

IDENTIFYING TREATMENT RESPONDERS TO A TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) OR TOPICAL CAPSAICIN IN PAINFUL KNEE OSTEOARTHRITIS: A PILOT SERIES OF N-OF-1 TRIALS

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Short title: *Ibuprofen gel or Capsaicin cream for my
painful knee osteoarthritis?*

Trial Registration: ClinicalTrials.gov (NCT03146689)

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SYNOPSIS

Title	Identifying treatment responders to a topical non-steroidal anti-inflammatory drug (NSAID) or topical capsaicin in painful knee osteoarthritis: a pilot series of n-of-1 trials
Short title	Topical NSAID or capsaicin in knee osteoarthritis: a pilot n-of-1 trial series
Chief Investigator	Prof Weiya Zhang
Objectives	<p>To identify individuals with a treatment response to a topical non-steroidal anti-inflammatory drug or capsaicin (primary).</p> <p>To examine pre-treatment differences between responders and non-responders, specifically focusing on synovial changes by ultrasonography and neuropathic-like characteristics of pain in osteoarthritis and to gather sufficient information to guide a definitive trial of predictors of response (secondary).</p> <p>To offer recommendations on the use of n-of-1 trials for individualised (precision) medicine in osteoarthritis (secondary).</p>
Trial Configuration	Series of n-of-1 randomised trials
Setting	Department of Academic Rheumatology, Clinical Sciences Building, Nottingham City Hospital, NG5 1PB
Sample size estimate	<p>The number of treatment cycles within each n-of-1 trial was set to three as this is the most commonly used number of cycles in n-of-1 trials in osteoarthritis [1, 2] and other conditions [3]. Furthermore, after the first few cycles, each additional cycle contributes little to the precision of the trial [4] so three cycles were deemed to be sufficient.</p> <p>The sample size for n of-1-trial series is based on the number of treatment periods rather than the number of participants. The primary outcome of this trial is to identify treatment response in individual participants. A response is defined as a minimum clinically important difference (MCID) of 0.5 SD between topical NSAID and capsaicin [1]. In order to detect this difference, 66 participants are required in a traditional parallel comparison trial, 33 in a one-cycle cross-over trial, or 11 in a series of individual patient (i.e., n-of-1) trials with three cycles. This would give 80% power at a significance level of 0.05 for the trial. Assuming only 50% of participants show a preferential response between treatments (i.e., have an MCID between the two treatments), 22 participants are required. The overall withdrawal rate for n-of-1 trials has been found to be approximately 20% [3], and this has been factored into the 50% that do not show a preferential response.</p> <p>This n-of-1 trial series is not powered for the exploratory multilevel regression modelling and it has therefore been termed a pilot. If, on</p>

	average, each participant provides the data for two full cycles, that yields 88 change-from-baseline pain scores for regression modelling. This was felt to be sufficient to provide an indication of the feasibility of using n-of-1 trials to examine predictors of response and provide some provisional conclusions.
Number of participants	22 participants
Eligibility criteria	People with knee osteoarthritis, defined as knee pain plus radiographic changes, will be eligible for inclusion. Knee pain must fall between 4-8 on the numerical rating scale (NRS). Participants with predominantly neuropathic-like pain or predominantly inflammatory phenotypes will be selected for inclusion.
Description of interventions	Two interventions will be used: Zacin (0.025% capsaicin cream) and Ibuprofen 5% w/w gel. Both treatments will be applied four times a day for four weeks.
Duration of study	Total: 18 months Per participant: maximum of 44 weeks Planned recruitment start date: March 2017
Randomisation and blinding	The treatment sequence for each participant will be randomised by the trial statistician who has no contact with the participants. Allocation will be via a centralised web-based system. Participants and investigators will be aware of the current treatment prescribed, however, they will not be aware of the order of treatments in the upcoming blocks.
Outcome measures	Primary efficacy variable will be pain severity using a 0-10 numerical rating scale (NRS). Secondary efficacy variables will be the participant's end-of-cycle treatment preference for pain relief and end-of-study overall preference.
Statistical methods	<ol style="list-style-type: none"> 1. Identification of participants with a preferential treatment response to ibuprofen gel or capsaicin cream. A preferential response is defined as an MCID of 0.5SD, which is equivalent to 1 point difference on the NRS, between ibuprofen gel and capsaicin cream for at least two of the three cycles. 2. Comparison between topical NSAID and capsaicin using a one way ANOVA for repeated measures test to investigate if any differences exist between the two treatments in our population of mainly neuropathic or mainly inflammatory participants 3. Exploratory, between-individual analysis to investigate any shared characteristics that are associated with response or non-response to the treatments. Multilevel regression modelling will be used for this purpose. <p>The participant's end-of-cycle treatment preference and end-of-study overall treatment preference (secondary endpoint) will be compared to their response status. This will serve to validate the NRS-based method for identifying individuals with a preferential treatment response and to offer advice for further n-of-1 trials in OA.</p>

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ANOVA	Analysis of Variance
BMI	Body Mass Index
CF	Informed Consent Form
CI	Chief Investigator overall
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HADs	Hospital Anxiety and Depression Scores
ICF	Informed Consent Form
IPD	Individual Patient Data
IUD	Intrauterine Device
IUS	Intrauterine System
KOOS	Knee injury and Osteoarthritis Outcome Score
KPIC	Knee Pain and Related Health in the Community survey
MCID	Minimum Clinically Important Difference
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIR	Neuro-Inflammation Ratio
NLDLA	Nottingham Logically Devised Line Drawing Atlas
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
PDQ	painDETECT Questionnaire

PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PA	Posterior-Anterior
PPT	Pressure Pain Threshold
QST	Quantitative Sensory Testing
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SH	Synovial Hypertrophy
SS	Symptom Severity
TS	Temporal Summation
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Arthritis Index
WPI	Widespread Pain Index

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Osteoarthritis (OA) is the commonest joint disorder [5] and can affect any moveable joint in the body, such as the knees and hips [6]. Approximately a quarter of individuals aged over 55 experience knee pain (attributable to knee OA) [7, 8]. The disease burden of OA is considerable, and with the trend for an ageing population and increase in obesity, these costs are likely to increase dramatically as the prevalence of OA increases [9].

Knee OA will often present with pain, stiffness, gelling, and “giving way” [10]. Pain is the most troubling issue for most OA sufferers [11, 12] and many of the management options for OA are aimed at reducing pain and thereby improving the quality of life of individuals. Two commonly recommended pharmacological treatments for knee OA are topical non-steroidal anti-inflammatory drugs (NSAIDs) and topical capsaicin. They are recommended by the National Institute for Health and Care Excellence (NICE) and other organisations as first- or second-line pharmacological treatments, respectively, for knee OA [5, 13, 14]. Our systematic reviews have demonstrated that both topical NSAIDs and capsaicin are effective and safe treatments for OA [15, 16]. Topical NSAIDs are believed to act by inhibiting prostanoind production, thereby reducing pain and inflammation [17]. Ultrasound-detectable synovial hypertrophy, an indicator of inflammation, appears to be a component of the structural changes that occur in osteoarthritic joints [18]. Topical NSAIDs may therefore target this component of pain in OA. Capsaicin is the substance that makes chilli peppers spicy and appears to act by interfering with the superficial pain-signalling nerves that drive chronic pain states [19]. Although capsaicin is most commonly used in neuropathic pain conditions such as diabetic neuropathy, it may also be useful for individuals with OA – a condition with different phenotypes, including neuropathic-type pain [12].

Despite evidence that topical NSAIDs and capsaicin are effective in OA, it is still unclear why they work for some people but not others. We are undertaking an individual patient data (IPD) meta-analysis to identify responders according to patient characteristics [20]. Although many trials report age, gender, body mass index (BMI), baseline pain, and disease severity, none report the presence of synovial hypertrophy or neuropathic-type pain. These two traits are of interest as they may be used to optimise the treatment effects of the two drugs in OA which work via different mechanisms to reduce pain. We therefore propose this **pilot** n-of-1 trial series.

N-of-1 trials are also called individual patient trials or single patient trials. They are within-individual, randomised, multiple cross-over trials [21]. In these trials, a single participant is given several treatments in a randomly determined order. The participant is assessed at the beginning and end of each treatment period and is also asked to indicate which treatment is preferred. The course is repeated to confirm the results. As with other trials in OA, response to treatment is commonly assessed using a Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) [22].

N-of-1 trials border between clinical care and clinical research, which allows the research findings to be more relevant and generalizable to the wider population [21]. Series of n-of-1 trials may be combined to examine shared characteristics between individuals that respond to a treatment [23, 24]. Although, this approach has been heralded as a promising way forward for precision medicine [23, 24], few have been implemented for this purpose.

This pilot trial will, in the first instance, investigate whether a person with OA, who has a different balance between inflammatory and neuropathic pain, shows a preference between these mechanistically different treatments. This may lead to a full trial to further investigate the differences between responders and non-responders and to confirm whether inflammation and neuropathic pain can be used as stratification markers for precision medicine.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

The purpose of this project is to investigate patients' preferential response, to identify baseline characteristics that may be associated with an improved response to topical NSAIDs and capsaicin, and to guide future use of n-of-1 trials for this approach.

PRIMARY OBJECTIVE

To identify individuals with a treatment response to topical NSAID or capsaicin

SECONDARY OBJECTIVES

To examine the baseline differences between responders and non-responders in multiple repeated treatment periods, specifically focusing on synovial changes by ultrasonography and neuropathic components of pain in OA. To gather sufficient information to guide a definitive trial of predictors of response.

To offer recommendations on the use of n-of-1 trials for individualised (precision) medicine in OA.

DETAILS OF PRODUCT(S)

Description

Ibuprofen 5% gel:

Ibuprofen Ph.Eur.

- Formulation: Gel for topical administration
- Concentration: 5% w/w

List of excipients: Ethylhydroxycellulose EP, Sodium Hydroxide EP, Benzyl alcohol EP, Isopropyl alcohol EP, Purified water EP

Marketing authorisation number: PL 10972/0045

- Pharmacological properties (from eMedicines Compendium [25])
- Licensed for rheumatic pain and available over-the-counter in the UK

“5.1 Pharmacodynamic properties

ATC code: M02A A13, Anti-inflammatory preparations, non-steroids for topical use.

The gel is for topical application. It contains the active ingredient, ibuprofen, a phenylpropionic acid derivative which exerts its anti-inflammatory and analgesic effects directly in inflamed tissues underlying the site of application, mainly by inhibiting prostaglandin biosynthesis. Because it is formulated in an aqueous/alcoholic gel, the preparation also exerts a soothing and cooling effect when applied to the affected area..

5.2 Pharmacokinetic properties

Specially formulated for external application, the active ingredient penetrates through the skin rapidly and extensively (approximately 22% of a finite dose within 48 hours), achieving high, therapeutically relevant local concentrations in underlying soft tissues, joints and the synovial fluid, whilst producing plasma levels that are unlikely to be sufficient to cause any systemic side-effects, other than in rare individuals who are hypersensitive to ibuprofen. Furthermore, there do not appear to be any appreciable differences between the oral and topical routes of administration regarding metabolism or excretion.”

Zacin 0.025% Cream:

- Capsaicin 0.025% w/w
- Formulation: Cream for topical application
- Concentration: 0.025% w/w
- List of excipients: Purified Water, Sorbitol Solution, Isopropyl Myristate, Cetyl Alcohol, White Soft Paraffin, Glyceryl Stearate and Peg-100, Stearate (Arlacel 165), Benzyl Alcohol

Manufacturer: Cephalon UK Limited

Marketing authorisation number: PL 16260/0028

- Pharmacological properties (from eMedicines Compendium [26])
- Licensed for OA pain and recommended by NICE [5]

“5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Topical products for joint and muscular pain, Capsaicin and similar agents, ATC code: M02A B01.

Although the precise mechanism of action of capsaicin is not fully understood, current evidence suggests that capsaicin exerts an analgesic effect by depleting and preventing reaccumulation of Substance P [the principal neurotransmitter] in peripheral sensory neurons. Substance P is thought to be the principal

chemomediator of pain impulses from the periphery to the central nervous system.

[Capsaicin only has an effect on pain nerve fibres and no other sensation is affected.]

5.2 Pharmacokinetic properties

Absorption after topical application is unknown. Average consumption of dietary spice from capsicum fruit has been estimated at 2.5g/person/day in India and 5.0g/person/day in Thailand. Capsaicin content in capsicum fruit is approximately 1% therefore dietary intake of capsaicin may range from 0.5-1mg/kg/day for a 50kg person. Application of two tubes of Zacin Cream 0.025% (90g) each week results in 3.21mg/day topical exposure. Assuming 100% absorption in a 50kg person, daily exposure would be 0.064mg/kg which is approximately one seventh to one eighth of the above mentioned dietary intake.”

Manufacture

Ibuprofen 5% w/w gel

- Manufacturer: The outpatient Nottingham University Hospitals pharmacy that will supply the medication for this trial stocks Ibuprofen 5% gel from various manufacturers.
- Marketing authorisation number: PL 10972/0045

Zacin 0.025% w/w cream

- Manufacturer: Cephalon UK Limited
- Marketing authorisation number: PL 16260/0028

Packaging and labelling

Standard pharmacy supplies will be used.

Storage, dispensing and return

Private prescriptions for the medications (one month of each) will be issued by a GMC registered physician (Professor David Walsh). Medication will be picked up from the Nottingham City Hospital outpatient pharmacy by the investigator at the beginning of each cycle. They will be stored in a locked drawer, accessible only to the investigator, until delivery to participants during home visits.

Participants will be advised to store the medication at room temperature (between 15- 25°C). Any unused medication will be collected at home visits and these will be disposed of at the hospital pharmacy.

Known Side Effects

Ibuprofen gel:

Interactions:

“Non-steroidal anti-inflammatory drugs may interact with blood pressure lowering drugs, and may possibly enhance the effects of anticoagulants, although the chance of either of these occurring with a topically administered preparation is extremely remote. Concurrent aspirin or other NSAIDS may result in an increased incidence of adverse reactions.” [25]

Side effects:

Side effects such as hypersensitivity, gastro-intestinal events, and renal events are extremely uncommon with topical application of ibuprofen.

Hypersensitivity, including:

- Non-specific allergic reaction and anaphylaxis
- Respiratory tract reactivity such as asthma, aggravated asthma, bronchospasm, or difficulty breathing
- Skin disorders such as rashes, itching, hives, purpura, angioedema, and bullous dermatoses (less commonly)

Large amounts applied topically may be associated with systemic effects, including hypersensitivity and asthma. Side effects associated with systemic use are:

Asthma – a degree of worsening

Cardiovascular events – a small increased risk of thrombotic events

Gastro-intestinal events – gastro-intestinal toxicity such as ulceration

Renal events – renal impairment in patients with a history of kidney problems

Zacin 0.025%:

Interactions: No interaction studies have been performed for Zacin. Because of the limited transdermal absorption from Zacin, interactions are unlikely.

Side effects:

Common or very common: transient warming sensation during initial few days of treatment

Rare: cough, eye irritation, sneezing

Frequency not known: dyspnoea, exacerbation of asthma

Reference Safety Information:

- BNF on medicinescomplete.com
- Patient Information Leaflet and Summary of Patient Characteristics from eMedicines Compendium

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

This will be a series of single participant (n-of-1) randomised controlled trials that aim to identify whether an individual has a preferential response to topical NSAID (ibuprofen) or capsaicin. Individuals involved in this trial will be given ibuprofen and capsaicin in a random order. The process (i.e., cycle) will be repeated three times to establish the response (Figure 1). There will be a washout period between treatments and cycles. The length of the wash-out period is dependent on the time taken for the pain score to return to the baseline level, but will be no more than 4 weeks.

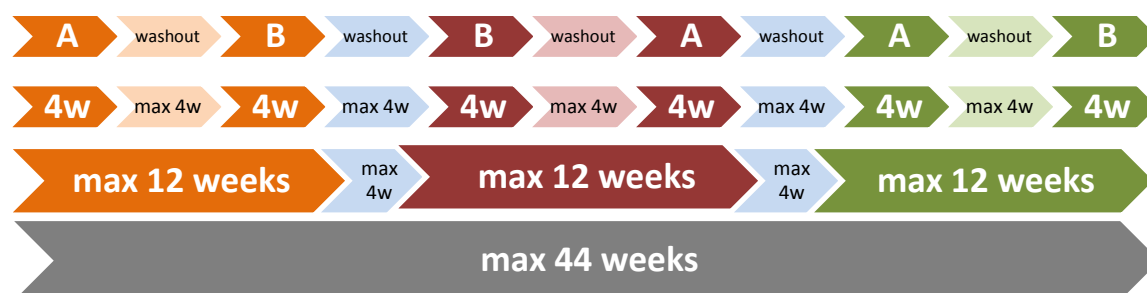


Figure 1 Study design for each participant. Where A= ibuprofen and B = capsaicin

Primary endpoint

Pain score before and after each treatment will be measured using a 0-10 numeric rating scale (NRS). Pain experienced in the most painful knee in the past week will be recorded. The following question will be asked for this purpose: "In the past week, on average, how intense was your knee pain rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'". Participant will be asked to circle only one number, as seen in Figure 2:

In the past week, on average, how intense was your knee pain rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (Circle only ONE number)

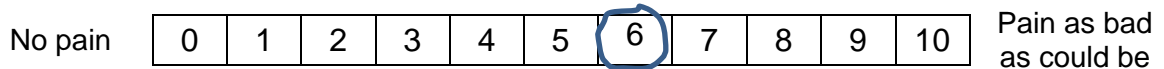


Figure 2 NRS 0-10 for pain intensity

At the end of each study period, participants will be asked the same question via phone call or text message and will be asked give a number between 0-10.

Secondary endpoint

- Participant's end-of-cycle treatment preference for pain relief: "Considering only the pain relief experienced in this most recent cycle, which treatment do you feel provided satisfactory pain relief?" Options: Topical NSAID, capsaicin, neither, or both
- Participant's end-of-study overall treatment preference: "Considering all the aspects of the treatment, including its effectiveness and ease of application, which treatment do you prefer?" Options: Topical NSAID, capsaicin, neither, or both
- Weekly pain score recorded in the participant diaries during treatment, using a 0-10 NRS as described above.

Safety endpoints

Not applicable

Stopping rules and discontinuation

Individual participants:

Participants experiencing serious AEs related to the study medications may be withdrawn. Should they choose to, participants may opt to leave the study at any point.

Parts of the trial/entire trial:

Both interventions are widely used in practice and are known to be safe and well-tolerated, so it is unlikely that the entire trial will need to be stopped due to the medications.

RANDOMIZATION AND BLINDING

A random sequence (AB or BA) will be generated for each study visit by DMcW. The randomisation sequence will be generated in unbalanced format using an online randomisation package (www.randomizer.org). The treatment cycle (AB or BA) corresponding to the randomised sequence will be recorded in sequentially numbered, sealed, opaque envelopes. After the consent and baseline assessment, the MP will open the

next envelope in strictly sequential order. The form will describe the treatment order for the cycle, will be filled in with the participant's ID, and will be signed and kept as a record of treatment allocation.

The process will be repeated at the beginning of each cycle (i.e., up to three times for each participant). Neither participant nor investigator will be able to determine the sequence before opening the envelope.

Once the random number is generated, both investigator and participant will be aware of the treatment sequence (i.e. whether the participant is going to start with ibuprofen or capsaicin). The drugs will then be delivered to the participant according to the sequence.

Randomisation is required in order to minimise the effect of potential of confounders, particularly those that are time-dependent, and ensures that the treatments are fairly compared [21].

Maintenance of randomisation codes and procedures for breaking code

Not applicable. Both the investigator and the participant will be aware of the treatment allocated by the time of the delivery of the treatments within each cycle. This is a pragmatic, non-blinded trial.

TRIAL/STUDY MANAGEMENT

The trial will be coordinated by the research team in Academic Rheumatology. As Principal Investigator and Trial Manager, Monica Persson will manage recruitment and the day to day running of the trial.

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Participant Duration: Each participant will be involved a maximum of 44 weeks. This involves 24 weeks on treatment (12 weeks on capsaicin and 12 weeks on ibuprofen). The variable washout periods will be a maximum of 20 weeks per participant (Figure 1). For participants that meet the responder criteria after the second treatment period, their involvement will be a maximum of 28 weeks.

Study Duration: The total study duration will be approximately 18 months, including 6 months recruitment and approximately 1 year to complete the last follow-up.

End of the Trial

The end of the study will be the last follow-up visit of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

The Knee Pain and Related Health in Community (KPIC) survey (n=9500), where 745 individuals have undergone standardised knee radiographs and ultrasound assessment of both knees, will form the source population for this trial. The KPIC participants were originally

recruited through postal questionnaires to eligible people selected by General Practice Surgery staff. Recruitment will be hypothesis-driven, whereby participants will be chosen based on the characteristics of interest (e.g. neuropathic-like pain, evidence of inflammation). Eligible KPIC participants that have indicated that they are interested in participating in other studies will be contacted via letter, including a patient information sheet (PIS) (Appendix 1 and 2). Those that return a ticked slip (using the provided pre-paid envelope) will be contacted via telephone where any initial questions can be answered and eligibility can be confirmed. If they are still interested in participation an appointment at the department will be made for them. At their first meeting they will be given an opportunity to ask any further questions and it will be confirmed that they are still eligible (e.g. have sufficiently marked knee pain). Signed consent will then be obtained (Appendix 3).

The initial approach for recruitment to the n-of-1 trial will be by the Principal Investigator (Monica Persson). The investigator will inform the participant of all aspects pertaining to participation in the study.

The participant will be given information sheets and consent forms before entering the trial. The purpose of the trial and treatments involved in the trial will be discussed fully with the participant. It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

Inclusion criteria

- Men and non-pregnant women
 - Premenopausal women will need to be on an acceptable contraceptive method*
- Aged 40-95 years
- Knee pain between 4-8 on the NRS
- Knee osteoarthritis – defined as knee pain plus radiographic changes, based on response to KPIC questionnaire response and KPIC radiographic findings
 - Knee pain: individuals with knee pain in and around the knee on most days for at least a month.
 - Radiographic changes: definite joint space narrowing and definite osteophytes (each scoring two or more on the Nottingham Line Drawing Atlas) in the tibiofemoral and/or patellofemoral compartments
- Predominantly neuropathic or inflammatory phenotypes based on response to KPIC questionnaire responses (not current status)
 - Predominantly neuropathic phenotype: painDETECT Questionnaire (PDQ) > 13 and synovial hypertrophy (SH) <4 mm
 - Predominantly inflammatory phenotype: SH > 4 mm and PDQ < 13
 - These threshold have been set in order to ensure that there is variation in the contribution of inflammation/neuropathic-like pain in the population studied. The primary recruitment plan will be to include participants according to the thresholds detailed above. However, if we cannot recruit enough people with the above thresholds, the PDQ and SH thresholds will be loosened to allow additional participants will be recruited. As PDQ and SH data will be analysed as a continuous outcome, the inclusion of participants with a mixture of

inflammatory/neuropathic-like pain will not affect the analyses or conclusions drawn from this study.

*Examples of acceptable contraceptive methods: Established use of oral, injected or implanted hormonal methods; placement of an intrauterine device (IUD) or intrauterine system (IUS); condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide; true abstinence (when this is in line with the preferred and usual lifestyle of the participant); or vasectomised partner.

Exclusion criteria

- Inability to give informed consent
- Daily use of oral NSAIDs for the last two weeks
- Prior regular use of Ibuprofen gel or Zacin on the affected knee(s)
- Terminal or untreated major mental illness
- Pregnancy or breastfeeding
- Hypersensitivity or allergy to topical NSAIDs, capsaicin, or other ingredients in the preparations. This includes individuals that experience attacks of asthma, urticaria, or acute rhinitis that are precipitated by NSAIDs
- Current treatment for stomach or duodenal ulcers
- Total joint replacement of affected joint
- Renal failure
- Taking anticoagulants

Expected duration of participant participation

Study participants will be participating in the study for a maximum of 44 weeks.

Removal of participants from therapy or assessments/Participant Withdrawal

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Participants will be withdrawn from the study if they withdraw their consent to remain under observation in the study, if they lose the capacity to consent, or if they are found to meet any of the exclusion criteria detailed above.

Withdrawn participants will be asked to provide the reasons for withdrawal and a final outcome measure, though both these are purely optional. For the latter, they will be asked to rate their NRS pain severity (which will be taken as the endpoint pain severity for that treatment if withdrawal occurs during a treatment block) and indicate their treatment preference.

Informed consent

All participants will provide written informed consent. The Informed Consent Form (Appendix 3) will be signed and dated by the participant at their first visit before they enter the trial. Participants will have received a PIS prior to enrolment to ensure that they have plenty of time to consider participating or not. The Investigator will explain the details of the trial and answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant and one will be kept by the Investigator.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

TRIAL / STUDY TREATMENT AND REGIMEN

Initial contact

Participants identified from the KPIC database that meet the eligibility criteria for this study will be sent a letter of invitation (Appendix 1), a Participant Information Sheet (Appendix 2), and a reply slip with a pre-paid envelope. Those who indicate that they are interested will be telephoned by the Investigator. Any questions that the participant may have can be fully discussed, and the investigator will ask brief screening questions to determine current eligibility. If the participant remains interested in the study, and appears to be eligible, an appointment to come to Academic Rheumatology will be agreed.

Department visit

At the department visit, current eligibility (e.g. sufficient knee pain severity) will be confirmed, the participant will be given another opportunity to ask any questions, and then written informed consent will be obtained. Participants will be informed of how to apply both study treatments and how the study outcomes will be assessed.

Instructions for applying study treatments

Participants will receive the following instructions (printed and verbally) for applying the study treatments:

Apply the allocated medication to your painful knee(s). If you only have pain in one knee, medication should only be applied to that knee. If you experience pain in both knees, you should apply the medication equally to both knees.

Zacin cream

Application

- Apply a *pea-sized* amount to your knee(s) four times a day
 - Leave a minimum of four hours between applications
 - Gently rub the cream in until it is no longer visible
- You can choose to apply the cream with your bare hands, wearing gloves, or using a plastic/credit card
 - If you are applying with your bare hands, ensure you wash your hands thoroughly with soap and water afterwards
- If you forget to use the cream, leave that dose and apply the next dose at the normal time

Ibuprofen gel

Application

- Apply a small amount (approximately half the length of a credit card) to your knee(s) four times a day
 - Leave a minimum of four hours between applications
 - Gently rub the gel in until it is no longer visible
- If you forget to use the cream, apply it as soon as you remember and then carry on as normal. Do not apply twice the amount at once to make up for a missed application.

Precautions

General precautions:

- Do not apply on broken or irritated skin
- Wash your hands immediately after application of the cream
- Do not get Ibuprofen or Zacin in your eyes, nose, and mouth. Avoid breathing in any vapours from the gel or cream
- Do not apply tight bandages over the knee after application of the gel or cream

Zacin cream:

- Avoid hot baths or showers immediately after applying the cream
 - You may find that avoiding baths or showers an hour before and after application of the cream reduces the burning feeling

Ibuprofen gel:

- Avoid excessive sunlight exposure to treated knees

Storage

- Keep the gel/cream at room temperature (below 25°C) with the lid on. Ensure it is left out of reach and sight of children

Participants will undergo baseline assessments prior to randomisation and treatment sequence allocation. Baseline assessments are comprised of:

- **Questionnaire** (Appendix 4)
 - **Pain intensity for each knee:** NRS 0-10 (see Figure 2)
NRS is a commonly used measure of pain intensity that involves participants selecting whole number between 0-10. Several formats exist for the NRS, but in general these comprise of a scale with whole integers (0 and 10) that is anchored by the terms “no pain” and “pain as bad as it could be” at either end [27]. Participants are asked to circle the number that best describes where their knee pain falls. The NRS can be administered verbally, such as via telephone, or graphically for the respondent to fill out [27]. A higher score indicates a higher pain intensity.
 - **Neuropathic-like pain:** modified painDETECT Questionnaire [28]
Various questions assess the nature of pain experienced, and a summary score between -1 and 38 is calculated. The score indicates the likelihood of the participant’s pain being neuropathic in nature, where a higher score makes neuropathic pain more likely. A threshold of PDQ>13 will be used to indicate possible neuropathic pain for inclusion to the study. For the analyses, the PDQ scores will be Rasch transformed as per Moreton et al [29] in order to convert the raw scores to interval-level data with improved goodness of fit.
 - **Function:** Knee Injury and Osteoarthritis Outcome Score (KOOS) dimension of Activities of Daily Living questionnaire [30]
Participants are asked to score the difficulty experienced when undertaking various activities of daily living, such as rising from sitting and taking off socks.

These scores are added up and a higher score indicates more functional impairment.

- **Illness perception including expectation of treatment:** Brief Illness Perception Knee Questionnaire) [31]
Participants are asked to score various questions around their perception of knee pain, including its impact of their life, its likely duration, and the concern caused by it. Participants are also asked to rate how much they think the treatments will help their knee pain. The scores may be added and a higher score presents a more threatening view of the illness.
- **Anxiety and depressive symptoms:** Hospital and Anxiety Depression Scores (HADs) [32]
HADs is a validated questionnaire comprised of seven questions for depression and seven for anxiety, with a maximum score of 21 for each. A higher score indicates that the participant is more likely to have a mood disorder. A cut-off of >8 will be used to determine the presence of either anxiety or depression [33].
- **Fibromyalgia screening questions**
Two main domains, the number of painful areas (widespread pain index, WPI) and the severity of symptoms such as fatigue (symptom severity, SS), are scored. Participants will be scored as likely to have fibromyalgia if they meet the following criteria:
 1. Pain is present in at least four of five regions
 2. Symptoms have been present for at least three months
 3. WPI ≥ 7 and SS ≥ 5 or WPI 4-6 and SS ≥ 9
- **Indicators of central aspects pain in the knee**
Eight questions from within the KPIC questionnaire that have been shown to associate with central pain mechanisms in OA.
- **Examination**
 - **Knee ultrasound to assess for any inflammation within the knee joint**
Both knee joints will be imaged using a Toshiba Aplio SSA-770A ultrasound machine with a multi-frequency (7–12 Hz). The supra-patellar, medial and lateral para-patellar recesses and medial and lateral tibio-femoral spaces of both knees will be assessed with knee flexion of approximately 20-30°. US detected changes will be defined according to definitions accepted by the OMERACT-7 Group [34]. The maximal synovial thickness and effusion depth will be measured in millimetres using the longitudinal axis. A Power Doppler assessment, which provides information on vascularity, will be focused on areas of synovial hypertrophy. A Positive Power Doppler signal will be recorded as present or absent.
 - **Quantitative Sensory Testing (QST) for pressure pain threshold (PPT) and temporal summation (TS)**
PPT and TS measures will be undertaken at seven sites, including the sternum and three specified sites around each knee using non-invasive QST.

Pressure pain thresholds (PPT) will be assessed using a hand-held pressure algometer (Somedic AB, Sweden) connected to a computer (HP ProBook 4520s). The algometer consists of a rod with a circular end (1cm²) that is placed perpendicular to the skin and pressure is applied at a gradually

increasing rate (standardised rate set at 30kPa/s) until the participant indicates that the sensation has changed from pressure to pain by pressing a button. The algometer is then immediately taken off the skin. Participants will be familiarised with the test by the research metrologist prior to the PPT test commencing. Gradual pressure will be applied to a fingernail of the dominant hand and the procedure will be carried out as described above.

The algometer will be used on seven pre-specified anatomical sites and this will comprise one cycle of PPT testing. The sites are: the sternum (3cm caudal to the sternal notch); the medial joint line (medial tibiofemoral joint line located medial to patellar ligament of both knees); the lateral joint line (lateral tibiofemoral joint line located lateral to the patellar ligament of both knees); and the proximal shins (both legs). The PPT cycle will be repeated three times with a 2 minute rest period in between each cycle.

Temporal summation (TS), also known as wind-up ratio or mechanical sensitivity, will be assessed using a 256 millinewton (mN) weighted pinprick stimulator. The stimulator will be applied perpendicular to the skin, 2cm distal to the infero-medial border of the patella of the knee to detect a sensation of sharpness or pain. The participant will be asked to rate their pain on an NRS of 0-100 where 0 indicates no pain or sharpness and 100 indicates the most intense pain or sharpness. This rating will be recorded. The stimulator will then be re-applied to the same site 10 times at a rate of one per second. At the end of the 10 pinpricks, participants will be asked to rate the pain or sharpness using the NRS and this will be recorded. The entire procedure will be repeated twice and the temporal summation will be calculated as the mean pain rating of both series of repetitive pinprick stimuli divided by the mean pain rating of both baseline NRS measures. The mechanical sensitivity will be calculated as the mean pain rating of both baseline NRS measures. Participants will be familiarised with the tests on their least affected knee. The tests will then be conducted using their most affected knee.

- **Muscle strength in quadriceps (thigh muscle)**

The “Nicholas Manual Muscle Tester” (Lafayette Instruments) will be used to assess the maximum voluntary quadriceps contraction. The participant will sit upright on a stable flat surface with no arm rests, with their thighs horizontal to the surface. Their knees will be bent at 90° and their feet raised off the floor. The Muscle Tester will be positioned at the bottom of the participant’s shin, just above the ankle. They will be asked to push against it, as hard as possible, in an attempt to straighten the leg against resistance provided by the research metrologist. This will be carried out three times on each leg and the mean value for each side will be recorded.

- **Height and weight**

BMI will be calculated as: $\frac{kg}{m^2}$

- **Knee radiography**

All participants will have had tibio-femoral and patello-femoral radiographs taken using a standardised protocol (standing posterior-anterior (PA) and skyline views) in the previous KPIC assessment. They will not be repeated for this study. The severity of radiographic changes, scored by Dr Gwen Fernandes using the Nottingham logically devised line drawing atlas (NLDLDA) [35], will be used.

Following the treatment allocation, participants will be given the medication for the first treatment period (Ibuprofen or Zacin). Detailed information about the study and how to fill in their participant diaries (Appendix 5) will also be given. Participants will be allowed to continue all regular medications throughout the trial, provided they have been on them for three months without a change in dose. Details of the regular medications will be recorded in the participant's questionnaire, which will be reviewed by the Principal Investigator together with the participant to ensure sufficient detail about the medications has been recorded. No new treatments, including exercise therapy, orthotics, or alternative therapies, are to be commenced during the treatment period. Oral rescue analgesia will be allowed, although the medication, dose, and frequencies of this will need to be recorded in the participant diary.

Treatment cycles one to three

Participants will be asked to score their pain in the past week using the 0-10 NRS before they begin four weeks treatment of the first allocated intervention (for the first cycle, their response from the questionnaire will be taken as the baseline). During the treatment period, they will be asked to record the pain intensity in their knee, the use of any rescue analgesia, and any adverse events (AE) experienced on a weekly basis in their diaries. At the end of the four week period, they will be contacted via text messaging or telephone call (according to their preference) to score their pain in the past week using the 0-10 NRS. At the end of each treatment cycle (i.e., after every other treatment period), they will also be asked to state their preferred treatment for pain relief. Participants then enter the washout period.

A home visit will be arranged as soon as possible following the end of the four week period, where the participant diary and unused medications will be collected and participants will be asked about AEs or any other concerns. Participants will be provided with the medication and diary for the subsequent treatment period. The University of Nottingham Lone Worker Policy (Appendix 6) and Academic Rheumatology Fieldwork Safety Policy (Appendix 7) will be followed.

During the washout period, participants will be contacted via text message or telephone call on a weekly basis and asked if their pain is back to "normal" (i.e., pre-treatment level) and to rate their pain "on a scale of 0-10, where 0 is no pain and 10 is pain as bad as it could be". Once the pain has returned to the baseline level or the washout period has reached four weeks they will be told to commence the next treatment the following day. The pain score received via text message or telephone call will be taken as their baseline pain score for that treatment period.

Participants will be informed of the mobile telephone number to text or call prior to the washout period and will be able to initiate contact outside of the weekly messages if they feel that their pain has returned to a pre-treatment level. They will be asked to score their pain and to initiate the next treatment.

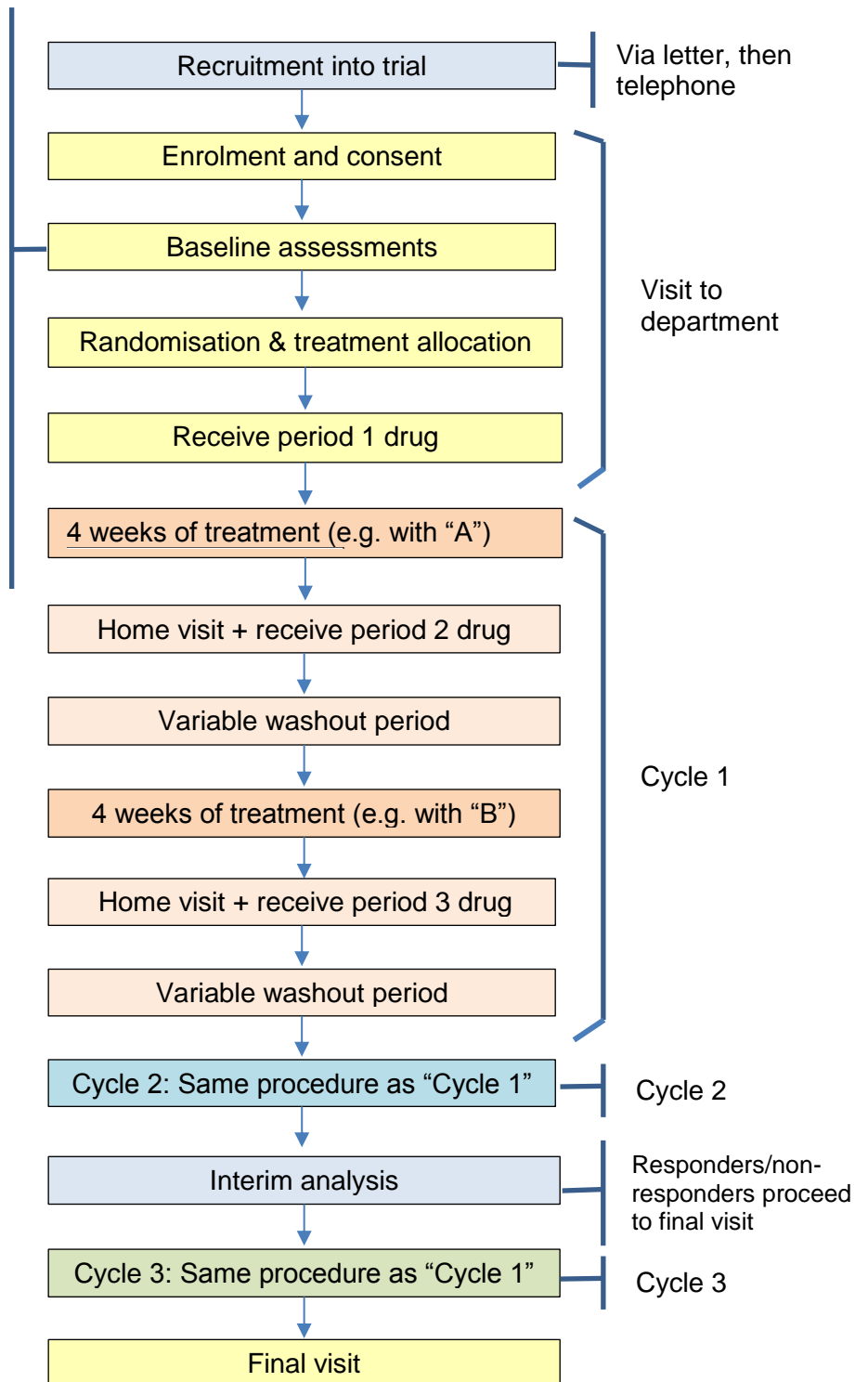
Following the end of cycle 2, an interim analysis will be carried out for each individual. Participants that meet the criteria for a responder or non-responder in the first two cycles will not need to undertake cycle 3. At this point they will have established their responder status and this will be unchanged by a third cycle. However, n-of-1 trials are a decision-making process between participants and physicians and the participants will be given the option to continue into the third cycle if they are unsure of their treatment preference based only on two cycles. Participants not meeting responder/non-responder criteria in the first two cycles will automatically continue with cycle 3 prior to their final visit.

Questionnaire

- NRS pain
- painDETECT
- KOOS ADL
- Illness Perception (Knee)
- HADS
- Fibromyalgia screening

Examinations

- Ultrasound
- QST
- Muscle strength
- Height and weight
- X-ray scoring



Concomitant and Rescue Medications and Treatments

Concomitant medications and treatments:

Concomitant medications and treatments can be continued throughout the trial, provided the participant has been on them for three months without a change in frequency or dose. This includes medications taken as required, and participants will be asked to maintain a similar routine throughout the study as they were on prior to enrolment.

Concomitant medications and treatments will be recorded in the questionnaire and any changes to these during the study will be recorded in the CRF (under "Any other concerns").

Rescue medications:

Participants may take any systemic medication of their preference as rescue medication and will need to record these in their participant diaries.

Non-permitted concomitant treatments and medications:

All topical treatments for the affected knee

Regular oral NSAIDs

Arthroplasty

Compliance

Compliance will not be formally assessed as this will not influence the interpretation of the primary, within-individual identification of responders. The number of responders may be conservative as we will not account for compliance.

Criteria for terminating trial

As both investigated treatments have been extensively studied in randomised controlled trials and are commonly used in clinical practice, it is unlikely that the trial will be stopped due to safety concerns.

If the trial is prematurely terminated participants will be asked to return all remaining medications. All returned medications will be given to the Nottingham City Hospital Outpatient Pharmacy for disposal.

STATISTICS

Methods

Monica Persson will conduct the statistical analyses, with the supervision and support of Professor Weiya Zhang. The data will be entered into MS Access and analysed using MS Excel and Stata SE 14 (StataCorp, College Station, Texas).

Individuals with different degree of neuropathic pain and synovial hypertrophy will be presented using a neuro-inflammation ratio (NIR) index. The NIR will be calculated by dividing the Rasch-transformed PDQ score by the SH score. Both the PDQ and SH scores will be normalised to a % scale by dividing the actual score by the maximum score on each scale before calculating the NIR. This makes the NIR a continuous index for the analysis. It can also be categorised into tertiles or dichotomised as

- NIR > 1 are predominantly neuropathic phenotype

- NIR < 1 are predominantly inflammatory phenotype

The following analyses will be undertaken:

1. It will be determined if individuals show a preferential response to topical NSAID, to capsaicin, or no preferential response.
 - a. A preferential response is defined as a between-drug difference in change from baseline scores equal to or larger than the minimum clinically important difference (MCID) of 1 point on the NRS [5, 36] for a treatment in at least two of the three treatment cycles.
 - b. The weekly NRS pain scores will be plotted for each participant to examine the response to treatments within each period. This may indicate whether weekly or monthly pain assessments are preferred
2. Treatment preferential response (as defined using NRS pain scores) will be explored across the participants
 - a. The number of treatment periods which showed a preferential response to topical NSAID or capsaicin. A one-way analysis of variance (ANOVA) for repeated measures test will be used to compare the pain reduction between topical NSAID and capsaicin in a maximum of 33 paired treatment periods (11 participants x 3 paired cycles)
 - i. Both treatments have proven efficacy in osteoarthritis and this analysis will indicate whether a statistically significant difference exists between the two treatments in our population of mainly neuropathic or mainly inflammatory participants
 - b. The number of participants who showed a preferential response to topical NSAID, capsaicin, or no preferential response will be presented
 - i. This indicates if response variation exists and provides evidence for the feasibility of n-of-1 trials to examine predictors of response to topical NSAIDs and capsaicin
3. In an exploratory, between-individual analysis, we will examine if there any associations between baseline characteristics (particularly the NIR) and response to topical NSAID, capsaicin, or non-response
 - a. Multilevel regression modelling will be performed. NRS pain will be the dependent variable. Independent variables will be: treatment, baseline characteristic, and an interaction term between treatment and baseline characteristic.

The participant's end-of-cycle treatment preference for pain relief (secondary endpoint) will be compared to their response status using NRS. Finally, the participant's end-of-study overall treatment preference (secondary endpoint) will be described and it will be noted whether overall preference is different from preference based on pain relief alone.

Interim analyses will occur at an individual level. Following the second treatment cycle, the pain data for that individual will be analysed. If they are found to show a response for either treatment at that point, they will not need to enter the third treatment cycle.

Sample size and justification

The number of treatment cycles within each n-of-1 trial was set to three as this is the most commonly used number of cycles in n-of-1 trials in OA [1, 2] and other conditions [3]. Furthermore, after the first few cycles, each additional cycle contributes little to the precision of the trial [4] so three cycles were deemed to be sufficient.

For n-of-1 trial series, the sample size is calculated based on the number of treatment periods rather than the number of participants [37]. The participants in n-of-1 trials are used as their own control (paired comparison) and the treatments tested are repeatedly used in the same participants. Each repetition is labelled a treatment cycle, which contains two treatment periods (A and B).

The sample size for series of n-of-1 trials can be derived from that of a classic, parallel comparative trial. For example, based on a MCID of 0.5 SD, the sample size for a classic parallel comparison is 66 participants (assuming 80% power at a significance level of 0.05). For a simple cross-over trial where each participant receives both A and B in random sequence, the equivalent sample size required is 33. For a series of n-of-1 trials, where each participant undergoes three cycles (i.e., three treatment repetitions), the equivalent sample size required is 11 participants, provided there are no carry over effects.

Design	Parallel	Cross-over	N-of-1 series with 3 cycles
Repetitions	Each participant receives A or B	Each participant receives A and B	Each participant receives A and B three times (each)
Sample size (80% power and 0.05 significance level)	66	33	11

The primary objective of this study is to identify preferential treatment response. This is defined as a MCID between topical NSAID (A) and topical capsaicin (B) within each paired comparison (cycle). If we use the same MCID of 0.5 SD (approximately one grade difference in a 0-10 NRS), we would need 11 participants to generate 33 paired comparisons (or 33 cycles or 66 treatment periods) in a random fashion. Assuming only 50% of participants show a preferential response between treatments, 22 participants are required. The overall withdrawal rate for n-of-1 trials has been found to be approximately 20% [3] and that has been factored into the 50% that do not show a preferential response.

This n-of-1 trial series is not powered for the exploratory multilevel regression modelling and it has therefore been termed a pilot. If, on average, each participant provides the data for two full cycles, that yields 88 change-from-baseline pain scores for regression modelling. This was felt to be sufficient to provide an indication of the feasibility of using n-of-1 trials to examine predictors of response and provide some provisional conclusions.

Assessment of efficacy

Endpoint	Variable	Timings	Parameter
Primary	0-10 NRS pain	Monthly (at beginning and end of each treatment period)	Change in NRS ($NRS_{\text{baseline}} - NRS_{\text{endpoint}}$) between treatments
Secondary	Treatment preference (pain relief)	End-of-cycle	Topical NSAID, capsaicin, neither, or both
Secondary	Treatment preference (overall)	End of cycle	Topical NSAID, capsaicin, neither, or both

Assessment of safety

The interventions reflect best practice and are being used as licensed. Spontaneously reported AEs will be recorded in the CRF. The seriousness and causality of the AEs will be determined, and any serious or unlisted adverse drug reactions (ADRs) will be reported via the Yellow Card scheme as recommended by the MHRA.

The safety of the medications has been established in previous studies and will not be analysed in this trial.

Procedures for missing, unused and spurious data

Missing data will not be imputed on an individual level. All efforts will be made to ensure that all necessary outcome data is captured. Should any data be missed, the reasons for this will be sought. Where outcome data is missing for a treatment period, participants will be labelled as non-responders for that period.

Definition of populations analysed

Primary analysis at the individual level will be based on all randomised participants. Secondary exploratory analyses will be performed on the full analysis set.

Full Analysis set: All randomised participants, who participated in at least one treatment and for whom at least one post-baseline assessment of the primary endpoint is available.

ADVERSE EVENTS

The interventions examined in this study reflect recommended best practice and are used as licensed. Therefore, the occurrence of adverse events as a result of participation in this study is not expected and adverse event data will not be systematically collected.

Self-reported adverse events in participants will be recorded in the CRF and their severity and causality will be determined by the Principal Investigator in conjunction with Professor Michael Doherty or Professor David Walsh. If it is determined to be an adverse drug reaction (ADR) that is serious or unlisted in the product information, the MHRA will be informed using the Yellow Card scheme. The information collected in the CRF will be used to collect the information required for reporting, but will not be analysed.

A summary of the ADRs reported using the Yellow Card scheme will be included in the final summary submitted to REC.

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms, and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. Furthermore, a scanned electronic copy will be saved in a secure University server folder accessible only to Monica Persson and her supervisors (WZ, DW, MD).

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms (Appendix 8)

Each participant will be assigned a study identity code number and this will be used on the study forms as well as other trial documents and the electronic database. This will be a randomly generated unique participant identifier.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Sample Labelling

Each participant will be assigned a trial identity code number for use on the samples, consent forms and other study documents and the electronic database.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall be made available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the trial risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

The results will be submitted for publication in peer review scientific journals and at conferences. The study may also be included in Monica Persson's PhD Thesis. A lay summary of the findings will be submitted to the Arthritis Research UK Pain Centre website. Participants will not be identified in any publications. Study participants will also be informed of the results, if requested.

USER AND PUBLIC INVOLVEMENT

User and public involvement has been sought during the design of the study. Members of the public will be asked to comment on and help develop information leaflets, the questionnaire design, and the study protocol.

STUDY FINANCES

Funding source

This study is funded by Nottingham University Hospitals Charity.

Participant stipends and payments

Participants will not be paid to participate in the trial. Travel expenses will be offered for the initial department visit, to a maximum of £20 per participant.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Professor Weiya Zhang

Signature: _____

Date: _____

Principal Investigator: Dr Monica Persson

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