# Co-designing acceptable, feasible trials to test drugs targeting prevention of post-traumatic osteoarthritis after knee injury: pipedream or reality?

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**Purpose:** Osteoarthritis (OA) occurring after trauma, post-traumatic osteoarthritis (PTOA) of the knee, has a window of opportunity for prevention- intervening after acute knee joint injury but before disease onset. Challenges associated with PTOA trial design and conduct include lack of stakeholder involvement, particularly in 'experimental medicine' studies. To enable high quality trial design, we set out to expand our understanding of key stakeholder views relating to potential barriers around feasibility and acceptability of trials and identify areas of agreement, differences, and uncertainty.

**Methods:** 2 parallel related processes were piloted: i) Two surveys of 2 stakeholder groups and ii) workshop delivery at an orthopaedic congress. Survey 1 (S1) was for healthcare professionals and researchers (HCP/R) attending the workshop. S1 was modified to Survey 2 (S2) for people with joint damage caused by injury, OA, or both (PJD). Those approached were either local involvement registry members or receiving a UK charity newsletter. Surveys were developed by co-author subgroups around 6 previously highlighted trial design considerations, identified by an international interdisciplinary group consensus exercise. They were refined by PJDs and live for 3 weeks. Anonymised data were collected and analysed in Qualtrics.

**Results:** 19 HCP/Rs responded to S1 and 30 PJDs responded to S2. There was general support for trials including experimental medicine studies testing pharmacological agents for PTOA. All HCP/Rs and 30/31(97%) of PJDs supported the development of new treatments that improved or delayed knee symptoms and damage to knee structure, favouring this over targeting symptoms or structure alone. 24/32(75%) of PJDs felt delaying knee structure damage was more important than improving knee symptoms, whereas 6/32(19%) of PJDs prioritised knee symptoms. Both stakeholder groups found it more acceptable to test agents in human experimental medicine studies as the expected future participant benefit increased (Figure 1) and as risk of subsequent PTOA increased: 17/29(58%) of PJDs & 7/14(50%) of HCP/Rs when risk of developing PTOA≤25%, compared with 27/29(93%) of PJDs & 11/14(78%) of HCP/Rs when risk≥75%.

By multiple answer questions, all drug delivery routes were acceptable, with oral intake being most acceptable (26/30[87%] PJD and 12/14[86%] HCP/R). Both groups suggested similar acceptability for intra-articular injection (73% PJD and 71% HCP/R) and transdermal (70% PJD and 71% HCP/R), which were more acceptable than systemic injections (43% PJD and 21% HCP/R). Groups agreed about target

populations, where most PJDs and HCP/Rs found it acceptable to test a new drug that may prevent PTOA in people with knee OA (27/29[93%] PJDs and all HCP/Rs), and in people with knee injury but no OA (21/29[72%] of PJDs and 11/14[79%] HCP/Rs), and first in human studies in these groups (25/29[86%] PJDs and 10/14[71%] HCP/Rs). 15/29[52%] PJDs found testing repurposed agents unacceptable or were neutral. Overall, PJDs appeared less risk-averse and more accepting of some trial design elements than HCP/Rs.

Around 60 people (including 2 PJDs) attended the workshop. Breakout group discussions largely reflected survey views. In addition, stratifying participants at trial enrolment by risk-benefit was felt to be ethical and acceptable. Stratifying using molecular testing for likely drug response was more acceptable than using characteristics such as sex, age, and BMI.

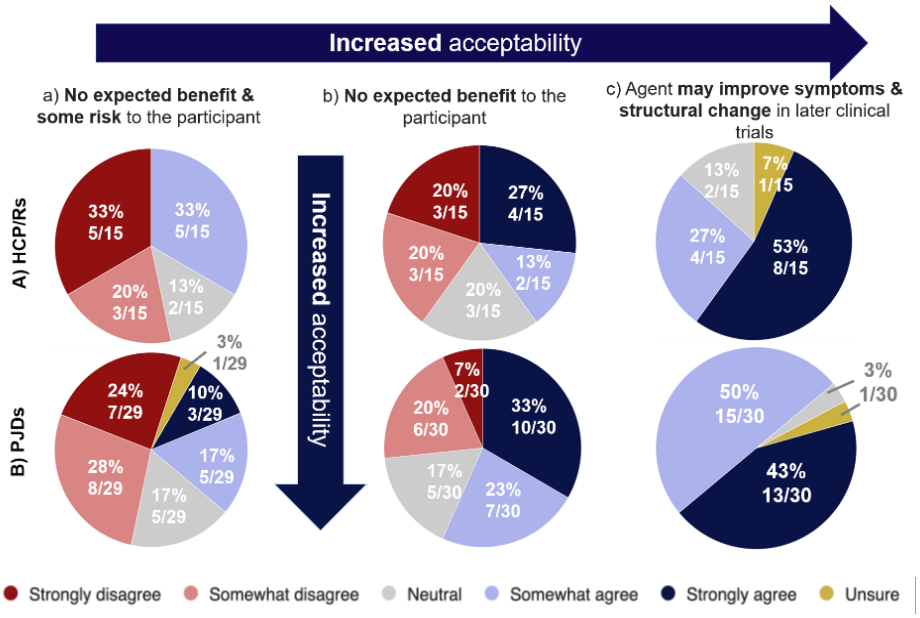


***Figure 1*:** Survey findings for (A) HCP/Rs and (B) PJDs. Respondents were asked about acceptability of testing agents in human experimental medicine studies and trials.

**Conclusion:** These findings provide preliminary evidence on the feasibility of trial design to prevent PTOA. They also highlight some differences in acceptability between stakeholder groups. Further consensus and involvement work to understand these perspectives is crucial for PTOA drug interventional study success. This includes further exploration of areas, such as optimal outcome measures and acceptability of testing agents in PTOA trials in those with different risk profiles and/or expected response. Developing prognostic markers predicting PTOA disease progression, as well as addressing other barriers in trial design such as those identified in this work would be beneficial. Collaborating across the international community, involving more people with knee injury with different risks of developing OA and those from industry/regulatory roles, will help refine approaches to PTOA trial design.