pinch Strength / Grip Strength / Grip Ability Test		X			X		X
Hand pain 0-10 numerical rating		X		X	X		X
Hand / whole body pain manikin		X		X	X		X
Global disease activity		X		X	X		X
AUSCAN / HADS		X		X	X		X
OAQoL / SF-12 / EQ-5D		X			X		X
Resource use		X			X		X
Hand OA medication change diary		X		X	X		X
Brief Medication Questionnaire				X	X		X
Concomitant meds monitoring		X	X	X	X	X	X

STUDY VISIT	**1** Screening	**2** Baseline	**3** Telephone	**4** Postal / telephone	**6** Clinic	**7** Telephone	**8** Clinic
DATE	**-3 weeks**	**0**	**1 month**	**3 months**	**6 months**	**9 months**	**12 months**
Adverse Event monitoring			X	X	X	X	X
Bilateral hand X-ray		X					X
Ultrasound (substudy centres only)		X					

7.0 Listing of Study Procedures

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

7.1 Informed Consent

Written informed consent will be obtained from each patient by a clinician (either the principal investigator or designee). Informed consent will be prepared according to the institutional requirements for informed consents. Patients who are candidates for the study must sign an informed consent prior to any study-specific procedures being performed, including any study specific screening procedures (see section 6.2) in accordance with the principles of Good Clinical Practice.

7.2 Physical Examination and Vital Signs

Vital signs including height and weight will be performed at screening, 6 and 12 months. Physical examination will also include examining both hands to document if any finger joints are painful, swollen or tender and to identify Heberdon's and Bouchard's nodes. This will be recorded on a homunculus to allow change in individual joints to be monitored during the study. Examination of the hands to document painful, swollen or tender joints will again be performed at 12 months. In addition patients will be asked about visual impairment (not corrected by glasses) at each visit and near visual acuity of each eye (with glasses where appropriate) will be recorded using a standard reading chart at baseline and 12 months[†]. This information will be documented in the study CRF and in the patient notes. Grip strength (JAMAR dynometer)[46] performed at each visit to gain a measure of hand ability. Equipment for functional tests will be purchased and provided to each site for use in the study. All equipment will be calibrated annually at each site and calibration documentation filed in the TMF.

7.3 Blood and urine analysis

7.3.1 Bloods and urine analysis for safety monitoring

Approximately 10ml of blood will be drawn for blood tests according to routine Yorkshire regional guidelines for hydroxychloroquine (and where applicable, at the physician's discretion) for monitoring of treatment safety. Safety of therapy will be assessed according to regional monitoring guidelines and will be determined by treatment strategy. Additional tests will need to be undertaken as guided by the physician according to the Yorkshire regional guidelines (see Appendix 5).

- Full blood count (FBC), liver function tests (LFT) and urea, electrolytes and creatinine (U&E) tests to be performed at screening and U&E to be repeated at 6 and 12 months for all subjects over 60 or at risk of renal impairment as per the regional guidelines for hydroxychloroquine use.
- Urine dipstick pregnancy test for female patients with child-bearing potential (see Appendix 1)

[†] According to BSR guidelines

7.3.2 Biological sub-study tests (Leeds only)

If a patient agrees to take part in the sub-study then additional samples will be taken at baseline:

- 18 ml serum (2 x 9 ml red-topped clotted tubes)
- 4 ml plasma for microparticles (1 x sodium citrate – blue topped)
- 4 ml EDTA (1 x 5ml purple topped tubes for DNA)
- 18 ml for analysis of immune changes in T cell subsets and PBMC storage for protein/RNA extraction (3 x 9 ml lithium heparin green top)
- 5 ml for RNA/gene expression profiling (2 x 2.5 ml clear top)

7.4 Medical history/demographic data

Medical history will be performed at baseline. This information will be documented in the study CRF and in the patient notes.

7.5 Imaging Assessments

Patients who agree to the study will have a hand radiograph of both hands at the baseline visit and again at 12 months. Plain radiographs of each hand will be taken (1 hand per film), as recommended by the OARSI taskforce for the design and conduct of clinical trials in patients with hand OA[50]. An x-ray protocol will be provided to each site. Briefly, a posteroanterior (PA) view will be taken, where the palmar aspect of the hand will be placed on the film with the fingers extended, separated slightly and spaced evenly and with the entire forearm placed flat against the X-ray table. A hand map will be provided to each trial site to aid reproducibility of positioning[50] and to ensure consistency of hand positioning between centres. An X-ray protocol will also be provided to each site to ensure reproducibility of image capturing between centres. In brief, the X-ray beam should be centered between the 2nd and 3rd MCPs with the central ray at 90° to the plane of the film. A consistent film-focal-distance of 100 cm should be maintained.

Baseline ultrasound imaging will be performed for one hand of all patients enrolled at the centres participating in the substudy. 6 centres (Leeds, Kings College London, Nottingham, Keele, Newcastle and Oxford) will participate in the ultrasound imaging substudy. All patients recruited at these sites will have baseline ultrasound imaging of the most painful (or dominant if both equally painful) hand. The IP joint and the 4 DIP, 4 PIP and 4 MCP joints of the dominant hand will be imaged globally in multiple planes. Domains scored will be greyscale synovitis, power Doppler signal and osteophytosis.

7.6 Clinical parameters

Response assessments will be performed at 0, 3, 6 and 12 months, with the exception of OAQoL, SF-12, and EQ-5D, which will be performed at 0, 6 and 12 months.

7.6.1 0-10 numerical rating scales - Patients will be asked to assess their average hand pain on a 0-10 11-point numerical rating scale. The scale ranges from “No pain” to “pain as bad as it could be”. The patient global assessment of the last 48 hours will also be recorded on a 0-10 11-point

numerical rating scale. The scale for the patients' assessment of overall activity of their arthritis ranges from "not active" to "extremely active". Patients will also be asked to assess pain in other joints on a 0-10 numerical rating scale and to indicate where they have pain by marking on a manikin. Numerical scales have been found to be reliable and demonstrate good face and criterion validity[51].

7.6.2 Hospital Anxiety and Depression Score (HADS) - patients will be asked to complete a hospital anxiety and depression score to assess depression and anxiety. The Hospital Anxiety and Depression Scale (HADS)[52] 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.

7.6.3 Osteoarthritis Quality of Life questionnaire (OAQoL) - a questionnaire to judge the effect of OA symptoms on quality of life.

7.6.4 Australian Canadian Osteoarthritis hand index (AUSCAN) questionnaire - the patient-centered self-administered Australian/Canadian (AUSCAN) Index is a reliable, responsive, well-validated and feasible tri-dimensional (pain, stiffness, and function) index developed specifically for hand OA studies and comprising five items for measuring hand pain, one for measuring hand stiffness and nine measuring physical function. The test-retest reliability (ICC = 0.70-0.90), internal consistency (Cronbach's alpha = 0.90-0.98), face, content and criterion validity (vs FIHOA, HAQ, Doyle Index, PGA, MDGA, grip strength, pinch grip and duration of morning stiffness) and responsiveness of the AUSCAN Index have been reported[41,53].

7.6.5 EQ-5D - 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[54]. EQ-5D 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[55].

7.6.6 SF-12 - 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).

7.6.7 Brief Medication Questionnaire – a self-report measure composed of 9 questions to monitor adherence which includes a 5-item Regimen Screen that asks patients how they took

each medication in the past week, a 2-item Belief Screen that asks about drug effects and bothersome features, and a 2-item Recall Screen about potential difficulties remembering. Whilst not infallible self-report is likely to identify at least 50% of non-adherent individuals[56,57].

7.6.8 Grip strength

Power grip (JAMAR dynomometer) measured in lbs according to the protocol by Mathiowetz et al[46].

7.7 Clinical Safety Evaluation/Adverse Events

During each visit the patient will be monitored and questioned by a member of the clinical staff for the occurrence of adverse events. At each of the study visits, patients will be questioned about the occurrence of new adverse events and changes in concomitant medications since the last visit, or the outcome of any adverse events reported at previous visits.

Only adverse events that occur after the signing of the consent form should be recorded on the adverse event page in the CRF. Recording should be done in a concise manner using standard, acceptable medical terms. The adverse events recorded should not be a procedure or a clinical measurement (i.e. a laboratory value or vital sign) but should reflect the diagnosis based on the abnormal measurement. However, if **a clinically significant** abnormal laboratory value occurs, this abnormality (but not the value itself) should be entered on the adverse event page. Any pre-existing conditions will be recorded on the medical history. Pre-existing conditions which worsen in severity or frequency during the study will be recorded on the Adverse Event CRF page. Refer to 8.7 for SAE reporting.

8.0 Pharmacovigilance

8.1 Defining adverse events (AEs)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with this treatment and can include:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests

In addition the following criteria may be used in order to collect protocol-defined *reportable adverse events* which do not meet the criteria for serious (below):

- requires medical or surgical intervention to prevent permanent impairment of function or permanent damage to body structure.

8.2 Defining Serious Adverse Events (SAEs)

A Serious Adverse Event is defined in general as an untoward (unfavourable) event, which:

- Is fatal. Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring within 30 days of the last administration of the study agent must be treated as an SAE and reported as such. All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAE and reported as such.
- Is life-threatening (see below)
- Requires or prolongs hospitalisation (see below)
- Results in persistent or significant disability or incapacity (see below)
- Results in a congenital anomaly or a birth defect
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above
- Any other significant clinical event, not falling into any of the criteria above, but which in the opinion of the investigator requires reporting.

Medical judgement should be exercised in deciding whether an SAE is serious in other situations. Important SAE/SARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one or the other outcomes listed in the definition above, should also be considered 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 study, the following are <u>not</u> considered a SAE, but will be recorded on the CRF:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.

- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the centre (e.g. stent removal after surgery).
- 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.

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the test article but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, i.e. related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

8.3 Defining Suspected Unexpected Serious Adverse Reactions (SUSARs)

Where an SAE is deemed to have been related to an IMP used within the trial the event is termed as a Serious Adverse Reaction (SAR).

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a Serious Adverse Reaction which also demonstrates the following characteristic of being unexpected:

Unexpected – An adverse event, the nature, seriousness, severity OR outcome of which is NOT consistent with the applicable product information (i.e. Summary of Product Characteristics [SmPC]).

The term 'severe' is used to describe the intensity (severity) of a specific event. This is not the same as 'serious' which is based on the patient/event outcome or action criteria.

All investigators should refer to the current trial supplied SmPC and manufacturer's SmPC for the brand being used for more specific details and potential drug interactions. These should not be reported as SUSARs, unless the nature, seriousness, severity or outcome is not consistent with the relevant product information.

8.4 Operational Definition & Reporting Adverse Events (AES)

Information about adverse events whether volunteered by the patient, discovered by investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the relevant CRFs. Adverse events related to the underlying disease under study or treatment for disease under study will be collected for all patients from the time of start of protocol treatment until 4 weeks post cessation of trial treatment.

8.5 Efficacy Endpoints and Disease Progression Events

All events that are unequivocally due to progression of moderate to severe hand osteoarthritis or lack of response should not be reported as an AE or SAE. This type of information will be captured in the study assessments. Disease progression would include: increased joint pain, increased stiffness, limited motion, and hospitalizations for OA-related procedures (joint replacement surgery, joint arthroscopy).

8.6 Reporting AEs

AEs will be collected for all patients and will be evaluated for duration and intensity according to the NCRI Common Toxicity Criteria. AEs & SAEs will be collected for all patients from first dose of protocol treatment until 30 days after the last dose of treatment with a protocol IMP (hydroxychloroquine). Information about AEs, whether volunteered by the patient, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the CRF with the following information:

1. its relationship to the study drug(s) (suspected/not suspected)
2. its duration (start and end dates or if continuing at final exam)

Where applicable the severity grade (mild, moderate, severe) will be recorded in the report as free text.

A copy of all reported AEs will be sent to the sponsor if requested.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event CRF. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome. Information about common side effects already known about the investigational drug can be found in the SmPC. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.7 Reporting SAEs

All SAEs occurring whilst on trial (until 30 days after the last treatment dose) must be recorded on the Serious Adverse Event Form and faxed to York Trials Unit (YTU) **within 24 hours** of the research staff becoming aware of the event.

Each SAE will be described by:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome
- causality, in the opinion of the investigator*
- whether the event would be considered expected or unexpected (see Section 13.3.2)*

**Assessment of causality and expectedness must be made by an authorised medic. If an authorised medic is unavailable, initial reports without causality and expectedness assessment should be submitted by a healthcare professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter.*

When determining whether an SAE is expected or not, please refer to the version of the SmPC supplied in the Investigator Site File or the latest updated version as instructed by York Trials Unit (YTU).

Please ensure that each SAE is reported separately and not combined on one SAE form.

The original form should also be posted to the YTU in real time and a copy retained at Site.

Any follow-up information should be faxed to YTU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached.

Investigators must report all SAEs to their host institution in line with their local arrangements.

8.8 Reporting SUSARs

All SAEs assigned by the local investigator (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 MHRA. All SUSARs should be reported in the same way as SAEs.

All SUSARs occurring whilst on trial (until 30 days after the last day of the last treatment) must be reported on a sponsor approved SAE form and faxed through to YTU within 24 hours (1 business day) of any member of the research team becoming aware of the SUSAR. All SUSARs must be reviewed by the CI or a nominated delegate. If the CI or delegated doctor is unavailable, initial reports without causality and expectedness assessment should be submitted to YTU within 24

hours, but must be followed up by medical assessment as soon as possible thereafter. PI SUSARs cannot be downgraded by the CI without agreement from the PI.

The YTU will chase missing data and seek confirmation from the CI on the occurrence of a SUSAR. The YTU will forward a confirmed SUSAR to the sponsor office with 24 hours (1 working day) of awareness of the event. The sponsor will submit the SUSAR to the MHRA and the responsible REC. If the YTU are unable to confirm the SUSAR with the CI or delegated representative they will contact the sponsor office who will instigate medical review from within the joint University of Leeds and Leeds Teaching Hospitals NHS Trust general trial Data Monitoring and Ethics Committee to confirm the event as a SUSAR.

The YTU will notify trial Principle Investigators of any confirmed SUSARs that occur within the trial. The Sponsor will report all confirmed SUSARs to the MREC and MHRA in accordance with their respective expedited reporting procedures and within the statutory time limits of **7** (death/life threatening events)/**15** (all other events) days with follow-up within 8 days of receiving the SUSAR report.

Fax number for reporting SAEs and SUSARs:

01904 321 387

8.9 Pregnancies

Pregnancy in patients participating on this study or their partners must be prevented as effectively as possible.

Site staff should notify the HERO trial coordinator of a pregnancy in a trial subject or the partner of a trial subject and the estimated due date using the Notification of Pregnancy form.

All protocol therapy must be stopped immediately if a pregnancy in a female patient occurs or is suspected. Patients withdrawn from treatment will still attend for follow-up assessments unless unwilling to do so and case report forms will continue to be collected. The pregnancy will be followed up for 12 weeks after an outcome (termination, abortion, birth).

8.10 Study Agent Accountability

The pharmacies will maintain a log of drug accountability and the release of all drugs, including drug dose to the research staff. The research staff will maintain detailed logs of subject number and deviations to protocol.

8.11 Development Safety Update Report (DSUR)

A DSUR must be submitted to the Sponsor for approval and then to the main REC and MHRA on the anniversary of the Clinical Trial Authorisation being granted. The CI must review and sign / date the report.

8.12 Responsibilities

Principal Investigator/ Chief Investigator (or nominated individual in CI's absence):

- Checking for SAEs when patients attend for treatment / follow up
- Medical judgement in assigning to SAEs, seriousness, causality and expectedness
- To ensure all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware and to provide further follow up information as soon as available.
- To report SAEs to local committees in line with local arrangements.
- To assign causality and expected nature of SAEs where it has not been possible to obtain local assessment.
- To undertake SAE review
- Review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and the Chief Investigator, local assessment will not be downgraded but the Chief Investigator may add comments prior to reporting to MHRA and Main REC
- To assign code to all SAEs suspected to be related to trial treatment using the MedDra Body
- System Organ Class coding, prior to submission of annual safety reports.

Sponsor:

- Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and main REC within required timelines with support from the YTU
- Notifying Investigators of SUSARs that occur within the trial.

HERO Trial Coordinator/YTU:

- Preparing annual safety reports in collaboration with appropriate members of the TMG to Competent Authority, main REC and Arthritis Research UK, periodic safety reports to TSC and DMEC as appropriate.
- Collating SAE information and feeding this to the TSC / DMEC
- Collecting SUSAR information, coordinating SUSAR review and expedited forwarding of complete SUSAR reports to the Sponsor in order to allow for reporting to Competent Authority (MHRA in UK) and main REC within required timelines.

TSC:

- In accordance with the Trial Terms of Reference for the TSC (see Appendix 3), periodically reviewing safety data and liaising with the DMEC regarding safety issues.

DMEC:

- In accordance with the Trial Terms of Reference for the DMEC (see Appendix 4), periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.0 Data collection, source data and confidentiality

9.1 General

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

York Trials Unit and all study centres will comply with all aspects of the Data Protection Act 1998 and operationally this will include:

- consent from patients 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 patient personal and clinical details
- consent from patients 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 patients for the data collected for the trial to be used to evaluate safety and develop new research.
- restriction of transfer of patient identifiable data between sites to the consent form.

9.2 Source Data

A case report form will be provided for each subject.

All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the case report form. Details of case report form completion and correction will be explained to the investigator. If the investigator authorizes other persons to make entries in the case report form, the names, positions, signatures, and initials of these persons must be supplied to the sponsor.

The investigator, or designated representative, should complete the case report form pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must 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 study. This list will be filed in both the trial master file and the investigator study file and updated as necessary. All clinically relevant data must 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 Study Visit.

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

9.3 Archiving

In line with the principles of GCP/UK Clinical trial Regulations guidelines, at the end of the trial, data will be securely archived at each participating centre for a minimum of 15 years. Arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed immediately. No records may be destroyed without first obtaining written permission from the Sponsor.

Patient notes (source data) should be annotated as per local instructions to ensure that they are stored for the same amount of time as the trial data in order to allow source data verification.

Study documentation/data must not be destroyed without the approval of the sponsor.

9.4 Protection of Patients

All records will be kept confidential and the patient's name will not be released at any time. Data sets for each subject will be identified by the patient enrolment number and initials only.

10.0 Statistical Considerations

10.1 Design

- Randomised double-blind clinical trial of hydroxychloroquine vs placebo
- N=252
- Final clinical evaluation at 12 months

10.2 Statistical Method

All analyses will be conducted on an intention to treat basis, including all randomised patients 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. All baseline data will be summarised by treatment group. Baseline data will be described descriptively. No formal statistical comparisons of baseline data will be undertaken. The flow of patients through the trial will be presented in a CONSORT diagram. The numbers of patients withdrawing from treatment will be summarised by treatment group.

The primary outcome (average overall hand pain severity over the past 2 weeks) will be measured at baseline, month 3, month 6 and month 12. The primary analysis will estimate the difference in '*average overall hand pain severity over the past 2 weeks'* at 6 months between the hydroxychloroquine and placebo groups using a linear mixed model (linear regression for correlated data) adjusting for the baseline measure and other important covariates (e.g. chronic drug use).

The secondary analyses will estimate treatment differences at 3 months and 12 months in the same linear mixed model. Other continuous secondary outcomes measured longitudinally at baseline, month 3, month 6 and month 12 will be analysed as the primary outcome. For the ordinal secondary outcomes measured longitudinally at baseline, month 3, month 6 and month 12, we will assume that the outcomes are continuous and analysis will be similar to the primary analysis. The assumptions underlying this model will be checked. All these models will estimate the differences between hydroxychloroquine and placebo in the secondary outcomes at 3 months, 6 months and 12 months adjusting for the same covariates as the primary analysis. Point estimates and their 95% confidence intervals will be presented.

All secondary outcomes will be described descriptively (mean, standard deviation, median, minimum and maximum for continuous data and counts and percentages for categorical data). The SF-12 will be summarised for all components. To minimise multiple testing, only the overall physical component score and mental component score will be analysed using a linear mixed model as described above. 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 non responders 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. We anticipate that there will be a single analysis at the end of the study.

10.3 Health Economics Analysis

Health economics evaluation will be carried out as part the HERO randomised controlled trial in order to determine the cost-effectiveness of using Hydroxychloroquine (the intervention) as part of a multi-drug regimen.

The intention-to-treat population will be used for all analyses, with resource use data collected from a NHS perspective.

Medication use will be estimated from the drug history summary collected during the trial, these will be itemised according to medication for hand pain, and other medication, further divided into sections for prescription and non-prescription medication. Health service use will be measured using a patient health services utilisation questionnaire developed for the HERO trial.

Utility will be measured using the EuroQol (EQ-5D-5L), deriving quality –adjusted life years (QALYs) for each participant. Data on the cost and utility measures will be collected at the same time points as for clinical outcomes, i.e. at baseline, 6 months and 12 months.

Unit cost of medications will be taken from the British National Formulary. Health service use cost will be derived from the annual NHS reference cost summary, identifying relevant healthcare resource group codes.

Future costs and outcomes will not be discounted as follow-up in the HERO trial is for 12 months.

The main analysis will be a within-trial analysis. A cost-effectiveness analysis using the primary outcome in the HERO trial, i.e. cost per unit of reduction in pain score (as measured on a NRS) and cost-utility analysis deriving cost per QALY saved will be conducted. For each analysis, the following summary measures will be estimated:

- Ratio measure: Incremental cost-effectiveness ratio obtained by dividing the incremental cost by the incremental health benefit.
- Difference measures: Net benefit will be calculated based on pre-specified thresholds.
- Probability measure: A Cost Effectiveness Acceptability Curve will be constructed.

Multiple imputation methods will be used to handle missing data, where needed.

10.4 Power Calculations

The primary outcome of the study is change in hand pain, measured on a 0-10 numerical rating scale, between baseline and 6 months. Our previous data from a 257 patient trial with ACR hand OA (SMOOTH: Self-management, joint protection education and exercise in hand osteoarthritis) and a 176 patient trial with ACR hand features and pain on most/all days (CAS-HA: Clinical Assessment Study of the Hand) give mean baseline pain scores of 5.06 (standard deviation, 2.079) and 5.50 (standard deviation, 2.5) respectively. In order to detect an effect size of 0.4, with 80% power and 5% significance, 99 patients would be required per arm. Allowing for a conservative 20% dropout, a total of 248 patients will therefore need to be recruited into the study. Since we will be recruiting at 9 centres, we will set a recruitment target of 28 patients for each centre, giving a total of 252 patients.

The trial is powered to detect an effect size of 0.4. This is equivalent to the reported effect size of NSAIDs as a treatment for hand OA obtained from two large studies with a total of 654 patients[58,59]. Moreover, with the estimated mean pain numerical rating scores and s.d., in this instance an effect size of 0.4 is equivalent to a 15% change on the pain scale, which lies within the minimal clinically important difference for change in pain in a randomised trial (10-20%)[60].

10.5 Safety Evaluation

Safety will be assessed by summarising incidence and type of adverse events through the 12 months of the study. All patients will be included in the safety assessment. The Chief Investigator(s) will include all serious and non-serious adverse events in a final study report. Adverse events will be recorded in the Case Record Form.

11.0 Trial Monitoring

11.1 Data Monitoring

The principal investigator will ensure that the trial will be appropriately monitored by ensuring that all the rights of the subjects are adequately protected, that the trial data are accurate, complete and verifiable from source documents and that the conduct of the trial is in compliance with the protocol and its subsequent amendments, with GCP and with applicable regulatory requirements.

The principal investigator will verify that for all patients a written informed consent was obtained before each subject's participation in the trial. The principal investigator will also ensure that all patients enrolled will be eligible according to the in- and exclusion criteria as defined in the protocol.

The study may be monitored and/or audited by the sponsor, the MHRA or the host organisation at any time as part of both organisations' commitment to maintaining the highest standards of GCP.

Monitoring will be conducted according to the HERO Monitoring SOP (Appendix I).

11.2 Quality Assurance

The Sponsor has systems in place to ensure that there is reporting and appropriate action taken in respect of:

(a) Serious breaches of GCP, the trial protocol and the Clinical Trial Authorisation.
(b) Urgent safety measures
(c) Protocol violations

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the trial; or
(b) The scientific value of the trial.

Investigators will promptly notify the Sponsor QA Office of the following within the required timeframe, once they become aware of:

(a) Serious breaches of GCP, the trial protocol and the Clinical Trial Authorisation.
(b) Urgent safety measures
(c) Protocol violations
(d) Any amendments to the trial
(e) Any changes the Clinical Trial Risk Assessment (form A).
(f) Any other issues as stated in the Research Sponsorship Agreement (RSA)

The Sponsor reserves the right to audit any site involved in the trial and authorisation for this is given via the RSA.

11.3 Trial Steering Committee

The trial steering committee will hold regular meetings to monitor the progress of the study. The committee will include an independent chair (Dr Andrew Oster, Consultant Rheumatologist, Oxford), 2 independent members (Dr Elspeth Wise, Professor Bruce Kidd), and a lay representative (Ms Jo Cumming, Arthritis Care Helplines Manager). See Appendix 3.

11.4 Data Monitoring and Ethics Committee

The study will be regularly reviewed by the data monitoring and ethics committee. This will be done to verify that data is being accurately recorded and documented. Further, the committee will routinely review study documents with an eye towards ensuring that the study protocol is accurately followed and GCP compliant. See Appendix 4.

The minutes/records of these meetings will be stored in the Division of Musculoskeletal Disease at Chapel Allerton Hospital and will be available to the sponsor upon request.

12.0 Ethical considerations

12.1 Good Clinical Practice

This clinical study was designed and shall be implemented and reported in accordance with the Medicines for Human Use Act 2004, and with the ethical principles laid down in the Declaration of Helsinki.

This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki, 1996 (South Africa). The institutional review board (IRB)/independent ethics committee (IEC) must review and approve the protocol and informed consent form before any subjects are enrolled. Before any protocol-required procedures are performed, the subject must sign and date the IRB/IEC-approved informed consent form.

12.2 Delegation of Investigator Duties

The investigator should ensure that all persons assisting with the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.
The investigator should maintain a list of co-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

12.3 Subject Information and Informed Consent

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An informed consent document (Patient Information Leaflet) that includes both information about the study and the consent form will be prepared and given to the subject at least 24 hours prior to the screening visit. The document must be translated (by an independent interpreter) into a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

At the screening visit, patients will be given the opportunity to ask questions and the nature and objectives of the study will be explained. A research nurse may help in this process but the study doctor is responsible for the informed consent discussions.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions, the study doctor. If an interpreter has been used to translate the study information and assist with the informed consent process then the process should be documented into the

patient's medical records. The interpreter should write their name, sign and date the consent form to signify that they have correctly interpreted the study information, that the patient understands the requirements for participation in the trial and has agreed to take part in the study.

The original signed consent document will be retained in the ISF. Other copies of the consent form are required:

- One copy of the informed consent document will be faxed to YTU and filed in the TMF
- One copy of the informed consent document will be kept in the patient's clinical notes where applicable. If a patient does not have clinical notes at the trial site the informed consent document will be filed in a separate folder.
- One copy will be given to the patient.

The screening period will provide further opportunity for a patient to re-consider and consent will be confirmed in the clinical notes at the baseline visit.
The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.
The investigator must inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

12.4 Confidentiality

Only the subject number and subject initials will be recorded in the case report form, and if the subject name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor, independent ethics committee (IEC)/ institutional review board (IRB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

12.5 Protocol Amendments

Requests for any amendments to the protocol must be sent to the sponsor by the chief investigator. The sponsor will determine whether said amendments are substantial or non-substantial prior to their submission to the appropriate bodies for approval. Patients should be re-consented to the study if the amendments affect the information they have received, patient safety, or if the change alters the type or quality of the data collected for the study. Patients should only be re-consented AFTER an amendment has been fully approved.

12.6 Approval of Clinical Study Protocol and Amendments

Before the start of the study, the clinical study protocol, informed consent document, and any other appropriate documents will be submitted to the REC, the MHRA and the sponsor with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements.

Investigational products can only be supplied to the sponsor after documentation on all ethical and legal requirements for starting the study has been received by the product provider. This documentation must also include a list of the members of the REC and their occupation and qualifications. If the REC will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. Formal approval by the REC should preferably mention the study title, study code, study site (or region or area of jurisdiction, as applicable), amendment number where applicable, and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met, including approval of the study by the local Research and Development department, the REC and the MHRA.

The REC, the MHRA and the sponsor must be informed of all subsequent protocol amendments and administrative changes, in accordance with local legal and sponsor requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should be revised.

The investigator must keep a record of all communication with the REC, the MHRA, and the sponsor. This also applies to any communication between the investigator (or coordinating investigator, if applicable) and the authorities.

Individual R&D permission will be required for all sites.

12.7 Ongoing Information for Independent Ethics Committee

Unless otherwise instructed by the REC and the sponsor, the investigator must submit to the REC, MHRA and the sponsor:

- Information on serious or unexpected adverse events (SUSARs) from the investigator's site, as soon as possible, and to the sponsor within 24 hours (one business day) of the research team becoming aware of them.
- Expedited safety reports from the sponsor, as soon as possible.
- Annual reports on the progress of the study.
- A copy of the annual safety/ Development Safety Update Report

12.8 Closure of the Study

The study must be closed at the site on completion. Furthermore, the sponsor or the investigator has the right to close this study site at any time. As far as possible, premature closure should occur after mutual consultation. Depending on local legislation, it may be necessary to inform the REC, the MHRA, the sponsor, any other regulatory authorities, the local pharmacy departments, and any other involved departments when the study site is closed.

12.9 Record Retention

Essential documents will be retained for 15 years after the end of the trial. However, because of international regulatory requirements, the sponsor may request retention for a longer period.
Essential documents include, but are not limited to:

- Signed informed consent documents for all subjects.
- Subject identification code list, screening log (if applicable) and enrolment log.
- Record of all communications between the investigator, the REC and the sponsor.
- Composition of the REC, and the sponsor
- List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures.

Copies of case report forms and documentation of corrections for all subjects.

- Investigational product accountability records.
- Record of any body fluids or tissue samples retained.
- All other source documents (subject medical records, hospital records, laboratory records, etc.).
- All other documents as listed in section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial).

Normally, these records will be held in the investigator's archives. If the investigator is unable to meet this obligation, he or she must ask the sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

13.0 Statement of indemnity

The University of Leeds is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent and non-negligent harm in the design and delivery of the trial protocol. Participating Trust's will provide indemnity for individuals working on the study through the NHS CNST scheme.

14.0 Publication Policy

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

In accordance with the Arthritis Research UK's 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 Arthritis Research UK as the study's funding source. When acknowledging Arthritis Research UK support, the grant reference number must be quoted.

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16.0 Appendices

Appendix 1 Definition of a Women of Childbearing Potential

A woman of childbearing potential (WCBP) is:

- A sexually mature woman (i.e. any female who has ever experienced menstrual bleeding) AND
- Who has not undergone a hysterectomy or who has not been postmenopausal for at least 24 consecutive months (i.e. who has had menses at any time within the preceding 24 consecutive months).

Appendix 2 American College of Rheumatology Classification Criteria for Osteoarthritis of the Hands.

Hand pain, aching, or stiffness and 3 or 4 of the following features:

- Hard tissue enlargement of 2 or more of 10 selected joints
- Hard tissue enlargement of 2 or more DIP joints
- Fewer than 3 swollen MCP joints
- Deformity of at least 1 of 10 selected joints

* The 10 selected joints are the second and third distal interphalangeal (DIP), the second and third proximal interphalangeal, and the first carpometacarpal joints of both hands. This classification method yields a sensitivity of 94% and a specificity of 87%. MCP = metacarpophalangeal.

Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601-10.

Appendix 3 Trial Steering Committee

Terms of reference

The Trial Steering Committee should meet once a year or more often as appropriate.

Specifically the terms of reference of the Trial Steering Committee are as follows:

- To provide overall supervision of the trial.
- To monitor and supervise the progress of the trial towards its interim and overall objectives, adherence to the protocol and patient accrual within the set time-frame.
- To review at regular intervals relevant information from other sources (e.g. other related trials), and recommend appropriate action (e.g. changes to trial protocol, stopping or extending the trial).
- To recommend appropriate action in light of points 1, 2 and 3 to ensure that the trial adheres to the Declaration of Helsinki and specifically that the rights, safety and well-being of the trial participants are the most important considerations, and prevail over the interests of science and society.
- To keep any issues discussed in the meetings or written in the minutes confidential, unless otherwise agreed.

It is also the responsibility of the Trial Steering Committee to:

- Approve any changes to the protocol during the course of the trial.
- Consider new information relevant to the trial, including reports from the Data Monitoring and Ethics Committee (DMEC) and the results of other studies, particularly if the results may have a direct bearing on the future conduct of the trial. On consideration of this information, the Trial Steering Committee should recommend appropriate action, such as changes to the trial protocol, additional patient information, or stopping or extending the study.
- Ensure that appropriate efforts are made to ensure that the results of the trial are adequately disseminated and that due consideration is given to the implementation of the results into clinical practice.

In addition, the Chairman should also:

- Be informed of any unexpected serious adverse events.
- Approve and sign the final report of the trial (for the funding body).
- The main purposes of Trial Steering Committee meetings are:
- To provide the overall supervision of the trial, in particular to monitor the progress of the trial, adherence to the protocol and patient safety.
- To maximise the chances of the trial completing within the timescales set and agreed by the funding body.
- To ensure that the trial is conducted to the rigorous standards set out in the MRC Guidelines for Good Clinical Practice and the DoH Research Governance proposals.

It is therefore essential that all members of the Trial Steering Committee attend each meeting.

Appendix 4 Data Monitoring and Ethics Committee Terms Of Reference & Confidentiality Agreement

Objective
The objective of the Data Monitoring and Ethics Committee (DMEC) is to independently monitor the safety data and related ethics of the trial.

Roles and Responsibilities
• Attend DMEC meetings and provide advice on availability for future DMEC meetings (non attendance at three successive meetings may lead to removal from the DMEC)
• To consider data monitoring plans and related ethical implications at the outset of the trial
• Agree to any relevant statistical analysis plans (e.g. DMEC plans, interim analysis plans)
• To monitor the safety and tolerability endpoint on a continuous basis
• To consider interim safety data at approximately four-month intervals or more frequently if any safety issues arise during the conduct of the trial, and data from the formal interim analysis plus any additional safety issues for the trial and relevant information from other sources (any recommendations relating to patient safety may be subject to expedited reporting to the Competent Authority)
• To review safety data to look for any emerging trends, including increases in severity or frequency of expected Serious Adverse Reaction such that they would require expedited reporting to the Competent Authority
• In the light of the above, and ensuring the ethical considerations are of prime importance, to report (following each DMEC meeting) to the Chief Investigator and YTU Principal Investigator and to recommend on the continuation of the trial (with consideration of the stopping rules as defined in the protocol). The DMEC reserve the right to recommend suspending recruitment between stage I and stage II of the trial if deemed necessary. To inform the decision of whether or not to suspend recruitment, overall response rates at day 28 of the third cycle will be presented to the DMEC as early indications of response.
• To consider any requests for release of interim trial data and to recommend to the Chief Investigator on the advisability of this
• In the event of further funding being required, to provide to the Chief Investigator appropriate information and advice on the data gathered to date that will not jeopardise the integrity of the study

Accountability & Escalation
The DMEC is accountable to the Chief Investigator and YTU Principal Investigator. The DMEC is responsible for escalating any issues for concern to the Chief Investigator and YTU Principal Investigator.

Confidentiality
All data and results from the trial must be kept confidential.

Data Transfer

No publically identifiable patient data will be transferred to the DMEC. Data will usually be transferred electronically to an appropriate professional email address or via standard postal routes. Where additional risk is identified, passwords or special delivery services will be used.

Appendix 5: Yorkshire Regional Guidelines For The Monitoring Of Adult Patients On Disease Modifying Drugs (DMARDS) Including Biologic Therapies. Fifth Edition. Revised March 2009

HYDROXYCHLOROQUINE **(4 / 3 / 2009)**

When commencing treatment the following will be considered:

1) Generally thought safe in pregnancy (but crosses placenta)
2) Renal and Hepatic impairment
3) Known ocular disease-
4) Potential drug interactions:
   - Amiodarone
   - Moxifloxacin
   - Ciclosporin
   - Digoxin
   - Antacids avoid within 4hrs
   - Anti-epileptics

Usually started at a dose of 200mg bd for the first 3 months and then reduced to 200mg daily as a maintenance dose if effective (aim for 3-5mg/Kg/day LEAN body weight). Routine blood / urine monitoring tests are not necessary other than those below.

ROUTINE TESTING when treatment commences

Baseline	FBC / U&E / LFT Opthalmological screening recommended if pre-existing ocular pathology or visual disturbance, impaired renal function or over the age of 60.
Repeat	Renal function every 6 months in those over 60 or at risk of renal impairment

Optician Screening : Recommend pre treatment assessment and annual visual acuity / fundoscopy and Amsler charting. Formal opthalmological screening is also suggested when :

1) A cumulative dose of 500grams, which is equivalent to 3.4 years of 200mg bd or 6.8 years of 200mg daily
2) If doses of > 6.5mg/kg/day are used. (= > 400mg/day for 60kg patient)

IF Photophobia / Haloes Field Defects / Reduced Acuity

Stop medication and contact local rheumatology service

HERO

Hydroxychloroquine Effectiveness in Reducing Symptoms of Hand Osteoarthritis: A Randomised, double-blind, placebo-controlled trial (ISRCTN 91859104)

STATISTICAL ANALYSIS PLAN (SAP)

Clinical Effectiveness Analysis

Version 2.1

York Trials Unit
Department of Health Sciences
University of York
York, YO10 5DD

Version date: 28/01/2016
Author: Ada Keding
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Independent Statistician: Hannah Buckley
Health Economist: Sarah Ronaldson

Document Version History

Version Number	Version Date	Summary of Changes
1.0	*18/11/2014*	*First full draft*
1.1	*01/05/2015*	*General updates* *- Protocol version updated (v6.0)* *- Restructuring and renumbering of document sections* *- Senior statistician confirmed* *- Data sources updated* *Changes following DMEC advice* *- Descriptive compliance analysis added* *- Subgroup analysis section added* *Changes and additions following team consultation* *- Definition of non-compliance confirmed for per protocol population and sensitivity analyses* *- Sensitivity analysis for time of outcome completion added* *- Secondary outcomes categorised into key outcomes for formal treatment analysis and descriptive only outcomes* *- Exclusion of premature data from withdrawing patients added*
1.2	*25/05/2015*	*General updates* *- Study specific CONSORT template added* *Changes after consultation with YTU statisticians and DMEC statistician* *- Change of secondary per protocol analysis to CACE as the more appropriate analysis for assessing the intervention effect for treatment compliers* *- Quality of life secondary outcomes categorised as key for full analysis* *- Third statistician added, who will be independent and responsible for unblinding* *- HCQ dose dropped from analysis covariates due to overlap with BMI covariate*
1.3	*15/06/2015*	*General updates* *- Trial health economist (Sarah Ronaldson) included in the list of required approval signatures and added as person with permission to access the analysis file directory* *Updates following YTU consultation and DMEC statistician advice*

Version Number	Version Date	Summary of Changes
		- *Exclusion of premature data from withdrawing patients revoked, all available data to be used in primary analysis*
2.0	*24/06/2015*	*Final analysis plan before handover of trial data, incorporating all changes of interim versions detailed above. Signed off by trial team.*
2.1	*28/01/2016*	*Confirmation of imaging data analysis following receipt of data and clinical review* - *Scoring and analysis of radiograph data confirmed* - *Scoring and analysis of ultrasound data confirmed* *Planned clinical review of compliance population* - *Definition of non-compliance criteria confirmed* *Primary Analysis* - *Addition of average grip strength at baseline as a covariate in the primary analysis (and any other analyses based on the primary model)* *Secondary outcomes* - *Designation of AUSCAN pain and function subscales as separate secondary outcomes*

Signatures of Approval

The sheet containing original wet ink signatures is held in the Trial Master File for all major analysis plan versions. A scanned image is inserted into the electronic document version.

SAP Version 2.1, 28 January 2016

Name	Trial Role	Signature	Date
Philip Conaghan	Principal Investigator		
Puvan Tharmanathan	Trial Co-ordinator		
Sarah Kingsbury	Trial Co-ordinator		
Ada Keding	Statistician		
Catherine Hewitt	Senior Statistician		
Val Wadsworth	Data Manager		

Glossary

AUSCAN	Australian/Canadian Hand Osteoarthritis Index
BMI	Body Mass Index
CACE	Complier Average Causal Effect
CMC	Carpometacarpal joints
CONSORT	Consolidated Reporting of Randomised Trials
CRF	Case Report Form
DICHOA	Disease Characteristics in Hand Osteoarthritis
DIP	Distal interphalangeal joints
EQ-5D-5L	EuroQol Quality of Life Measure (5 response option version)
HADS	Hospital Anxiety and Depression Scale
HCQ	Hydroxychloroquine
ITT	Intention to Treat
MCP	Metacarpophalangeal joints
NRS	Numeric Rating Scale
NSAE	Non-serious Adverse Event
NSAID	Nonsteroidal Anti-Inflammatory Drug
OA	Osteoarthritis
OAQoL	Osteoarthritis Quality of Life Measure
PIP	Proximal interphalangeal joints
PJC	Painful joint count
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SF-12	Short Form Health Survey
SJC	Swollen joint count
TJC	Tender joint count
VAS	Visual Analogue Scale

Contents

1. Introduction

1.1 The HERO Trial

Recent studies have indicated that synovitis (inflammation in the joints) is prevalent in osteoarthritis (OA) and is associated with pain in knee and hand OA. Hydroxychloroquine (HCQ) is used in routine practice at treating synovitis in inflammatory arthritides such as rheumatoid arthritis, is widely used anecdotally as a treatment for OA and has been shown to be effective at reducing pain. Hydroxychloroquine has an excellent safety profile, with toxicity generally associated with sustained periods of use that due to the natural history of hand OA are unlikely to be an issue. Treating patients with moderate to severe OA hand symptoms with hydroxychloroquine may be a practical and safe treatment option to reduce synovitis and therefore reduce pain, and may be of particular use in the primary care setting. The HERO trial aims to determine the analgesic efficacy of hydroxychloroquine as a treatment for painful hand OA in a randomised controlled trial (RCT).

1.2 Research Objectives

Primary Objective

1. Determine the effectiveness of hydroxychloroquine as a treatment for hand osteoarthritis

Secondary Objectives

1. Determine the cost effectiveness of hydroxychloroquine
2. Determine whether baseline ultrasound synovitis is associated with response to treatment with hydroxychloroquine

1.3 Scope of Statistical Analysis Plan

This analysis plan exclusively covers details of the statistical analysis of treatment efficacy in the HERO Trial, including the ultrasound sub-study. Any analyses addressing the economic analysis as well as any additional planned analyses are detailed elsewhere.

2. Trial Design

2.1 Summary

The HERO trial is a 2-arm, multi-centre, randomised, double-blind, placebo-controlled trial with randomisation at the patient level. The two treatment arms are:

(1) Hydroxychloroquine (HCQ, active treatment)

Participants are prescribed a single daily dose between 200 mg and 400 mg of HCQ (based on participant's calculated ideal body weight), taken orally as 200 mg capsules with or just after food for 12 months. The active drug can be used in combination with drugs licensed for use in pain management of OA.

(2) Placebo

Participants in the placebo group are prescribed matching placebo capsules for 12 months containing a lactose and magnesium stearate blend and are taken as the active treatment capsules. The placebo drug can be used in combination with drugs licensed for use in pain management of OA.

Full details of the background and design of the trial are given in the study protocol (latest version at time of writing: Version 6.0, 19/03/2015).

2.2 Sample Size

The primary outcome of the HERO trial is the average overall hand pain severity over the past 2 weeks, measured on an 11-point, 0-10 numerical rating scale (NRS), at 6 months follow-up. Data from two previous trials (SMOOTH and CAS-HA) give mean baseline pain scores of 5.06 (SD=2.08) and 5.50 (SD=2.50) respectively.

The HERO trial is powered to detect a standard effect size of 0.4, which is the reported effect size of NSAIDs as a treatment for hand OA obtained from two large studies with a total of 654 patients. The effect size is equivalent to an approximate reduction in pain of 0.8 score points (or 15%) on the numerical pain rating scale. This lies within the minimal clinically important difference for change in pain in a randomised trial (10-20%).

In order to detect an effect size of 0.4 with 80% power and 5% significance, 99 patients are required per arm. Allowing for a conservative 20% dropout, the total required sample size is 238 patients. With the recruitment target for nine study centres set at 28 patients per centre, the total target sample size is 252 patients.

2.3 Randomisation

Randomisation is performed by the manufacturer of all active and placebo drugs (Sharp Clinical Ltd.) using random permuted blocks and random number tables to order drug bottles in a 1:1 ratio of drug and placebo.

Blinded bottles are supplied to the hospital pharmacy units in the order of the randomisation schedule. When a patient consents to participate in the trial, a prescription for the study drug is given to the patient, and the pharmacy at the trial site issues bottles of the study drug in the order that it was provided to them.

2.4 Blinding

Treatment allocation is concealed from the investigator, patients and the blinded assessor for the full duration of the trial. Study drugs are supplied to the hospital pharmacy unit in the order of the randomisation schedule prepared by Sharp Clinical Ltd.

A master list detailing which patients are taking HCQ or placebo is held by Leeds General Infirmary Trials Pharmacy. Site-specific code break envelopes are also held at each site pharmacy. Any unblinded patients are withdrawn from the trial.

The statistician conducting the analyses will remain blind to treatment allocation until after the primary analysis has been completed and verified.

2.5 Follow-up

Following two clinic visits at screening and baseline, all participants who consent to participate in the HERO trial are followed up for up to 12 months. A detailed account of the data collection schedule is presented in Table 1.

The main follow-up points are at 3, 6 and 12 months post-randomisation, at which the majority of patient reported outcomes are collected. Patients return to clinic at 6 and 12 months, whereas 3 month follow-up is either by clinic visit, telephone call or postal questionnaire. The nurse, doctor or trial administration team attempt to arrange follow-up visits within the visit window (+/- 21 days) for each follow-up point. Additional safety data is collected at 1 month, 9 months and 13 months over the telephone.

3. Outcomes

3.1 Primary Outcome

- Overall hand pain severity (NRS over last 2 weeks) at 6 months follow-up

Participants are asked to rate their average overall hand pain on a 0-10 (11-point) numerical rating scale (NRS). The anchor question is: *"On average, how would you rate your overall hand pain during the last 2 weeks?".* Response options range from 0 ("*no pain*") to 10 ("*pain as bad as it could be*").

3.2 Secondary Outcomes

A) Clinical Outcomes

Structural assessment at screening or baseline and 12 months

- Bilateral hand X-ray

Patient reported at baseline, 3 months, 6 months and 12 months

- Overall hand pain severity (NRS over last 48 hours and 2 weeks; VAS over last 48 hours and 2 weeks)
- Pain severity in the most painful joint (NRS over last 48 hours and 2 weeks; VAS over last 48 hours and 2 weeks)
- Pain severity in the most painful thumb (NRS over last 48 hours)
- Global arthritis activity (NRS over last 48 hours)
- Satisfaction with hand function (NRS over last 48 hours)
- Hand pain/aching/stiffness (over last month)
- AUSCAN (over last 48 hours)
- Pain in all joints (NRS over last 48 hours)

Patient reported at 3 months, 6 months and 12 months

- Global improvement in hand problem (compared to first seen)
- Global improvement in hand pain (compared to first seen)
- Global improvement in ability to use hands (compared to first seen)

Clinical measurements by investigator at baseline, 6 months and 12 months

- Count of painful, swollen and tender joints
- Grip Strength (Jamar)

Bilateral hand X-ray

Plain radiographs of each hand will be taken (1 hand per film). Radiographs will be scored using the Kallman scale, which showed the highest sensitivity to change and high intra-reader reproducibility and inter-reader reliability in a study comparing four scoring methods for the radiological assessment of hand OA. The Kallman scale scores 22 joints (all but the metacarpophalangeal joints) for 6 radiological features according to a semi-numerical scale: osteophytes (0-3), joint space narrowing (0-3), subchondral bone sclerosis (0-1), subchondral bone cysts (0-1), lateral bony deviation (>15°; 0-1) and bone erosion (0-1), with the total combined score for both hands ranging from 0-220. The mean score for each feature as well as the mean score for each feature by joint group (DIP, PIP/IP, CMC and STT) are also calculated for analysis.

Overall hand pain severity

Participants are asked to rate their average overall hand pain on an 11-point NRS. The anchor questions are: *"On average, how would you rate your overall hand pain during the last 2 weeks?"* and *"On average, how would you rate your overall hand pain during the last 48 hours?"*. Response options range from 0 ("*no pain*") to 10 ("*pain as bad as it could be*"). Participants are also asked to rate their hand pain on a 100mm continuous VAS ranging from "*no pain*" on the left to "*worse possible pain*" on the right. The anchor questions are: "*On average, how would you rate your overall hand pain during the last 2 weeks? Mark on the line below.*" and "*On average, how would you rate your overall hand pain during the last 48 hours? Mark on the line below.*" Research staff then measure the distance of the placed mark from the left in millimetres, resulting in a score from 0 to 100.

Pain severity in the most painful joint

Participants are asked to rate their average hand pain in their most painful joint on an 11-point NRS. The anchor questions are: *"On average, how would you rate your pain in the most painful joint in your hands during the last 2 weeks?"* and *"On average, how would you rate your pain in the most painful joint in your hands during the last 48 hours?".* Response options range from 0 ("*no pain*") to 10 ("*pain as bad as it could be*"). Participants are also asked to rate their worst joint pain on a 100mm continuous VAS ranging from "*no pain*" on the left to "*worse possible pain*" on the right. The anchor questions are: "*On average, how would you rate your pain in the most painful joint in your hands during the last 2 weeks? Mark on the line below.*" and "*On average, how would you rate your pain in the most painful joint in your hands during the last 48 hours? Mark on the line below.*" Research staff then measure the distance of the placed mark from the left in millimetres, resulting in a score from 0 to 100.

Pain severity in the most painful thumb

Participants are asked to rate their average thumb pain in their most painful thumb on an 11-point NRS. The anchor question is: *"On average, how would you rate your base of thumb pain, in the worst thumb, in the last 48 hours?".* Response options range from 0 ("*no pain*") to 10 ("*pain as bad as it could be*").

Global arthritis activity

Participants are asked to judge their arthritis activity on an 11-point NRS. The anchor question is: *"Over the last 48 hours, how active do you think your hand arthritis has been?".* Response options range from 0 ("*not very active*") to 10 ("*extremely active*").

Satisfaction with hand function

Participants are asked to rate their hand function on an 11-point NRS. The anchor question is: *"How satisfied have you been with your hand function over the last 48 hours?".* Response options range from 0 ("*very satisfied*") to 10 ("*not at all satisfied*").

Hand pain/aching/stiffness

Participants are asked to estimate the frequency of their hand problems on a 5-point Likert scale. The anchor question is: *"In the last month, have you had pain or aching or stiffness in your hands including your fingers and thumbs?".* Response options are "*No days*", "*Few days*", "*Some days*", "*Most days*", "*All days*".

AUSCAN

The Australian Canadian Osteoarthritis Hand Index (AUSCAN) is a self-report assessment measuring pain (5 items), stiffness (1 item) and function (9 items) during the preceding 48 hours. All items are rated on a scale of 0 (none) to 4 (extreme), resulting in a total score from 0 to 60. Subscale scores for pain (range 0-20) and function (range 0-36) will be derived.

Pain in all joints

Participants are asked to rate their average overall joint pain on an 11-point NRS. The anchor question is: *"On average, how would you rate your pain in all your joints (i.e. not just your hands), over the last 48 hours?".* Response options range from 0 ("*no pain*") to 10 ("*pain as bad as it could be*").

Global improvement in hand problems

Participants are asked to rate any improvement of their hand problem, hand pain and ability to use their hands compared to when they were first seen as part of this study on a 6-point Likert scale. Response options are "*Completely recovered*", "*Much better*", "*Better*", "*No change*", "*Worse*", "*Much worse*".

Count of painful, swollen and tender joints

For each hand, all 15 joints (4 distal interphalangeal, 5 proximal interphalangeal, 5 metacarpophalangeal and 1 carpometacarpal) are assessed by investigators separately for pain, swelling and tenderness using response options 0 (not present), 1 (present), 2 (not assessed) or 3 (joint replaced). Outcomes will be summarised as painful joint count (PJC), swollen joint count (SJC) and tender joint count (TJC), each with a score range of 0 to 28.

Grip Strength (Jamar)

Grip strength of both hands is being assessed by using a Jamar device when the participant is in clinic. Grip strength is recorded in pounds (lbs) for three attempts as well as a mean recording for each hand.

B) Quality of Life Outcomes

Patient reported at baseline, 6 months and 12 months

- OAQoL
- SF-12
- HADS
- EQ-5D-5L

OAQoL
The Osteoarthritis Quality of Life (OAQoL) is a questionnaire to judge the effect of OA symptoms on quality of life and consists of 38 statements, which participants mark as "*True*" or "*Not true*". The questionnaire is scored by summing the number of 'true' responses, resulting in a score from 0-38.

SF-12
The SF-12 is a generic health status measure and a short form of the SF-36 health survey. It consists of 12 questions measuring 8 domains (Physical, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health) rated over the past month. Questions have 3 or 5 response categories, and responses are summarised into a physical and mental component score (PCS and MCS). Outcomes range from 0 (lowest level of health) to 100 (highest level of health).

HADS
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. The components of the anxiety and depression scales are indicated on the questionnaire.

EQ-5D-5L
The EQ-5D is a standardised measure of current health status developed by the EuroQol Group for clinical and economic appraisal. The EQ-5D consists of five questions, each assessing a different quality of life dimension (Mobility, Self-care, Usual activities, Pain/Discomfort and Anxiety/Depression). Each dimension is rated on five levels: no problems (score=1), slight problems (score=2), moderate problems (score=3), severe problems (score=4) and extreme problems (score=5). A weighted and population referenced summary index can be derived to give a score between 1 (perfect health) and 0 (death). For the purpose of the present analysis, only scores of the individual dimensions will be utilised. The summary index will be derived and analysed separately as part of the cost utility analysis.

3.3 Adherence Outcomes

- Non-compliance notice
- Brief medication questionnaire
- Pill Counts

Non-compliance notice
Each time a period of non-compliance is identified for a patient by the investigators, a notice of non-compliance is completed. Each period is detailed as start and end date (if known), occurrence before or after 6 month follow-up, estimated duration in days, type of non-compliance (partial/intermittent or no study medication at all) as well as reasons for non-compliance (if known).

Brief medication questionnaire
The brief medication questionnaire is a self-report measure to monitor adherence. It consists of four questions relating to the regimen of any medications taken in the week, any medications that bothered participants in any way, the level of concern around different issues of medication adherence and any medications that were discontinued in the past six months. As a self-report, the questionnaire is not expected to give comprehensive and reliable adherence estimates but is intended as a supplementary compliance indicator.

Pill Counts
Trial participants are asked to return any unused drugs to the pharmacy, and pharmacies are keeping a log of any trial medications dispensed and returned. As patient medication return and pharmacy log return are anticipated to be sporadic, pill counts are not expected to give comprehensive and reliable adherence estimates but are intended as a supplementary compliance indicator.

3.4 Safety Outcomes

- Adverse Events
- Visual Acuity
- Vitals
- Bloods

Adverse Events
During each study visit patients are monitored and questioned by a member of the clinical staff for the occurrence of new adverse events or the outcome of any adverse events reported at previous visits. Serious and non-serious adverse events (NSAEs and SAEs) are recorded in terms of date of onset, diagnosis (if applicable), description, seriousness, suspected relatedness to study treatments, expectedness, treatment and outcome.

Visual Acuity
Visual acuity is recorded as a print size read test for the left and right eye (recorded as N6, N8 or unable to read N8) and an Amsler Grid test for the left and right eye (recorded as Normal vision or Abnormal vision). The outcome will be reported as change / no change compared to baseline.

Vitals
Blood pressure (in mmHG), Pulse (in beats/min), Weight (in kg), Height (in m) and Temperature (in °C) are recorded at screening, 6 months and 12 months.

Bloods

Biochemistry and Haematology outcomes are collected at screening, and Urea and Creatinine are collected at follow-up if the participant is over 60 years of age or at risk of renal impairment.

3.5 Baseline Measures

- Pain elsewhere (pain manikin)
- Onset of hand pain
- Duration of hand pain (over the past 12 months)
- Ultrasound synovitis score

Pain elsewhere (pain manikin)
Patients mark on a printed pain manikin with 14 distinct areas (arm and leg joints, neck and back) if they had suffered from any swelling, pain or stiffness in the last three months that lasted for more than six weeks in each area.

Onset of hand pain
Participants are asked for an estimate of when their hand pain first started. Response options are: "Within the last 12 months", "1 year to less than 5 years", "5 years to less than 10 years, "10 years or more".

Duration of hand pain
Participants are asked to estimate on how many days they have had hand pain over the last 12 months. Response options are: "Less than 7 days", "1 to 4 weeks", "More than 1 month but less than 3 months", "3 months or more".

Ultrasound Scores
Baseline ultrasound imaging is performed for the most painful hand (or dominant hand if both equally painful) of all patients enrolled at the centres participating in the ultrasound sub-study (Leeds, Kings College London, Nottingham, Keele, Newcastle and Oxford). The CMC joint (thumb), 4 DIP, 5 PIP (including thumb) and 5 MCP (including thumb) joints of the dominant hand are imaged globally in multiple planes. Domains scored will be greyscale synovitis, power Doppler signal and osteophytosis. A semi-quantitative scoring system will be used for greyscale synovitis (0-3, positive score ≥2) and power Doppler (0-3, positive score ≥1), and osteophytosis will be scored as being absent or present, in line with DICHOA (Disease Characteristics in Hand OA). For each patient, a positive score for each feature is assigned if at least one joint (of 15 joints assessed) is positive. A total positive outcome for each patient is defined as having a positive greyscale or power Doppler score.

3.6 Other Collected Data

- Demographics
- Medical History
- Pain elsewhere (pain manikin)
- Concomitant Therapy

- Steroid Use
- Resource Use Data

Demographics

At screening, the following demographic data are recorded: Age, Gender, Ethnicity (Caucasian, South Asian, East Asian, Afro-Caribbean, Other), Smoking (Never, Current, Previous, number of smoking years, number of cigarettes per day), Drinking (alcohol units per week), Employment (Employed full time, Employed part time, Self-employed, Unemployed, Retired), Job type (Heavy manual, Repetitive use of hands, Prolonged keyboarding, None).

Medical History

At screening, the presence and stability of the following medical conditions or events are recorded: Hypertension, Hypercholesterolemia, Ischaemic heart disease, Other cardiovascular disease, Cerebrovascular disease, Peripheral vascular disease, Asthma, Emphysema/ chronic bronchitis, Other pulmonary disease, Diabetes, Peptic ulcer disease, Inflammatory bowel disease, Other GI disease, Renal disease, Chronic liver disease, Epilepsy, Nervous system disease, Depression, Endocrine disease, Inflammatory arthritis, Allergies, Cancer, Surgery, Other.

Pain elsewhere (pain manikin)

Patients complete the pain manikin as at baseline at follow-up.

Concomitant Therapy

Treatment regimens for any continuing and new concomitant oral and topical medication (for hand pain and other) as well as concomitant therapies for hand pain were collected by investigators as appropriate at each follow-up time point. Medications will be grouped according to class by the trial team for the purpose of analysis.

Steroid Use

Each time a patient reports the use of steroids, a notice of steroid use is completed by the investigators. Each use is categorised as intramuscular, intravenous, intra-articular or oral together with date of administration and occurrence before or after 6 month follow-up.

Resource Use Data

Participants complete questions about their use of health care services and other medical expenditures at baseline, 6 months and 12 months. These data will be used in the health economic analysis only.

3.7 Data Collection Schedule

For an overview of the timing of different data collection see Table 1.

Table 1: HERO Data Collection Schedule

Study Visit	1	2	3	4	5	6	7	8
Purpose	Screening	Baseline	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up
Time	max - 3 weeks	0	+ 1month	+ 3 months	+6 months	+ 9 months	+ 12 months	+ 13 months
Type	Clinic	Clinic	Telephone	Cli / Post / Tel	Clinic	Telephone	Clinic	Telephone
Demographics / Medical history	•							
Pain elsewhere (pain manikin)	•			•	•		•	
Hand pain onset and duration		•						
Bilateral X-ray	○	○					•	
Overall hand pain severity		•		•	❖		•	
Pain in most painful joint		•		•	•		•	
Pain in most painful thumb		•		•	•		•	
Global arthritis activity		•		•	•		•	
Satisfaction with hand function		•		•	•		•	
Hand pain/ aching/ stiffness		•		•	•		•	
AUSCAN		•		•	•		•	
Pain in all joints		•		•	•		•	
Global hand improvements				•	•		•	
Painful joint count		•			•		•	
Grip strength (JAMAR)		•			•		•	
OAQoL/ EQ-5D/ SF-12/ HADS		•			•		•	
Brief Medication Questionnaire				•	•		•	
Steroid Use / Non-compliance			○	○	○	○	○	○
Adverse Events			○	○	○	○	○	○
Visual acuity	•				•		•	
Concomitant therapy	•	○	○	○	○	○	○	○
Resource use		•			•		•	
Ultrasound synovitis score		○						
Vitals / Bloods		•			○		○	

• Mandatory data collection ○ Conditional data collection ❖ Primary outcome

4. Data

4.1 Data Sources

- Case Report Forms (CRFs)
    - Screening form
    - Patient Baseline questionnaire
    - Patient 3 months follow-up questionnaire
    - Patient 6 months follow-up questionnaire
    - Patient 12 months follow-up questionnaire
    - Investigator 1 month follow-up questionnaire
    - Investigator 3 months follow-up questionnaire
    - Investigator 6 months follow-up questionnaire
    - Investigator 9 months follow-up questionnaire
    - Investigator 12 months follow-up questionnaire
    - Investigator 13 months follow-up questionnaire
    - NSAE forms
    - Notice of steroid use or non-compliance
    - Medication logs

- Study Management Database
    - Match of patient IDs and pack IDs
    - Questionnaire due and return dates
    - Withdrawal logs
    - Pill counts (from returned bottles)

- YTU Trial Management Data
    - SAE details
    - NSAE reporting dates and details

- Leeds Trial Site
    - Radiograph scores
    - Ultrasound scores

- Sharp Clinical Ltd
    - Treatment allocations (matched to pack IDs)

All data will be available in csv format before being imported to the statistical analysis software.

4.2 Data Management and Verification

CRFs will be received in paper format by York Trials Unit and scanned in by the data management team. A copy of the CRFs with the variable names from the database is kept in the Trial Master File.

Comprehensive data validation algorithms have been incorporated into the processing of each CRF, including checks for completeness, internal consistency as well as appropriate data formatting and range checks. The data management team will document any violations of these validation rules. Interim data sets will be handed over to the statistician for reporting purposes. Any identified inconsistencies at these points will be queried with recruitment sites or resolved between the trial team, data team and statisticians and changes made to 'soft locked' data as appropriate. At the end of the trial, a final 'hard locked' dataset will be handed over to the trial statistician.

The statistician will conduct further data checks including checks for duplicate responses and date chronology across questionnaires. The statistician will generate any derived variables as required. Any decision rules, data changes and assumptions made by the statistician following receipt of the final dataset from data management will be documented in a Trial Assumptions Form.

The statistician will not make any changes to the resource use data and will release a copy of these together with cleaned demographics and other required variables to the trial health economist.

4.3 Relevant Standard Operating Procedures

Data and documents relevant to the statistician will be kept in a Statistical Master File on the R: drive (secure YTU drive) following the directory structure detailed in the YTU SOP "DS01 Directory structure and version control". Access to this folder will be restricted to the trial statisticians and health economist at York Trials Unit (Ada Keding, Catherine Hewitt and Sarah Ronaldson) and the YTU data management team. Other relevant YTU SOPs or guidance documents that will be followed in the conduct of this trial include: S01 Statistical Considerations; SG02 Statistical Reporting.

5. Analysis

5.1 Principles

Analyses will be on intention to treat (ITT) basis, analysing participants as part of the group they were randomised to. All analyses will be conducted in Stata version 13 or later, using 2-sided significance tests at the 5% significance level. Results will be presented with 95% confidence intervals where appropriate. The statistician conducting the analyses will remain blind to treatment allocation until completion of the primary analysis, after which the independent statistician will make the labels for treatments A and B available.

5.2 Descriptives

5.2.1 Trial Progression

The flow of participants through the trial will be presented in a CONSORT flow diagram (see Appendix). Summaries of the numbers of participants screened, eligible and randomised will be given, and reasons for exclusion will be listed. Frequencies of dropout (death, dropout from treatment, follow-up or trial) will be presented by trial arm.

5.2.2 Baseline Data

All participant baseline data (demographics and medical history from the screening form, baseline measures of pain elsewhere, hand pain history and ultrasound synovitis score as well as any outcome measures from the baseline questionnaire) will be summarised descriptively by trial arm for all randomised participants and all participants included in the primary analysis. No formal statistical comparisons will be undertaken. Continuous measures will be reported as means, standard deviations, minimum, maximum and interquartile ranges; and categorical data will be reported as frequencies and percentages.

5.2.3 Compliance

Compliance with the trial drug regimens will be summarised descriptively using non-compliance notices and pill counts. Periods of non-compliance will be summarised by treatment arm and overall as the number of patients for whom any time of non-adherence to the drug regimen has been reported, the average length of time of such non-compliance as well as its timing in relation to the trial follow-up time points. Pill counts will be summarised by treatment arm and overall as the number pills dispensed grouped by mean daily dose (200mg, 300mg or 400mg), the number of patients for whom return pill counts were available and the difference between expected and actual pill returns (frequencies and percent) for these patients.

5.3 Analysis of the Primary Outcome

5.3.1 Primary Analysis

Analysis population

The ITT analysis population for the primary analysis will include all patients in their randomised groups with available outcome data (NRS pain rating over the past 2 weeks at 3, 6 or 12 months follow-up) as well as complete baseline covariates specified for the analysis.

Descriptives

Participant baseline data for all participants included in the primary analysis will be summarised descriptively and reported alongside baseline data for all participants. Unadjusted descriptives of overall hand pain severity during the last 2 weeks (NRS) at all follow-up time points will be presented in tabular format as well as graphically. The proportion of patients with missing primary outcome data at each time point will be reported.

Analysis Model Definition

A covariance pattern linear mixed effects model will be used to compare hand pain severity scores over the 12 months follow-up between HCQ treatment and placebo treatment. The treatment effect estimate from this model at 6 months follow-up will form the primary end point. Effects of interest and baseline covariates (details below) will be specified as fixed effects, and the correlation of observations within patients over time will be modelled by a covariance structure to describe the random effects. The mixed model will provide increased statistical power by utilising all patients with outcomes for at least one follow-up time point.

The outcome modelled will be hand pain severity at 3, 6 and 12 months. The model will include as fixed effects: time, treatment group and time-by-treatment interaction, adjusting for hand pain severity at baseline, average grip strength at baseline (average between left and right hand), age, gender, BMI and concomitant analgesic use at baseline. Different covariance structures for the repeated measurements that are available in the analysis software will be explored, and the most appropriate pattern will be used for the final model based on the model information criteria (AIC).

Analysis Model Output

The primary endpoint will be the estimate of the effect of the intervention at 6 months, which will be presented with 95% confidence intervals and associated p-values in addition to adjusted means for each treatment group. In addition to the primary endpoint, estimates of the effect of the intervention on NRS pain scores at 3 months and 12 months will also be extracted from the primary analysis model and presented with 95% confidence intervals and associated p-value.

Model Assumptions

Model assumptions of normality of the standardised residuals and of homogeneity of variance of the standardised residuals against fitted values will be checked. If the model assumptions are in doubt, the outcome data will be transformed prior to analysis. If the specified mixed model fails to converge with the parameters specified as above, individual regressions at each time point will be undertaken instead. The assumption of missing at random will be explored as part of the sensitivity analyses.

Primary Analysis Verification

Analysis of the primary outcome will be checked by the senior blinded statistician, including the derivation of applicable variables and analysis code. Following the verified primary analysis, treatment allocations will be unblinded by the independent statistician, and the senior statistician will verify that the final analysis report is correct.

5.3.2 Secondary Analyses

Adherence adjusted analysis

While ITT analysis will give an unbiased treatment effect estimate, it may underestimate the effect of complying with the treatment. Therefore the primary endpoint of pain severity at 6 months follow-up will be re-analysed to obtain a complier average causal effect of treatment (CACE). CACE analysis will adjust for the same baseline covariates as the primary analysis.

Treatment compliers are defined as the subset of participants of the ITT primary analysis population who adhered to the regimen of the treatment they were allocated to and did not violate the trial protocol in any substantial way. The following criteria will be used to define *non*-compliance:

- Receipt of a corticosteroid injection to the hand at any time before 6 months follow-up
- Receipt of any non-hand corticosteroid injections (including intramuscular or intravenous injections) within 8 weeks before the patient's 6 month follow-up
- Receipt of more than one non-hand corticosteroid injection at any time before 6 months follow-up
- Receipt of any oral corticosteroids within 3 months before 6 months follow-up
- Receipt of more than one week's course of oral corticosteroids at any time before 6 months follow-up
- Study medication not used as prescribed for more than 2 weeks duration before 6 months follow-up
- Withdrawal from treatment or follow-up at any time before 6 months follow-up

A panel including the clinical project manager, trial statistician and other appropriate members of the study team reviewed the compliance criteria using blinded data prior to data analysis. The number of patients to whom the non-compliance criteria apply will be summarised descriptively for each criterion and in total by treatment arm and overall. Participant baseline data for compliers and non-compliers will be summarised descriptively.

Analyses accounting for missingness

The number and proportion of patients with missing primary outcome data will be reported at each time point by treatment group and overall. Missing data will be explored in order to assess if it is likely to be missing at random. Baseline characteristics for participants with any missing primary outcome data will be summarised descriptively and reported alongside baseline data for participants with complete data. Average pain scores over time will be plotted for patients with baseline only, 6 months only and those with baseline and 6 months to see if the missing data is related to the observed pain scores.

In order to investigate the impact of missing data, any baseline predictors of non-response at 6 months follow-up will be included as covariates in the primary analysis model. Non-response will be defined as the absence of a valid pain score, and predictors will be identified initially by individual logistic regressions followed by a combined regression using $p<0.10$.

If there are substantial missing data, then a multiple imputation sensitivity analysis will be carried out, imputing the primary outcome and any missing covariates. This will be detailed further in an updated SAP prior to any analyses being conducted.

5.3.3 Sensitivity Analyses

Analysis accounting for receipt of rescue medication

The proportion of patients receiving either increased concomitant analgesic medication (increased dose or addition of any NSAIDs, opioids or paracetamol) or a steroid injection to hand joints at any time as well as their combined proportion will be reported by treatment group and their timing in relation to the trial follow-up time points. If sufficient numbers of patients received rescue medications and the proportions differ between the treatment groups, a sensitivity analysis to explore the underlying difference between HCQ and placebo accounting for receipt of these medications will be carried out. Analyses will follow the appropriate methods described in White et al. (2001), depending on the nature of the data.

Analysis using patients with confirmed osteoarthritis using imaging data at baseline

OA diagnosis at baseline was confirmed by Kallman radiograph scores as well as ultrasound osteophyte data where available. A confirmed OA diagnosis is established if a patient has a radiograph osteophyte score of ≥ 2 in any joint, a positive ultrasound osteophyte score (where available) in any joint, or a radiograph joint space narrowing score of ≥ 2 in any joint. In order to assess the robustness of the trial results to fulfilment of radiographic / ultrasonic criteria for OA, a sensitivity analysis will be carried out, repeating the primary analysis for patients with confirmed OA diagnosis only. Patients without available radiograph data at baseline will be excluded from this analysis.

Analysis using patient data collected within 21 days of due dates

Recruitment sites were advised to arrange follow-ups within +/- 21 days of the appropriate calendar month since randomisation, i.e. since the baseline visit. However some variability in the timing of follow-up visits and questionnaire returns is expected. Time differences between due and actual follow-up times will be calculated and presented descriptively (mean, standard deviation, median, minimum, and maximum) at each time point by trial arm and in total. In order to assess the robustness of the trial results in relation to the timing of follow-up, a sensitivity analysis will be carried out, repeating the primary analysis for follow-up data collected within +/- 21 days of the appropriate due date.

5.3.4 Subgroup Analyses

Analysis by extent of structural damage

An exploratory sub-group analysis by the extent of structural damage at baseline based on radiographic data will be performed. We hypothesise that HCQ treatment will differ according to degree of structural damage. As there are no existing cut-off scores in the literature, the distribution of the total Kallman radiograph score across the study population will be reviewed, and an analytically and clinically sensible cut-off will be chosen to distinguish between mild to moderate and severe structural damage. An interaction term between randomised treatment group and this radiograph score dichotomisation (Mild/Moderate versus Severe) will be added to the primary analysis model in order to ascertain any differential treatment response. Results from this analysis will be used to generate hypotheses for future studies.

5.4 Analysis of Secondary Outcomes

Descriptive statistics including the extent of missing data will be presented for all secondary outcomes by trial arm at the time points collected and presented graphically where appropriate. The ITT analysis population for the analysis of secondary outcomes will include all patients in their randomised groups with available respective outcome data and complete specified covariates.

Continuous secondary end points

Given the large number of secondary outcomes, these were categorised by the trial team into key outcomes of interest for which treatment group differences will be formally analysed, and those outcomes for which descriptive statistics will be reported only.

The primary analysis mixed model will be repeated for the following continuous secondary outcomes, adjusting for the outcome at baseline where applicable. Treatment effect estimates with 95% confidence intervals will be presented for each outcome and model assumptions checked. A more simple regression will be performed for the Kallman total radiograph score, for which follow-up data is collected at a single time point (12 months).

- Pain severity in the most painful joint (NRS over last 2 weeks)
- AUSCAN Pain subscale score
- AUSCAN Function subscale score
- Grip Strength (left hand)
- Grip Strength (right hand)
- Kallman total radiograph score
- OAQoL
- SF-12 Physical Component Score
- SF-12 Mental Component Score

Descriptive statistics only and graphical representations over time will be presented for the following continuous secondary outcomes.

- Overall hand pain severity (NRS over last 48 hours)
- Overall hand pain severity (VAS over last 48 hours)
- Overall hand pain severity (VAS over last 2 weeks)
- Pain severity in the most painful joint (NRS over last 48 hours)
- Pain severity in the most painful joint (VAS over last 48 hours)
- Pain severity in the most painful joint (VAS over last 2 weeks)
- Pain severity in the most painful thumb
- Global arthritis activity
- AUSCAN Total score
- Kallman radiograph score – Osteophytes (total and x 4 joint groups)
- Kallman radiograph score – Joint space narrowing (total and x 4 joint groups)
- Kallman radiograph score – Subchondral bone cyst (total and x 4 joint groups)
- Kallman radiograph score – Subchondral bone sclerosis (total and x 4 joint groups)
- Kallman radiograph score – Lateral bone deviation (total and x 4 joint groups)

- Kallman radiograph score – Bone erosion (total and x 4 joint groups)
- Satisfaction with hand function
- Hand pain/aching/stiffness
- Pain in all joints
- HADS Anxiety
- HADS Depression

Agreement between NRS and VAS measurements of the same outcome (Overall hand pain severity over 48 hours, Overall hand pain severity over 2 weeks, Pain severity in the most painful joint over 48 hours, Pain severity in the most painful joint over 2 weeks) will be explored using the kappa statistic.

Categorical secondary end points

The following outcomes will be presented descriptively as frequencies and percentages by trial arm at each available follow-up time point.

- Hand pain/aching/stiffness
- Count of painful joints (PJC)
- Count of swollen joints (SWC)
- Count of tender joints (TJC)
- Global improvement in hand problem
- Global improvement in hand pain
- Global improvement in ability to use hands
- EQ-5D-5L Mobility
- EQ-5D-5L Self-care
- EQ-5D-5L Usual activities
- EQ-5D-5L Pain/Discomfort
- EQ-5D-5L Anxiety/Depression

5.5 Ultrasound Sub-Study

For centres participating in the ultrasound sub-study, greyscale synovitis (average score over 15 joints), power Doppler signal (average score over 15 joints) and osteophytosis (average proportion of positive joints) will be reported descriptively in total and by randomised treatment arm. In four separate analyses (greyscale synovitis, power Doppler synovitis, total synovitis, and osteophytosis), an interaction term between randomised treatment group and the scoring dichotomisation for each feature (positive or negative) will be added to the primary analysis model in order to ascertain any differential treatment response.

5.6 Safety Analyses

Adverse Events

Frequencies of any reported adverse events (NSAEs and SAEs) will be summarised by trial arm and overall. Figures will include a breakdown by type of event and suspected relatedness to treatment. The number and percent of patients experiencing at least one adverse event as well as the average

number of adverse events per patient will be presented. All adverse events will be included in individual subject line listings.

Vitals and Bloods

Vital signs will be summarised descriptively at each time point. Changes from baseline will also be reported. Any changes from baseline in haematology and chemistry values will be summarised descriptively for each time point.

5.7 SAP Departures from the Protocol

Any details specified in the HERO protocol that have been amended in this analysis plan are detailed in Table 2.

Table 2: SAP Departures from Protocol

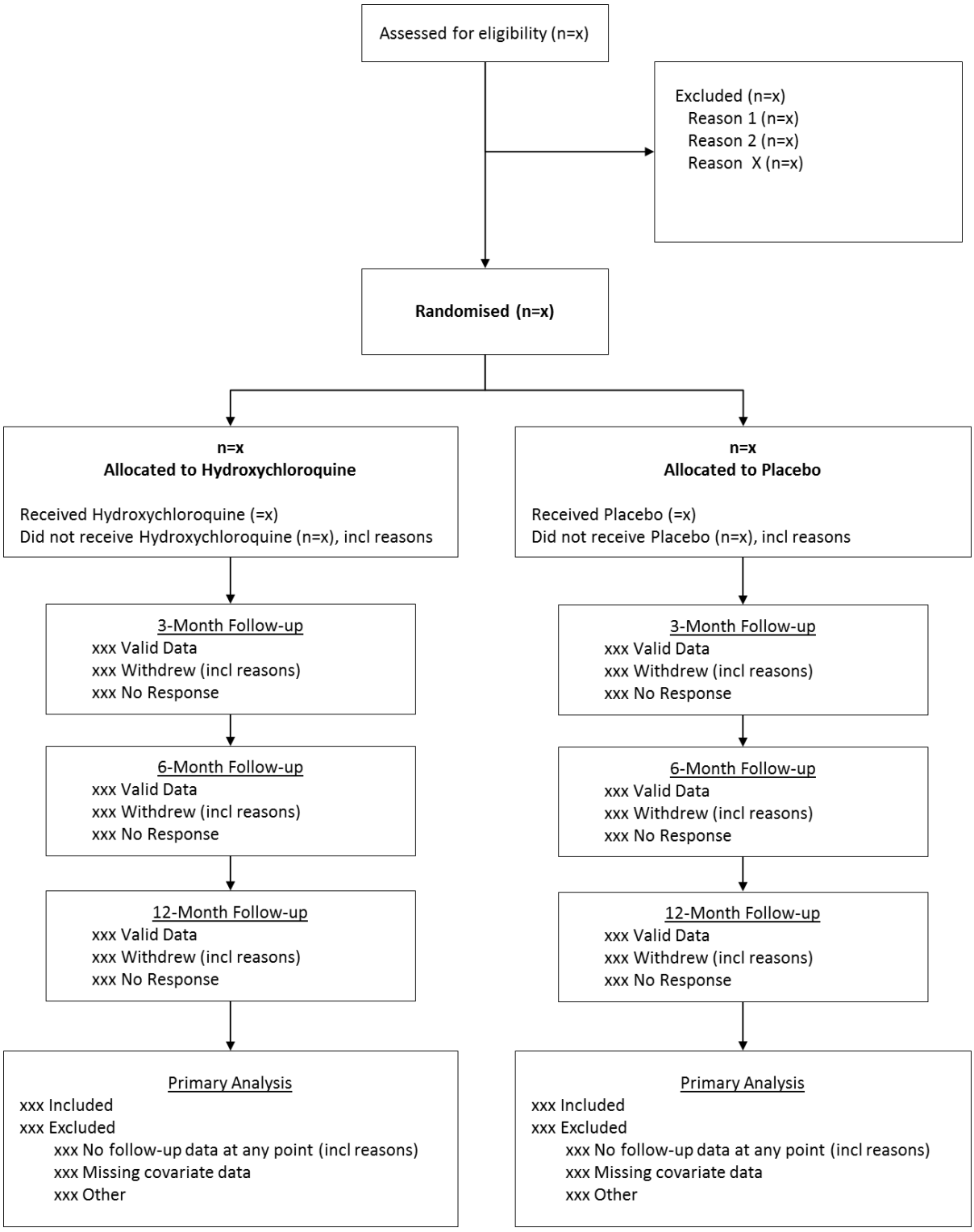
Protocol Version 6.0 (19/03/2015)	Statistical Analysis Plan	Reason for Change
Analysis by intention to treat only	Additional CACE analysis	To additionally estimate the treatment effect for treatment compliers.
Analysis of all continuous secondary outcomes to be carried out as for the primary outcome (i.e. linear mixed model)	Treatment effect to be formally analysed for ten key secondary outcomes and reported descriptively for remaining secondary outcomes	Full analysis of 54 secondary outcomes was not deemed appropriate, both in terms of clinical usefulness and for reasons of multiplicity. Key secondary outcomes were selected by the study team a priori.

6. References

White, I.R., Bamias, C., Hardy P., Pocock, S. and Warner, J. (2001). Randomized clinical trials with added rescue medication: some approaches to their analysis and interpretation. Statistics in Medicine, **20**(20): p. 2995-3008.

7. Appendices

7.1 CONSORT Flow Diagram



Appendix

Appendix 3

Amendments to Protocol and Statistical Analysis Plan

Amendment 1 18.07.12. Clarifications and corrections to protocol. Non-pharmacological therapies, including physiotherapy and splinting, added to the list of 'new therapies' which should not be started during the study unless essential.

Amendment 2: 18.07.12. Eligibility criteria and outcome measures updated, randomisation process altered and pharmacovigilance reporting amended (prior to initiation of recruitment), The following exclusion criteria were added to the study: Evidence of plaque psoriasis; Any new hand OA treatment in the previous 2 months, including physiotherapy and provision of new hand splint; Planned hand surgery in the next 6 months; Melanoma or non-skin cancer in the past 3 years; Epilepsy; Unexplained visual impairment not corrected by glasses. Allowance to re-screen patients who are deemed ineligible at screening due to a temporary status which is likely to change (e.g. recent steroid injection).
The following outcome measures were updated: Pinch strength and grip strength functional tests removed from protocol; Snapshot drug diary removed from protocol; Primary outcome changed from 21-point to 11-point NRS following revised recommendations.
Change to randomisation process – randomisation to be provided by Sharp Clinical Ltd and not by York Trials Unit.
Change to pharmacovigilance reporting – SAEs/AEs/SUSARs to be reported to and escalated by York Trials Unit and not directly to the Sponsor. Unblinding process clarified.
Dipstick pregnancy testing to be completed at 12 months for all female participants of child bearing potential.

Amendment 3: 18.09.12. Clarification of visit procedures, blood tests at baseline and maximum window between screening and baseline (21 days).

Amendment 4: 21.09.12 No amendments to protocol. New document created as cover letter to GPs inviting them to be involved in identifying participants for the study. Change in principle investigator at four peripheral sites: Dr Toby Garrood replaced Dr David Scott at Guys' and St Thomas's NHS Foundation Trust; Dr Ajit Menon replaced Dr Peter Dawes at Haywood Hospital, Stoke-on-Trent NHS Foundation Trust; Dr Fiona Clarke replaced Dr John Dickson at James Cooke University Hospital; and Dr Charles Mackworth-Young replaced Dr Fiona Watt at Imperial College NHS Foundation Trust.

Amendment 5: 20.12.12. Protocol amended to allow screening x-ray, where required, to be captured according to the specific baseline x-ray protocol and used as the baseline trial x-ray if the participant is enrolled in the study. Clarification of eligibility criteria.

Amendment 6: 20.12.12. Clarification of procedure for use of Jamar dynomometer.

Amendment 7: 28.06.13. Increase of window between screening and baseline and around study visits. Update protocol to allow two-week IMP holiday in case of AE. Update to x-ray scoring following revision of guidelines. Addition of recruiting site. Clarification of exclusion criteria to exclude any form of psoriasis.

Amendment 8: 02.07.2013 Clarification of dose calculations.

Amendment 9, 20.05.2015, clarification of protocol to ensure protocol, CRFs and SAP were consistent. Removal of outcome from the protocol - 'Severity rating of participant nominated main functional problem over the past 2 days'. Protocol updated to allow non-hand IA steroid. Revision to allow 12 month x ray to be completed at 13 months if required.

SAP Amendment 1.1: 01.05.2015.

General updates: Protocol version updated (v6.0); Restructuring and renumbering of document sections; Senior statistician confirmed; Data sources updated. Changes following DMEC advice: Descriptive adherence analysis added; Subgroup analysis section added. Changes and additions following team consultation: Definition of non-adherence confirmed for per protocol population and sensitivity analyses; Sensitivity analysis for time of outcome completion added; Secondary outcomes categorised into key outcomes for formal treatment analysis and descriptive only outcomes; Exclusion of premature data from withdrawing patients added.

SAP Amendment 1.2: 25.05.2015.

General updates: Study specific CONSORT template added. Changes after consultation with YTU statisticians and DMEC statistician: Change of secondary per protocol analysis to CACE as the more appropriate analysis for assessing the intervention effect for treatment compliers; Quality of life secondary outcomes categorised as key for full analysis; Third statistician added, who will be independent and responsible for unblinding; HCQ dose dropped from analysis covariates due to overlap with BMI covariate.

SAP Amendment 1.3: 15.06.2015.

General updates: Trial health economist (Sarah Ronaldson) included in the list of required approval signatures and added as person with permission to access the analysis file directory. Updates following YTU consultation and DMEC statistician advice: Exclusion of premature data from withdrawing patients revoked, all available data to be used in primary analysis.

SAP Amendment 2.1: 28.01.2016.

Confirmation of imaging data analysis following receipt of data and clinical review: Scoring and analysis of radiograph data confirmed, Scoring and analysis of ultrasound data confirmed, Planned clinical review of adherence population: Definition of non-adherence

criteria confirmed. Primary Analysis: Addition of average grip strength at baseline as a covariate in the primary analysis (and any other analyses based on the primary model). Secondary outcomes: Designation of AUSCAN pain and function subscales as separate secondary outcomes.

We confirm that the outcomes in our published protocol were the outcomes pre-specified before the trial commenced and there have been no changes to the primary outcome since inception of the trial.

Deviations from Statistical Analysis Plan:

1. As part of the secondary analyses, multiple imputation was planned to be conducted only in the event of substantial missing data and to be detailed in an updated analysis plan. As other planned missing data analyses were not applicable (no significant predictors of missingness that had not already been included in the primary analysis), multiple imputation was conducted for completeness, even though the rate of attrition was as expected. The specification of the imputation was straightforward, using existing covariates of the primary analysis as predictors, and therefore no updated statistical analysis plan was issued.

2. Painful swollen and tender joints were listed as categorical outcomes in the statistical analysis plan. These are in fact count data (count of joints out of 30) and were therefore analysed descriptively as other continuous outcomes.

Appendix 4 - Supplementary methods

Eligibility Criteria

Inclusion criteria

Patients were included if they met the following criteria:

- Patient-reported inadequate response/toxicity to their existing medication (to include paracetamol, oral NSAID or opioid).
- Moderately severe symptoms (≥4/10 on a 0-10 visual analogue scale) at screening.
- Symptoms for more than half of days in the last 3 months.
- Fulfil the American College of Rheumatology criteria for OA.
- Radiograph of the hands in the past 5 years with changes consistent with OA.
- No change in the average weekly dose of analgesics (including NSAIDs) for at least 4 weeks.
- Has used chondroitin or glucosamine for at least 4 months with no change to the average weekly dose, is not using or is willing to stop using if recently started.
- Be able to adhere to the study visit schedule and other protocol requirements.
- Capable of giving informed consent and the consent must be obtained prior to any screening procedures.

Exclusion criteria

Patients were excluded from the study for any of the following reasons:

- Presence of inflammatory arthritis (e.g. gout, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, seronegative spondylarthropathy, Lyme disease) or fibromyalgia
- Evidence of psoriasis
- OA of the 1st carpometacarpal joint and no symptomatic OA in other hand joints.

- Oral, intramuscular, intra-articular, or intravenous steroids or use of other anti-synovial agents (e.g.slow-acting anti-rheumatic drugs such as methotrexate, sulfasalazine) during the last 2 months
- Any new hand OA treatment in the previous 2 months, including physiotherapy and provision of new hand splint.
- Planned hand surgery in the next 6 months.
- Sensitivity, anaphylaxis or allergy to hydroxychloroquine or any other 4-aminoquinoline compound.
- Unexplained visual impairment that is not corrected by glasses or presence of any eye problems.
- Pregnant or lactating
- Use of any investigational (unlicensed) drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer.
- Evidence of serious uncontrolled concomitant medical condition, including cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine, GI disease or epilepsy, which in the opinion of the investigator makes them unsuitable for the study
- Uncontrolled disease states, such as moderate/severe asthma or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids
- Melanoma or non-skin cancer in the past 3 years
- IA hyaluronans to the hand joints within the last 6/12
- Intolerance to lactose
- Significant haematological or biochemical abnormality
    - Haemoglobin ≤ 8.5 g/dL
    - WCC $\leq 3.5 \times 10^9$/L
    - Neutrophils $\leq 1.5 \times 10^9$/L
    - Platelets $\leq 100 \times 10^9$/L

- ALT > 2 times ULN for the laboratory conducting the test.
- Creatinine > 1.5 times ULN for the laboratory conducting the test

Potential participants who were deemed ineligible at screening were allowed a second screening visit if ineligibility status was a temporary status which was likely to change (for example, recent corticosteroid injection).

Outcome Measures

Primary Outcome

Overall hand pain severity (NRS over last 2 weeks) at 6 months follow-up. Participants were asked to rate their average overall hand pain on a 0-10 (11-point) numerical rating scale (NRS). The anchor question is: *"On average, how would you rate your overall hand pain during the last 2 weeks?".* Response options range from 0 ("*no pain*") to 10 ("*pain as bad as it could be*").

Secondary Outcomes

Clinical Outcomes

Structural assessment at screening or baseline and 12 months

- Bilateral hand X-ray

Patient reported at baseline, 3 months, 6 months and 12 months

- Overall hand pain severity (NRS over last 48 hours and 2 weeks; VAS over last 48 hours and 2 weeks)
- Pain severity in the most painful joint (NRS over last 48 hours and 2 weeks; VAS over last 48 hours and 2 weeks)
- Pain severity in the most painful thumb (NRS over last 48 hours)

- Global arthritis activity (NRS over last 48 hours)
- Satisfaction with hand function (NRS over last 48 hours)
- Hand pain/aching/stiffness (over last month)
- AUSCAN (over last 48 hours)
- Pain in all joints (NRS over last 48 hours)

Patient reported at 3 months, 6 months and 12 months

- Global improvement in hand problem (compared to first seen)
- Global improvement in hand pain (compared to first seen)
- Global improvement in ability to use hands (compared to first seen)

Clinical measurements by investigator at baseline, 6 months and 12 months

- Count of painful, swollen and tender joints
- Grip Strength (Jamar)

Quality of Life Outcomes

Patient reported at baseline, 6 months and 12 months

- Osteoarthritis Quality of Life (OAQoL)
- SF-12
- Hospital Anxiety and Depression Scale (HADS)
- EQ-5D-5L

Adherence Outcomes

- Non-adherence criteria
- Brief medication questionnaire
- Pill Counts

Safety Outcomes

- Adverse Events
- Vitals (height, weight, blood pressure, pulse, temperature, visual impairment)
- Bloods (Baseline full blood count (FBC), liver function tests (LFT), urea, electrolytes and creatinine (U&E) and U&E repeated at 6 and 12 months for all subjects over 60 or at risk of renal impairment as per the regional guidelines for hydroxychloroquine use).

Baseline Measures

- Pain elsewhere (pain manikin)
- Onset of hand pain
- Duration of hand pain (over the past 12 months)
- Ultrasound synovitis score

Other Collected Data

- Demographics
- Medical History
- Pain elsewhere (pain manikin)
- Concomitant Therapy
- Steroid Use
- Resource Use Data

Ultrasound substudy

The ultrasound assessment was performed at baseline only on the worse affected hand (or dominant hand if both equally affected). The following joints were assessed: 1st CMC, all MCPJ, all PIPJ and all DIPJ (15 joints). Each joint was scored for synovitis and osteophytes. Synovitis was graded using a semi-quantitative (0-3) score using both gray scale (GS) and power Doppler (PD) modalities. Only the presence or absence of osteophytes was recorded.

For all the joints a longitudinal scan over the dorsum and volar aspect of the joint was undertaken. For the CMC joint, only a volar scan was required. If pathology was suspected, a transverse scan was undertaken to confirm the finding.

Hand radiographs

Plain radiographs of each hand (1 hand per film) were taken at baseline and 12 months. A posteroanterior (PA) view was taken, where the palmar aspect of the hand was placed on the film with the fingers extended, separated slightly and spaced evenly and with the entire forearm placed flat against the X-ray table. A hand map was provided to each trial site to aid reproducibility of positioning (58) and to ensure consistency of hand positioning between centres. An X-ray protocol was also provided to each site to ensure reproducibility of image capturing between centres. In brief, the X-ray beam was centered between the 2nd and 3rd MCPs with the central ray at 90° to the plane of the film. A consistent film-focal-distance of 100 cm was maintained.

Radiographs were scored using the Kallman scale, which showed the highest sensitivity to change and high intra-reader reproducibility and inter-reader reliability in a study comparing four scoring methods for the radiological assessment of hand OA (59). The Kallman scale scores 24 joints (all but the metacarpophalangeal joints) for 6 radiological features according to a semi-numerical scale: osteophytes (0-3), joint space narrowing (0-3), subchondral bone sclerosis (0-1), subchondral bone cysts (0-1), lateral bony deviation (>15°; 0-1) and bone erosion (0-1), with total scores ranging from 0-208 (60). A proportion of radiographs were re-scored for reliability and reproducibility

Statistical Analysis

The following gives further details on secondary analyses that could not be fully outlined within the scope of the manuscript.

CACE (Complier Average Causal Effect) analysis

Non-adherence was defined in the statistical analysis plan as a binary variable indicating that one or more of the following criteria applied:

- Receipt of a corticosteroid injection to the hand at any time before 6 months follow-up
- Receipt of any non-hand corticosteroid injections (including intramuscular or intravenous injections) within 8 weeks before the patient's 6 month follow-up
- Receipt of more than one non-hand corticosteroid injection at any time before 6 months follow-up
- Receipt of any oral corticosteroids within 3 months before 6 months follow-up
- Receipt of more than one week's course of oral corticosteroids at any time before 6 months follow-up
- Study medication not used as prescribed for more than 2 weeks duration before 6 months follow-up
- Withdrawal from treatment or follow-up at any time before 6 months follow-up

BMQ and pharmacy records were not included due to poor data quality. For the purpose of CACE analysis, all patients in the placebo group were considered non-adherent. CACE was implemented using instrumental variable regression (*ivregress* in Stata) (1), predicting the outcome at the primary end point of 6 months, using treatment allocation as the instrument and allowing for the constraint that treatment allocation only affected the outcome through the treatment that has been adhered to. The analysis adjusted for covariates of the primary analysis model. Assuming that the same proportion of participants in the placebo group would have adhered to the intervention if they had been offered it (which should be achieved

by way of randomisation), the group differences from this model provide an estimate of the treatment effect among patients adhering to the treatment.

Multiple Imputation

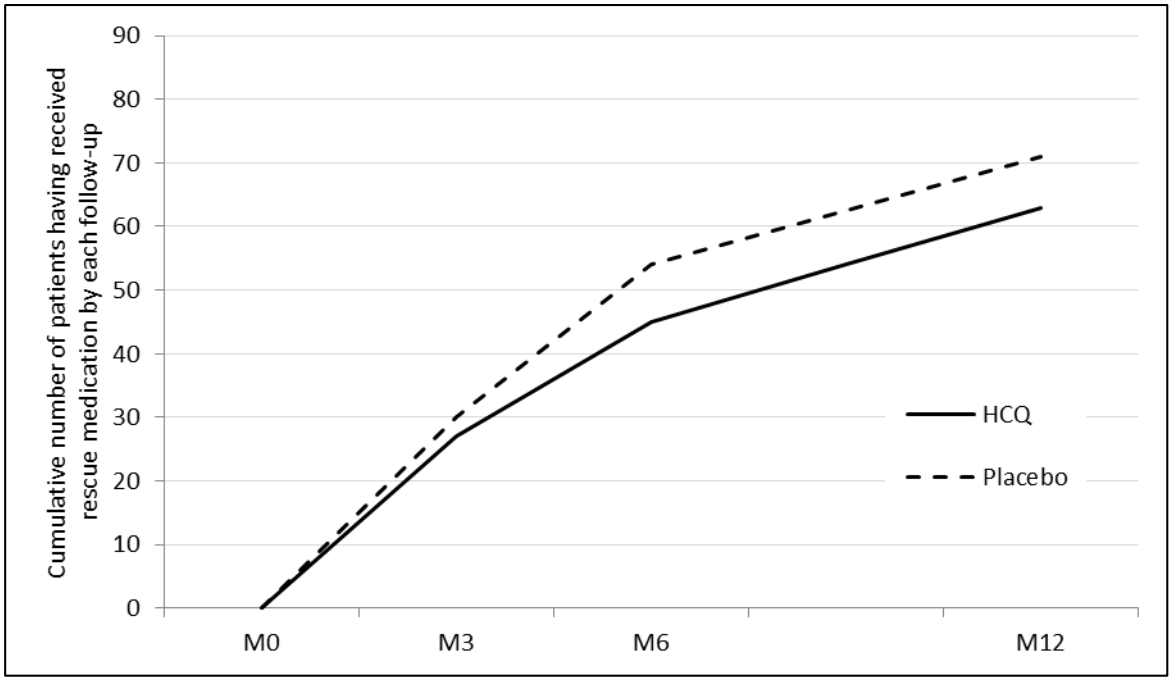
In order to account for missing data, multiple imputation by chained equations was used (*mi impute chain (reg)* in Stata), with estimates being based on 20 imputed data sets. Missing primary outcome data at any time point as well as missing grip strength at baseline were imputed from available outcome data and all available fixed-effect baseline covariates of the primary analysis (age, gender, analgesic medication use, BMI, grip strength, allocation) as predictors.

Adjustment for receipt of rescue medication

There was a slight difference in the trajectories of rescue medication receipt over time, with fewer patients requiring rescue between 3 and 6 months in the HCQ arm (see below). To take account of the timing, we chose the approach of using rescue medication as a time dependent covariate (having received rescue medication by each follow-up time) to assess treatment effects when accounting for these group differences (2).

References

1. Angrist JD, Imbens GW, Rubin DB**.** Identification of causal effects using instrumental variables. JASA. 1996;91(434):444-55.
2. White IR, Bamias C, Hardy P, Pocock S, Warner J. Randomized clinical trials with added rescue medication: some approaches to their analysis and interpretation. Stat Med. 2001;20(20):2995-3008.



337 .

338 **Cumulative number of patients having received rescue medication, by treatment allocation**

Appendix 5 – Supplementary Tables and Figures

Appendix Table 1: HERO Data Collection Schedule

Study Visit	1	2	3	4	5	6	7	8
Purpose	Screening	Baseline	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up
Time	max - 3 weeks	0	+ 1month	+ 3 months	+6 months	+ 9 months	+ 12 months	+ 13 months
Type	Clinic	Clinic	Telephone	Cli / Post / Tel	Clinic	Telephone	Clinic	Telephone
Demographics / Medical history	•							
Pain elsewhere (pain manikin)	•			•	•		•	
Hand pain onset and duration		•						
Bilateral X-ray	○	○					•	
Overall hand pain severity		•		•	❖		•	
Pain in most painful joint		•		•	•		•	
Pain in most painful thumb		•		•	•		•	
Global arthritis activity		•		•	•		•	
Satisfaction with hand function		•		•	•		•	
Hand pain/ aching/ stiffness		•		•	•		•	
AUSCAN		•		•	•		•	
Pain in all joints		•		•	•		•	
Global hand improvements				•	•		•	
Painful joint count		•			•		•	
Grip strength (JAMAR)		•			•		•	
OAQoL/ EQ-5D/ SF-12/ HADS		•			•		•	
Brief Medication Questionnaire				•	•		•	
Steroid Use / Non-adherence			○	○	○	○	○	○
Adverse Events			○	○	○	○	○	○
Visual acuity	•				•		•	
Concomitant therapy	•	○	○	○	○	○	○	○
Resource use		•			•		•	
Ultrasound synovitis score		○						
Vitals / Bloods		•			○		○	

• Mandatory data collection ○ Conditional data collection ❖ Primary outcome

AUSCAN = Australian/Canadian Hand Osteoarthritis Index; Hospital Anxiety and Depression Scale = HADS; OAQoL = Osteoarthritis Quality of Life

Appendix Table2: Intended daily dose of study drug at baseline

	HCQ n=124	Placebo n=124
200 mg	7 (5.6%)	14 (11.3%)
300 mg	85 (68.5%)	90 (72.6%)*
400 mg	32 (25.8%)	20 (16.1%)
Average dose, N	124	124
Mean (SD)	320.2 (52.54)	304.8 (52.35)
Median (min, max)	300 (200, 400)	300 (200, 400)

* includes one patient randomised in error, dose was decided but study drug not dispensed

Appendix Table3: Sensitivity Analyses

Sensitivity Analysis using patients with confirmed OA based on radiographs/ ultrasound data*						
	HCQ		Placebo		Difference	
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	p-value
3 months	82	5.35 (4.76, 5.95)	89	5.63 (5.07, 6.19)	0.28 (-0.34, 0.90)	0.38
6 months	82	5.61 (5.02, 6.20)	89	5.36 (4.79, 5.93)	-0.25 (-0.89, 0.39)	0.44
12 months	82	5.40 (4.80, 6.01)	89	5.35 (4.78, 5.93)	-0.05 (-0.70, 0.60)	0.88
Sensitivity Analysis using time of response as a continuous variable†						
	HCQ		Placebo		Difference	
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	p-value
3 months	113	5.66 (5.32, 6.00)	119	5.78 (5.45, 6.11)	0.12 (-0.36, 0.59)	0.63
6 months	113	5.61 (5.29, 5.93)	119	5.69 (5.38, 6.00)	0.09 (-0.36, 0.53)	0.71
12 months	113	5.50 (5.06, 5.94)	119	5.52 (5.09, 5.95)	0.02 (-0.60, 0.64)	0.59

* Linear mixed effects model with fixed effects of treatment, time and treatment by time interaction, adjusted for baseline hand pain, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use (subset of patients with available x-ray data and confirmed hand OA based on imaging)

† Linear mixed effects model with fixed effects of treatment, time and treatment by time interaction, adjusted for baseline hand pain, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use, and random slope of time for each patient

Appendix Table 4: Secondary outcomes

Appendix Table 4.1: Overall hand pain severity (NRS over last 48 hours) over time by trial arm

Time	HCQ	Placebo
Baseline N	124	121
Mean (SD)	6.9 (1.66)	6.8 (1.76)
Median (minimum, maximum)	7 (2, 10)	7 (2, 10)
3 months N	110	119
Mean (SD)	5.5 (2.21)	5.8 (2.09)
Median (minimum, maximum)	5.5 (0, 9)	6 (0, 10)
6 months N	107	103
Mean (SD)	5.5 (2.05)	5.4 (2.42)
Median (minimum, maximum)	6 (1, 9)	6 (0, 10)
12 months N	92	97
Mean (SD)	5.4 (2.28)	5.3 (2.59)
Median (minimum, maximum)	6 (0, 10)	5 (0, 10)

Appendix Table 4.2: Overall hand pain severity (NRS over last 48 hours) over time by trial arm

Time	HCQ	Placebo
Baseline N	124	123
Mean (SD)	69.0 (17.20)	68.8 (16.48)
Median (minimum, maximum)	73 (20, 96)	70 (8, 100)
3 months N	110	119
Mean (SD)	53.1 (24.81)	56.9 (23.75)
Median (minimum, maximum)	55 (1, 96)	60 (0, 99)
6 months N	107	103
Mean (SD)	54.7 (22.95)	55.6 (25.00)
Median (minimum, maximum)	59 (5, 95)	60 (1, 98)
12 months N	92	98
Mean (SD)	53.0 (27.10)	52.6 (27.38)
Median (minimum, maximum)	55 (0, 100)	56.5 (1, 95)

Appendix Table 4.3: Overall hand pain severity (VAS over last 2 weeks) over time by trial arm

Time	HCQ	Placebo
Baseline N	124	123
Mean (SD)	67.3 (14.27)	66.9 (15.27)
Median (minimum, maximum)	68.5 (16, 95)	68 (10, 100)
3 months N	110	119
Mean (SD)	52.6 (22.92)	57.0 (21.98)
Median (minimum, maximum)	52.5 (4, 99)	58 (0, 98)
6 months N	107	103
Mean (SD)	54.8 (20.83)	53.8 (23.96)
Median (minimum, maximum)	59 (9, 94)	57 (4, 99)
12 months N	92	98
Mean (SD)	53.6 (24.76)	53.9 (25.43)
Median (minimum, maximum)	56.5 (9, 100)	57.5 (1, 95)

Appendix Table 4.4: Hand pain or aching or stiffness over time by trial arm

Time	HCQ	Placebo
Baseline		
No days	0 (0%)	0 (0%)

Few days	0 (0%)	2 (2%)
Some days	6 (5%)	7 (6%)
Most days	46 (37%)	44 (36%)
All days	72 (58%)	70 (57%)
Missing	0 (0%)	0 (0%)
3 months		
No days	0 (0%)	0 (0%)
Few days	12 (11%)	10 (8%)
Some days	26 (24%)	23 (19%)
Most days	33 (30%)	42 (35%)
All days	39 (35%)	44 (37%)
Missing	0 (0%)	0 (0%)
6 months		
No days	1 (1%)	2 (2%)
Few days	9 (8%)	9 (9%)
Some days	22 (21%)	16 (16%)
Most days	29 (27%)	48 (47%)
All days	46 (43%)	27 (26%)
Missing	0 (0%)	1 (1%)
12 months		
No days	0 (0%)	3 (3%)
Few days	10 (11%)	10 (10%)
Some days	20 (22%)	18 (18%)
Most days	27 (29%)	30 (31%)
All days	35 (38%)	37 (38%)
Missing	0 (0%)	0 (0%)

Appendix Table 4.5: Pain severity in the most painful joint (NRS over last 48 hours) over time by trial arm

Time	HCQ	Placebo
Baseline N	124	123
Mean (SD)	7.3 (1.53)	7.4 (1.56)
Median (minimum, maximum)	8 (3, 10)	8 (2, 10)
3 months N	110	119
Mean (SD)	6.1 (2.31)	6.3 (2.24)
Median (minimum, maximum)	6.5 (0, 10)	7 (0, 10)
6 months N	107	103
Mean (SD)	6.3 (1.99)	5.9 (2.42)
Median (minimum, maximum)	7 (1, 10)	6 (0, 10)
12 months N	92	96
Mean (SD)	5.9 (2.34)	5.9 (2.67)
Median (minimum, maximum)	6 (0, 10)	6.5 (0, 10)

Appendix Table 4.6: Pain severity in the most painful joint (VAS over last 48 hours) over time by trial arm

Time	HCQ	Placebo
Baseline N	124	123
Mean (SD)	73.0 (16.79)	74.2 (16.08)
Median (minimum, maximum)	77 (21, 99)	77 (11, 100)
3 months N	110	119
Mean (SD)	58.8 (25.30)	60.9 (25.47)
Median (minimum, maximum)	63.5 (4, 95)	65 (0, 99)
6 months N	107	103
Mean (SD)	58.3 (23.49)	59.4 (26.01)
Median (minimum, maximum)	62 (10, 100)	65 (1, 99)

12 months N	92	98
Mean (SD)	57.4 (26.15)	56.8 (27.77)
Median (minimum, maximum)	62.5 (0, 100)	63.5 (1, 100)

Appendix Table 4.7: Pain severity in the most painful joint (VAS over last 2 weeks) over time by trial arm

Time	HCQ	Placebo
Baseline N	124	123
Mean (SD)	73.8 (14.91)	74.0 (16.08)
Median (minimum, maximum)	77 (24, 99)	77 (12, 100)
3 months N	110	119
Mean (SD)	58.1 (25.04)	62.7 (24.44)
Median (minimum, maximum)	61 (5, 96)	67 (0, 99)
6 months N	107	103
Mean (SD)	60.5 (21.88)	57.6 (26.22)
Median (minimum, maximum)	64 (11, 99)	64 (3, 99)
12 months N	92	98
Mean (SD)	58.5 (25.75)	58.1 (27.42)
Median (minimum, maximum)	63 (5, 100)	64.5 (0, 100)

Appendix Table 4.8: Pain severity in the most painful thumb over time by trial arm

Time	HCQ	Placebo
Baseline N	123	122
Mean (SD)	5.9 (2.84)	5.5 (2.88)
Median (minimum, maximum)	7 (0, 10)	6 (0, 10)
3 months N	110	117
Mean (SD)	5.0 (2.96)	4.9 (2.82)
Median (minimum, maximum)	5 (0, 10)	5 (0, 10)
6 months N	107	103
Mean (SD)	5.3 (2.63)	4.9 (2.96)
Median (minimum, maximum)	6 (0, 10)	5 (0, 10)
12 months N	92	98
Mean (SD)	5.0 (2.95)	4.6 (2.95)
Median (minimum, maximum)	5 (0, 10)	5 (0, 10)

Appendix Table 4.9: Number of painful joints over time by trial arm

Time	HCQ	Placebo
Baseline N	124	123
Mean (SD)	8.3 (5.87)	8.8 (7.13)
Median (minimum, maximum)	7 (0, 30)	7 (0, 30)
6 months N	104	103
Mean (SD)	5.9 (6.35)	7.0 (8.06)
Median (minimum, maximum)	4 (0, 30)	4 (0, 30)
12 months N	92	98
Mean (SD)	4.9 (5.25)	6.5 (7.80)
Median (minimum, maximum)	3 (0, 22)	3 (0, 30)

Appendix Table 4.10: Number of swollen joints over time by trial arm

Time	HCQ	Placebo
Baseline N	124	123
Mean (SD)	3.8 (4.20)	3.4 (4.37)
Median (minimum, maximum)	3 (0, 20)	1 (0, 22)
6 months N	104	103

Mean (SD)	2.0 (2.76)	1.8 (2.66)
Median (minimum, maximum)	0 (0, 13)	1 (0, 15)
12 months N	92	97
Mean (SD)	2.0 (3.07)	2.1 (2.67)
Median (minimum, maximum)	1 (0, 15)	1 (0, 11)

Appendix Table 4.11: Number of tender joints over time by trial arm

Time	HCQ	Placebo
Baseline N	124	123
Mean (SD)	10.4 (6.27)	10.9 (7.33)
Median (minimum, maximum)	10 (0, 27)	9 (0, 30)
6 months N	104	103
Mean (SD)	7.3 (6.57)	8.4 (8.14)
Median (minimum, maximum)	5 (0, 30)	6 (0, 30)
12 months N	92	98
Mean (SD)	7.4 (6.88)	7.8 (7.97)
Median (minimum, maximum)	5 (0, 30)	6 (0, 30)

Appendix Table 4.12: Global arthritis activity over time by trial arm

Time	HCQ	Placebo
Baseline N	123	123
Mean (SD)	7.0 (1.72)	6.9 (1.86)
Median (minimum, maximum)	7 (3, 10)	7 (2, 10)
3 months N	110	119
Mean (SD)	5.4 (2.35)	5.8 (2.18)
Median (minimum, maximum)	5 (0, 10)	6 (0, 10)
6 months N	106	103
Mean (SD)	5.8 (2.17)	5.5 (2.45)
Median (minimum, maximum)	6 (1, 10)	6 (0, 10)
12 months N	92	97
Mean (SD)	5.4 (2.41)	5.4 (2.73)
Median (minimum, maximum)	6 (0, 10)	6 (0, 10)

Appendix Table 4.13: Satisfaction with Hand Function over time by trial arm

Time	HCQ	Placebo
Baseline N	122	123
Mean (SD)	6.4 (2.02)	6.4 (1.87)
Median (minimum, maximum)	7 (0, 10)	6 (0, 10)
3 months N	110	119
Mean (SD)	5.4 (2.17)	5.5 (2.16)
Median (minimum, maximum)	6 (0, 10)	6 (0, 10)
6 months N	107	103
Mean (SD)	5.4 (2.00)	5.3 (2.44)
Median (minimum, maximum)	6 (0, 10)	5 (0, 10)
12 months N	92	97
Mean (SD)	5.3 (2.51)	5.0 (2.72)
Median (minimum, maximum)	6 (0, 10)	5 (0, 10)

Appendix Table 4.14: Global Improvement in Hand Problem over time by trial arm

Time	HCQ	Placebo
3 Months		
Completely recovered	0 (0%)	0 (0%)

Much better	9 (8%)	10 (8%)
Better	37 (34%)	31 (26%)
No change	40 (36%)	59 (50%)
Worse	20 (18%)	17 (14%)
Much worse	4 (4%)	2 (2%)
Missing	0 (0%)	0 (0%)
6 Months		
Completely recovered	0 (0%)	0 (0%)
Much better	12 (11%)	12 (12%)
Better	32 (30%)	29 (28%)
No change	36 (34%)	43 (42%)
Worse	26 (24%)	15 (15%)
Much worse	1 (1%)	3 (3%)
Missing	0 (0%)	1 (1%)
12 Months		
Completely recovered	0 (0%)	1 (1%)
Much better	14 (15%)	19 (19%)
Better	20 (22%)	14 (14%)
No change	32 (35%)	32 (33%)
Worse	22 (24%)	29 (30%)
Much worse	4 (4%)	3 (3%)
Missing	0 (0%)	0 (0%)

Appendix Table 4.15: Global Improvement in Hand Pain over time by trial arm

Time	HCQ	Placebo
3 Months		
Completely recovered	0 (0%)	0 (0%)
Much better	9 (8%)	12 (10%)
Better	40 (36%)	29 (24%)
No change	36 (33%)	57 (48%)
Worse	21 (19%)	18 (15%)
Much worse	4 (4%)	3 (3%)
Missing	0 (0%)	0 (0%)
6 Months		
Completely recovered	0 (0%)	0 (0%)
Much better	13 (12%)	12 (12%)
Better	31 (29%)	32 (31%)
No change	34 (32%)	39 (38%)
Worse	25 (23%)	17 (17%)
Much worse	4 (4%)	3 (3%)
Missing	0 (0%)	0 (0%)
12 Months		
Completely recovered	1 (1%)	1 (1%)
Much better	11 (12%)	21 (21%)
Better	24 (26%)	14 (14%)
No change	29 (32%)	29 (30%)
Worse	22 (24%)	30 (31%)
Much worse	5 (5%)	2 (2%)
Missing	0 (0%)	1 (1%)

Appendix Table 4.16: Global Improvement in Hand Function over time by trial arm

Time	HCQ	Placebo
3 Months		

Completely recovered	0 (0%)	0 (0%)
Much better	4 (4%)	8 (7%)
Better	31 (28%)	23 (19%)
No change	53 (48%)	69 (58%)
Worse	19 (17%)	17 (14%)
Much worse	3 (3%)	2 (2%)
Missing	0 (0%)	0 (0%)
6 Months		
Completely recovered	0 (0%)	0 (0%)
Much better	6 (6%)	10 (10%)
Better	27 (25%)	18 (17%)
No change	45 (42%)	57 (55%)
Worse	28 (26%)	16 (16%)
Much worse	1 (1%)	2 (2%)
Missing	0 (0%)	0 (0%)
12 Months		
Completely recovered	0 (0%)	3 (3%)
Much better	7 (8%)	12 (12%)
Better	20 (22%)	18 (18%)
No change	31 (34%)	28 (29%)
Worse	33 (36%)	33 (34%)
Much worse	1 (1%)	4 (4%)
Missing	0 (0%)	0 (0%)

Appendix Table 4.17: AUSCAN Total score over time by trial arm

Time	HCQ	Placebo
Baseline N	123	121
Mean (SD)	35.5 (8.69)	36.7 (9.02)
Median (minimum, maximum)	36 (11, 56)	37 (10, 57)
3 months N	108	115
Mean (SD)	32.6 (11.93)	34.0 (10.84)
Median (minimum, maximum)	34 (5, 58)	33 (2, 57)
6 months N	104	101
Mean (SD)	32.2 (10.22)	32.8 (11.90)
Median (minimum, maximum)	33 (5, 53)	34 (4, 59)
12 months N	90	98
Mean (SD)	31.6 (11.45)	31.8 (13.84)
Median (minimum, maximum)	32 (7, 57)	35.5 (0, 58)

Appendix Table 4.18: Pain severity in all joints over time by trial arm

Time	HCQ	Placebo
Baseline N	123	121
Mean (SD)	6.7 (2.01)	7.0 (1.89)
Median (minimum, maximum)	7 (0, 10)	7 (0, 10)
3 months N	110	117
Mean (SD)	5.6 (2.32)	5.7 (2.26)
Median (minimum, maximum)	6 (0, 9)	6 (0, 10)
6 months N	107	103
Mean (SD)	6.0 (1.99)	6.0 (2.21)
Median (minimum, maximum)	6 (1, 10)	6 (1, 10)
12 months N	91	96
Mean (SD)	5.7 (2.41)	5.6 (2.60)
Median (minimum, maximum)	6 (1, 10)	6 (0, 10)

Appendix Table 4.19: HADS Anxiety over time by trial arm

Time	HCQ	Placebo
Baseline N	124	122
Mean (SD)	7.0 (4.11)	6.6 (3.98)
Median (minimum, maximum)	7 (0, 18)	6 (0, 16)
6 months N	106	102
Mean (SD)	6.3 (4.31)	5.6 (3.68)
Median (minimum, maximum)	6 (0, 17)	5 (0, 15)
12 months N	92	98
Mean (SD)	6.0 (4.15)	5.5 (4.27)
Median (minimum, maximum)	5 (0, 17)	5 (0, 18)

Appendix Table 4.20: HADS Depression over time by trial arm

Time	HCQ	Placebo
Baseline N	124	122
Mean (SD)	4.6 (3.31)	4.4 (3.02)
Median (minimum, maximum)	4 (0, 15)	3 (0, 13)
6 months N	106	102
Mean (SD)	4.4 (3.84)	3.5 (2.93)
Median (minimum, maximum)	3 (0, 18)	3 (0, 13)
12 months N	92	98
Mean (SD)	4.0 (3.82)	3.7 (3.14)
Median (minimum, maximum)	3 (0, 18)	3 (0, 14)

Appendix Table 4.21: EQ-5D Mobility over time by trial arm

Time	HCQ	Placebo
Baseline, N	124	123
No problems	52 (42%)	52 (42%)
Slight problems	37 (30%)	27 (22%)
Moderate problems	27 (22%)	31 (25%)
Severe problems	8 (6%)	12 (10%)
Unable to walk	0 (0%)	0 (0%)
Missing	0 (0%)	1 (1%)
6 Months, N	107	103
No problems	45 (42%)	37 (36%)
Slight problems	27 (25%)	31 (30%)
Moderate problems	26 (24%)	25 (24%)
Severe problems	8 (7%)	10 (10%)
Unable to walk	0 (0%)	0 (0%)
Missing	1 (1%)	0 (0%)
12 Months, N	92	98
No problems	37 (40%)	40 (41%)
Slight problems	26 (28%)	24 (24%)
Moderate problems	22 (24%)	23 (23%)
Severe problems	7 (8%)	9 (9%)
Unable to walk	0 (0%)	1 (1%)
Missing	0 (0%)	1 (1%)

Appendix Table 4.22: EQ-5D Self-Care over time by trial arm

Time	HCQ	Placebo
Baseline, N	124	123
No problems	87 (70%)	77 (63%)

Slight problems	24 (19%)	30 (24%)
Moderate problems	12 (10%)	13(11%)
Severe problems	1 (1%)	2 (2%)
Unable to wash or dress oneself	0 (0%)	0 (0%)
Missing	0 (0%)	1 (1%)
6 Months, N	107	103
No problems	79 (74%)	73 (71%)
Slight problems	16 (15%)	17 (17%)
Moderate problems	11 (10%)	9 (9%)
Severe problems	0 (0%)	4 (4%)
Unable to wash or dress oneself	0 (0%)	0 (0%)
Missing	1 (1%)	0 (0%)
12 Months, N	92	98
No problems	70 (76%)	73 (74%)
Slight problems	13 (14%)	15 (15%)
Moderate problems	8 (9%)	8 (8%)
Severe problems	1 (1%)	2 (2%)
Unable to wash or dress oneself	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)

Appendix Table 4.23: EQ-5D Usual Activities over time by trial arm

Time	HCQ	Placebo
Baseline, N	124	123
No problems	27 (22%)	25 (20%)
Slight problems	50 (40%)	55 (45%)
Moderate problems	37 (30%)	34 (28%)
Severe problems	10 (8%)	7 (6%)
Unable to do usual activities	0 (0%)	1 (1%)
Missing	0 (0%)	1 (1%)
6 Months, N	107	103
No problems	38 (36%)	31 (30%)
Slight problems	33 (31%)	36 (35%)
Moderate problems	29 (27%)	28 (27%)
Severe problems	7 (7%)	8 (8%)
Unable to do usual activities	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)
12 Months, N	92	98
No problems	33 (36%)	32 (33%)
Slight problems	35 (38%)	33 (34%)
Moderate problems	19 (21%)	27 (28%)
Severe problems	4 (4%)	6 (6%)
Unable to do usual activities	1 (1%)	0 (0%)
Missing	0 (0%)	0 (0%)

Appendix Table 4.24: EQ-5D Pain / Discomfort over time by trial arm

Time	HCQ	Placebo
Baseline, N	124	123
None	1 (1%)	2 (2%)
Slight	14 (11%)	14 (11%)
Moderate	78 (63%)	75 (61%)
Severe	30 (24%)	28 (23%)
Extreme	1 (1%)	2 (2%)
Missing	0 (0%)	2 (2%)

6 Months, N	107	103
None	0 (0%)	0 (0%)
Slight	33 (31%)	29 (28%)
Moderate	53 (50%)	54 (52%)
Severe	18 (17%)	20 (19%)
Extreme	3 (3%)	0 (0%)
Missing	0 (0%)	0 (0%)
12 Months, N	92	98
None	1 (1%)	5 (5%)
Slight	28 (30%)	37 (38%)
Moderate	43 (47%)	33 (34%)
Severe	17 (18%)	22 (22%)
Extreme	2 (2%)	1 (1%)
Missing	1 (1%)	0 (0%)

Appendix Table 4.25: EQ-5D Anxiety / Depression over time by trial arm

Time	HCQ	Placebo
Baseline, N	124	123
None	64 (52%)	73 (59%)
Slight	35 (28%)	30 (24%)
Moderate	21 (17%)	19 (15%)
Severe	2 (2%)	0 (0%)
Extreme	1 (1%)	0 (0%)
Missing	1 (1%)	1 (1%)
6 Months, N	107	103
None	64 (60%)	67 (65%)
Slight	22 (21%)	28 (27%)
Moderate	16 (15%)	8 (8%)
Severe	4 (4%)	0 (0%)
Extreme	0 (0%)	0 (0%)
Missing	1 (1%)	0 (0%)
12 Months, N	92	98
None	53 (58%)	62 (63%)
Slight	28 (30%)	26 (27%)
Moderate	7 (8%)	9 (9%)
Severe	3 (3%)	1 (1%)
Extreme	0 (0%)	0 (0%)
Missing	1 (1%)	0 (0%)

63 **Appendix Table 4.26: Kallman radiograph score – Osteophytes**

	HCQ	Placebo	Total
Total			
Baseline N	94	94	188
Mean (SD)	15.1 (9.96)	16.8 (10.81)	16.0 (10.40)
Median (minimum, maximum)	13 (0, 40)	15 (1, 46)	13.5 (0, 46)
12 months N	79	78	157
Mean (SD)	15.9 (10.27)	18.2 (11.49)	17.0 (10.92)
Median (minimum, maximum)	13 (0, 40)	16.5 (1, 48)	15 (0, 48)
Change from Baseline N	79	78	157
Mean (SD)	0.4 (0.77)	0.5 (0.83)	0.4 (0.80)
Median (minimum, maximum)	0 (-2, 3)	0 (0, 4)	0 (-2, 4)
DIP			
Baseline N	94	94	188
Mean (SD)	6.6 (4.49)	8.2 (5.55)	7.4 (5.09)
Median (minimum, maximum)	6 (0, 19)	7.5 (0, 21)	7 (0, 21)
12 months N	79	78	157
Mean (SD)	6.9 (4.62)	8.7 (5.84)	7.8 (5.32)
Median (minimum, maximum)	7 (0, 19)	8 (0, 21)	7 (0, 21)
Change from Baseline N	79	78	157
Mean (SD)	0.2 (0.45)	0.2 (0.50)	0.2 (0.47)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
PIP/IP			
Baseline N	94	94	188
Mean (SD)	6.6 (5.71)	6.5 (5.42)	6.5 (5.55)
Median (minimum, maximum)	5 (0, 23)	5 (0, 24)	5 (0, 24)
12 months N	79	78	157
Mean (SD)	6.9 (5.92)	7.1 (5.87)	7.0 (5.88)
Median (minimum, maximum)	5 (0, 23)	6 (0, 24)	5 (0, 24)
Change from Baseline N	79	78	157
Mean (SD)	0.2 (0.50)	0.2 (0.57)	0.2 (0.54)
Median (minimum, maximum)	0 (0, 3)	0 (-1, 2)	0 (-1, 3)
CMC			
Baseline N	94	94	188
Mean (SD)	1.4 (1.58)	1.56 (1.69)	1.5 (1.63)
Median (minimum, maximum)	1 (0, 6)	1 (0, 6)	1 (0, 6)
12 months N	79	78	157
Mean (SD)	1.51 (1.62)	1.6 (1.70)	1.6 (1.65)
Median (minimum, maximum)	1 (0, 6)	1 (0, 6)	1 (0, 6)
Change from Baseline N	79	78	157
Mean (SD)	0.0 (0.11)	0.1 (0.22)	0.0 (0.18)
Median (minimum, maximum)	0 (0, 1)	0 (0, 1)	0 (0, 1)
STT			
Baseline N	94	94	188
Mean (SD)	0.5 (0.80)	0.6 (0.99)	0.6 (0.90)
Median (minimum, maximum)	0 (0, 3)	0 (0, 5)	0 (0, 5)
12 months N	79	78	157
Mean (SD)	0.5 (0.80)	0.7 (1.08)	0.6 (0.95)
Median (minimum, maximum)	0 (0, 3)	0 (0, 5)	0 (0, 5)
Change from Baseline N	79	78	157
Mean (SD)	0.0 (0.28)	0.0 (0.23)	0.0 (0.25)
Median (minimum, maximum)	0 (-2, 1)	0 (0, 2)	0 (-2, 2)

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Appendix Table 4.27: Kallman radiograph score – Joint Space Narrowing

	HCQ	Placebo	Total
Total			
Baseline N	94	94	188
Mean (SD)	14.7 (9.47)	16.9 (10.20)	15.8 (9.88)
Median (minimum, maximum)	13.5 (0, 35)	15 (0, 40)	14 (0, 40)
12 months N	79	78	157
Mean (SD)	15.7 (9.61)	18.4 (10.97)	17.0 (10.37)
Median (minimum, maximum)	15 (0, 33)	17 (0, 46)	15 (0, 46)
Change from Baseline N	79	78	157
Mean (SD)	0.7 (1.14)	1.0 (1.57)	0.8 (1.38)
Median (minimum, maximum)	0 (-2, 4)	1 (-3, 7)	1 (-3, 7)
DIP			
Baseline N	94	94	188
Mean (SD)	7.3 (4.75)	8.7 (4.88)	8.0 (4.85)
Median (minimum, maximum)	7 (0, 18)	8 (0, 19)	8 (0, 19)
12 months N	79	78	157
Mean (SD)	7.6 (4.72)	9.4 (5.32)	8.5 (5.09)
Median (minimum, maximum)	8 (0, 18)	9.5 (0, 20)	9 (0, 20)
Change from Baseline N	79	78	157
Mean (SD)	0.2 (0.65)	0.5 (0.96)	0.4 (0.83)
Median (minimum, maximum)	0 (-2, 2)	0 (-2, 4)	0 (-2, 4)
PIP/IP			
Baseline N	94	94	157
Mean (SD)	5.2 (4.90)	5.9 (5.37)	5.5 (5.14)
Median (minimum, maximum)	4 (0, 19)	4 (0, 19)	4 (0, 19)
12 months N	79	78	157
Mean (SD)	5.7 (5.00)	6.5 (5.84)	6.1 (5.42)
Median (minimum, maximum)	4 (0, 16)	4 (0, 21)	4 (0, 21)
Change from Baseline N	79	78	157
Mean (SD)	0.3 (0.72)	0.3 (0.88)	0.3 (0.80)
Median (minimum, maximum)	0 (-3, 3)	0 (-3, 4)	0 (-3, 4)
CMC			
Baseline N	94	94	188
Mean (SD)	0.9 (1.34)	1.0 (1.41)	0.9 (1.37)
Median (minimum, maximum)	0 (0, 5)	0 (0, 6)	0 (0, 6)
12 months N	79	78	157
Mean (SD)	1.0 (1.43)	1.0 (1.41)	1.0 (1.42)
Median (minimum, maximum)	0 (0, 5)	0 (0, 6)	0 (0, 6)
Change from Baseline N	79	78	157
Mean (SD)	0.1 (0.42)	0.1 (0.42)	0.1 (0.42)
Median (minimum, maximum)	0 (-1, 2)	0 (-2, 1)	0 (-2, 2)
STT			
Baseline N	94	94	188
Mean (SD)	1.2 (1.49)	1.4 (1.54)	1.3 (1.51)
Median (minimum, maximum)	1 (0, 5)	1 (0, 6)	1 (0, 6)
12 months N	79	78	157
Mean (SD)	1.4 (1.56)	1.4 (1.52)	1.4 (1.54)
Median (minimum, maximum)	1 (0, 5)	1 (0, 6)	1 (0, 6)
Change from Baseline N	79	78	157
Mean (SD)	0.1 (0.32)	0.1 (0.55)	0.1 (0.45)
Median (minimum, maximum)	0 (0, 1)	0 (-2, 2)	0 (-2, 2)

67 **Appendix Table 4.28: Kallman radiograph score – Subchondral bone cyst**

	HCQ	Placebo	Total
Total			
Baseline N	94	94	188
Mean (SD)	4.7 (3.26)	4.1 (2.52)	4.4 (2.92)
Median (minimum, maximum)	4 (0, 14)	4 (0, 13)	4 (0, 14)
12 months N	79	78	157
Mean (SD)	5.3 (3.38)	4.5 (2.56)	4.9 (3.01)
Median (minimum, maximum)	5 (0, 14)	4 (0, 12)	5 (0, 14)
Change from Baseline N	79	78	157
Mean (SD)	0.6 (0.98)	0.6 (1.09)	0.6 (1.03)
Median (minimum, maximum)	0 (-1, 4)	0 (-1, 5)	0 (-1, 5)
DIP			
Baseline N	94	94	188
Mean (SD)	2.3 (1.56)	1.9 (1.40)	2.1 (1.50)
Median (minimum, maximum)	2 (0, 6)	2 (0, 5)	2 (0, 6)
12 months N	79	78	157
Mean (SD)	2.5 (1.62)	2.3 (1.58)	2.4 (1.60)
Median (minimum, maximum)	2 (0, 6)	2 (0, 6)	2 (0, 6)
Change from Baseline N	79	78	157
Mean (SD)	0.2 (0.54)	0.4 (0.81)	0.3 (0.70)
Median (minimum, maximum)	0 (-1, 3)	0 (-1, 4)	0 (-1, 4)
PIP/IP			
Baseline N	94	94	188
Mean (SD)	1.9 (1.92)	1.6 (1.60)	1.8 (1.77)
Median (minimum, maximum)	1 (0, 8)	1 (0, 7)	1 (0, 8)
12 months N	79	78	157
Mean (SD)	2.2 (2.01)	1.7 (1.66)	1.9 (1.85)
Median (minimum, maximum)	2 (0, 8)	1 (0, 8)	1 (0, 8)
Change from Baseline N	79	78	157
Mean (SD)	0.3 (0.56)	0.1 (0.50)	0.2 (0.54)
Median (minimum, maximum)	0 (0, 2)	0 (-1, 2)	0 (-1, 2)
CMC			
Baseline N	94	94	188
Mean (SD)	0.3 (0.56)	0.3 (0.60)	0.3 (0.58)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
12 months N	79	78	157
Mean (SD)	0.4 (0.61)	0.36 (0.60)	0.4 (0.6)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
Change from Baseline N	79	78	157
Mean (SD)	0.1 (0.30)	0.1 (0.32)	0.1 (0.31)
Median (minimum, maximum)	0 (0, 1)	0 (-1, 1)	0 (-1, 1)
STT			
Baseline N	94	94	188
Mean (SD)	0.1 (0.39)	0.2 (0.41)	0.2 (0.40)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
12 months N	79	78	157
Mean (SD)	0.2 (0.45)	0.2 (0.43)	0.2 (0.44)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
Change from Baseline N	79	78	157
Mean (SD)	0.0 (0.28)	0.0 (0.16)	0.0 (0.23)
Median (minimum, maximum)	0 (-1, 2)	0 (0, 1)	0 (-1, 2)

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Appendix Table 4.29: Kallman radiograph score – Subchondral bone sclerosis

	HCQ	Placebo	Total
Total			
Baseline N	94	94	188
Mean (SD)	6.6 (4.46)	7.4 (4.81)	7.0 (4.65)
Median (minimum, maximum)	6 (0, 19)	6.5 (0, 18)	6 (0, 19)
12 months N	79	78	157
Mean (SD)	6.7 (4.59)	7.9 (4.93)	7.3 (4.78)
Median (minimum, maximum)	6 (0, 19)	8 (0, 19)	6 (0, 19)
Change from Baseline N	79	78	157
Mean (SD)	0.2 (0.54)	0.3 (0.60)	0.3 (0.57)
Median (minimum, maximum)	0 (0, 2)	0 (-1, 2)	0 (-1, 2)
DIP			
Baseline N	94	94	188
Mean (SD)	3.0 (2.1)	3.6 (2.33)	3.3 (2.21)
Median (minimum, maximum)	3 (0, 8)	3 (0, 8)	3 (0, 8)
12 months N	79	78	157
Mean (SD)	3.1 (2.08)	3.7 (2.37)	3.4 (2.25)
Median (minimum, maximum)	3 (0, 8)	4 (0, 8)	3 (0, 8)
Change from Baseline N	79	78	157
Mean (SD)	0.2 (0.43)	0.1 (0.48)	0.1 (0.43)
Median (minimum, maximum)	0 (0, 2)	0 (-1, 2)	0 (-1, 2)
PIP/IP			
Baseline N	94	94	188
Mean (SD)	2.5 (2.57)	2.8 (2.73)	2.7 (2.65)
Median (minimum, maximum)	2 (0, 9)	2 (0, 10)	2 (0, 10)
12 months N	79	78	157
Mean (SD)	2.6 (2.65)	3.1 (2.78)	2.8 (2.71)
Median (minimum, maximum)	2 (0, 9)	2 (0, 10)	2 (0, 10)
Change from Baseline N	79	78	157
Mean (SD)	0.1 (0.25)	0.1 (0.32)	0.1 (0.29)
Median (minimum, maximum)	0 (0, 1)	0 (0, 1)	0 (0, 1)
CMC			
Baseline N	94	94	188
Mean (SD)	0.7 (0.85)	0.7 (0.85)	0.7 (0.85)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
12 months N	79	78	157
Mean (SD)	0.7 (0.83)	0.7 (0.84)	0.7 (0.83)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
Change from Baseline N	79	78	157
Mean (SD)	0.0 (0.11)	0.0 (0.11)	0.0 (0.11)
Median (minimum, maximum)	0 (0, 1)	0 (0, 1)	0 (0, 1)
STT			
Baseline N	94	94	188
Mean (SD)	0.4 (0.72)	0.3 (0.61)	0.4 (0.67)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
12 months N	79	78	157
Mean (SD)	0.4 (0.72)	0.3 (0.62)	0.4 (0.67)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
Change from Baseline N	79	78	157
Mean (SD)	0.0 (0.11)	0.0 (0.20)	0.0 (0.16)
Median (minimum, maximum)	0 (0, 1)	0, (-1, 1)	0 (-1, 1)

71 **Appendix Table 4.30: Kallman radiograph score – Lateral bone deviation**

	HCQ	Placebo	Total
Total			
Baseline N	94	94	188
Mean (SD)	1.1 (1.61)	1.2 (1.64)	1.2 (1.62)
Median (minimum, maximum)	0.5 (0, 9)	1 (0, 8)	1 (0, 9)
12 months N	79	78	157
Mean (SD)	1.2 (1.68)	1.5 (1.70)	1.4 (1.69)
Median (minimum, maximum)	1 (0, 9)	1 (0, 6)	1 (0, 9)
Change from Baseline N	79	78	157
Mean (SD)	0.2 (0.46)	0.2 (0.61)	0.2 (0.54)
Median (minimum, maximum)	0 (0, 2)	0 (-1, 3)	0 (-1, 3)
DIP			
Baseline N	94	94	188
Mean (SD)	0.5 (0.95)	0.6 (1.08)	0.6 (1.01)
Median (minimum, maximum)	0 (0, 5)	0 (0, 6)	0 (0, 6)
12 months N	79	78	157
Mean (SD)	0.5 (0.83)	0.8 (1.17)	0.6 (1.01)
Median (minimum, maximum)	0 (0, 4)	0 (0, 5)	0 (0, 5)
Change from Baseline N	79	78	157
Mean (SD)	0.1 (0.32)	0.2 (0.46)	0.1 (0.40)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
PIP/IP			
Baseline N	94	94	188
Mean (SD)	0.3 (0.89)	0.3 (0.71)	0.3 (0.80)
Median (minimum, maximum)	0 (0, 5)	0 (0, 4)	0 (0, 5)
12 months N	79	78	157
Mean (SD)	0.5 (1.02)	0.4 (0.79)	0.4 (0.91)
Median (minimum, maximum)	0 (0, 5)	0 (0, 4)	0 (0, 5)
Change from Baseline N	79	78	157
Mean (SD)	0.1 (0.34)	0.0 (0.30)	0.1 (0.33)
Median (minimum, maximum)	0 (0, 2)	0 (-1, 2)	0 (-1, 2)
CMC			
Baseline N	94	94	188
Mean (SD)	0.2 (0.53)	0.3 (0.65)	0.3 (0.59)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
12 months N	79	78	157
Mean (SD)	0.3 (0.57)	0.3 (0.62)	0.3 (0.59)
Median (minimum, maximum)	0 (0, 2)	0 (0, 2)	0 (0, 2)
Change from Baseline N	79	78	157
Mean (SD)	0.0 (0.0)	0.0 (0.11)	0.0 (0.08)
Median (minimum, maximum)	0 (0, 0)	0 (0, 1)	0 (0, 1)
STT			
Baseline N	94	94	188
Mean (SD)	0.0 (0.15)	0.0 (0.00)	0.0 (0.10)
Median (minimum, maximum)	0 (0, 1)	0 (0, 0)	0 (0, 1)
12 months N	79	78	157
Mean (SD)	0.0 (0.11)	0.0 (0.00)	0.0 (0.08)
Median (minimum, maximum)	0 (0, 1)	0 (0, 0)	0 (0, 1)
Change from Baseline N	79	78	157
Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
Median (minimum, maximum)	0 (0, 0)	0 (0, 0)	0 (0, 0)

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Appendix Table 4.31: Kallman radiograph score – Bone erosion

	HCQ	Placebo	Total
Total			
Baseline N	94	94	188
Mean (SD)	0.6 (1.37)	0.8 (1.48)	0.7 (1.42)
Median (minimum, maximum)	0 (0, 9)	0 (0, 7)	0 (0, 9)
12 months N	79	78	157
Mean (SD)	0.8 (1.75)	1.0 (1.73)	0.9 (1.74)
Median (minimum, maximum)	0 (0, 9)	0 (0, 8)	0 (0, 9)
Change from Baseline N	79	78	157
Mean (SD)	0.2 (0.59)	0.2 (0.44)	0.2 (0.52)
Median (minimum, maximum)	0 (0, 3)	0 (0, 2)	0 (0, 3)
DIP			
Baseline N	94	94	188
Mean (SD)	0.4 (0.80)	0.6 (1.15)	0.5 (0.99)
Median (minimum, maximum)	0 (0, 5)	0 (0, 6)	0 (0, 6)
12 months N	79	78	157
Mean (SD)	0.5 (1.06)	0.7 (1.26)	0.6 (1.16)
Median (minimum, maximum)	0 (0, 5)	0 (0, 6)	0 (0, 6)
Change from Baseline N	79	78	157
Mean (SD)	0.1 (0.49)	0.1 (0.35)	0.1 (0.42)
Median (minimum, maximum)	0 (0, 3)	0 (0, 2)	0 (0, 3)
PIP/IP			
Baseline N	94	94	188
Mean (SD)	0.2 (0.65)	0.2 (0.68)	0.2 (0.67)
Median (minimum, maximum)	0 (0, 4)	0 (0, 4)	0 (0, 4)
12 months N	79	78	157
Mean (SD)	0.3 (0.85)	0.3 (0.79)	0.3 (0.82)
Median (minimum, maximum)	0 (0, 4)	0 (0, 4)	0 (0, 4)
Change from Baseline N	79	78	157
Mean (SD)	0.1 (0.29)	0.0 (0.19)	0.1 (0.25)
Median (minimum, maximum)	0 (0, 2)	0 (0, 1)	0 (0, 2)
CMC			
Baseline N	94	94	188
Mean (SD)	0.0 (0.25)	0.0 (0.00)	0.0 (0.18)
Median (minimum, maximum)	0 (0, 2)	0 (0, 0)	0 (0, 2)
12 months N	79	78	157
Mean (SD)	0.1 (0.29)	0.0 (0.16)	0.0 (0.24)
Median (minimum, maximum)	0 (0, 2)	0 (0, 1)	0 (0, 2)
Change from Baseline N	79	78	157
Mean (SD)	0.0 (0.11)	0.0 (0.16)	0.0 (0.14)
Median (minimum, maximum)	0 (0, 1)	0 (0, 1)	0 (0, 1)
STT			
Baseline N	94	94	188
Mean (SD)	0.0 (0.15)	0.0 (0.00)	0.0 (0.10)
Median (minimum, maximum)	0 (0, 1)	0 (0, 0)	0 (0, 1)
12 months N	79	78	157
Mean (SD)	0.0 (0.11)	0.0 (0.00)	0.0 (0.08)
Median (minimum, maximum)	0 (0, 1)	0 (0, 0)	0 (0, 1)
Change from Baseline N	79	78	157
Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
Median (minimum, maximum)	0 (0, 0)	0 (0, 0)	0 (0, 0)

Appendix Table 4.32: Number of other painful joints (from pain manikin)

Time	HCQ	Placebo
Baseline N	124	123
Mean (SD)	5.8 (2.78)	5.9 (3.11)
Median (minimum, maximum)	6 (0, 12)	5 (0, 14)
3 months N	110	119
Mean (SD)	5.2 (2.87)	5.4 (3.14)
Median (minimum, maximum)	5 (0, 13)	5 (0, 14)
6 months N	107	103
Mean (SD)	5.3 (2.94)	5.6 (3.29)
Median (minimum, maximum)	5 (0, 14)	5 (0, 14)
12 months N	92	98
Mean (SD)	5.2 (2.94)	5.3 (3.41)
Median (minimum, maximum)	5 (0, 14)	5 (0, 14)

Appendix Table 4.33 Pill Counts Dispensed and Returned (Bottle 1)

	HCQ		Placebo	
	N	Pill Count	N	Pill Count
Mean Daily Dose: 200mg				
Dispensed	7	186	14	186
Expected Use	7	91	14	91
Expected Return	7	95	14	95
Actual Returned with Pills, mean (SD)	4	97.5 (11.93)	10	101.2 (10.03)
Difference Returned-Expected , mean (SD)	4	2.5 (11.93)	10	6.2 (10.03)
Mean Daily Dose: 300mg				
Dispensed	85	186	90*	186
Expected Use	85	136	90	136
Expected Return	85	50	90	50
Actual Returned with Pills, mean (SD)	47	60.2 (23.01)	48	51.1 (15.37)
Difference Returned-Expected , mean (SD)	47	10.2 (23.01)	48	1.1 (15.37)
Mean Daily Dose: 400mg				
Dispensed	32	186	20	186
Expected Use	32	182	20	182
Expected Return	32	4	20	4
Actual Returned with Pills, mean (SD)	15	22.3 (17.41)	12	16.8 (20.31)
Difference Returned-Expected , mean (SD)	15	18.3 (17.41)	12	12.8 (20.31)

* includes one patient randomised in error, dose was decided but study drug not dispensed

Appendix **Table 4.34: Pill Counts Dispensed and Returned (Bottle 2)**

	HCQ		Placebo	
	N	**Pill Count**	**N**	**Pill Count**
Mean Daily Dose: 200mg				
Dispensed	5	186	13	186
Expected Use	5	91	13	91
Expected Return	5	95	13	95
Actual Returned with Pills, mean (SD)	4	94.5 (23.10)	9	105.3 (25.33)
Difference Returned-Expected , mean (SD)	4	-0.5 (23.10)	9	10.3 (25.33)
Mean Daily Dose: 300mg				
Dispensed	73	186	79	186
Expected Use	73	136	79	136
Expected Return	73	50	79	50
Actual Returned with Pills, mean (SD)	41	66.7 (26.29)	36	64.8 (37.00)
Difference Returned-Expected , mean (SD)	41	16.7 (26.29)	36	14.8 (37.00)
Mean Daily Dose: 400mg				
Dispensed	28	186	17	186
Expected Use	28	182	17	182
Expected Return	28	4	17	4
Actual Returned with Pills, mean (SD)	13	22.2 (18.63)	8	20.6 (13.54)
Difference Returned-Expected , mean (SD)	13	18.2 (18.63)	8	16.6 (13.54(

Appendix Table 2.35: Pill Counts Dispensed and Returned (Bottle 3)

	HCQ		Placebo	
	N	**Pill Count**	**N**	**Pill Count**
Mean Daily Dose: 200mg				
Dispensed	4	186	12	186
Expected Use	4	91	12	91
Expected Return	4	95	12	95
Actual Returned with Pills, mean (SD)	2	100.5 (0.71)	4	107.0 (12.03)
Difference Returned-Expected , mean (SD)	2	5.5 (0.71)	4	12.0 (12.03)
Mean Daily Dose: 300mg				
Dispensed	67	186	65	186
Expected Use	67	136	65	136
Expected Return	67	50	65	50
Actual Returned with Pills, mean (SD)	17	64.4 (30.17)	13	63.2 (42.13)
Difference Returned-Expected , mean (SD)	17	14.4 (30.17)	13	13.2 (42.13)
Mean Daily Dose: 400mg				
Dispensed	26	186	15	186
Expected Use	26	182	15	182
Expected Return	26	4	15	4
Actual Returned with Pills, mean (SD)	3	18.0 (2.65)	2	11.0 (15.56)
Difference Returned-Expected , mean (SD)	3	14.0 (2.65)	2	7.0 (15.56)

Appendix Table 4.36: Pill Counts Dispensed and Returned (Bottle 4)

	HCQ		Placebo	
	N	**Pill Count**	**N**	**Pill Count**
Mean Daily Dose: 200mg				
Dispensed	4	186	9	186
Expected Use	4	91	9	91
Expected Return	4	95	9	95
Actual Returned with Pills, mean (SD)	2	74.0 (29.70)	1	111 (-)
Difference Returned-Expected , mean (SD)	2	-21.0 (29.70)	1	16 (-)
Mean Daily Dose: 300mg				
Dispensed	49	186	55	186
Expected Use	49	136	55	136
Expected Return	49	50	55	50
Actual Returned with Pills, mean (SD)	5	101.0 (78.74)	9	67.9 (49.23)
Difference Returned-Expected , mean (SD)	5	51.0 (78.74)	9	17.9 (49.23)
Mean Daily Dose: 400mg				
Dispensed	22	186	12	186
Expected Use	22	182	12	182
Expected Return	22	4	12	4
Actual Returned with Pills, mean (SD)	0	-	0	-
Difference Returned-Expected , mean (SD)	0	-	0	-

Appendix Table 5: Safety outcomes

Appendix Table 5.1: Serious Adverse Events

	HCQ 7 events	Placebo 8 events	Total 15 events
Relatedness to IMP			
Unrelated to IMP	4 (57.1%)	8 (100%)	12 (80.0%)
IMP (blind not broken)	1 (14.3%)	0 (0.0%)	1 (6.7%)
IMP (unblinded)	2 (28.6%)	0 (0.0%)	2 (13.3%)
Resolution			
Recovered	5 (71.4%)	2 (25.0%)	7 (46.7%)
Recovering	0 (0.0%)	2 (25.0%)	2 (13.3%)
Recovered with sequelae	0 (0.0%)	1 (12.5%)	1 (6.7%)
Not recovered	2 (28.6%)	3 (37.5%)	5 (33.3%)
Patients			
Number of patients with one or more adverse events	7 (5.6% of 124 randomised)	8 (6.5% of 124 randomised)	15 (6.0% of 248 randomised)
Average number of SAEs per patient (Mean, SD)	0.056 (0.232)	0.065 (0.247)	0.060 (0.239)

Appendix Table 5.2: Non-Serious Adverse Events

	HCQ 153 events	Placebo 135 events	Total 288 events
Severity			
Mild	112 (73.2%)	88 (65.2%)	200 (69.4%)
Moderate	38 (24.8%)	47 (34.8%)	85 (29.5%)
Severe	2 (1.3%)	0 (0.0%)	2 (0.7%)
Missing	1 (0.7%)	0 (0.0%)	1 (0.4%)
Relatedness to IMP			
Unrelated	32 (20.9%)	46 (34.1%)	78 (27.1%)
Unlikely to be related	78 (51.0%)	71 (52.6%)	149 (51.7%)
Possibly related	37 (24.1%)	14 (10.4%)	51 (17.7%)
Probably related	6 (3.9%)	4 (3.0%)	10 (3.5%)
Definitely related	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients			
Number of patients with one or more adverse events	61 (49.2% of 124 patients randomised)	53 (42.7% of 124 patients randomised)	134 (54.0% of 248 patients randomised)
Average number of NSAEs per patient (Mean, SD)	1.2 (1.77)	1.1 (1.68)	1.2 (1.72)

Appendix Table 5.3: Blood pressure (in mmHG)

	HCQ	Placebo	Total
Systolic blood pressure			
Baseline, N	124	124	248
Mean (SD)	136.8 (20.14)	136.8 (19.25)	136.8 (19.66)
Median (minimum, maximum)	136 (92, 191)	136 (97, 222)	136 (92, 222)
6 months, N	104	103	207
Mean (SD)	133.7 (19.29)	133.5 (14.67)	133.6 (17.10)
Median (minimum, maximum)	131.5 (96, 200)	134 (96, 170)	134 (96, 200)
12 months, N	92	98	190
Mean (SD)	134.0 (20.69)	134.8 (15.67)	134.4 (18.23)
Median (minimum, maximum)	131.5 (88, 216)	137 (95, 175)	135 (88, 216)
Change from Baseline, N	92	98	190
Mean (SD)	-2.7 (15.40)	-2.6 (15.65)	-2.7 (15.49)
Median (minimum, maximum)	-5 (-33, 71)	-0.5 (-62, 45)	-1.5 (-62, 71)
Diastolic blood pressure			
Baseline, N	124	124	248
Mean (SD)	78.4 (10.01)	78.1 (9.19)	78.2 (9.59)
Median (minimum, maximum)	78.5 (55, 110)	78.5 (57, 100)	78.5 (55, 110)
6 months, N	104	103	207
Mean (SD)	76.5 (8.86)	77.3 (8.86)	76.9 (8.85)
Median (minimum, maximum)	76 (58, 101)	77 (55, 96)	76 (55, 101)
12 months, N	92	98	190
Mean (SD)	77.1 (8.81)	78.9 (9.73)	78.0 (9.32)
Median (minimum, maximum)	77.5 (52, 104)	79 (55, 99)	78 (52, 104)
Change from Baseline, N	92	98	190
Mean (SD)	-1.9 (9.40)	0.5 (9.26)	-0.7 (9.38)
Median (minimum, maximum)	-3.5 (-22, 31)	1 (-21, 28)	-1 (-22, 31)

Appendix Table 5.4: Pulse (in beats/min)

	HCQ	Placebo	Total
Baseline, N	124	124	248
Mean (SD)	72.0 (9.90)	71.3 (10.16)	71.6 (10.02)
Median (minimum, maximum)	72 (52, 96)	72 (48, 104)	72 (48, 104)
6 months, N	104	103	207
Mean (SD)	71.2 (11.0)	72.2 (9.76)	71.7 (10.38)
Median (minimum, maximum)	72 (47, 101)	71 (56, 102)	71 (47, 102)
12 months, N	92	98	190
Mean (SD)	71.9 (9.74)	73.1 (10.22)	72.5 (9.98)
Median (minimum, maximum)	71 (53, 101)	72 (54, 105)	72 (53, 105)
Change from Baseline, N	92	98	190
Mean (SD)	0.7 (8.44)	1.6 (11.05)	1.1 (9.86)
Median (minimum, maximum)	1.5 (-18, 20)	0.5 (-23, 30)	1 (-23, 30)

Appendix Table 5.5: Temperature (in °C)

	HCQ	Placebo	Total
Baseline, N	121	123	244
Mean (SD)	36.4 (0.42)	36.5 (0.49)	36.4 (0.46)
Median (minimum, maximum)	36.3 (34.7, 37.5)	36.5 (35, 37.6)	36.4 (34.7, 37.6)
6 months, N	102	100	202
Mean (SD)	36.4 (0.45)	36.4 (0.46)	36.4 (0.45)
Median (minimum, maximum)	36.4 (35.1, 37.3)	36.4 (35.1, 37.4)	36.4 (35.1, 37.4)
12 months, N	89	96	185
Mean (SD)	36.3 (0.48)	36.5 (0.42)	36.4 (0.46)
Median (minimum, maximum)	36.4 (34.5, 37.6)	36.5 (35.4, 37.4)	36.4 (34.5, 37.6)
Change from Baseline, N	86	95	181
Mean (SD)	0.0 (0.53)	-0.0 (0.49)	0.0 (0.51)
Median (minimum, maximum)	0 (-1.7, 1.8)	0 (-1.2, 1.2)	0 (-1.7, 1.8)

Appendix Table 5.6: BMI (in Kg/m^2)

	HCQ	Placebo	Total
Baseline, N	124	124	248
Mean (SD)	28.4 (5.36)	29.3 (6.23)	28.8 (5.82)
Median (minimum, maximum)	28 (15, 45)	28 (19, 45)	28 (15, 45)
6 months, N	102	101	203
Mean (SD)	28.7 (5.29)	29.0 (6.1)	28.8 (5.72)
Median (minimum, maximum)	28 (16, 43)	27 (19, 44)	28 (16, 44)
12 months, N	91	96	187
Mean (SD)	28.4 (5.69)	29.2 (6.07)	28.8 (5.89)
Median (minimum, maximum)	28 (15, 48)	27.5 (19, 43)	28 (15, 48)
Change from Baseline, N	91	96	187
Mean (SD)	-0.3 (2.54)	0.2 (1.64)	-0.1 (2.14)
Median (minimum, maximum)	0 (-11, 10)	0 (-7, 5)	0 (-11, 10)

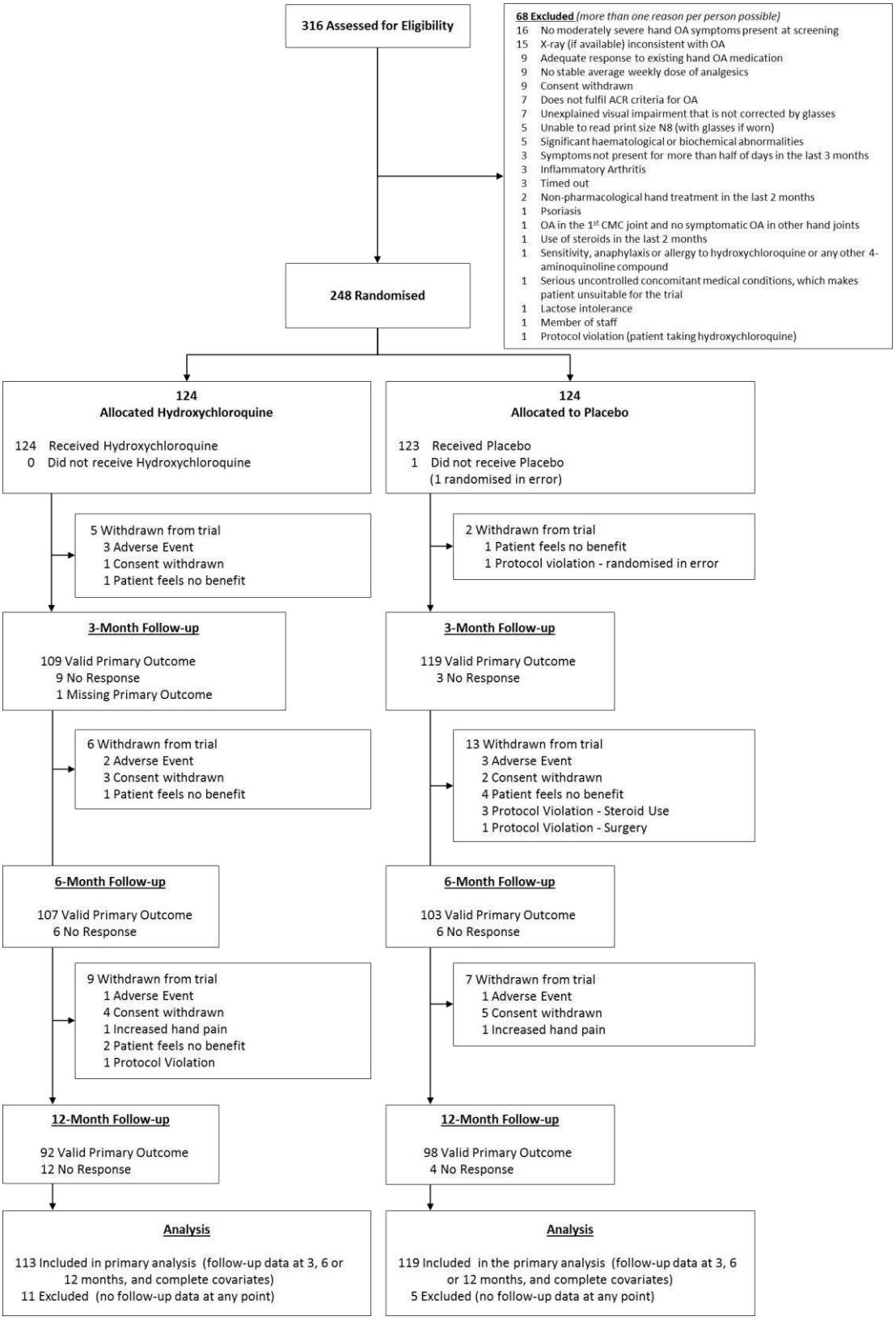
Appendix Table 5.7: Haematology outcomes

	HCQ	Placebo	Total
WBC (x10^9/L)			
Baseline, N	124	124	248
Mean (SD)	6.8 (1.95)	6.7 (1.56)	6.7 (1.76)
Median (minimum, maximum)	6.4 (3.7, 13.1)	6.6 (3.7, 11.4)	6.5 (3.7, 13.1)
Hb (g/dL)			
Baseline, N	124	124	248
Mean (SD)	13.7 (1.06)	13.5 (1.09)	13.6 (1.07)
Median (minimum, maximum)	13.7 (10.6, 17.3)	13.5 (10.4, 16.3)	13.6 (10.4, 17.3)
PLT (x10^9/L)			
Baseline, N	124	124	248
Mean (SD)	263.9 (53.85)	256.6 (54.95)	260.3 (54.42)
Median (minimum, maximum)	259 (161, 466)	250.5 (139, 494)	254 (139, 494)
Neutrophils (x10^9/L)			
Baseline, N	124	124	248
Mean (SD)	3.9 (1.39)	4.0 (1.24)	4.0 (1.31)
Median (minimum, maximum)	3.7 (1.6, 9.5)	3.7 (1.7, 7.9)	3.7 (1.6, 9.5)

Appendix Table 5.8: Urea & Creatinine

	HCQ	Placebo	Total
Urea			
Baseline, N	124	124	248
Mean (SD)	5.7 (1.33)	5.8 (1.66)	5.8 (1.50)
Median (minimum, maximum)	5.8 (2.9, 9.5)	5.7 (2.9, 12.8)	5.8 (2.9, 12.8)
6 months, N	71	67	138
Mean (SD)	6.2 (1.49)	5.8 (1.47)	6.0 (1.49)
Median (minimum, maximum)	6.2 (2.6, 10.4)	5.5 (3, 9.6)	6 (2.6, 10.4)
12 months, N	62	66	128
Mean (SD)	6.1 (1.45)	5.8 (1.62)	5.9 (1.54)
Median (minimum, maximum)	5.9 (3, 9.2)	5.6 (3.5, 10.4)	5.7 (3, 10.4)
Change from Baseline to M6, N	71	67	138
Mean (SD)	0.0 (0.90)	-0.2 (1.10)	-0.1 (1.00)
Median (minimum, maximum)	-0.1 (-1.8, 2.1)	-0.2 (-4.2, 2.5)	-0.2 (-4.2, 2.5)
Change from Baseline to M12, N	62	66	128
Mean (SD)	-0.1 (1.08)	-0.1 (1.31)	-0.1 (1.20)
Median (minimum, maximum)	-0.1 (-2.5, 3.4)	-0.2 (-4.4, 3.6)	-0.2 (-4.4, 3.6)
Creatinine			
Baseline, N	124	124	248
Mean (SD)	71.9 (15.06)	69.5 (15.46)	70.7 (15.28)
Median (minimum, maximum)	69 (46, 124)	67 (43, 126)	68 (43, 126)
6 months, N	71	68	139
Mean (SD)	75.8 (16.41)	70.5 (15.17)	73.2 (15.98)
Median (minimum, maximum)	71 (50, 129)	67 (48, 109)	70 (48, 129)
12 months, N	63	67	130
Mean (SD)	73.1 (14.67)	68.9 (16.76)	70.9 (15.86)
Median (minimum, maximum)	70 (50, 116)	63 (45, 120)	68 (45, 120)
Change from Baseline to M6, N	71	68	139
Mean (SD)	-0.5 (10.96)	-0.2 (7.82)	-0.4 (9.52)
Median (minimum, maximum)	0 (-31, 50)	-2 (-20, 22)	-1 (-31, 50)
Change from Baseline to M12, N	63	67	130
Mean (SD)	-3.0 (9.9)	-1.0 (7.94)	-2.0 (8.96)
Median (minimum, maximum)	-1 (-26, 17)	-2 (-23, 20)	-1.5 (-26, 20)

Appendix Figure 1: CONSORT Flow Diagram

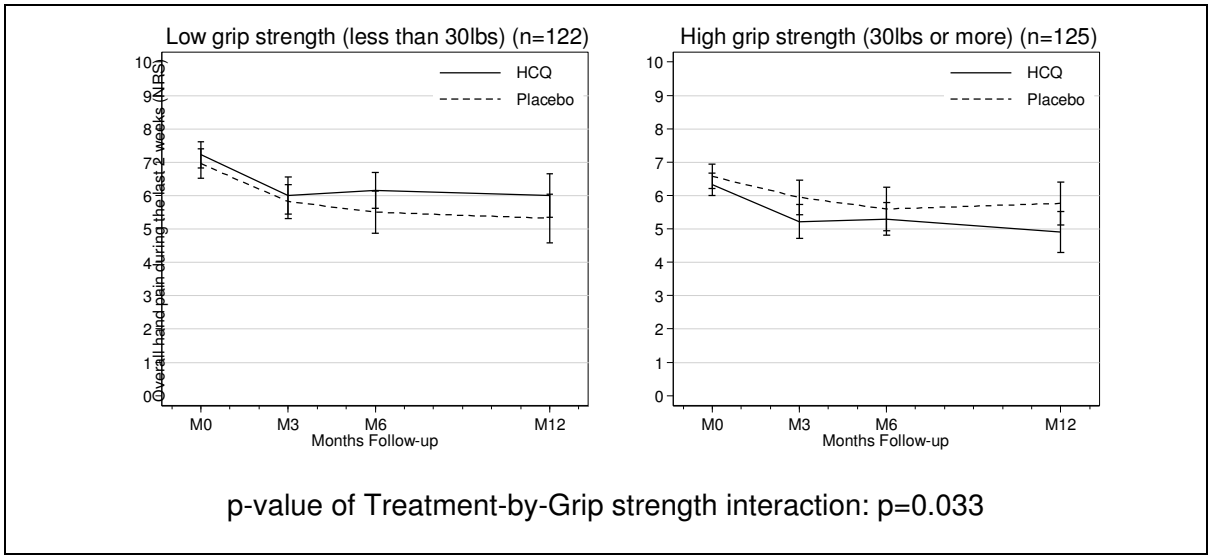


Follow-up categories: Valid primary outcome – Patient returned questionnaire and primary outcome data was available; Missing primary outcome – Patient returned questionnaire and primary outcome data was invalid or missing; No response – Patient did not return questionnaire

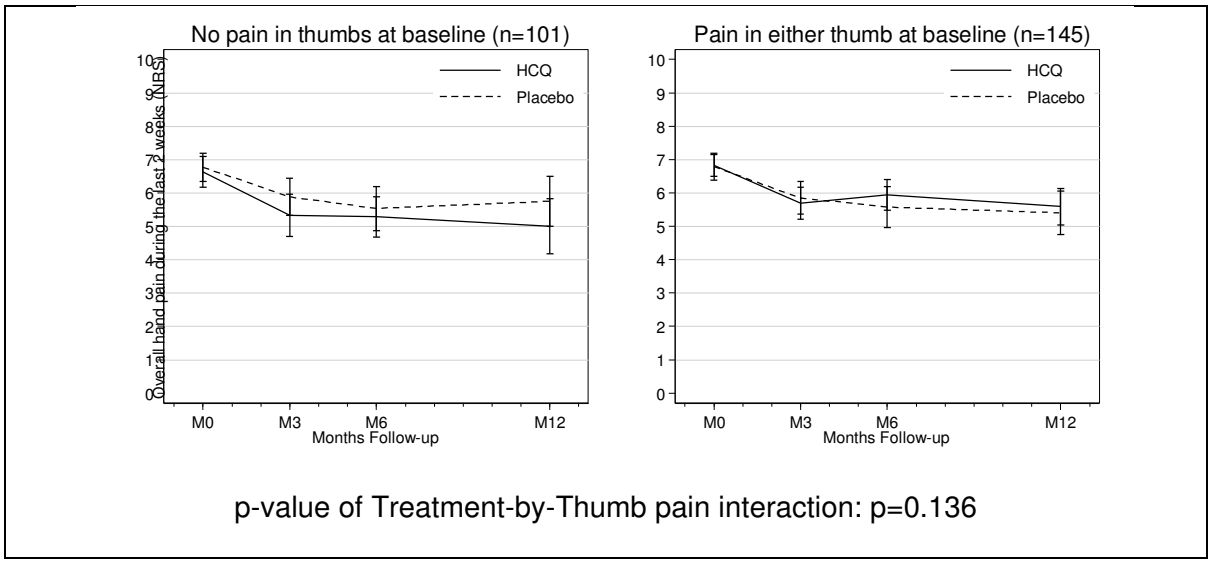
Appendix Figure 1: CONSORT Flow Diagram

CMC = carpometacarpal; OA = osteoarthritis; ACR = American College of Rheumatology;

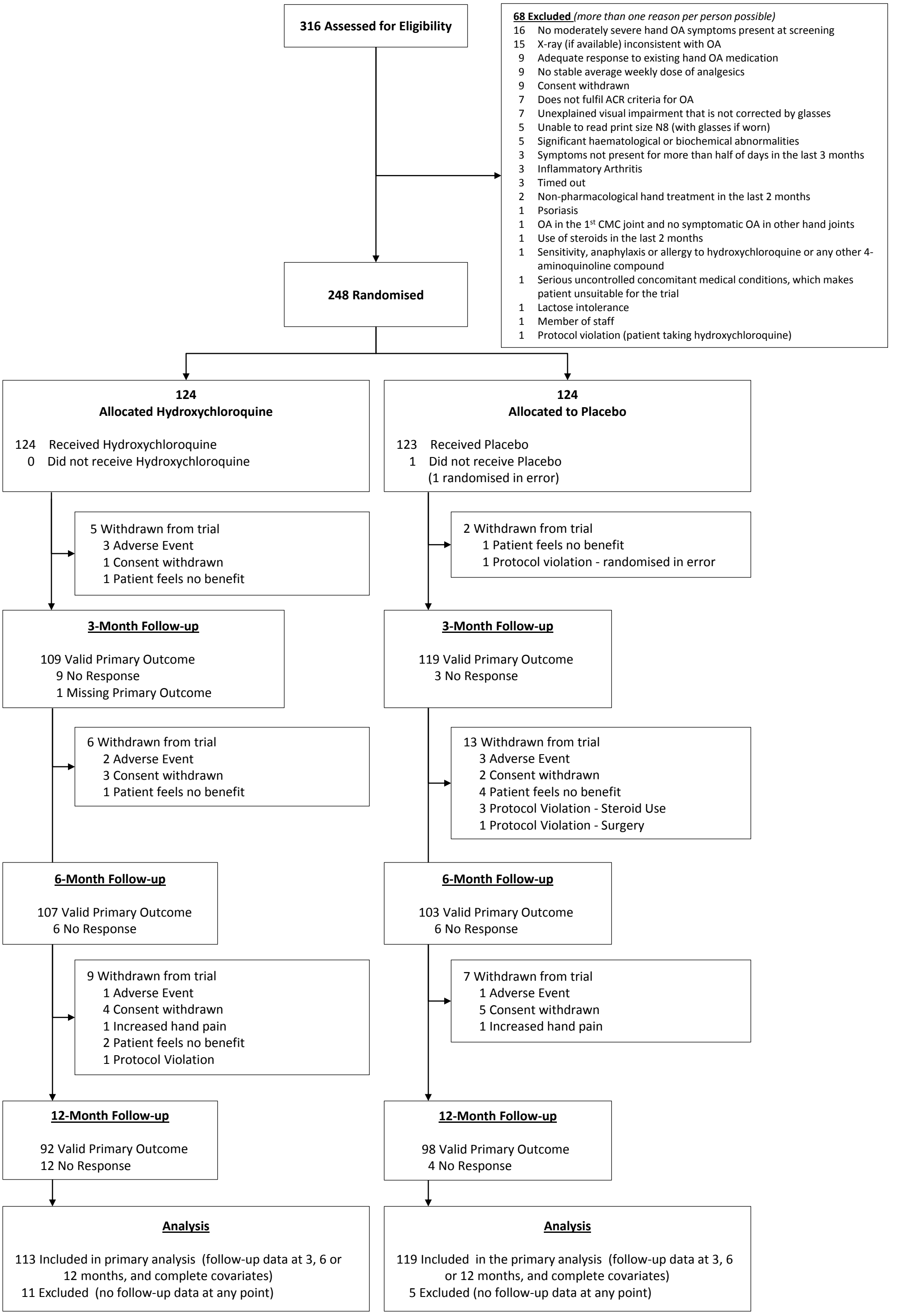
Appendix Figure 2: Average grip strength at 6 and 12 months follow-up by treatment group and baseline grip strength



Appendix Figure 3: Hand Pain NRS (past two weeks) over time by baseline pain in either thumb



Appendix Figure 1: CONSORT Flow Diagram



Follow-up categories: Valid primary outcome – Patient returned questionnaire and primary outcome data was available; Missing primary outcome – Patient returned questionnaire and primary outcome data was invalid or missing; No response – Patient did not return questionnaire

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Appendix 2-4
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Appendix 2-4
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10, App Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	10, App Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11-12, Figure 1, Tables 2, 3, Appendix Table 4
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10-11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12-13, Figure 1, Table 3, Appendix Table 4, Appendix Figure 2, 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12, Appendix Table 5
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15-16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-16

Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	6, Appendix 1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	4, 17

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.