IMPROVING ENROLMENT IN CLINICAL TRIALS THROUGH CO-DESIGN WITH PARTICIPANTS: DEVELOPMENT OF THE I-PARTICIPATE APROACH

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Nick Bansback, PhD

Professor, School of Population and Public Health, University of British Columbia

Decision Science Lead, Centre for Advancing Health Outcomes, St Paul's Hospital

Disclosures and Acknowledgments

The studies described were funded by CIHR and The Arthritis Foundation (US)
No members of the team have current or former relationships with commercial entities

Study 1 –An analysis of clinical trials registered on ClinicalTrials.gov co-authors include UBC researchers: **Alexander C.T. Tam**, Jack Smith, Mark J. Harrison, and Srinivas Murthy
Study 2 – Incorporating the Patient Voice into Clinical Trial Design To Increase Enrolment
Alexander C.T. Tam, Kevin Kennedy (both UBC), Lily Waddell, Jeffrey N. Katz, Elena Losina (all Harvard) Liana Fraenkel (Yale) Jason Kim (Arthritis Foundation)

Colleagues have critically reviewed previous versions of slides to mitigate potential bias

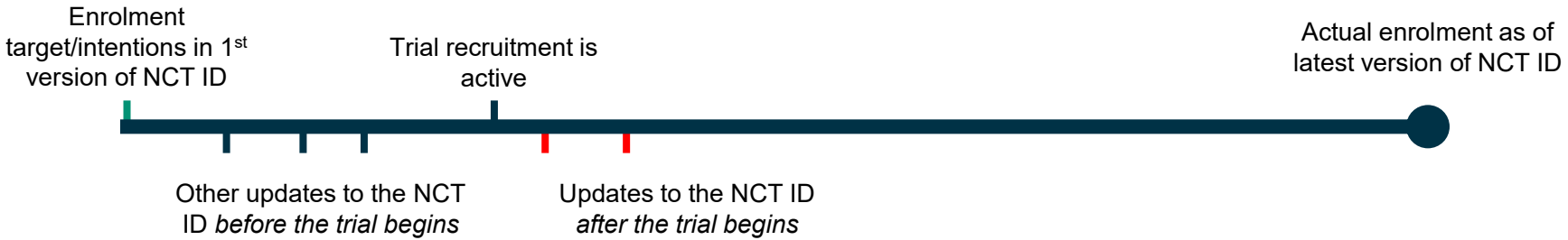
The work was conducted on the traditional and unceded territory of the Coast Salish Peoples, including the territories of the xwməθkwəy̓əm (Musqueam), Skwxwú7mesh (Squamish), Stó:lō and Səl̓ílwətaʔ/Selilwitulh (Tsleil- Waututh) Nations

Background

- **Clinical trials** are **essential** for advancing medical knowledge, improving patient care and outcomes.
- However, **many clinical trials fail** - lower than required patient enrolment a key reason.
- **Low enrolment** to a clinical trial reduces statistical power meaning intended research question may not be answered.
- **Exposes patients to risk** associated with interventions, wastes research dollars, and raises many ethical questions.
- Studies in US and UK have previously estimated the proportion of trials with **low enrolment ranges between 19 and 37%** (Carlisle 2015)_

How big a problem is low enrolment in Canada?

- In a previous study, we extracted information from *ClinicalTrials.gov* where intended enrolment is a mandatory field. (Tam, Bansback et al. Under Review)
- And compared *intended/targeted enrolment* versus the actual enrolment as of the time of data extraction.

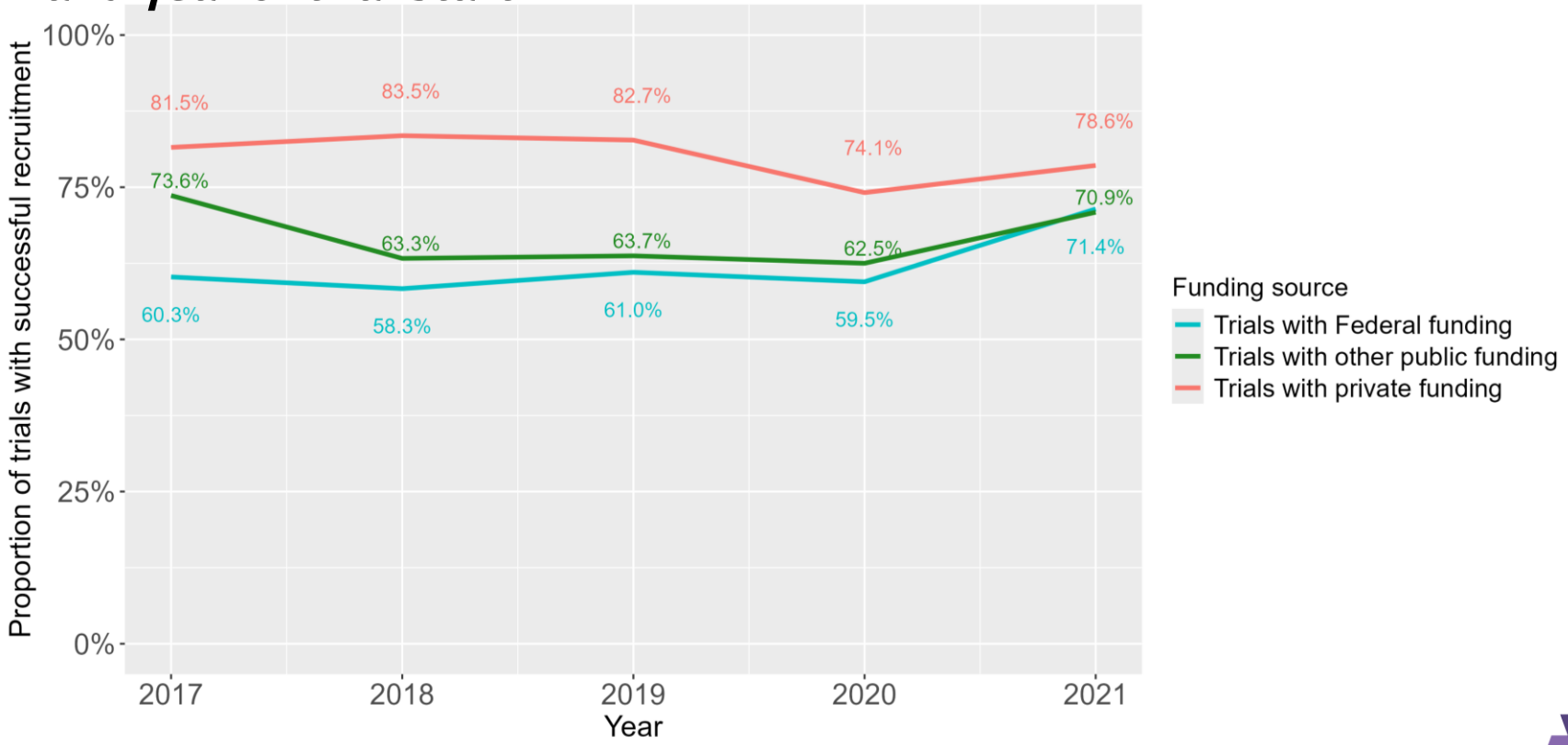


- We used a ratio of ≥0.85 to indicate recruitment success (Carlisle et al. 2015)
- Explored associations between trial-level factors and recruitment success

About 1 in 3 clinical trials in Canada fail to enrol the desired number of patients

- Of 2,213 trials that met our study inclusion, 681 trials (31%) were unsuccessful with recruitment
  - 130,648 participants were recruited into these trials unsuccessful with recruitment
- Clinical trials that fail to enrol are not necessarily a ‘failure’ – some can still meet statistical inference, provide useful information on secondary endpoints or adverse events.
- But many trials that met enrolment required additional funding and time (difficult to measure in clinicaltrials.gov)
- Several modifiable aspects of trial design were associated with recruitment success (e.g. multicentre studies, being a trial that does not require travel to a physical study site, having active comparators)

Proportion of trials that successfully recruited, by funding source and year of trial start



Why is this such a problem?

- Typical research grant:

  "*We will enrol 120 patients in the next year which is feasible because*
  - *we see 100 patients per month who meet inclusion criteria, so conservatively estimate 10% will enrol ….*"
    or
  - *our pilot study recruited 10 patients in 1 month so extrapolating to 9 other sites over 1 year we estimate ….*"

- Relatively little research in asking patients – the potential participants in the clinical trial – whether they would enrol, and what the barriers and facilitators to their participation are.
- And efforts to enrol often exacerbate exclusion of under-represented populations.

Circulation

ORIGINAL RESEARCH ARTICLE

Women's Participation in Cardiovascular Clinical Trials From 2010 to 2017

Xurui Jin, MD

BACKGROU
death among
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METHODS:
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disease population (participation prevalence ratio; a ratio of 0.8 to 1.2 suggests comparable prevalence and good representation).

RESULTS: We identified 740 completed cardiovascular trials including a total of 862 652 adults, of whom 38.2% were women. The median female-to-male ratio of each trial was 0.51 (25th quartile, 0.32; 75th quartile, 0.90) overall and varied by age group (1.02 in ≤55 year old group versus 0.40 in the 61- to 65-year-old group), type of intervention (0.44 for procedural trials versus 0.78 for lifestyle intervention trials), disease type (0.34 for acute coronary syndrome versus 3.20 for pulmonary

How can potential participants help inform modifiable clinical trial design decisions such that enrolment is increased?

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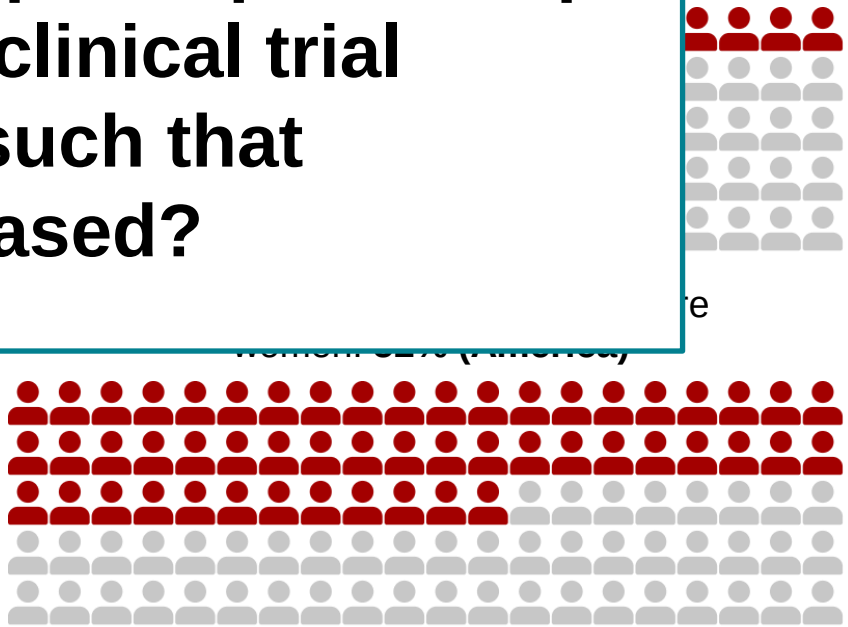

The **I**mproving **PA**tient **R**ecruitment into **T**rials by el**ICI**ting **P**references **A**nd Trad**E**-offs (**I-PARTICIPATE**) APPROACH

Step 1: Understand patients' barriers and motivators for participating in a future trial and identify modifiers of trial design that address these factors.

Step 2: Quantify how eligible participants weigh trade-offs among modifiable trial design features, and examine how these trade-offs differ across key patient subgroups.

Step 3: Estimate the increase in enrolment achieved by shifting from a default trial design to a patient-informed trial design that integrates patients' preferences.

Step 4: Calculate the expected budget implications associated with shifting from the default design to the patient-informed designs.

Case Study: Post traumatic osteoarthritis (PTOA) → will provide implications for cardiology trials

- Individuals who sustain ACL injury are at high risk to develop Post Traumatic OsteoArthritis (PTOA), which accounts for nearly 12% of all cases of knee osteoarthritis
- Early work has suggested that intra-articular injections and/or oral medications (metformin) could reduce the development of PTOA
- Arthritis Foundation wanted to fund a trial – but recognized that this would be a difficult study to enrol patients for.

    - Most patients post ACL injury are symptom free
    - They *might* develop knee OA, in the *future*
    - The treatments *might* work
    - But *might* cause side-effects
    - If you enrol, you *might* be randomized to placebo

Step 1: Barriers and motivators

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American College of Rheumatology
Empowering Rheumatology Professionals

Patient Perceptions of Medication Therapy for Prevention of Posttraumatic Osteoarthritis Following Anterior Cruciate Ligament Injury: A Qualitative Content Analysis

Lily M. Waddell,[1] Donald P. Mitchener,[1] Kelly C. Frier,[1] Morgan H. Jones,[2] Elena Losina,[2] Nick Bansback,[3] Liana Fraenkel,[4] Jason S. Kim,[5] Jeffrey N. Katz,[2] Faith Selzer,[2] and Adam Easterbrook[3]

Objective. Posttraumatic osteoarthritis (PTOA) accounts for nearly 12% of osteoarthritis incidences and often occurs after anterior cruciate ligament (ACL) tear. Ensuring the uptake of preventive treatments for PTOA requires that investigators and clinicians understand factors influencing patients to seek preventive therapies. This qualitative, descriptive study aimed to assess individuals' willingness to adopt a medication therapy for PTOA prevention following ACL injury.

Methods. We enrolled participants who had an ACL tear within two years of enrollment. Study individuals participated in a semistructured interview or focus group. We reviewed audio transcriptions for accuracy, and then organized the data inductively, beginning with open coding of audio transcriptions using NVivo 12. Finally, using a qualitative content analysis approach, we identified, revised, and constructed themes and subthemes.

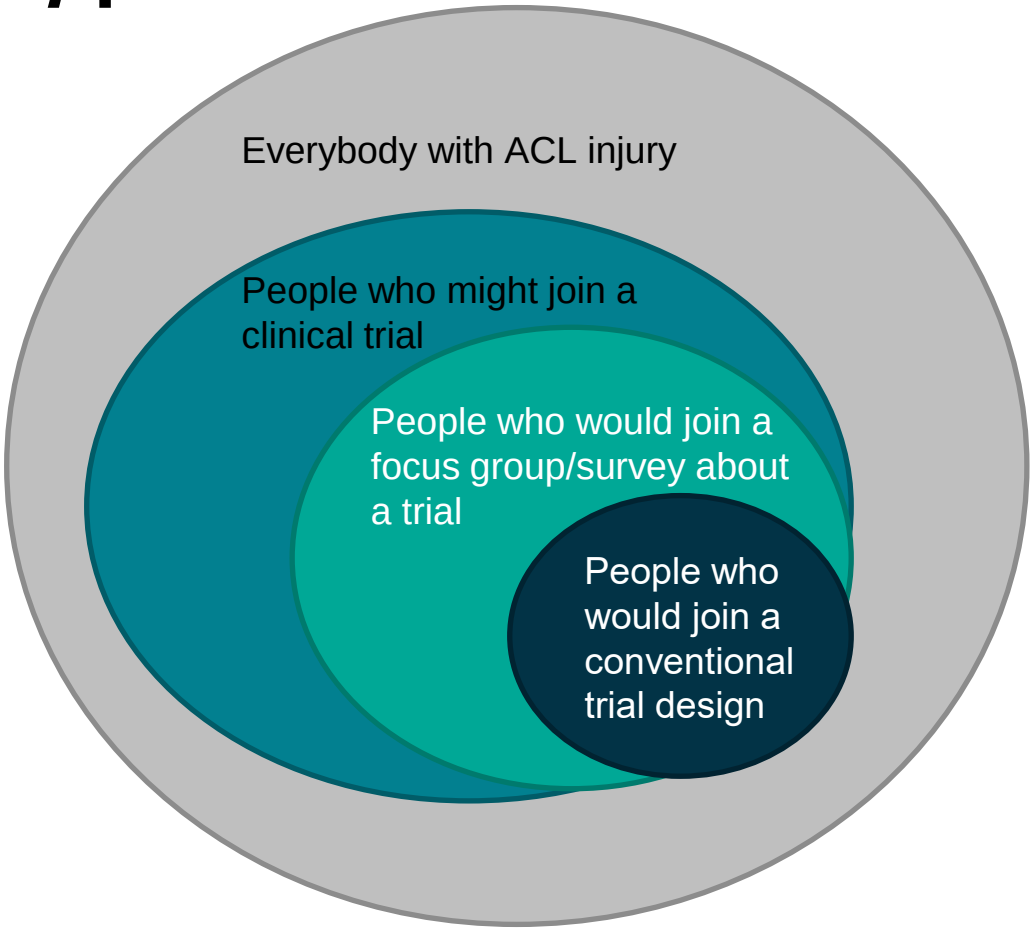
Results. Twenty-five individuals (mean age 25 years, 60% women) participated. Participants were an average of 10 months after injury (mean 310 days, 95% confidence interval [CI] 249–371) and reported a mean Knee Injury and Osteoarthritis Outcome Score pain score of 80.3 (95% CI 74.5–86.2). We identified three main themes related to general treatment for PTOA (eg, unwanted side effects), medication treatment for PTOA (eg, concern about pill size and dose frequency), and clinical trial attributes (eg, time commitment).

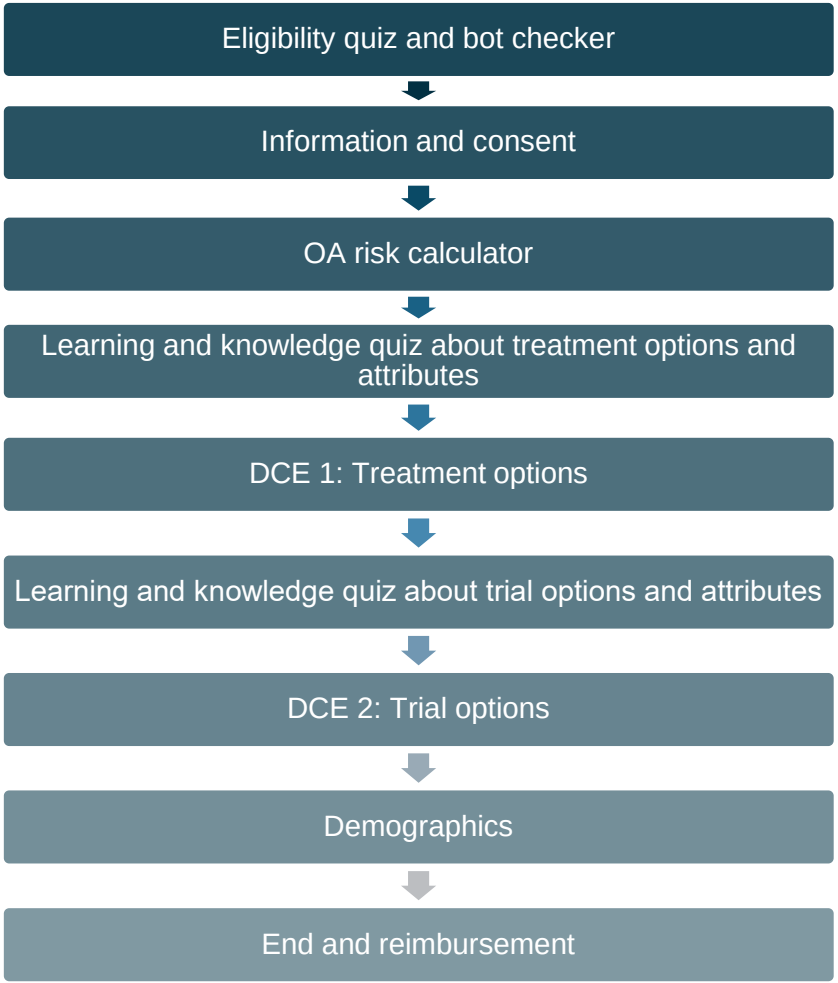
Conclusion. Although participants expressed great interest in trying medication therapy for PTOA prevention, there was variability in which components of treatment mattered to them. Our results stress the importance of using qualitative approaches such as this one to inform the design of trials and treatments that real-world patients will pursue

- 25 individuals with an ACL injury who would be eligible for the trial.
  - Quota sampled to include representation of gender and racialized groups
- While great interest in a treatment, concerns about:
  - chance of benefit & side-effects,
  - Injection, pill size and frequency,
  - time commitment,
  - distance to site,
  - inclusiveness,
  - who invites you,
  - other factors.

Step 2: Quantify preferences and trade-offs

- Survey of potential trial population
- Participants recruited from orthopedic sports medicine clinics at an academic medical center, supplemented by Reddit and Facebook ACL forums, ResearchMatch
- Participants received a $20 Amazon e-gift card for completing the survey.
- The target population resided in North America, was aged 18-45, and had a self-reported ACL injury diagnosed by advanced imaging in the past five years.




Eligibility quiz and bot checker
Information and consent
OA risk calculator
Learning and knowledge quiz about treatment options and attributes
DCE 1: Treatment options
Learning and knowledge quiz about trial options and attributes
DCE 2: Trial options
Demographics
End and reimbursement

Discrete Choice Experiment 1: Treatment

Based on your characteristics, 22* out of 100 people like you will develop knee arthritis in the next 20 years (only 10* out of 100 people without an ACL will develop knee arthritis). Would you consider taking a treatment that would reduce your risk of developing knee arthritis?

	Treatment A	Treatment B	I prefer to choose neither option
Effectiveness in reducing chance of developing arthritis and related pain in the next 20 years (and potential for future joint replacement)	50% reduction (11 out of 100 people will develop knee arthritis)	25% reduction (18 out of 100 people will develop knee arthritis)	0% reduction (22 out of 100 people will develop knee arthritis)
Type of treatment	A pill every day for the next 12 months and physical therapy 2 times a week for 6 months	One time Injection into your knee and physical therapy 2 times a week for 6 months	Physical therapy 2 times a week for 6 months
Side effects	Very rare chance (~6 in 100,000 people) of developing a very serious condition	Mild nausea/diarrhea that typically goes away after 2 weeks, but possibly persistent increase in bowel movements	No nausea/diarrhea
Other potential benefits	Potentially delay the onset of diabetes	None	None
Out-of-pocket cost	$10 per month	$100 per month	$0
Which do you prefer?			
	☐	☐	☐

*individualized based on OA risk score

Discrete Choice Experiment 1: Treatment

Based on your characteristics, 22* out of 100 people like you will develop knee arthritis in the next 20 years (only 10* out of 100 people without an ACL will develop knee arthritis). Would you consider taking a treatment that would reduce your risk of developing knee arthritis?

	Treatment A	Treatment B	I prefer to choose neither option
Effectiveness in reducing chance of developing arthritis and related pain in the next 20 years (and potential for future joint replacement)	25% reduction (18 out of 100 people will develop knee arthritis)	50% reduction (11 out of 100 people will develop knee arthritis)	0% reduction (22 out of 100 people will develop knee arthritis)
Type of treatment	One time Injection into your knee and physical therapy 2 times a week for 6 months	A pill every day for the next 12 months and physical therapy 2 times a week for 6 months	Physical therapy 2 times a week for 6 months
Side effects	Very rare chance (~6 in 100,000 people) of developing a very serious condition	No nausea/diarrhea	No nausea/diarrhea
Other potential benefits	Potentially delay the onset of diabetes	Potentially delay the onset of some cancers	None
Out-of-pocket cost	$50 per month	$50 per month	$0
Which do you prefer?			
	☐	☐	☐

*individualized based on OA risk score

Discrete Choice Experiment 2: Trial

Based on your characteristics, 22* out of 100 people like you will develop knee arthritis in the next 20 year. Would you consider participating in a trial that would test new treatments that might reduce your risk of developing knee arthritis?

	Trial A	Trial B	I would not participate
Proposed effectiveness in reducing chance of developing osteoarthritis and related pain (and potential for future joint replacement)	20% reduction (i.e. X out of 100 people will develop knee osteoarthritis)	50% reduction (i.e. Z out of 100 people will develop knee osteoarthritis)	0% reduction (i.e. Y out of 100 people will develop knee osteoarthritis)
Known Side-effects	Mild nausea/diarrhea that typically goes away after 2 weeks, but possibly persistent increase in bowel movements	Very rare chance (~6 per 100,000 patient-years) of developing lactic acidosis which is a very serious condition	None
Who invites you to participate in the trial	Phone call/email from research coordinator	Surgeon/doctor at pre-op visit	N/A
What happens at the end of trial	If you are on the placebo, you are provided free medication for 1 year if it is shown to be effective	Nothing	N/A
Compensation	$25 per hour	$50 per hour	$0
Other benefits	Support groups/ ask an expert sessions	Routine MRI and physiotherapy	N/A
Distance to study visits	30 mins	60 mins	N/A
Inclusiveness	People who represent populations invite me to participate in the trial	Materials are available in different languages	N/A
	Which do you prefer?		
	☐	☐	☐

*individualized based on OA risk score

Analysis

- Various quality checks to ensure only responses from informed and engaged respondents are included
- Conditional and mixed logit modelling to estimate the relative importance of each attribute level
- Latent class modelling to find subgroups of individuals with similar preferences
- Predictions based on relative odds compared to opt out

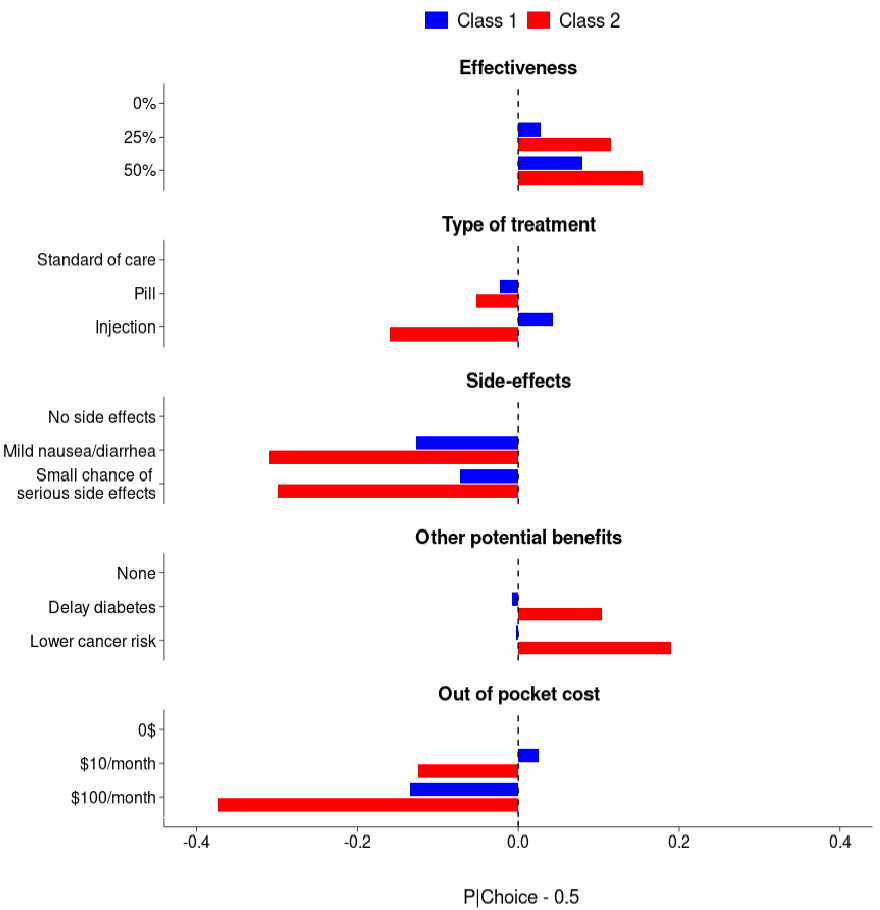
Results - demographics

- A total of 268 legitimate responses were included after excluding bots
- 102 participants (37%) were 18-30 years old, and 173 (63%) were female.
- 179 participants (66%) reported at least weekly knee pain, 73 (27%) monthly pain, and 21 (8%) never had pain
- Many participants (105, 39%) were aware of their knee problem daily, even without current pain.

	Total (%)
Sex	
Female	169 (63%)
Male	99 (37%)
Age	
18 to 29	98 (37%)
30 to 45	170 (63%)
Ethnicity	
White	173 (65%)
Black	35 (13%)
Asian	26 (10%)
Hispanic	24 (9%)
Other	10 (4%)
Know somebody with arthritis	139 (51.9%)
Number of medications (not for knee)	
None	114 (43%)
1-2	123 (46%)
3-4	28 (10%)
5+	3 (1%)
Regular use of supplements	
None	96 (36%)
Daily	124 (46%)
Weekly	32 (12%)
Monthly	16 (6%)
Pain in knee after ACL injury	
Never	21 (8%)
Monthly	73 (27%)
Weekly	91 (34%)
Daily	75 (28%)
Always	8 (3%)
Awareness of knee problem	
Never	10 (4%)
Monthly	57 (21%)
Weekly	72 (27%)
Daily	102 (38%)
Constantly	27 (10%)

Results – DCE 1 (Treatment)

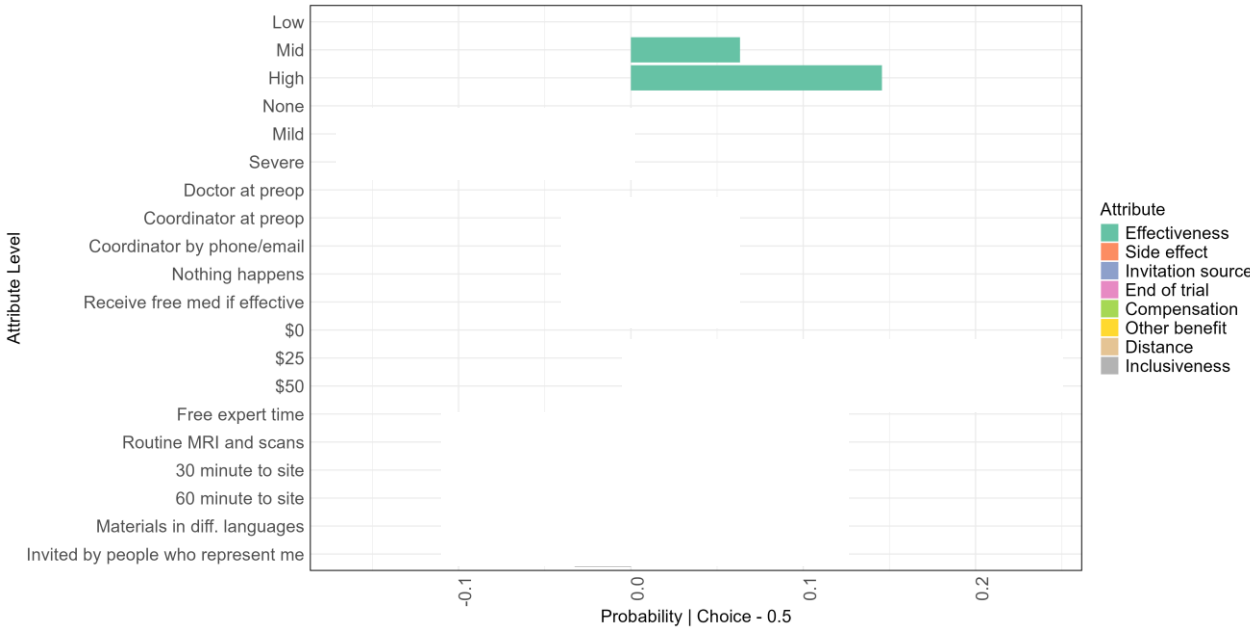
- 60% of respondents would take a treatment (not opt out)
- Preference for pill vs injection not clear



Kennedy K, Waddell L, Easterbrook A, Katz JN, Jacobs C, Jones M, Selzer F, Losina E, Fraenkel L, Bansback N. Preferences for post-traumatic osteoarthritis prevention strategies in individuals with anterior cruciate ligament injury. Arthritis Care & Research. In Press

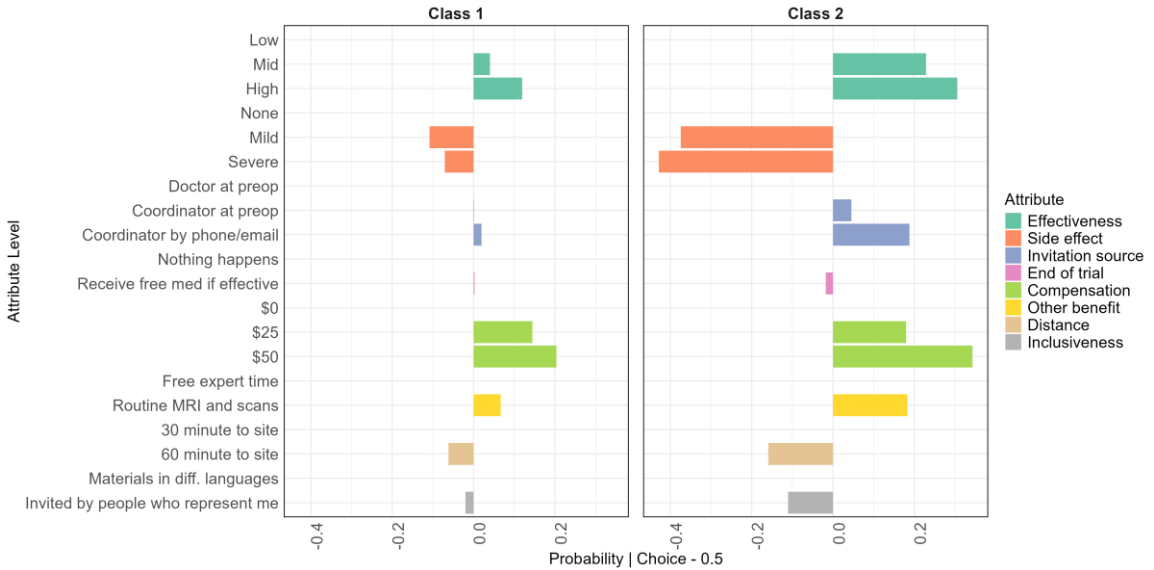
Results – DCE 2 (Trial): Average preferences

- Preference for trials with a high likelihood of effectiveness.
- Any risk of side-effects was an important deterrent.
- Compensation was important and for many, would outweigh the risk of rare or even very small side-effects.
- Free routine MRI and 60 minute distance to site also important.
- Inclusiveness and what happens at the end of the trial were relatively unimportant.



Results – DCE 2(Trial): latent class preferences

- Class 1 (79% of respondents): More likely to participate in trials generally. Any compensation was important
- Class 2 (29% of respondents): Less likely to participate in trials generally, A higher compensation of $50 vs $25 was important.
- A greater proportion of Class 1 participants reported being motivated to participate because they wanted to help others compared to Class 2 participants.



Step 3: Estimate pote
increases in enrolme

- Increasing financial incentives could considerably encourage enrolment by 14 – 23%
- Offering MRI and physiotherapy could increase enrolment by 7%.
- More sites to shorten distance could increase enrolment by 6%.
- Providing research materials in different languages could increase enrolment by 3%
- Some distinct patterns for class 2 – e.g. phone call from coordinator

Step 4: Calculate expected budget implications

Impact of changing compensation

Default design
N=200, $10 per visit, 6 visits
Total cost of patient compensation = $12,000

I-PARTICIPATE design
N=200, **$25** per visit, 6 visits
Total cost of patient compensation = **$30,000**

10 patients per month = 20 months recruitment
Cost per month to run trial = $50,000
Total cost for trial = $50,000*20+ $12,000
= $1,012,000

12 patients per month = 16.6 months recruitment **(15% increase in enrolment)**
Cost per month to run trial = $50,000
Total cost for trial = $50,000***16.6** + **$30,000**
= **$860,000**

Step 4: Calculate expected budget implications

Impact of adding a site

Default design	I-PARTICIPATE design
N=200, 5 sites	N=200, **6 sites**
10 patients per month over 5 sites = 20 months recruitment Cost per site per month = $10,000 Total cost for trial = $10,000*5*20 = $1,000,000	11 patients per month over 6 sites = 18.2 months recruitment **(7% increase in enrolment)** Cost per site per month = $10,000 Total cost for trial = $10,000***6*18.2** = **$1,092,000**

Discussion

- Limitations
  - Response bias - participants in the study may be more likely to participate in clinical trials generally.
  - The DCE could not capture all nuances of an intervention, such as more detailed side-effects, costs, or administration mode.
  - It's unclear if participants fully understood all attributes, such as being given a placebo.
  - Effectiveness of the approach still under investigation

- Inclusiveness
  - The study did not find meaningful socio-demographic differences between classes, likely due to the sampling strategy and sample size.
  - However, the approach used could still be valuable for considering inclusiveness in clinical trial design, as underrepresented demographics may prioritize different attributes.
    - E.g what design changes would increase participation of women in cardiology trials?

Conclusion

- I-PARTICIPATE is an approach to design clinical trials that we believe can increase participant enrolment.
- Approach not relevant for every trial, and each trial will be different
- The I-PARTICIPATE approach is inexpensive compared to cost of the trial itself, but does take time to conduct – propose it is done alongside pilot/feasibility trial.
- Would help convince grant reviewers on the feasibility of proposed trials
- An opportunity for Cardiology trials? – we are looking for opportunities

THANK YOU

NICK.BANSBACK@UBC.CA