Participant Information Sheet
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Title of Study: Ibuprofen gel or Capsaicin cream for my painful knee osteoarthritis?

Name of Researcher(s):	Weiya Zhang	Chief Investigator
	Monica Persson	Principal Investigator
	Michael Doherty	Medical Expert
	David Walsh	Co-supervisor
	Joanne Stocks	QST assessor
	Gwen Fernandes	X-ray assessor
	Aliya Sarmanova	Ultrasound assessor
	Daniel McWilliams	Treatment allocator

We would like to invite you to take part in our research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear. If you decide to take part you may keep this leaflet. Thank you for reading this.

What is the purpose of the study?

Approximately one in four individuals over the age of 55 experience knee pain due to knee osteoarthritis. Most treatments for osteoarthritis are aimed at reducing pain and this is often the most troubling issue for individuals with osteoarthritis. Unfortunately, pain relief is often inadequate and this may be because pain can be influenced by a number of different factors and there may be a mismatch between an individual's characteristics and the treatment that is most likely to target their source of pain. There is a large variation between individuals with osteoarthritis and we are interested in two particular traits: individuals with "neuropathic pain" and individuals with "inflammatory pain". Neuropathic pain is often described as sharp, burning, or shooting pain often present at rest as well as on movement which is caused by nerve damage. Inflammatory pain is caused by inflammation and is often described as pain and stiffness at rest, which is improved by movement. It is often associated with swelling and increased warmth of the joint.

Treatment guidelines for knee osteoarthritis consistently recommend two treatments that are applied directly to the knee: topical capsaicin and topical non-steroidal anti-inflammatory drugs (NSAIDs). These treatments come as creams or gels and are applied directly to the painful joint. Topical capsaicin is the substance that makes chilli peppers spicy and acts on superficial pain-signalling nerves. Topical NSAIDs are a group of drugs that include ibuprofen and act by reducing inflammation.

The purpose of this study is to try to identify individuals who benefit from either topical NSAID or capsaicin. We are then interested in identifying any characteristics, including neuropathic and inflammatory aspects of their pain, that are shared between those that respond to either treatment.

This trial will not be able to give a definitive answer regarding which characteristics are related to a response to either drug, but to collect the relevant information that would allow us to design a full study to confirm this.

Why have I been invited?

You are being invited to take part because you have reported knee pain in other studies in our department and have kindly indicated that you would be willing to receive further information about other research studies. You should read this information sheet in detail before deciding whether you wish to take part or not.

We are inviting 22 participants like you to take part in this study.

Do I have to take part?

No. You should only take part in this study if you want to. It is entirely up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. You are free to withdraw at any time, without having to give a reason and without your decision affecting your treatment, care, or legal rights

What will happen to me if I take part?

If you are happy to take part in this study, you will be contacted by telephone by one of our research team to arrange an appointment to come to the department. Please see page 4 for an illustration of your overall path through the trial, should you choose to participate.

Your initial appointment will take approximately two to three hours. A brief review of your medical history will be undertaken to ensure you are eligible to enrol in the trial. You will be given the opportunity to ask any questions you have about the study prior to signing a consent form. You will fill in a questionnaire and have a series of assessments. Please see pages 5-6 for a description of what to expect at each point of contact during this study.

During this study, you will be given two medications: Ibuprofen gel (an NSAID) and Zacin (capsaicin) cream in random order for your painful knee(s). Each treatment will take 4 weeks to complete before switching to the other. The process (cycle) will be repeated up to three times according to your response. You will be shown how to apply both medications and will receive the medication and a participant diary.

Starting on the day after your first hospital visit, you will need to apply the given medication to your knee(s) four times a day for four weeks. If you have pain in both knees, you should apply the medication to both. If only one knee is painful, you will only need to apply medication to the painful knee. You will be asked to record the use of any extra pain medications you have taken, how often you have missed an application of the study drugs, and to rate your knee pain on a weekly basis. At the end of the four weeks, we will send you a text message (SMS, short message service) to ask you to rate your average pain over the last week. You will receive the question in a text message and will only need to respond with the answer (for example, 5). If you are unfamiliar with using text messaging, we can explain the process at the department visit. Alternatively, if you would prefer to receive a telephone call instead of using text messaging, we can do this instead. We will then arrange a home visit to collect your unused medications from the previous treatment period and completed participant diary. We will give you the new medication and participant diary for the next treatment period. The home visits will occur between 9:00 – 17:00 on weekdays. If you are employed, we can arrange for a visit to your work or wherever is most convenient for you.

You will then have a "treatment break" phase until your pain again becomes severe enough to treat. During the "treatment break" period, we will contact you weekly via telephone or text message to ask you to rate your current pain on a scale of 0-10. You are also encouraged to contact us via text message or telephone if you feel that your pain has returned to the level that needs to be treated. Once your pain has returned to the required levels, we will inform you that you are ready for the next treatment period.

Duration:

Because of the variable length of the break periods, the duration of each participant's involvement in the research will vary. It will range from approximately **four to ten months**. In total, we expect the study to take approximately 18 months.

Essential study requirements:

- Medication use: You will need to apply the medication to your knee(s) four times a day throughout the treatment periods. See page 7 for further information about applying the medication.
- Availability for all points of contact: We will ask that you are available for all points of contact (department visit at beginning of trial, home visits at the end of each treatment period, and weekly text messages during break periods). We aim to be flexible in order to facilitate your participation, and ask that you inform us of any periods where you are not available so that we can rearrange a suitable time.
- Use of participant diary: If you experience any side effects or need to take extra pain medication, we ask that you record this in the participant diary.

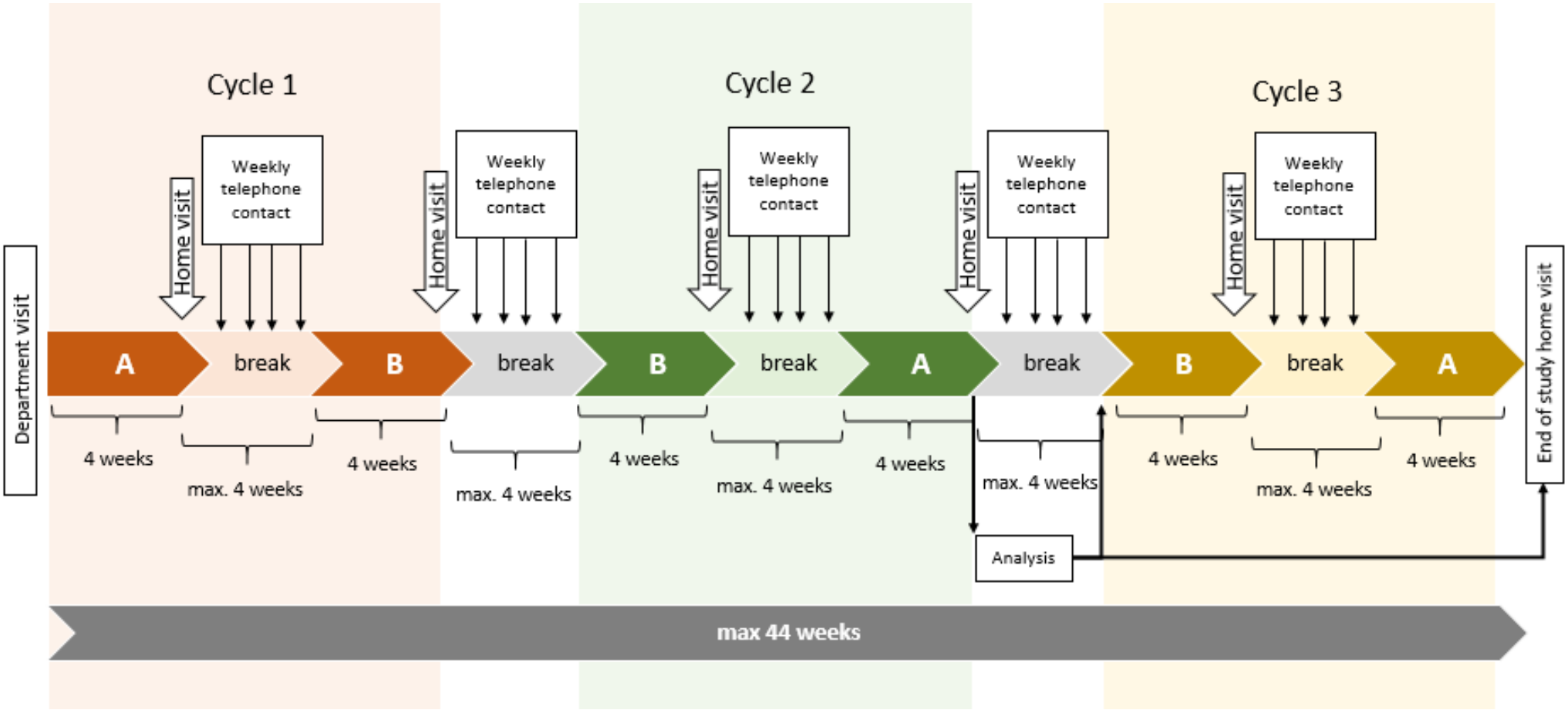

Figure 1 Each participant's journey through the trial. Where A = ibuprofen gel and B = capsaicin cream (note that the order of A and B is randomly determined)

Details of what will happen at each point of contact			
Contact type	**What will happen**	**Frequency**	**Duration**
Department visit	**Questionnaire** • Pain severity • Nature of the pain • Presence of other pain • Physical activity • Perceptions regarding illness and treatment expectations • Emotional state You will have been asked these questions in our previous studies so will hopefully be familiar with them. We would like as up-to-date information as possible and are therefore asking you to answer these questions again. **Assessments** • **Height and weight** • **Ultrasound** An ultrasound machine will be used to image both your knee joints for any underlying swelling. This is a non-invasive procedure; it does not involve any exposure to ionizing radiation and has no detrimental side effects. • **Muscle Strength** Measurement of muscle strength of your hands, knees (thigh muscles) and hips using a hand held machine. Measurements will be done three times in succession. • **Quantitative Sensory Testing (QST)** QST will be used to measure how sensitive your nerves are to changes in mechanical pressure or sharpness. Pressure sensitivity is tested by using a probe to apply pressure to specific sites including your knee, shin, and the front of your chest. To test for sensitivity to sharpness a "pinprick" stimulator will be applied to your skin and you will be asked to rate the pain or sharpness you experience on a given scale. The stimulator will be applied on your knee for less than a second each time. The "pinprick" stimulators are designed not to puncture your skin and the devices are always disinfected before application. So that you know what to expect, the researcher will demonstrate the tests on one of your	One-off	2-3 hours

	hands or your other knee. Any sensation of pain or pressure will be mild and temporary in nature. **Receive information** • We will explain how to apply the medications and how to fill in the participant diary **Receive medication and participant diary** • We will provide you with the medication and participant diary for the first treatment period		
Home visits	**Return medication and participant diary** • We will collect the participant diary and any unused or partially used medication • We will look through the diary and discuss any issues you may have experienced **Receive medication and participant diary** • We will provide you with the medication and participant diary for the subsequent treatment period	Every 1-2 months (5 times total)	15-30 minutes
End of study home visit	**Return medication and participant diary** • We will collect the participant diary and any unused or partially used medication • We will look through the diary and discuss any issues you may have experienced **Pain rating** • You will be asked to rate the severity of your knee pain in the last week using a questionnaire **Treatment preference** • You will be asked which treatment you preferred	One-off	30 minutes
Weekly telephone contact during "break"	**Pain rating** • You will be asked to rate your pain on a scale of 0-10, and will be informed whether or not to commence the next treatment.	Weekly during the "break" periods"	Less than five minutes

Table 1 What will happen at each point of contact

Medication information

Ibuprofen gel and Zacin cream are both safe and licensed treatments for osteoarthritis. They are applied directly to the knee and very little medication is absorbed into the bloodstream.

Ibuprofen gel contains ibuprofen, a non-steroidal anti-inflammatory drug that reduces inflammation.

Zacin contains capsaicin, the same substance that makes chilli peppers spicy. Similarly to the burning felt when you eat a chilli, application of Zacin is often associated with a temporary warming or burning sensation. This is due to the nature of the medication and it is important that you continue to use Zacin as recommended. This warming or burning sensation will subside as you continue to use the medication.

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

The medications are not recommended for use during pregnancy. Pregnant women should therefore not take part in this study and neither should women who plan to become pregnant during the study. If you could become pregnant, you must use an effective method of birth control during the course of this study. If you do become pregnant, you will need to inform us.

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

Expenses and payments

Participation in this study is entirely voluntary. You will receive no payment for your participation however your travel costs to and from the City Hospital will be reimbursed (up to £20).

What are the possible disadvantages and risks of taking part?

Disadvantages:

- Medications may not provide you with adequate pain relief.
    - You will be able to take extra medication if this is the case
    - We will not ask you to stop taking any medications that have been helpful for you in the past, and only hope to target the "excess" pain you are feeling on top of what is covered by your regular medications
    - We hope that you understand that the findings of this research may help others in the future
- You will have to be available for contact.
    - We have tried to minimise the inconvenience for you. This includes:
        - We will cover the travel expenses required for your initial department visit
        - We will carry out home visits rather than asking you to come into the department
            - These will occur between 9:00 – 17:00 on weekdays. If you are in employment, we could arrange for a visit to your place of work if it is more convenient
        - Text message contact during break periods. This means that you can reply when you have some spare time and do not have to rely on being contactable at a set time. Should you prefer to be contacted via telephone calls, we are able to do this instead of text messaging.
        - You will only need to fill in our patient diary at the end of each treatment week. This means that the time spent on filling out information for the study is minimised

Risks:

- You may experience short-term side effects with the medications. However, as only a little medication is absorbed into the bloodstream the treatments generally do not interact with any tablets you may be taking and are relatively safe. Below we have summarised some side effects that have been described for the treatments:
- Zacin cream
    - Common to very common: As previously mentioned, you will most likely experience a transient warming or burning feeling on application.
        - This will subside with continued applications
        - To minimise this, avoid taking a hot bath or shower just before or after applying the cream
    - Rare: cough, eye irritation, and sneezing
- Ibuprofen gel
    - Side effects such as hypersensitivity (rashes and other skin irritation, allergic reactions, asthma and other breathing difficulties), digestive conditions, and kidney problems are extremely uncommon when ibuprofen is applied to the skin
    - Photosensitivity, or a reaction similar to an allergic reaction to sunlight, may occur and this is minimised by avoiding excessive exposure of the knees to sunlight

- When large amounts are applied to the skin, ibuprofen gel may be associated with side effects such as: a degree of worsening of asthma, hypersensitivity to the medication, a small increased risk of blood clots, a worsening in kidney function in those with pre-existing kidney problems, and digestive conditions such as ulcers.
    - It is therefore important that you follow the application instructions and do not apply more than the recommended amount.

What are the possible benefits of taking part?

We cannot promise the study will help you, but as you are taking two treatments that have been shown to be effective for pain management in osteoarthritis, you may find that these medications will reduce your pain. Furthermore, the results of this study may be used to guide a definitive trial that could improve the management of people with knee osteoarthritis by improving the effectiveness of pre-existing medications by tailoring the treatment to the possible source of pain.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to Dr Monica Persson (telephone number: 0115 823 1759) who will do her best to answer your questions. If this achieves no satisfactory outcome, you should then contact the Ethics Committee Secretary, Mrs Louise Sabir, Division of Therapeutics and Molecular Medicine, D Floor, South Block, Queen's Medical Centre, Nottingham, NG7 2UH. Telephone 0115 8231063. E-mail louise.sabir@nottingham.ac.uk.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) is currently stored on a secure database within Academic Rheumatology following your consent for this to occur when you last participated in a study with us. If you state that you do not wish to be contacted regarding future studies your personal details will be destroyed when the results from the study have been analysed.

All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

Although what you say in the interview is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)

All the procedures outlined above are being carried out for research purposes only and your GP will not routinely be informed of your participation in the study. However, if it is felt that it would benefit your medical care if we inform your GP of your examination or investigation findings, this will be discussed with you at the appointment. We will only write to your GP to inform them of the examination and investigation findings if you confirm that you are happy for us to do so. If you wish to inform your GP of your involvement in the trial, we can provide another copy of this information sheet for their reference.

What will happen to the results of the research study?

We hope that the results of the study will lead to a better understanding of knee osteoarthritis and may help us plan a definitive trial that could be used to guide future management. Results from the study will be shared with the scientific community by submitting for publication in scientific and medical journals and presentation in medical scientific meetings. We will share the results to patients by providing lay summaries on the Arthritis Research UK Pain Centre website. Depending on the findings from this study, we may also use the results to plan and conduct a large, definitive trial. Finally, this study will be included in the PhD of Dr Monica Persson.

You will not be named or identified in the reports of this study.

Who is organising and funding the research?

This study is organised by members of staff in Academic Rheumatology, a department of the University of Nottingham based at the City Hospital. The study is being funded by Nottingham University Hospitals Charity, a local NHS Trust charity.

Who has reviewed the study?

This study has been reviewed and given a favourable opinion by the University of Nottingham Medical School Ethics Committee

Further information and contact details

Principal Investigator: Monica Persson
Email: monica.persson@nottingham.ac.uk
Address:
A26 Academic Rheumatology
Clinical Sciences Building
Nottingham City Hospital
NG5 1PB
Office telephone: 0115 823 1759
Work mobile (for texting during break periods): 07593399754