Bone & Joint Research

Supplementary Material

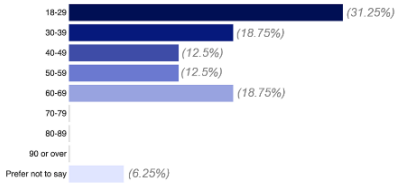
10.1302/2046-3758.139.BJR-2024-0109

Demographics of respondents

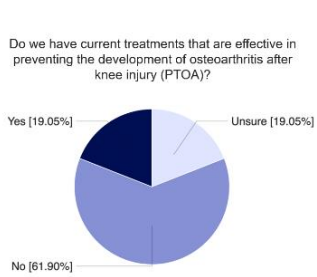
Good demographic representation:

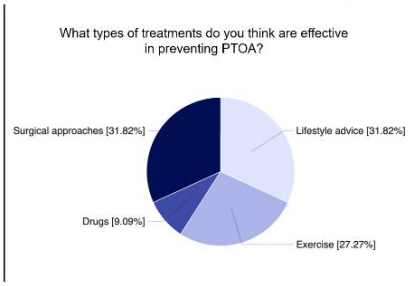
- Equal contribution from Males *(50%)* and Females *(47%)*
- Ethnically diverse: White *(56%)*, Asian or Asian British *(19%)* and Mixed/Multiple *(12.5%)*

Wide range of age groups, with majority being aged between 18-29



Current strategies for prevention of PTOA



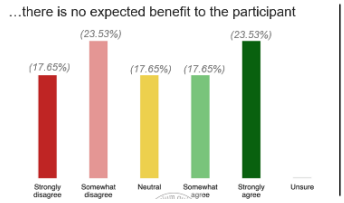


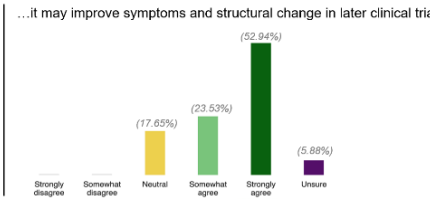
About studies seeking to prevent PTOA

There was a consensus that we need to develop more treatments to prevent PTOA (85%)

Human experimental medicine studies were more acceptable if treatment had the potential to improve both symptoms and prevent structural damage

In your opinion, testing agents in human experimental medicine studies is acceptable if...





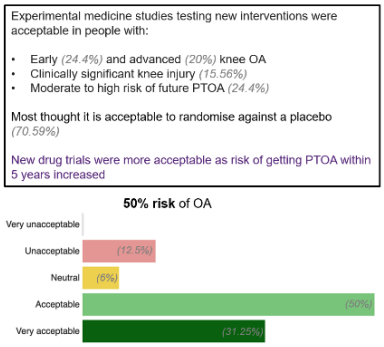
Study design

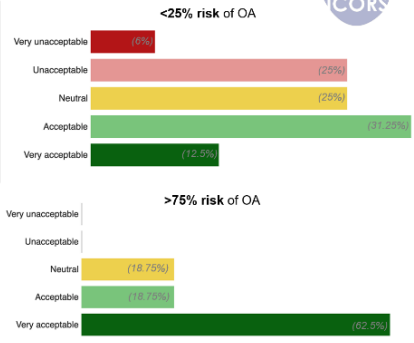
Experimental medicine studies testing new interventions were acceptable in people with:

- Early *(24.4%)* and advanced *(20%)* knee OA
- Clinically significant knee injury *(15.56%)*
- Moderate to high risk of future PTOA *(24.4%)*

Most thought it is acceptable to randomise against a placebo *(70.59%)*

New drug trials were more acceptable as risk of getting PTOA within 5 years increased

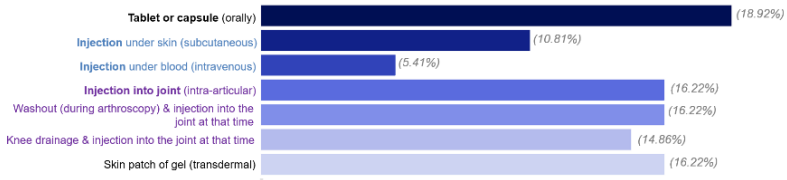




Intervention population, delivery and timing

Population: A reasonably safe new drug that may prevent PTOA can be tested in:

- Small numbers of healthy, young individuals *(69%)*
- People with knee OA *(100%)*
- People with knee injury but no OA *(75%)*



Delivery: All routes of drug delivery are acceptable
Timing: drugs given 2-4 week after injury is acceptable if treatment prevents PTOA and improves symptoms

Fig a. Provisional Survey 1 results presented at International Combined Orthopaedic Research Societies (ICORS), including responses from some people with joint damage caused by knee injury and/or osteoarthritis (PJDs) who had reviewed and trialled the survey, hence why these are different to the final Survey 1 results presented in the manuscript. These results were amended to only present the views of healthcare professionals, clinicians, and/or researchers (HCP/Rs). OA, osteoarthritis; PTOA, post-traumatic osteoarthritis.

Table i. Group A discussion summary around the question: 'How do we design studies/trials that are feasible?'.

Prompt question	Overview of key points of consensus or barrier reported by the group
a) Considering all aspects of practicalities, what is the shortest and what is the longest window that would be practical for taking/prescribing an experimental treatment (appreciating different targets may have different requirements)?	• The group thought that the optimal time of intervention based on current knowledge would be near to the knee injury. This would ideally be between 12 to 24 hours after injury but depending on treatment pathways. This would allow those involved in participant recruitment to feasibly approach, enrol, and collect some baseline data at an appropriate time. • It was thought that the practical time for this would be within the first week after injury, although some in the group thought that this may be too late for some types of treatment to have an effect. • There was less interest shown in the group for intervening in the later stages of injury or in early disease, however this was defined.
b) Thinking about drug treatments specifically, is a systemic treatment only okay if it is an oral tablet/capsule and not an injection under the skin or into a vein? Is an injection into a joint more attractive than a tablet? What	• The consensus was that none of these potential routes would be prohibitive so long as there is clear evidence to back up the decision for the treatment administration route. This would depend on the trial

about if several injections needed to be given over time. What are the considerations here?	design and prior findings from relevant studies (preclinical, human) • The group thought that it is crucial to the design of the trial to be clear on the evidence for options for route of administration and that the standard of care package that they would receive in addition is clearly defined and stated to the patient, alongside any additional/new treatment which would be received. • Injection of drug directly into the joint (intra-articular injection) was felt by some to be more attractive as it may help to minimize some of the side effects experienced with systemic treatments such as oral tablets. This route had the potential additional advantage of removing fluid during the procedure (though this was also an intervention and should be documented). • Administering several injections was thought to be acceptable, so long as they were given between 6 and 12 months after the injury. It was felt that patient adherence could be an issue with longer treatment periods.
c) Thinking about timing of a trial intervention and the timing of existing treatments such as surgical interventions or physiotherapy interventions, how feasible would it be to enrol people into randomized trials (of any type of intervention) around this time, i.e. early after an injury)? What are the possible challenges of recruiting patients into trials at this time? What if taking part limited other interventions people could have? What are the solutions?	• Timing and length of intervention depends on the type/nature of patient's existing treatment, as well as other treatment being offered. A potential challenge would be that patients may not be able to take 'usual' pain medication as it may interfere with the trial treatment. Therefore, the group thought that it would be important to clearly outline/define to the patient what they are able to do as part of their existing/standard of care and what is controlled/additional by participating in the trial. • The group also discussed the importance of delivering information to participants about the risk associated with OA at the time of injury. It is not clear that this is universally discussed or understood by patients, therefore it should be necessary to incorporate this as part

	of the clinical discussion that occurs between clinical staff and patients if trials are going to be relevant to them. • Other challenges highlighted involved those relating to patient compliance and adherence during the trial in this population.

OA, osteoarthritis.

Table ii. Group B discussion summary around the question: 'How do we design studies/trials that are acceptable?'.

Question	Overview of key points reported by the group
a) Does a new treatment need to successfully prevent both symptoms and joint degeneration to be acceptable? Would a treatment that either only prevented knee symptoms or only prevented joint degeneration ever be acceptable? Does a treatment always need to help symptoms?	• The group preferred new treatments that prevent both symptoms and joint degeneration, as these are two effects of arthritis that should be addressed. • Introducing new treatments that prevent symptoms may help improve patient adherence. • There could be a problem with treating everyone at the time of their injury, as only 50% will go on to develop OA. • Younger people may not consider fully (or be concerned about) the implications of later OA, which could reduce recruitment.
b) What is the acceptable balance of risk vs benefit for experimental medicine studies using new drugs? Does this differ from longer-term trials aiming for patient benefit, i.e. how safe do drugs need to be in these settings? Does this differ between people with an injury and people with early OA? Is it okay to give a patient a treatment with the potential to prevent OA when the risk of getting OA is undefined in that individual?	• The group felt that there was a problem with treating individuals at the time of injury, when the risk of getting OA in that individual was undefined. Accurate prediction models and the identification of early OA biomarkers which identify those at higher risk would address this. This consideration is less important if the treatment is also reducing symptoms of knee injury, which would benefit all patients. • Accurate prediction models are needed, and the group discussed the importance of recruiting a young patient population. It is often easier to recruit older patients to trials, as they have a better understanding of risks associated with trials and what enrolling/consenting to a trial involves. Older patients may be more familiar with the impact of OA whereas younger patients may be more focused on returning to sports participation at the same level. • The duration of treatment is also an important factor to consider in terms of acceptability, as well as the rate of drop-out under varying trial conditions (which might suggest issues with acceptability e.g. unacceptable side effect profile etc). • The group considered that short intervention periods rather than long-term continuous treatment would be more acceptable to the patient and more cost-effective.

	• There was emphasis on the importance of considering the cost-benefit ratio to individuals and society. It is important to think about the long-term benefits associated with a trial, how much trials (and interventions) with long-term benefits will cost, and whether certain types of interventions are worthwhile if we are not sure about their risk-benefit ratio. • The group thought it was acceptable to include in trials less tested drugs if they were supported by coherent arguments from animal/veterinary models, such as those showing likely benefits in the long term.
c) How acceptable are studies of new drugs, as opposed to other therapies like surgical interventions or exercise interventions? Would drug studies need to be 'superimposed' on standard care, and what would standard care be?	• Countries (the example of South Korea was given), have high rate of meniscal replacement/transplant surgery in young, asymptomatic populations compared to ACL repair (this is due to having a high incidence of discoid meniscus, a congenital abnormality associated with future degeneration). Findings suggest that surgery is more beneficial than conservative treatment and is accepted by these young patients, which illustrates that (at least in South Korea) young individuals may accept surgical interventions as a potential way to prevent future OA. The group discussed that this might suggest that young asymptomatic individuals may also accept a drug treatment if the evidence for it reducing later OA was established. • It is important to consider when it would be deemed acceptable to offer surgical interventions (either as part of usual care, or as a trial intervention?) to patients when we are not sure if they have a high risk of OA progression in the next 10 years. Would it be deemed acceptable to operate on asymptomatic patients? The group were not sure. • It is also important to consider sex-specific outcomes relating to surgery or other treatments.

ACL, anterior cruciate ligament; OA, osteoarthritis.

Table iii. Group C discussion summary around the topic: 'Key considerations around design of experimental medicine studies in this area'.

Question	Overview of key points reported by the group
a) Is risk stratification (assessing people and allocating them to low, medium, or high risk of OA groups) and selecting people at high risk for targeting particular treatments (in trials, or later in the clinic) acceptable or not? How much risk of OA over 5 years is sufficient to justify being considered at 'moderate to high risk'?	• The group discussed how people could be identified and potentially selected based on high, medium, and low risk and whether genetics could be used, in particular risk profiling according to groups of genes (in an overall risk score looking across the genome) rather than individual genes. The group saw potential in this. • One of the issues at the moment for experimental design and novel targets is that we still don't understand the full pathogenesis of the disease, therefore it's crucial to further our understanding of the disease. We can use different models (including pre-clinical ones) to help predict better what are the measurable outcomes for a particular target to study which may help with the stratification. It's important to know the cause and pathogenesis before we can stratify the risk. • If we are trying to stratify people into trials based on areas like lifestyle changes, such as exercise, there is a risk that people will change their trial groups/strata, as behaviours can also change which could affect trial integrity. There could be biases in terms of people being included in particular groups and also discomfort on any grouping based on non-modifiable risk factors e.g. age, sex. In saying this, the group recognised that lifestyle and amount people exercise are likely to be important factors in risk. The group felt that, rather than stratifying on overall risk factors for PTOA, it may instead be better to stratify based on specific molecular biomarkers for intervention target (there was high consensus for this). This can include stratifying based on likely effect of target by having molecular/mechanistic readout of engagement with targets. • In terms of ethical considerations - if you don't stratify with the aim of showing efficacy by benefiting patients in certain groups, based on what we have seen in OA, you may fail to identify efficacious treatment options that could help patients in the future. • Overall, there was support in the group for stratification as an enabler. However, it is important to carefully consider the trial eligibility criteria, as if they are too narrow (i.e. too small a target group), then you will not be able to recruit to the trial (to the point above). It's therefore important to consider

	which endpoints are relevant, and to consider selecting participants who may benefit the most.
b) How much experience should we have of drugs before they are used in humans in an experimental medicine setting e.g. should they always be drugs repurposed from other diseases or is it ok to use newer drugs that have only been tested for safety in healthy individuals?	• The group agreed on the importance of testing new drugs that haven't been tested in this setting before, and there was agreement that without testing new medicines there would be no progress in this field. In saying this, both new and repurposed drugs are needed. • It is important to have preclinical evidence to support which new drugs would be tested i.e., that this was compelling and ensuring that that drugs have 'passed' the relevant safety tests and measures. This can include having evidence from animal preclinical testing and human cell/organ culture models as well as phase I 'healthy human' studies. • The design of the trial was also a topic of conversation, and it was agreed by the group that blinding of interventions (both active and comparator) in this setting is essential (i.e. masking of intervention for patient and clinician). Placebo group needs to receive basic 'standard of care' treatment (i.e. ensuring we are not taking treatment away from patients when they enter trials). The group agreed that usual care in this setting is difficult to standardise as a 'standard of care', and depends on which pathway a patient is in and probably which country they are in.
c) Is it more attractive to design studies of new treatments that are targeted at the time of the injury or in people found to have persistent symptoms or higher risk 1 to 2 years after their injury?	• Ideally, we would want to treat patients at the time of their injury rather than later, but the group felt that this is not usually feasible due to the way most healthcare systems (e.g. UK NHS) realistically function. • It would be useful to think about whether it would be possible to fast-track patients to be seen in clinics who may be candidates for trials. This raised the question of which patients should be fast tracked and how they could be identified.

OA, osteoarthritis; PTOA, post-traumatic osteoarthritis.

Supplementary Material 2, Survey (1) text:

ICORS 2022 prevention of post-traumatic osteoarthritis (PTOA) pre-workshop survey

Thank you for taking the time to complete this ICORS 2022 survey. We want to hear from clinicians, researchers and people living with osteoarthritis or who have had a knee injury. The survey will ask you about research aimed at preventing osteoarthritis specifically after knee joint injury, so called 'post-traumatic osteoarthritis' of the knee (we have abbreviated this to PTOA throughout).

The survey responses will be presented as part of ICORS 2022 and used to inform research in this area. The survey is now live and will be open until midnight on 31st August. It should take no more than 20 minutes to complete. The survey does not collect any personal identifiable information so you will never be linked to your responses. Taking part is entirely voluntary. We would ask that you answer from your own knowledge and perspective. If you feel unsure, you can tick 'unsure'. You can miss out any question and do not need to give a reason. The survey is aimed at people who are 18 years and older.

Author 9 at Imperial College London and Author 8 at University of Cardiff are carrying out this survey. If you have a question about the survey, please contact us.

About current strategies for prevention of post-traumatic osteoarthritis (PTOA)

1. I am a (select the one that most applies):
    - researcher (clinician)
    - researcher (non-clinician)
    - healthcare professional (orthopaedic surgeon)
    - healthcare professional (physiotherapist)
    - healthcare professional (other)
    - person with osteoarthritis/experience of past knee injury
    - member of public with an interest in a condition
    - carer
    - other
    - prefer not to say

If other, please specify below:

2. In your opinion, do we have current treatments that are effective in preventing the development of osteoarthritis after knee injury (PTOA)?
    - yes/no/not sure

3. If you selected yes, what types of treatments do you think are effective in preventing PTOA? (please select all that apply)
    - Surgical approaches/drugs/exercise/lifestyle advice/other

4. To what extent do you agree or disagree with the following statements? *(strongly disagree, somewhat disagree, neutral, somewhat agree, strongly agree, unsure)*
    - We do not need to develop or test more treatments to prevent PTOA

- We should test existing treatments more to understand if they prevent PTOA
- We should develop new treatments that improve knee symptoms.
- We should develop new treatments that improve or slow down damage to the knee structure
- We should develop new treatments that improve or slow down knee symptoms and damage to the knee structure

About studies seeking to prevent post-traumatic osteoarthritis (PTOA)

5. Do you feel you know the difference between a clinical trial, an experimental medicine study and a feasibility study?
    - Yes/no/unsure

Please consider the following scenario for questions 6 to 8

Researchers are carrying out a human experimental medicine study to see if a drug is retained in the joint over time and has the expected effects on its target when injected into the knee. In people giving consent, the drug is injected into the knee in the days before their planned total knee replacement surgery. At surgery, the removed joint tissues are retained as well as a blood and urine sample. Drug concentrations are measured in these samples after surgery. The drug may have some side effects, but these are expected to be uncommon at the dose given.

6. In your opinion, testing agents in human experimental medicine studies acceptable if: *(strongly disagree, somewhat disagree, neutral, somewhat agree, strongly agree, unsure)*
    a. there is no expected benefit to the participant
    b. there is no expected benefit and some risk to the participant
    c. the agent being tested may improve symptoms only in later clinical trials
    d. the agent being tested may improve symptoms and structural change in later clinical trials

7. In which groups is it acceptable to offer experimental medicine studies testing new interventions? (*select all that apply)*
    - When a person has knee osteoarthritis with early or mild knee symptoms
    - When a person has knee osteoarthritis with severe knee symptoms
    - When a person has experienced knee injury and is shown to be at moderate to high risk of future PTOA
    - Any person who has experienced a clinically significant knee injury
    - Healthy individuals without knee injury or osteoarthritis
    - None of the above
    - Unsure

8. Is it acceptable to carry out 'randomised controlled studies' in this setting (where there is typically a 50:50 chance of getting the active treatment or a dummy treatment or 'placebo'), so long as all participants also receive standardised best care?
    - Yes/no/unsure/depends on the type of study or trial

About risk and benefit

9. Please tell us how acceptable it is to test a new drug in a clinical trial or experimental medicine setting that delays or seeks to prevent PTOA considering the following scenarios.

a) **Changing risks of PTOA for an individual** *(very unacceptable, unacceptable, neutral, acceptable, very acceptable, not sure)*

When a person is estimated to have a...
- 25% risk or less of developing osteoarthritis within 5 years
- 50% risk of developing osteoarthritis within 5 years
- 75% risk or more of developing osteoarthritis within 5 years

b) **Considering drug safety** (*very unacceptable, unacceptable, neutral, acceptable, very acceptable, not sure)*

When a drug is well-tolerated and reasonably safe when tested in…
- preclinical experiments, but not yet tested in humans (first in man)
- small numbers of healthy, young individuals
- people with knee osteoarthritis
- people with knee injury but no osteoarthritis
- people with other conditions, but not osteoarthritis (repurposed)

c) **Considering how a drug is predicted to work** *(very unacceptable, unacceptable, neutral, acceptable, very acceptable, not sure)*

When a drug...
- improves symptoms, such as knee pain and stiffness and is predicted to prevent joint damage
- improves knee symptoms, such as pain and stiffness with no effect on joint damage
- slows/improves joint damage with unknown effect on knee symptoms
- slows/improves joint damage with no effect on knee symptoms
- improves knee symptoms such as knee pain and stiffness and slows/improves joint damage

About how a drug might be taken

10. In which ways do you think it would be acceptable to take a drug that seeks to prevent or delay PTOA of the knee after a person has a knee injury? (*select all that apply)*
    - Tablet or capsule (orally)
    - Injection under skin (subcutaneous)
    - Injection into blood (intravenous)
    - Injection into joint (intra-articular)
    - Washout (during arthroscopy) and injection into joint at that time
    - Knee drainage and injection into joint at that time
    - Skin patch or gel (transdermal)
    - I don't think any of these ways are acceptable
    - Unsure

Frequency of drug administration

11. How acceptable is it to be given an intra-articular injection into the knee joint, with a drug that seeks to prevent or delay PTOA as… *(very unacceptable, somewhat unacceptable, neutral, somewhat acceptable, very acceptable, unsure)*

a) a single injection within 2 weeks of injury
b) a single injection within 4-6 weeks of injury
c) weekly injections over 3-4 weeks
d) monthly injections over 3 months
e) monthly injections over 6 months
f) 3 monthly injections over 1 year

Timing of intervention

12. Treatment at or close to the time of joint injury (within first 2-4 weeks) would be acceptable if the treatment… (*strongly disagree, somewhat disagree, neutral, somewhat agree, strongly agree, unsure)*

a) improved symptoms of the knee injury but with no effect on later PTOA risk
b) may prevent later OA, but does not affect knee symptoms
c) may prevent later OA and improves knee symptoms

Clinical and patient Insight – to target from 1st response

13. As a clinician, when would you be willing to talk to a patient about an experimental medicine study testing a new intervention (*select all that apply)*

- at time of knee injury (first visit at emergency room or clinic, within first week after injury)
- at time of arthroscopy or other planned first intervention
- at time of ligament reconstruction surgery
- at time of period of rehabilitation/physiotherapy/exercise advice
- at time of planned joint replacement surgery
- not willing to discuss at any of these times
- not applicable (I am not a clinician)

14. As an individual with past knee injury or with osteoarthritis, when do you think it is acceptable to participate in an experimental medicine study testing a new intervention *(select all that apply)*

- at time of knee injury (first visit at emergency room or clinic, within first week after injury)
- at time of arthroscopy or other planned first intervention
- at time of ligament reconstruction or arthroscopic surgery
- at time of start of rehabilitation period/physiotherapy/exercise advice
- at time of persisting/troublesome knee symptoms after injury
- at time of planned joint replacement surgery
- not willing to discuss at any of these times
- not applicable (I am not a person with lived experience of these conditions)

About you

We would like to gather some optional information on your background to ensure

balance and diversity in this exercise. If you do not wish to provide this information, please select the 'prefer not to say' option.

15. What is your age?
    - 18-29
    - 30-39
    - 40-49
    - 50-59
    - 60-69
    - 70-79
    - 80-89
    - 90 or over
    - Prefer not to say

16. How would you best describe your ethnic origins?
    - Asian or Asian British
    - Black, Black British, Caribbean or African
    - Mixed or multiple ethnic groups
    - White
    - Other ethnic group
    - Prefer not to say

17. What is your preferred gender identity?
    - Female
    - Male
    - Other
    - Prefer not to say

Contact and update

The workshop at ICORS, Edinburgh on 'Prevention of post-traumatic osteoarthritis: research needs and barriers' is on **Wednesday 7th September from 11-12.30pm** in Lecture theatre 3, Appleton tower. We will present the findings of this survey and include a facilitated discussion of opinions on testing new treatments seeking to prevent or slow PTOA of the knee.

Please join us at this important discussion and save the date in your diary!

18. Are you planning to attend the workshop?
    - Yes/no/ unsure

19. If yes, are you most interested in participating in discussion groups on:
    - Experimental medicine study design
    - Perspectives on feasibility of studies seeking to prevent OA
    - Perspectives on acceptability of studies seeking to prevent OA
    - Not applicable/none of these

If you would like to hear more about the planned workshop and/or help us develop further work in this area, please get in touch with us.

We thank you for your time spent taking this survey.
Your response has been recorded.

Supplementary Material 3, Survey (2) text

Prevention of post-traumatic osteoarthritis survey aimed at people with lived experience

Thank you for taking the time to complete this survey. We want to hear from people living with knee osteoarthritis or who have had a clinically significant knee injury. The survey will ask you about research aimed at preventing osteoarthritis that occurs specifically after knee joint injury, so called 'post-traumatic osteoarthritis' of the knee (we have abbreviated this to PTOA throughout).

The survey is live and will be open until midnight on **Monday 19th June 2023**. It should take no more than 20 minutes to complete. The survey does not collect any personal identifiable information so you will never be linked to your responses. Taking part is entirely voluntary. We would ask that you answer from your own knowledge and perspective. If you feel unsure, you can tick 'unsure'. You can miss out any question and do not need to give a reason. The survey is aimed at people who are 18 years and older.

Author 9 at Imperial College London, with honorary affiliation to Oxford University, and Author 8 at Cardiff University are carrying out this survey. The survey data will help to inform future experimental medicine and clinical trial design. If you have a question about the survey, or how the findings from the survey will be used, please contact us.

About current strategies for prevention of post-traumatic osteoarthritis (PTOA)

1. Are you an individual living with knee osteoarthritis OR who has had a clinically significant knee injury?
    - yes/no

Note: *For a knee injury to be clinically significant, we mean that you were not able to put your weight through the knee normally for at least 48 hours and that you saw a doctor and/or had an MRI that showed you had injured a structure within the knee. Typically your knee would swell as part of this injury*

2. *Please indicate which of the below you have (select all that apply):*
    - Knee osteoarthritis
    - Current knee injury
    - Past knee injury
    - Knee replacement (due to previous knee OA)
    - Other
    - None of the above

If other, please specify below:

3. In your opinion, do we have current treatments that are effective in preventing the development of osteoarthritis after knee injury (PTOA)?
    - yes/no/not sure

4. If you selected yes, what types of treatments do you think are effective in preventing PTOA? (please select all that apply)

- Surgical approaches/drugs/exercise/lifestyle advice/other

5. To what extent do you agree or disagree with the following statements? *(strongly disagree, somewhat disagree, neutral, somewhat agree, strongly agree, unsure)*

Note: *Below, knee symptoms include things like knee pain, knee stiffness or knee swelling*

- We do not need to develop or test more treatments to prevent PTOA
- We should test existing treatments more to understand if they prevent PTOA
- We should develop new treatments that only improve knee symptoms
- We should develop new treatments that only improve or slow down damage to the knee structure
- We should develop new treatments that improve or slow down knee symptoms and damage to the knee structure

Drag and drop the below statements in order of importance, from what you believe is deemed most important (1) to least important (3)

- We should develop new treatments that only improve knee symptoms
- We should develop new treatments that only improve or slow down damage to the knee structure
- We should develop new treatments that improve or slow down knee symptoms and damage to the knee structure

About studies seeking to prevent post-traumatic osteoarthritis (PTOA)

6. Do you feel you know the difference between a clinical trial, an experimental medicine study and a feasibility study?
    - yes/no

Below are the definitions for each type of research/study mentioned in question 5. Feel free to refer back to these definitions to assist you with answering future questions where needed.

Clinical trials are studies which test new treatments and measure their effects on human health outcomes. Trials are essential to the development of new medical treatments and help us to understand whether they work as expected and check they are sufficiently safe. They tend to be long, in large groups of people with a condition, and therefore expensive.

Experimental medicine studies compare the effect of treatments or interventions in humans in a clinical study like a clinical trial, but generally focus on looking at a short term 'experimental' early measurements like a blood marker or other response, to get an early indication of whether a drug or other intervention might be working or not. Unlike clinical trials, they do not collect human health outcomes or answer the question as to whether the treatment improves symptoms or disease, but provide 'proof of concept' for later larger clinical trials testing this. In theory they are smaller, shorter and faster than full clinical trials and give evidence supporting (or stopping) the next stage.

Feasibility studies are done before a main study to investigate whether the main study can be done, usually in smaller numbers and as such do not give a definitive answer to the research question. However, they improve the chances of continuing to

run a study that can answer this question in the future. They assist with planning the trial design, and improving the quality and success of recruitment to trials that may follow. For example, can patients who are willing to take part be identified within a particular time window, and from which routes. In theory they are smaller, shorter and faster than full clinical trials and support (or prevent) the next stage.

Please consider the following scenario for questions 6 to 8

Researchers are carrying out a human experimental medicine study to see if a drug is retained in the joint over time and has the expected effects on its target when injected into the knee. In people giving consent, the drug is injected into the knee in the days before their planned total knee replacement surgery. At surgery, the removed joint tissues are retained as well as a blood and urine sample. Drug concentrations are measured in these samples after surgery. The drug may have some side effects, but these are expected to be uncommon at the dose given.

7. In your opinion, testing agents in human experimental medicine studies acceptable if: *(strongly disagree, somewhat disagree, neutral, somewhat agree, strongly agree, unsure)*
    a. there is no expected benefit to the participant
    b. there is no expected benefit and some risk to the participant
    c. the agent being tested may improve symptoms only in later clinical trials
    d. the agent being tested may improve symptoms and structural change in later clinical trials

8. In which groups is it acceptable to offer experimental medicine studies testing new interventions? (*select all that apply)*
    - When a person has knee osteoarthritis with early or mild knee symptoms
    - When a person has knee osteoarthritis with severe knee symptoms
    - When a person has experienced knee injury and is shown to be at moderate to high risk of future PTOA
    - Any person who has experienced a clinically significant knee injury
    - Healthy individuals without knee injury or osteoarthritis
    - None of the above
    - Unsure

9. Is it acceptable to carry out 'randomised controlled studies' in this setting (where there is typically a 50:50 chance of getting the active treatment or a dummy treatment or 'placebo'), so long as all participants also receive standardised best care?
    - Yes/no/unsure/depends on the type of study or trial

About risk and benefit

Changing risks of PTOA for an individual

10. How acceptable do you think it is to test a new drug in a clinical study that seeks to prevent PTOA when a person is estimated to have a… *(very unacceptable, unacceptable, neutral, acceptable, very acceptable, not sure)*
    - 25% risk or less of developing osteoarthritis within 5 years
    - 50% risk of developing osteoarthritis within 5 years

- 75% risk or more of developing osteoarthritis within 5 years

Considering drug safety

11. How acceptable do you think it is to test a new, well-tolerated and reasonably safe drug in a clinical study that seeks to prevent PTOA in… (*very unacceptable, unacceptable, neutral, acceptable, very acceptable, not sure)*
    - preclinical experiments, but not yet tested in humans (first in man)
    - small numbers of healthy, young individuals
    - people with knee osteoarthritis
    - people with knee injury but no osteoarthritis
    - people with other conditions, but not osteoarthritis (repurposed)

Considering how a drug is predicted to work

12. How acceptable do you think it is to test a new drug in a clinical study that seeks to prevent PTOA when a drug… (*very unacceptable, unacceptable, neutral, acceptable, very acceptable, not sure)*
    - improves symptoms, such as knee pain and stiffness and is predicted to prevent joint damage
    - improves knee symptoms, such as pain and stiffness with no effect on joint damage
    - slows/improves joint damage with unknown effect on knee symptoms
    - slows/improves joint damage with no effect on knee symptoms
    - improves knee symptoms such as knee pain and stiffness and slows/improves joint damage

About how a drug might be taken

There are various different challenges associated with recruiting patients to studies and trials and keeping them in the study. One of the considerations is the method and frequency by which a drug is given.

13. In which ways do you think it would be acceptable to take a drug that seeks to prevent or delay PTOA of the knee after a person has a knee injury? (*select all that apply)*
    - Tablet or capsule (orally)
    - Injection under skin (subcutaneous)
    - Injection into blood (intravenous)
    - Injection into joint (intra-articular)
    - Washout (during arthroscopy) and injection into joint at that time
    - Knee drainage and injection into joint at that time
    - Skin patch or gel (transdermal)
    - I don't think any of these ways are acceptable
    - Unsure

Frequency of drug administration

14. How acceptable is it to be given an intra-articular injection into the knee joint, with a drug that seeks to prevent or delay PTOA as… *(very unacceptable, somewhat unacceptable, neutral, somewhat acceptable, very acceptable, unsure)*

a) a single injection within 2 weeks of injury
b) a single injection within 4-6 weeks of injury
c) weekly injections over 3-4 weeks
d) monthly injections over 3 months
e) monthly injections over 6 months
f) 3 monthly injections over 1 year

Timing of intervention

15. Treatment at or close to the time of joint injury (within first 2-4 weeks) would be acceptable if the treatment… (*strongly disagree, somewhat disagree, neutral, somewhat agree, strongly agree, unsure)*
    a) improved symptoms of the knee injury but with no effect on later PTOA risk
    b) may prevent later OA, but does not affect knee symptoms
    c) may prevent later OA and improves knee symptoms

16. Considering your condition, when do you think it is acceptable to take part in an experimental medicine study testing a new treatment? *(select all that apply)*
    - At time of knee injury (first visit at emergency room/A&E or clinic, within first week after injury)
    - At time of arthroscopy or other planned first intervention
    - At time of ligament reconstruction or keyhole surgery
    - At time of start of rehabilitation period/physiotherapy/exercise advice
    - At time of persisting/troublesome knee symptoms after injury
    - At time of planned joint replacement surgery
    - Not willing to discuss at any of these times
    - Not applicable (I am not a person with lived experience of these conditions)

About you

We would like to gather some optional information on your background to ensure balance and diversity in this exercise. If you do not wish to provide this information, please select the 'prefer not to say' option.

15. What is your age?
    - 18-29
    - 30-39
    - 40-49
    - 50-59
    - 60-69
    - 70-79
    - 80-89
    - 90 or over
    - Prefer not to say

16. How would you best describe your ethnic origins?
    - Asian or Asian British
    - Black, Black British, Caribbean or African
    - Mixed or multiple ethnic groups
    - White
    - Other ethnic group
    - Prefer not to say

17. What is your preferred gender identity?
- Female
- Male
- Other
- Prefer not to say

Contact and update

Thank you very much for taking the time to complete this survey. The results of this survey will be used to understand how we develop trials of new treatments in this area.

If you would like to hear more about the planned workshop and/or help us develop further work in this area, please get in touch with us.

We thank you for your time spent taking this survey.
Your response has been recorded.

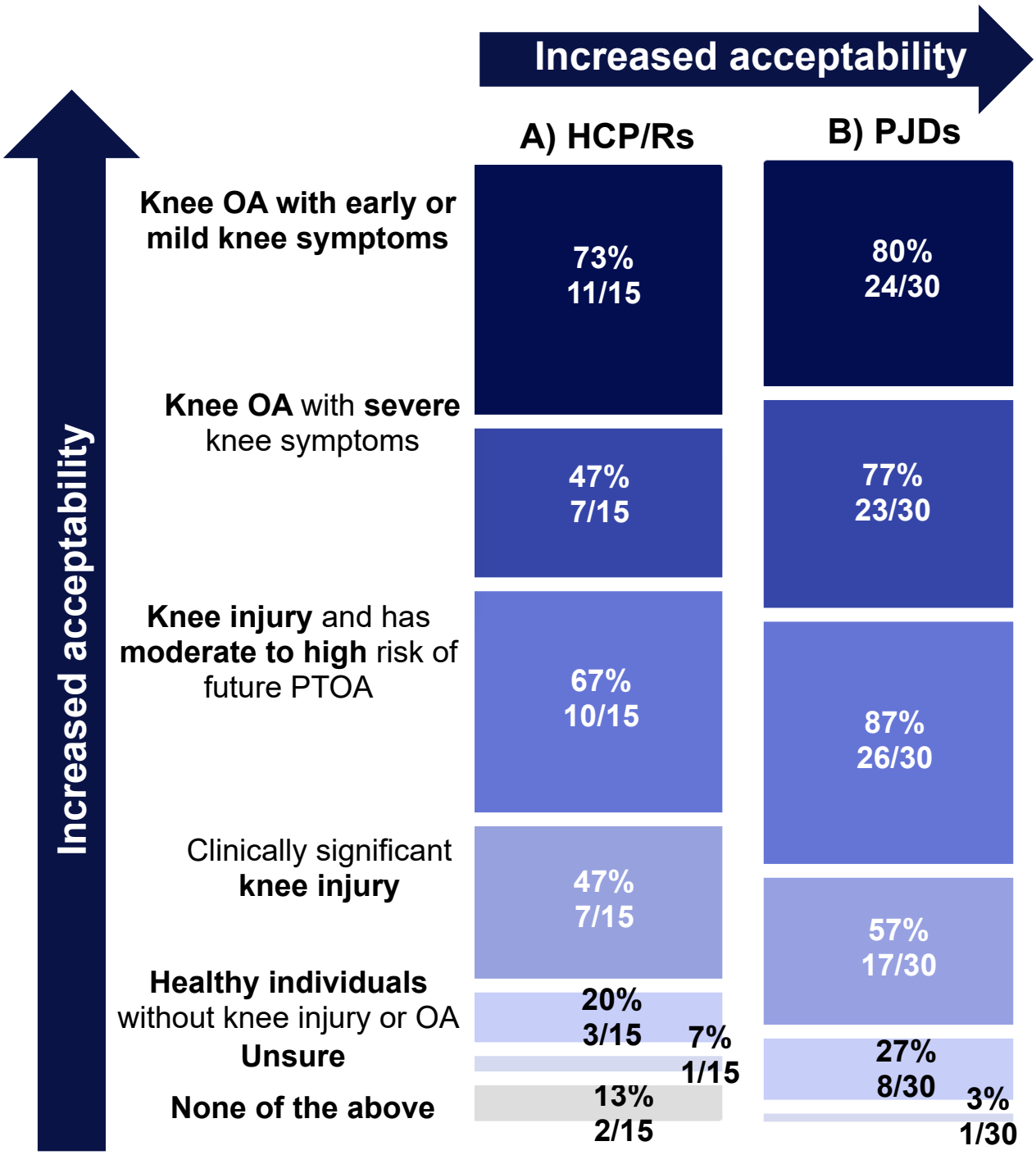


Fig b. Findings from surveys when respondents were asked about how acceptable they thought offering experimental medicine studies testing new interventions to different target groups is.

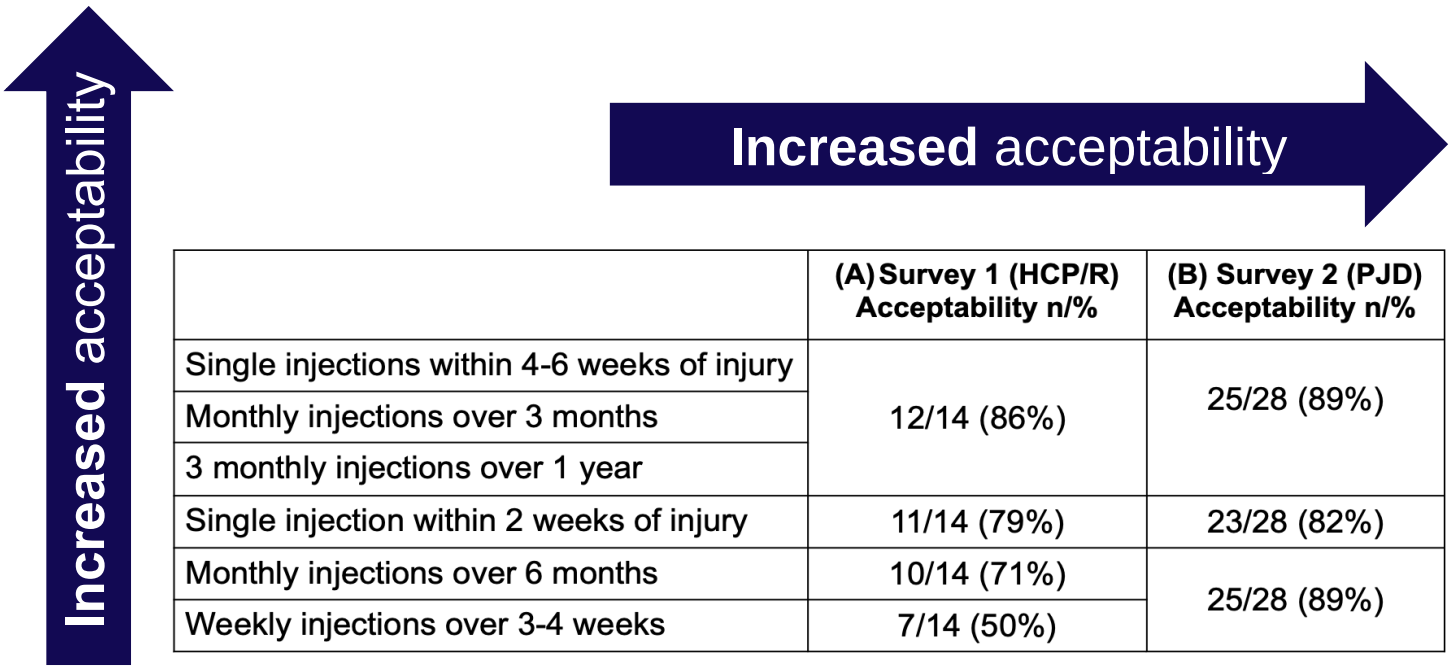
Survey findings for (A) HCP/Rs from Survey 1 and (B) PJDs from Survey 2. Multiple answers could be selected. 15 HCP/R respondents gave a total of 41 responses and 30 PJD respondents gave a total of 99 responses. Responses/respondents and

percentages for each stakeholder group are shown in the figure. HCP/Rs, healthcare professionals, clinicians, and/or researchers; OA, osteoarthritis; PJDs, people with joint damage caused by knee injury, osteoarthritis, or both; PTOA, post-traumatic osteoarthritis.

(A) Survey 1 (HCP/R)		(B) Survey 2 (PJD)	
Target population	**Acceptability n/%**	**Target population**	**Acceptability n/%**
Knee OA	14/14 (100%)	Knee OA	27/29 (93%)
Small number of healthy & young individuals	11/14 (79%)	First in human	25/29 (86%)
Knee injured, no OA		Knee injured, no OA	21/29 (72%)
First in Human	10/14 (71%)	Small number of healthy & young individuals	16/29 (55%)
With knowledge that it works in other conditions, but not OA (repurposed)	8/14 (57%)	With knowledge that it works in other conditions, but not OA (repurposed)	11/29 (38%)

Fig c. Findings from surveys when respondents were asked about how acceptable they thought it was to test a drug that is well-tolerated and reasonably safe in different target groups.

Survey findings for (A) HCP/Rs from Survey 1 and (B) PJDs from Survey 2. Responses/respondents and percentages for each stakeholder group are shown in the figure. HCP/Rs, healthcare professionals, clinicians, and/or researchers; OA, osteoarthritis; PJDs, people with joint damage caused by knee injury, osteoarthritis, or both.



	(A) Survey 1 (HCP/R) Acceptability n/%	(B) Survey 2 (PJD) Acceptability n/%
Single injections within 4-6 weeks of injury	12/14 (86%)	25/28 (89%)
Monthly injections over 3 months		
3 monthly injections over 1 year		
Single injection within 2 weeks of injury	11/14 (79%)	23/28 (82%)
Monthly injections over 6 months	10/14 (71%)	25/28 (89%)
Weekly injections over 3-4 weeks	7/14 (50%)	

Fig d. Findings from surveys when respondents were asked about how acceptable they thought a drug that seeks to prevent or delay post-traumatic osteoarthritis as an intra-articular injection into the knee joint over different frequencies is.

Survey findings for (A) HCP/Rs from Survey 1 and (B) PJDs from Survey 2. Responses/respondents and percentages for each stakeholder group are shown in the figure. HCP/Rs, healthcare professionals, clinicians, and/or researchers; PJDs, people with joint damage caused by knee injury, osteoarthritis, or both.