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RecUrrant Intra-articular Corticosteroid injections in Osteoarthritis: the RUblCOn mixed-methods study

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Extended Research Article

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Disclaimer

This report contains transcripts of interviews conducted in the course of the research, or similar, and contains language which may offend some readers.

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This article

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Abstract

Background: Intra-articular corticosteroid injections are an adjunct to core treatments for osteoarthritis. The National Institute for Health and Care Research Health Technology Assessment programme commissioned this research to address uncertainty around the long-term benefits and potential risks associated with recurrent intra-articular corticosteroid injections.

Objectives:

1. Characterise current intra-articular corticosteroid injection practice.
2. Establish longer-term effects and safety of single and recurrent intra-articular corticosteroid injections.
3. Explore views and experiences of patients and clinicians.
4. Assess the priorities/feasibility for future research.

Methods: A cohort study of incident osteoarthritis patients (2005–20) was performed using United Kingdom primary care data (Clinical Practice Research Datalink) linked to hospital data (Hospital Episode Statistics). Incidence of first intra-articular corticosteroid injection was stratified by age, calendar year, gender and geographical region. Longer-term outcomes included incident pain medication and joint replacement. Instrumental variables based on practice preference for intra-articular corticosteroid injection were used in primary analyses. Safety was assessed with propensity score matching and a self-controlled cohort, with outcomes (mortality, bleeding, hemarthrosis, wound infection, diabetes, stroke, ischaemic heart disease, myocardial infarction) assessed at 6 months.

Semistructured telephone/videocall interviews were conducted (patients = 38, primary care clinicians = 19), with inductive thematic analysis used to investigate views and experiences of intra-articular corticosteroid injections.

A three-round modified Delphi study with patients ($n = 41$), healthcare professionals ($n = 25$) and academics/researchers ($n = 25$) was performed to identify future primary research priorities and feasibility.

Results: There were 23,899 (10.8%) osteoarthritis patients receiving intra-articular corticosteroid injections (40% received > 1 injection). Incidence of intra-articular corticosteroid injection at 5-year follow-up was lowest for elbow (5.2%) and highest for shoulder (13.6%). Incidences remained stable for all joints between 2005 and 2019 but varied between regions {3.8 [95% confidence interval 3.4 to 4.1] to 1.4 [95% confidence interval 1.3 to 1.5] injections per 100 patient-years}. Intra-articular corticosteroid injection for knee osteoarthritis was associated with lower incident use of several pain medications at 5-year follow-up; recurrent knee intra-articular corticosteroid injections were associated with greater risk reduction. In primary analyses intra-articular corticosteroid injection was associated with a lower 5-year cumulative incidence of knee replacement (number needed to treat 17, 95% confidence interval 12 to 40), but not hip replacement. In certain analyses, incidences of diabetes, ischaemic heart disease and myocardial infarction were numerically higher with intra-articular corticosteroid injections but 95% confidence interval spanned the null; there were no significant associations with other outcomes.

Qualitative interviews demonstrated clinicians were more cautious about administering intra-articular corticosteroid injections compared to patients considering receiving intra-articular corticosteroid injections. Patients valued intra-articular corticosteroid injections; however, access was variable, with contributory factors including clinician concerns about the evidence base and their individual competence and confidence performing intra-articular corticosteroid injections.

The Delphi research priority list included 14 questions covering long-term effects, clinical and cost-effectiveness, outcomes measurement, comparison to other treatments, provision, safety, identifying responders, maximising benefits, patient experience, delaying joint replacement and dosage.

Limitations: Observational analyses: Possibility of residual confounding. Qualitative research: Self-selecting nature of participation; and while the funding remit focussed on primary care, qualitative findings suggest orthopaedic consultants are key stakeholders. Delphi study: Unable to engage commissioners.

Conclusions: Overall, in the UK, intra-articular corticosteroid injection use is unchanged over 15 years; however, there was wide regional heterogeneity. We observed a sustained reduction in usage of certain pain medications after intra-articular corticosteroid injections. Intra-articular corticosteroid injections appear generally safe, although more research is needed on potential safety signals, particularly diabetes and cardiovascular events.

Future work: A Delphi study with key stakeholders identified 14 priority questions to guide future intra-articular corticosteroid injection research. Work exploring regional variation in intra-articular corticosteroid injection access would be beneficial.

Study registration: This study is registered as ISRCTN32433800; Independent Scientific Advisory Committee (ISAC) for the Medicines and Healthcare Products Regulatory Agency (ISAC protocol no. 20_067RA).

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List of abbreviations

APC	admitted patient care	NNT	number needed to treat
BMI	body mass index	NSAID	non-steroidal anti-inflammatory drug
BNSSG CCG	Bristol North Somerset & South Gloucestershire Clinical Commissioning Group	OA	osteoarthritis
CI	confidence interval	OARSI	Osteoarthritis Research Society International
COPD	chronic obstructive pulmonary disease	OHS	Oxford Hip Score
CPRD	Clinical Practice Research Datalink	OID	organisational information document
CRN	Clinical Research Network	OKS	Oxford Knee Score
DVT	deep vein thrombosis	ONS	Office for National Statistics
EQ-VAS	EQ visual analogue scale	OPCS-4	Office of Population Censuses and Surveys Version 4
EQ-5D-3L	EuroQol-5 Dimensions, three-level version	PEP-R	Patient Experience Partnership in Research
FCP	first contact physiotherapists	PPI	patient and public involvement
GP	general practice	PPIE	patient and public involvement and engagement
GPs	general practitioners	PROM	patient-reported outcome measure
HES	hospital episode statistics	PS	propensity score
HR	hazard ratio	RCT	randomised controlled trial
IACI	intra-articular corticosteroid injection	REC	Research Ethics Committee
ICD-10	<i>International Statistical Classification of Diseases and Related Health Problems, Tenth Revision</i>	RRs	relative risks
IHD	ischaemic heart disease	RUBICON	RecUrrant Intra-articular Corticosteroid injections in Osteoarthritis
IMD	Index of Multiple Deprivation	SD	standard deviation
IV	instrumental variable	SMD	standardised mean difference
LRTI	lower respiratory tract infection	URTI	upper respiratory tract infection
MI	myocardial infarction	UTI	urinary tract infection
MICE	multiple imputation using chained equations	WE ReACH	West of England Research Facilitation in Community and Healthcare
NICE	National Institute for Health and Care Excellence		

Plain language summary

Osteoarthritis is a common joint condition causing pain and disability. After treatments like pain medication and exercise, using a steroid and local anaesthetic injection into the joint may help with pain. However, little is known about the long-term effects of these injections, especially when used repeatedly. We used three approaches to find out more about steroid injections.

First, we used data already collected on 220,125 patients with osteoarthritis in United Kingdom primary care to assess how commonly steroid injections were used, what the long-term benefits were, and if they were safe. Second, we interviewed 38 patients and 19 healthcare professionals about their views and experiences of injections. Third, patients, healthcare professionals and researchers (91 people in total) completed surveys to help identify important questions for future research about steroid injections.

We found one in nine patients with osteoarthritis received a steroid injection. Of these patients, 4 in 10 received repeat injections. However, there was variation between different United Kingdom regions/areas in how many patients received injections. Fewer patients having injections went on to start taking pain medications in the longer term compared with patients not having injections. For patients with knee osteoarthritis, this reduction in pain medication usage was larger for those receiving repeated injections than for patients receiving a single injection. Overall, steroid injections appeared to be safe. Some results suggested there might be a higher risk of diabetes and heart problems in patients having injections, although statistically speaking we could not rule this out as being a chance finding and the increased risk was not seen in an important sensitivity analysis. Healthcare professionals were cautious about giving injections, often concerned about their ability to perform injections correctly. Fourteen future research questions about steroid injections were identified, including how they compare to other treatments, and if they are good value for money.

Scientific summary

Background

Osteoarthritis (OA) is the most common musculoskeletal condition worldwide and it is a global public health burden. It is an irreversible and progressive disease, associated with pain, morbidity, functional decline and loss in quality of life. Intra-articular corticosteroid injections (IACIs) are an adjunct to core treatments for osteoarthritic joint pain such as weight loss and exercise, and are recommended by the UK's National Institute for Health and Care Excellence (NICE) for this purpose. Evidence for this recommendation was limited and based on data indicating a short-term benefit of repeated IACIs for pain relief in knee OA.

The benefits and risks of single and recurrent use of IACIs in different joints affected by OA remain unknown. Furthermore, there is concern that IACI use could become more common in future for reasons such as the predicted increasing prevalence of OA, to bridge longer waiting times before undergoing joint replacement, or as an alternative treatment for people who do not wish to undergo surgery or in those where surgery is not an option due to significant comorbidities. The National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme therefore commissioned this research to explore the use of IACIs in OA.

Objectives

1. To characterise the current practice of IACIs for OA.
2. To establish the longer-term effects and safety of single and recurrent IACIs.
3. To explore the views and experiences of patients and clinicians for IACIs.
4. To identify priorities and associated feasibility considerations for future primary research.

Methods

Observational work

An observational cohort study was performed using UK primary care data (Clinical Practice Research Datalink GOLD) linked to hospital data [Hospital Episode Statistics (HES)]. Patients ≥ 20 years old with a first diagnosis of ankle/foot, elbow, hand, hip, knee, shoulder or wrist OA between 2005 and 2019 were eligible for inclusion. Those receiving IACIs were identified.

To establish the current practice of IACI use, the incidence of first injection per 100 person-years and prevalence were estimated for each joint, and stratified by calendar year, gender and geographical region. Injections per OA patient and mean number of injections per injected patient's joint were calculated. Median time from OA diagnosis to injection was calculated per each joint.

To establish the longer-term effects of IACIs, we analysed patients who had not already been referred to orthopaedic surgery. Primary outcomes were incident pain medication prescriptions and joint replacement. Among those who received joint replacement, secondary outcomes included: complications [stroke, myocardial infarction (MI), thrombosis, joint infection], reoperation and patient-reported outcome measures. Instrumental variable (IV) analyses were conducted using two-step Poisson regression. Index date for the IV was 6 months after OA diagnosis date and IV was defined as practice preference for IACI use in the year prior to the index date (single and recurrent use considered separately, compared to non-use). Outcomes were measured at 1 and 5 years from the index date. For primary outcomes, propensity score (PS) matching was carried out in secondary analyses.

To establish the safety of IACIs, primary outcomes assessed were mortality, bleeding, hemarthrosis, infection, diabetes, stroke, ischaemic heart disease (IHD) and MI. We calculated incidence of outcomes per 100 person-years during

6 months after the first IACI (in patients with OA who received an injection) and after OA diagnosis (in patients with OA who did not receive an injection). Follow-up was censored at subsequent OA diagnosis, IACI, joint replacement or death. Incidence was further stratified by joint. To avoid duplicate events we excluded patients with previous diabetes, stroke, IHD and MI for those events. To minimise confounding we applied PS matching 2 : 1 by several confounders. We also performed a self-controlled cohort analysis using only IACI patients and comparing 6 months after OA versus 6 months after first injection for the same patient, adjusting by age.

Qualitative work

One-to-one semistructured in-depth telephone/videocall interviews were carried out with patients and primary care clinicians. We conducted an inductive thematic analysis to investigate their views and experiences of IACIs.

Delphi study

A three-round modified Delphi study was performed with patients ($n = 41$), healthcare professionals ($n = 25$) and academics/researchers ($n = 25$) to identify future primary research priorities and feasibility considerations. We attempted, but failed to recruit commissioners. In the Round 1 questionnaire, participants generated up to five potential research topics related to IACIs for OA. These responses were collated and grouped to develop candidate research questions. Literature searches were conducted and questions with a lack of evidence were included in the next round. In Round 2, importance ratings (1–9; not important to very important) were assigned to each question. Those questions given an importance rating of 7–9 by $\geq 70\%$ of participants were carried forward. In Round 3, participants were provided with the group ratings and the rating process was repeated to develop the final research priority list.

Results

Observational work

Of the 220,125 OA patients identified (58.8% women; mean age of 65 years), 23,899 (10.8%) patients were injected on or after diagnosis. Patients with shoulder (15%) and knee (13%) OA had a higher prevalence of injection at any time after diagnosis. The least injected joints were the elbow and wrist (6% and 9%, respectively). Of those injected, 40% had more than one injection. The joints with most injections per patient were the knee and hand (mean of two injections per injected patient). The earliest injected joints were the shoulder (median time of 94 days after OA diagnosis) and knee (median 295 days). Incidence of first injection after OA diagnosis was higher in women. Incidence of first injection in any joint was higher in Yorkshire and The Humber, and East Midlands with incidences of 3.8 (95% confidence interval 3.4 to 4.1) and 3.4 (3.0 to 3.7) injections per 100 person-years. The regions with the lowest injection usage were South East with 1.2 (1.1–1.3) injections per 100 person-years, and South West with 1.4 (1.3–1.5). Incidences of injections were stable for all joints during the study period, except for a significant decline for all joints in 2020 during the COVID-19 pandemic.

With regard to examining longer-term effects, the number of patients included in analyses of OA at each joint was up to 5180 for ankle, 16,775 for hand, 35,159 for hip, 83,188 for knee and 3007 for shoulder (elbow and wrist not analysed due to insufficient sample size). In the main IV analyses, single IACI for hand OA was associated with lower incident use of several pain medications at 1-year follow-up: oral non-steroidal anti-inflammatory drug [NNT = 14 (11–45)], oral glucocorticosteroids [NNT = 31 (27–135)], paracetamol [NNT = 10 (9–114)] and partial opioids [NNT = 5 (4–12)]. Incident or repeated use of most pain medications studied were similarly reduced over 5-year follow-up after a single IACI for knee OA. For patients with knee OA, generally larger reductions in incident pain medication use were observed after recurrent IACI use than were observed after single IACI use: for example repeat IACI relative risk (RR) = 0.39 (0.23–0.65) for initiating partial opioids during 5-year follow-up, while single IACI RR = 0.62 (0.37–0.87). IV analyses likewise found single IACI associated with lower 5-year cumulative incidence of knee replacement: NNT = 17 (12–40), but no association with hip replacement. In secondary analyses, PS matching suggested that recurrent use of IACI for hand, hip or knee OA was associated with lower rates of incident use of partial opioids at 5-year follow-up. However, rates of hip and knee replacement at 5-year follow-up were higher in the PS-matched IACI group. IACI was found to have no adverse impact on secondary outcomes after joint replacement.

With regard to examining safety, 197,301 patients remained after exclusions (58.6% women; mean age 65.5 years). 8241 (9.35%) patients were injected. When stratifying by joint, there were no significant differences between crude incidence rates of adverse events following OA diagnosis (excluding those who received an IACI) compared to following an injection. After PS matching (1 : 2), we arrived at a sample size of 8327 injected patients matched to 16,654 non-injected patients. PS-matched analysis with Cox regression showed no statistically significant results for all outcomes after a single IACI: a hazard ratio (HR) of 0.97 (0.48–1.95) for mortality, 1.22 (0.26–5.78) for infection, 1.50 (0.63–3.60) for diabetes, 0.81 (0.32–2.10) for cerebrovascular disease, 6.21 (0.94–40.92) for MI and 2.49 (0.96–6.48) for IHD. Results were similar for repeated IACI use, as they were in Fine-Gray regression analyses controlling for the competing risk of death. Self-controlled cohort analyses pointed towards the null effect for all outcomes with a similar risk in 6 months after OA diagnosis as in 6 months after injection.

Qualitative work

We interviewed 38 patients and 19 primary care clinicians. We identified six themes in the interviews with patients: variation in access; awareness of IACIs; views of risk and trust; effectiveness of IACIs; variation in onset and effect duration; and an alternative to undesirable treatments. In the interviews with clinicians we identified an overarching theme of caution and competence, under which eight subthemes are included: confidence and (dis)comfort with practical procedures; risk of adverse outcomes; training; uncertainty about evidence and guidelines; technical uncertainties; IACIs use on the OA pathway; perceived benefits and impacts of IACIs; and the possibility of placebo. Clinicians were more cautious about administering IACIs compared with patients considering receiving IACIs. Patient access to IACIs varied, with contributory factors including clinician concerns about the evidence base and clinicians concerns about their individual competence and confidence to perform IACIs.

Delphi study

All three Delphi rounds were completed by 75 participants (82% from the first round; 34 patients, 21 healthcare professionals and 20 academics). A total of 310 research topics were generated in Round 1, from which 26 research questions were developed. None had been robustly answered by previous research and therefore all were included in the Round 2 questionnaire. In Round 2, 14 research questions were retained; all 14 were prioritised in Round 3 and included in the final research priority list. The 14 questions were as follows:

1. What are the long-term effects of repeated IACIs for OA?
2. What outcomes are important to patients having IACIs for OA?
3. Are IACIs as good as other non-surgical treatments at reducing OA symptoms?
4. Can the duration of benefit from IACIs for OA be increased?
5. When in the OA treatment pathway should patients be offered IACIs?
6. How many IACIs is it safe for patients with OA to receive?
7. Do IACIs reduce OA symptoms?
8. Are IACIs for OA good value for money for the NHS?
9. Is it possible to predict which patients are most likely to benefit from IACIs for OA?
10. Do IACIs for OA delay the need for joint replacement?
11. What are patients' experiences of having IACIs for OA?
12. What is the best dose of IACIs to use for patients with OA?
13. What type of corticosteroid works the best for OA?
14. Do IACIs help people with OA to do exercises/physiotherapy?

Conclusions

Intra-articular corticosteroid injections are commonly used for treating patients with OA with around one out of nine patients diagnosed with OA receiving an IACI. Of those, 40% received more than one IACI. The most injected joints were the shoulder and knee, and median time from OA to first injection for those joints was < 1 year. The use of injections has been unchanged over the past 15 years. However, there was wide heterogeneity in use of injections between UK regions, with qualitative work suggesting that this may relate to the skills, confidence and training of primary care healthcare professionals to perform IACIs. There was evidence that IACIs were associated with a sustained

reduction in usage of several pain medications (up to 5 years post-injection), and a reduction in partial opioids at 1 year after single IACI for OA in any of the joint sites studied. For knee OA, larger reductions in incident pain medication use were observed after recurrent IACI use compared with single IACI use. A single IACI for knee OA may delay knee replacement with no adverse effect on postsurgical outcomes, although this finding requires confirmation in future studies. The safety of IACIs appears acceptable overall, with no increase in incidence of mortality, infection or bleeding at 6 months compared to after OA diagnosis. However, in certain analyses the incidences of diabetes, IHD and MI were numerically higher in the IACI group and approached borderline statistical significance, which require further investigation. This may be due to residual confounding and low number of outcomes, with these findings not present when using self-controlled methods. There was no dose–response observed in these analyses for single compared to recurrent IACIs.

Both patients and clinicians valued the potential of IACIs to relieve OA symptoms and improve quality of life. Variability in patients' access to treatment appeared to be related to clinicians' confidence in delivering injections and their concerns about the evidence base. Variation in dose frequency and timing may reflect clinicians' uncertainty about their familiarity with and the evidence base contained within current guidance. Despite variation in effectiveness, patients preferred IACIs to other forms of pain medication and to delay or avoid surgery. IACIs were used across the whole OA pathway, but most often as an adjunct treatment before surgery was offered.

A robust consensus technique with key stakeholders identified 14 priority research questions to guide future research into IACIs for OA, covering long-term effects, clinical and cost-effectiveness, outcome measurement, comparison to other treatments, provision, safety, identifying responders, maximising benefits, patient experience, delaying the need for joint replacement, and dosage. Additionally, work exploring regional variation in IACI access would be beneficial to help ensure patients with OA have equal access to IACIs across the UK.

Study registration

This study is registered as ISRCTN32433800; Independent Scientific Advisory Committee (ISAC) for the Medicines and Healthcare Products Regulatory Agency (ISAC protocol no. 20_067RA).

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Chapter 1 Introduction

Background

Osteoarthritis (OA) is the most common musculoskeletal condition worldwide¹ and it is a global public health burden.² OA is the commonest form of arthritis. It is an irreversible and progressive disease, which is associated with pain, morbidity, functional decline and reduced quality of life. OA of the hip and knee joint is one of the leading causes of global disability.³ It is also associated with substantial healthcare system and societal costs.⁴ Due to population ageing and increases in risk factors like obesity, the prevalence of OA is increasing, as is the need for joint replacement.⁵ Global estimates show that 10–15% of adults 60 years and older have some degree of joint OA.⁶ It has been estimated that by 2050, 130 million people will be affected by OA globally and of these, 40 million (31%) will be severely disabled by this disease.⁷ In the UK, data from Arthritis Research UK suggest that one-third of people aged 45 years and older are affected by OA, which represents 8.75 million people.⁸

The current common treatment regimens for OA reduce pain and may improve function, however these treatment strategies have no impact on disease incidence or progression. The Osteoarthritis Research Society International (OARSI) guidelines for the non-surgical management of knee OA recommends treatment modalities such as biomechanical interventions, intra-articular corticosteroid injections (IACIs), exercise (land-based and water-based), self-management and education, strength training and weight management.¹ In the UK, people with OA are usually managed in primary care [general practice (GP)] and treated without surgery. Management of OA includes core treatments (patient education and advice, exercise, weight loss and use of assistive devices) and may include physical therapy (physiotherapy, insoles or orthoses) and pharmacotherapy (paracetamol and topical or oral non-steroidal anti-inflammatory drugs (NSAIDs) as a first-line treatment for pain). A proportion of patients with OA proceed to secondary care (hospital) management which can include invasive treatment options like joint replacement.

Intra-articular corticosteroid injection preparations are frequently mixed with a local anaesthetic, to help pain and to reduce inflammation within the joint. The National Institute for Health and Care Excellence (NICE) Clinical Guideline for OA: care and management, recommends the use of IACIs as an adjunct to core treatments for the relief of moderate-to-severe uncontrolled pain in people with OA.⁹ Evidence for this recommendation was based on limited data which indicated a short-term benefit of repeated IACIs for pain relief in knee OA.^{10–13} The *British National Formulary* recommends repeat injections at intervals of 7–35 days and that no joint should be treated more than four times per year. Between the time of publication of the NICE guidance in 2014 and the application for this research grant, further studies and meta-analyses focussing on the benefits of IACIs for OA management had been published or presented.^{14–18} The overall evidence from these further studies suggests a short-term benefit of IACIs on pain relief, with mild or no evidence of adverse effects associated with IACIs.

Robust evidence on the longer-term benefits and potential risks associated with recurrent use of IACIs for OA is urgently warranted for several reasons. These include (1) the prevalence of OA being expected to rise over coming years, thus it is likely that more IACIs will be used in patients with OA, (2) concerns that IACIs may be used more frequently in the future to bridge longer waiting times for joint replacement which continue to lengthen in the UK especially after the COVID-19 pandemic¹⁹ and (3) concerns that IACIs will be increasingly used as an alternative treatment for people for whom surgery is not considered a viable option, for example due to comorbidities and/or excessive body mass index (BMI).

Presently there is limited and inconsistent evidence available regarding the recurrent use of IACIs for OA. Small observational cohort studies comprising people with OA followed up in the longer term have suggested a link between IACIs, particularly recurrent injections, and adverse outcomes within the joint such as joint degeneration or radiological OA progression with bone and cartilage damage.^{20,21} These findings were supported by a recent randomised controlled trial (RCT) involving 140 patients with symptomatic knee arthritis which observed that intra-articular triamcinolone (a commonly used formulation of IACI) administered every 3 months over 2 years resulted in greater cartilage volume loss with no significant benefit on pain compared with placebo.²² The authors concluded that their findings did not support

the use of long-term repeated IACIs for the management of pain or structural progression in OA patients, and in fact indicated there may be more cartilage loss in people receiving repeated IACIs.²³ These trial results contrast the findings of a single-centre RCT comparing the long-term effects of IACIs compared with saline in 68 patients with symptomatic knee OA; intra-articular triamcinolone administered every 3 months over 2 years resulted in significant improvement in pain and stiffness in the IACI group over the study period.²⁴ No adverse local effects in the knee were reported. The authors concluded that repeated IACIs appeared to be safe for managing knee OA.

Evidence about the practice and patterns of use of IACIs is needed, as this is important to help guide switching, augmentation or dosing of treatment in relation to clinical outcomes. Data on the current practice and patterns of use of IACIs after treatment initiation in the UK and globally are very limited. In a recent review that aimed to examine the dosing regimen and frequency of IACIs for osteoarthritic knees, it was noted that the published literature concerning the frequency of IACIs was non-existent and that all published information on this topic appeared to be based on expert opinion (level 5 evidence).²⁵ Analysis of 9 years of follow-up data from the US OA Initiative comprising of knee osteoarthritis patients suggested that about 60% of participants who received IACIs had an average age of 69 years and received only one injection.²⁶ During the follow-up period, 24% continued treatment with IACIs while 17% switched treatment to hyaluronic acid injections. The results suggested that the decision to continue or switch treatment was dependent on symptoms experienced after the initial injection. Limitations of the current evidence include the use of observational designs, which are limited by reverse causation bias, with inadequate adjustment for residual confounding, methodological limitations of the RCTs which include small sample sizes, single-centre design, samples in trials limited to osteoarthritic knees, and the inconsistent results reported. Taking all the evidence together suggests that currently the longer-term clinically important benefits and risks associated with IACIs for OA remain unclear. Data on patterns of use of IACIs after treatment initiation as well as factors influencing these patterns are also unavailable. Furthermore, little is known about the views, experiences and preferences of patients and clinicians for IACIs when managing OA and their opinions on important areas for future research.

Evidence explaining why this research is needed now

The work described within this report was performed in response to a National Institute for Health and Care Research Health Technology Assessment (NIHR HTA) research commissioning brief entitled 'Recurrent intra-articular corticosteroid injections in OA (HTA no 18/103)'. Therefore the rationale for undertaking this research work was appropriately justified in the initial commissioning brief published by the NIHR and updated in the 'Background' section of this report.

Research aims and objectives

We undertook the RecUrrant Intra-articular Corticosteroid injections in Osteoarthritis (RUBICOn) study, detailed within this report. The aims of RUBICOn were to:

1. Establish the current practice of use of IACIs for the treatment of joint pain due to OA within the UK.
2. Establish the longer-term effects of the use of single and recurrent IACIs.
3. Explore the views and experiences of patients and clinicians regarding the use of IACIs.
4. Identify priorities and associated feasibility considerations for future primary research in this area.

Following the direction of the NIHR HTA commissioning brief, our objectives were to use routinely collected UK observational healthcare data [Clinical Practice Research Datalink (CPRD GOLD), Hospital Episode Statistics (HES) and National Patient-Reported Outcome Measures (PROMs) data] to determine the use, safety and effect of IACIs for OA (aims 1 and 2). The large size and depth of these routinely collected healthcare datasets would allow rapid and efficient assessment of interventions such as IACIs used for OA in numerous body joints in a generalisable sample of patients that is of sufficient size to achieve satisfactorily powered analyses.

Formal qualitative interviews were used to explore patient and clinician views and experiences regarding the use of IACIs (aim 3). Finally, a Delphi consensus survey of patients, clinicians, researchers and commissioners was undertaken to identify future research priorities related to IACIs used for OA and to identify any associated feasibility considerations about performing future primary research within this area (aim 4).

Structure of this report

[Chapter 2](#) describes the data sources (CPRD GOLD, HES and PROMs) used in [Chapters 3–5](#), and also describes the data linkage.

[Chapters 3–5](#) report the work performed using the routinely collected UK observational healthcare datasets. [Chapter 3](#) examines the use of IACI over a 15-year period. [Chapter 4](#) reports the longer-term effects of single IACIs and recurrent IACIs used in various osteoarthritic joints. [Chapter 5](#) reports on the safety of IACIs when used for OA.

[Chapter 6](#) describes the qualitative research examining the views and experiences of patients and clinicians regarding IACIs for OA.

[Chapter 7](#) reports the Delphi consensus survey to identify future research priorities for IACIs used in OA.

[Chapter 8](#) summarises the conclusions from the research contained within this report, details the patient and public involvement (PPI) for this work, and identifies areas for future research.

Chapter 2 Data sources used in *Chapters 3–5*

Clinical Practice Research Datalink GOLD

The CPRD GOLD is an electronic database of UK pseudo-anonymised primary care health records, administered by the Medicines and Healthcare Products Regulatory Agency. The UK NHS primary care is provided free of charge through general practitioners (GPs), with almost the entirety of the population registered to a local GP practice.²⁷ GPs act as the 'gatekeepers' to other services and secondary care in the UK NHS, providing clinical consultations to registered patients and providing subsequent non-emergency healthcare, prescriptions, diagnostic tests or referral to secondary care where necessary. CPRD GOLD captures digital GP notes from consultations, including patient symptoms, test results, diagnoses, clinical measurements (e.g. height, weight and smoking status), immunisations and medicines prescribed. CPRD GOLD also captures information from letters and/or discharge reports sent from secondary care providers (hospitals) to the GP the patient is registered with. As such CPRD GOLD contains a longitudinal medical record of both primary and secondary care clinical events and referrals for each enrolled patient. At the time of data extraction (September 2020), CPRD GOLD covered 4.8% of the UK population, and cumulatively contained data covering approximately 19 million people from over 900 GP practices spread across the country. The database has been shown to be representative of the UK in terms of age, sex and ethnicity.²⁷ Symptoms, diagnoses, operations, procedures and other health-related information are recorded into CPRD GOLD and mapped to Read codes. Prescriptions data are mapped to Dictionary of medicines and devices (dm + d) and GemScript codes. Extensive work has been carried out to demonstrate the validity of coding in CPRD GOLD,²⁸ including for musculoskeletal conditions.²⁹

Clinical Practice Research Datalink GOLD data for the period 1 January 2005 to 28 August 2020 were extracted for patients whose data quality was flagged as 'acceptable' for clinical research and with a recorded diagnosis of OA identified using joint-specific Read code lists (see [Appendix 1, Table 26](#)) among enrolled GP practices with at least 1 year of 'up to standard' data uploaded. The 'up to standard' quality flag is assigned by CPRD GOLD based on data quality checks at the GP practice level. Separate cohorts were created for each joint studied: ankle/foot, elbow, hand, hip, knee, shoulder and wrist. We treated each unique CPRD patient ID ('patid') as a different patient as this has previously been shown to be a valid approach to handling the small number of patients transfers between CPRD registered GP practices.³⁰

Data linkage

To enhance analyses, several data were linked to CPRD GOLD patient records, including the Office for National Statistics (ONS) all-cause mortality registry,³¹ Index of Multiple Deprivation (IMD) based on Lower Super Output Area of patient's postcode, secondary care HES data and PROMs. These datasets were linked in a probabilistic manner by NHS Digital. A rank score was created based on patient-identifiable fields, provider codes, operation codes and dates, with the highest score of 1 given if identical information on patient-identifiable fields were recorded in both databases.³²

Hospital episode statistics

Clinical Practice Research Datalink GOLD was linked to HES admitted patient care (APC), which covers NHS hospitals and independent sectors that provide NHS services in England. At the time of writing, HES included APC data from 1997 onwards. All data recorded in HES are routinely submitted by the contributing hospitals for reimbursement purposes. HES is an administrative dataset; however, inpatient records have been used extensively for research purposes in recent years, including previous NIHR-funded work³³ resulting in high-impact publications.³⁴

For each hospital admission recorded in HES APC, information is available on hospital diagnoses and procedures, administrative details (such as date of admission and discharge) and basic sociodemographic data (such as ethnic

background). Diagnoses are coded using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10), and the procedure undertaken using the Office of Population Censuses and Surveys.

Patient-reported outcome measures database

In 2009, NHS England introduced the routine collection of PROMs associated with certain elective surgeries including primary hip and knee replacement.^{35,36} The PROMs Database contains patients' perspectives of knee or hip operations through self-completed questionnaires at the time before surgery (baseline) and at 6 months post-operatively, with an initial focus on four procedures: primary knee/hip replacement, hernia repair and varicose vein surgery. For joint replacement, the Oxford Knee Score (OKS) and Oxford Hip Score (OHS) are used to measure joint pain and function from the patient's perspective with 12 questions and 5 possible responses (each scored 0–4), giving a score ranging from 0 (worst) to 48 (best).^{37,38} In addition, EuroQol-5 Dimensions, three-level version (EQ-5D-3L) collected for all surgeries is included in the PROMs Database. EQ-5D-3L is a quality of life measure including two parts: the EQ-5D index and EQ Visual analogue scale (EQ-VAS). The former contains five questions and three possible responses for each of five subscales: mobility, self-care, daily activities, pain or discomfort, and depression or anxiety.³⁹ The raw score has been weighted according to UK preferences to represent the whole UK society, resulting in a score (EQ-5D utility index) ranging from –0.59 (worst state) to 1.00 (best state). The EQ-VAS is a patient self-assessment of their health in general with a score of 0 (the worst imaginable) to 100 (best imaginable).³⁵

Data curation

Curator software (Oxford University Innovation, Oxford, UK)⁴⁰ was used to perform advanced data curation on CPRD GOLD, ONS mortality, IMD, HES APC and PROMs datasets. From these five linked datasets and for each cohort (ankle/foot, elbow, hand, hip, knee, shoulder and wrist), Curator generated a distinct pre-analytical patient centric.CSV file containing all the necessary variables to perform the planned analyses.

Ethics and scientific approval

The study protocol (20_067RA) was approved via CPRD Research Data Governance (RDG) process, with feedback from the independent scientific advisory committee provided on 16 October 2020. No additional ethics approval was required as this study used pseudo-anonymised routinely collected data from CPRD GOLD.

Chapter 3 Current practice of IACI use: a cohort study using CPRD

Introduction

According to the OA guidelines (NG226) from NICE,⁴¹ IACIs are recommended as an adjunct to core treatments for the relief of moderate-to-severe uncontrolled pain in people with OA. We aimed to characterise the use of IACI in a large number of patients with OA in UK primary care over the last 15 years.

Methods

Data and participants

Clinical Practice Research Datalink GOLD data between 1 January 2005 and 28 August 2020 were extracted as described in [Chapter 2](#). All patients newly diagnosed with OA of any joint were included. We excluded patients with age < 20 years or BMI < 15 at the age of OA diagnosis, or patients with a referral for orthopaedic surgery prior to OA diagnosis date.

Variables

We used two main variables for the analyses, date of diagnosis of OA and site, assessed by Read codes and date of injections. Injections were assessed using two different sets of codes: product codes, that record when corticosteroid injection where prescribed, and Read codes, that record procedures, that is, when an injection was injected, with their respective dates. We also used age at OA diagnosis (calculated from the year of birth), sex as recorded in GP data and geographical region of residence.

Statistical analysis

We extracted counts of OA per joint. We described the percentage of female, and mean age at first OA diagnosis for each joint. We produced counts of injections and product injected by site. Number of injected patients, percentage of patients injected, injections per patient and percentage of injected patients with more than one injection were calculated for each joint. We also calculated median time to injection since OA diagnosis for the first to sixth injection per osteoarthritis site.

For incidence we calculated 1- to 5-year incidence as number of injections per person time, starting follow-up time at OA diagnosis and censoring at death, and prevalence of first injection or any injection after OA by joint. Incidence of first injection after osteoarthritis was also calculated by calendar year, with a burn-in period 2005–6, as the amount of patient-years were too low to obtain stable estimates. Incidence per 100 person-years of injections was also calculated by age group and sex, by joint. Finally, we computed incidence rates of injection in OA patients by UK region and joint.

Results

Diagnosis of osteoarthritis

We identified a total of 220,125 patients diagnosed with OA. Of those 58.9% were female, and the mean age at first OA diagnosis was 65.4 years with a standard deviation (SD) of 12.4. The most frequent sites were knee (106,890, 48.6%), hip (50,970, 23.2%) and hand (27,820, 12.6%). [Table 1](#) shows the number of diagnosed patients, percentage of females and the mean age at diagnosis by OA site. There were 17,230 (7.8%) patients with osteoarthritis of more than one joint. [Appendix 1, Table 27](#) shows the number of patients with each combination of joint OA and the percentage of female and mean age at first osteoarthritis diagnosis for the whole cohort.

Injection product and site

Of the 220,125 OA-diagnosed patients, 52,461 (23.8%) patients were prescribed an injectable corticosteroid, with a total of 144,542 prescriptions. The most used products were methylprednisolone acetate, accounting for 110,926 (76.7%) injections, with 64,064 (44.3%) of those being in combination with lidocaine hydrochloride. Triamcinolone acetonide was the second most used product, accounting for 27,492 injections.

Patients with a Read code indicating that an injection into a joint was performed were 35,329 (16.0%), with a total of 79,065 injections. [Appendix 1, Table 28](#) shows the concordance between recorded injection site according to the Read code and the registered OA site. Of all injections recorded, 34,846 (44.1%) did not have a code that specified which joint was being treated. After that, the most common joints injected according to Read codes were knee ($n = 26,189$) and shoulder ($n = 13,563$).

Injected patients and number of injections after osteoarthritis diagnosis

[Table 2](#) shows the number of patients injected, the number of injections per patient and the number of patients with more than one injection. There were a total of 23,899 (10.9%) patients who received at least one IACI on or after their OA date. Patients with multiple OA (with OA diagnoses in more than one joint/site) received the highest proportion of injections after or on diagnosis, with 19% of them injected, followed by patients with shoulder OA (15%) and knee OA

TABLE 1 Number of diagnosed patients, percentage of females and mean age at diagnosis by OA site between 2005 and 2020

Osteoarthritis site	N	Female (%)	Mean age (years) at first OA diagnosis
Knee	106,890	56.0	65.6
Hip	50,970	57.7	66.7
Hand	27,820	72.4	62.8
Multiple joints	17,230	63.7	66.6
Ankle or foot	8550	52.5	61.2
Shoulder	5490	52.7	67.9
Wrist	2351	59.4	66.0
Elbow	824	30.0	61.8
Total	220,125	58.8	65.4

TABLE 2 Number of injections, OA patients, percentage of injected patients and injections per patient after OA diagnosis

OA site	Injections	Injected patients	OA patients	Injections per OA patient	Injections per injected patient	OA patients injected (%)	Injected patients with > 1 injection (%)
Ankle/foot	1226	662	8550	0.14	1.9	7.74	37.0
Elbow	78	53	824	0.09	1.5	6.43	26.4
Hand	4054	2085	27,820	0.15	1.9	7.49	38.4
Hip	5793	3422	50,970	0.11	1.7	6.71	33.3
Knee	28,938	13,391	106,890	0.27	2.2	12.53	42.9
Multiple joints	7452	3266	17,230	0.43	2.3	18.96	45.6
Shoulder	1362	815	5490	0.25	1.7	14.85	34.8
Wrist	355	205	2351	0.15	1.7	8.72	30.2

(13%). The least injected joints were the hip (6%) and elbow (7%). As for the percentage of injected patients with more than one injection, the knee and hand were the most common joints multiply injected (excluding patients with multiple OA) with 43% and 38% of injected patients with more than one injection, respectively and approximately two injections per injected patient in for both joints. [Appendix 1, Table 29](#) shows similar metrics for injections performed to patients before OA diagnosis was recorded.

Time to injection since osteoarthritis diagnosis

Time to injection from OA diagnosis varied depending on the site of OA ([Table 3](#)). For the first injection, the time since OA diagnosis were shortest for shoulder OA (median 0.3 years) and knee OA (median 0.7 years). The joints where a first injection was given the longest time after diagnosis were the elbow (median 2.1 years) and the hand (median 2.1 years). The second injection median time from OA was approximately 1 year after the first injection (median time first injection was 0.9 years after OA and second, 2 years after OA).

Overall prevalence and incidence

Cumulative IACI uptake over time after OA diagnosis was higher in those with multiple joint OA with an incidence of 9.0% at 1 year and of 15.7% at 5 years. Those with shoulder and knee OA had a 5-year incidence of 13.6% and 10.8%, respectively. Elbow and hip OA had the lowest 5-year incidence of injection (5.2% and 5.6%, respectively). [Table 4](#) shows both prevalence and cumulative incidence of injection for 1–5 years after OA diagnosis in each joint. [Appendix 1, Table 30](#) shows yearly incidence and prevalence of only the first injection for each joint after OA.

Incidence of first injection after osteoarthritis

For most joints, the incidence of first injection after OA increases gradually with age and peaks around 40 to 49 years old for most joints and stays stable or slightly declines after that as shown in [Figure 1](#). The incidence [95% confidence interval (CI)] for patients 60–69 years for each joint were: ankle/foot 1.6% (1.4% to 1.9%), elbow 1.3% (0.8% to 2.2%), hand 1.4% (1.3% to 1.5%), hip 1.4% (1.3% to 1.5%), knee 2.4% (2.3% to 2.5%), multiple joints 3.7% (3.5% to 4.0%), shoulder 3.0% (2.5% to 3.5%) and wrist 2.1% (1.6% to 2.7%). Incidence was higher for women than for men in all age groups, especially for knee and hip injections with an incidence of 2.2% (2.1% to 2.2%) in men and 2.7% (2.6% to 2.7%) in women for knee, and 1.2% (1.1% to 1.3%) in men and 1.5% (1.5% to 1.6%) in women for hip.

Incidence by region

The use of IACI varied greatly by UK geographical region ([Figure 2](#)). For all joints combined the region with the highest incidence of injections was Yorkshire and The Humber with a rate of 3.8 (3.5–4.1) injections per 100 patient-years with OA, followed by the East Midlands with 3.4 (3.1–4.7) and Northern Ireland with 3.4 (3.2–3.5). The regions with the lowest incidence of injections were the South East Coast with 1.2 (1.1–1.3) and the South West with 1.4 (1.3–1.5). This ranking was mostly conserved when looking at each joint separately, as shown in [Figure 2](#).

Incidence by year

[Figure 3](#) shows temporal trends for the use of IACI among OA patients over time. For all individual joints, there was a stable incidence throughout 2007–19 period, without a clear trend upwards or downwards. In all cases there was a higher than 50% decrease in the incidence of first intra-articular injection in 2020 for all joints.

Discussion

Our large cohort of over 220,000 participants with OA is consistent with clinical knowledge and previous literature, with the majority being female and diagnosed in their 60s.⁴² Similarly, knee, hip and hand were (in this order) the most commonly affected sites, also in line with previous literature.⁴³ Clinically diagnosed OA has been previously validated in CPRD GOLD and shown to have a high positive predictive value close to 80%.²⁹

Osteoarthritis guidelines (NG226) by NICE recommend the use of IACIs as an adjunct to core treatments for the relief of moderate-to-severe uncontrolled pain in people with OA.⁴¹ This may explain why only 35,329 (16%) of participants received at least one injection in our study. Unfortunately, almost half of the recorded injections did not have information on injection site, which we recognise as a study limitation inherent in the data available to us. Out of those

TABLE 3 Number of injections and median years from OA diagnosis to injection for injections after OA diagnosis

Osteoarthritis site	First injection		Second injection		Third injection		Forth injection		Fifth injection		Sixth injection	
	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median
Ankle/foot	662	1.2	245	2.2	117	3.3	63	3	44	4.4	31	3.8
Elbow	53	2.1	14	3.5	< 5	2.1	< 5	4.6	< 5	4.1	< 5	4.3
Hand	2085	1.5	801	2.4	396	2.9	251	3.3	152	3.9	107	5.1
Hip	3422	1.5	1141	2.8	510	3.4	267	4.5	138	4.6	82	5.3
Knee	13,391	0.7	5747	1.6	3077	2.5	1876	3	1239	3.5	857	3.9
Multiple joints	3266	1.2	1489	2.2	811	3	490	3.6	316	4.1	226	4.6
Shoulder	815	0.3	284	1.3	118	2.4	57	2.8	32	4	22	3.8
Wrist	205	1	62	2.1	30	2.8	17	2.5	13	3	6	2.4

TABLE 4 Yearly prevalence and cumulative incidence of injections (up to 1 per person-year) after OA by joint

	Ankle/foot (%)	Elbow (%)	Hand (%)	Hip (%)	Knee (%)	Shoulder (%)	Wrist (%)	Multiple joints (%)
Prevalence (years)								
1	1.78	1.58	1.38	1.65	3.08	6.21	2.34	4.20
2	2.50	2.79	2.40	2.50	4.25	8.03	3.23	6.15
3	3.19	3.28	3.21	3.18	5.02	8.89	4.04	7.41
4	3.82	3.76	3.75	3.67	5.65	9.64	4.81	8.47
5	4.22	4.25	4.24	4.06	6.11	10.40	5.23	9.27
Incidence (years)								
1	3.61	2.06	3.13	2.75	6.89	10.11	4.47	8.95
2	4.63	3.16	4.25	3.87	8.38	11.79	5.61	11.47
3	5.43	4.13	4.97	4.62	9.41	12.59	6.38	13.17
4	6.13	4.73	5.56	5.13	10.17	13.24	6.98	14.63
5	6.60	5.22	6.05	5.58	10.77	13.61	7.32	15.66

with details available on injection site, knee and shoulder were the most common joints injected. Looking at cumulative uptake over time after OA diagnosis, those with multiple joint disease had the highest incidence, at 9% at 1 year and rising to almost 16% at 5 years. Comparatively, those with shoulder and knee OA had a 5-year cumulative incidence of almost 14% and 11%, respectively. Conversely, people with elbow and hip OA were the least commonly injected, with a 5-year incidence of 5.2% and 5.6%, respectively. This is likely due to perceived difficulties in the injection of both joints, and particularly the hip joint which requires some form of imaging guidance that is not routinely available in primary care.

The incidence of joint injections increased with age in most sites and peaked at ages between 60 and 79 years old, to then decline in older participants. Incidence was numerically higher in women compared to men for most OA sites, and this pattern was most apparent in knee OA. This fits with previous literature about the incidence and demographics of people who have OA.⁴²

We noticed heterogeneity in the incidence of intra-articular injections in people with OA across different UK regions. Incidence was higher for most OA sites among patients registered in GP practices in the East Midlands, Yorkshire and The Humber, and Northern Ireland. Rates were lower in the South East and South West. The reasons for this may be multifactorial such as local or regional clinical guidance, competency of individual GPs and physiotherapists to perform injections within primary care, how healthcare services are set up in different geographical regions and/or how GPs and physiotherapists in different regions interpret the evidence base for IACI.

We did not identify clear changes in the use of IACIs among OA patients over time, with most incidence rates overlapping in the period 2007 between 2019, other than a clear decline in 2020 during the COVID-19 pandemic. The stability in the incidence rates over time up until 2019 suggests that there have been no major changes in the evidence base relating to IACI or their availability to change practice on a national level. However, the decline in IACI use in 2020 for all joints during the COVID-19 pandemic was likely related to (1) the potential impact of national guidance suggesting the risk of increased susceptibility to COVID-19 when having steroid injections was not known and that the severity of any COVID-19 infection may be increased⁴⁴ and (2) the reduced access to care for patients with musculoskeletal conditions during the COVID-19 pandemic.⁴⁵ Similar reductions in the number of intra-articular injections during the COVID-19 pandemic have been observed elsewhere internationally.⁴⁶

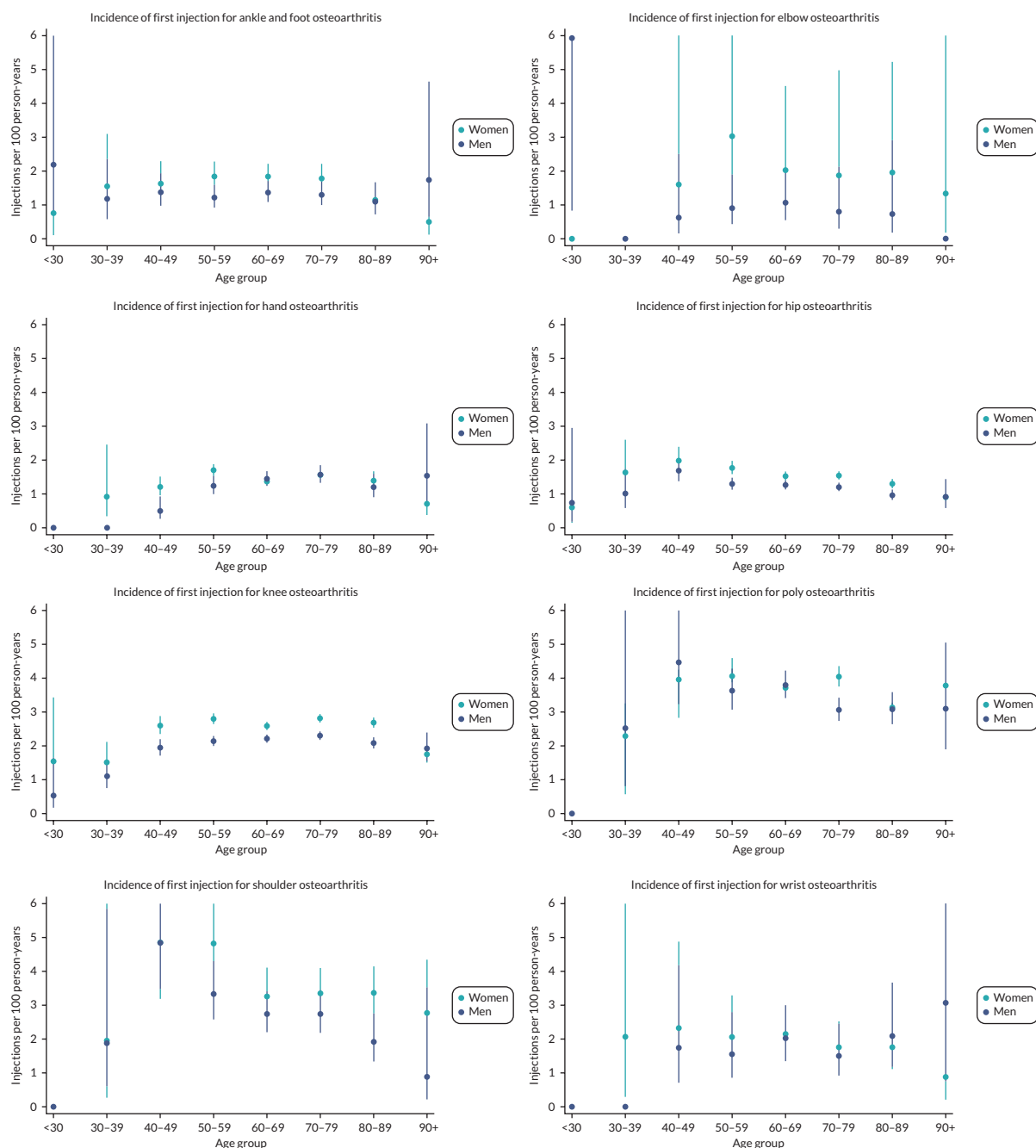


FIGURE 1 Incidence per 100 person-years of injections after OA by joint, age group and sex.

Strengths and limitations

One of the main strengths of the analysis is the inclusion of over 220,000 OA patients in a large national cohort, representative of the general population according to age, sex²⁷ and geographical region.⁴⁷ This, in conjunction with the continuous nature of data capture over time (average follow-up among all enrolled patients in CPRD GOLD at the point of data extraction was 13.5 years), makes this study – to the best of our knowledge – the largest UK descriptive study of frequency and timing of IACI use for OA. Given the cohort size we were able to analyse seven anatomical joints separately, and provide age, sex and region-specific rates.

However, it is possible that hospital-based or privately administered IACI like ultrasound-guided ones were missed in our primary care-based study, which we recognise as a study limitation. The IACI Read codes did not specify joint laterality, so we were unable to distinguish whether recurrent injections were performed at the same or opposite joint.

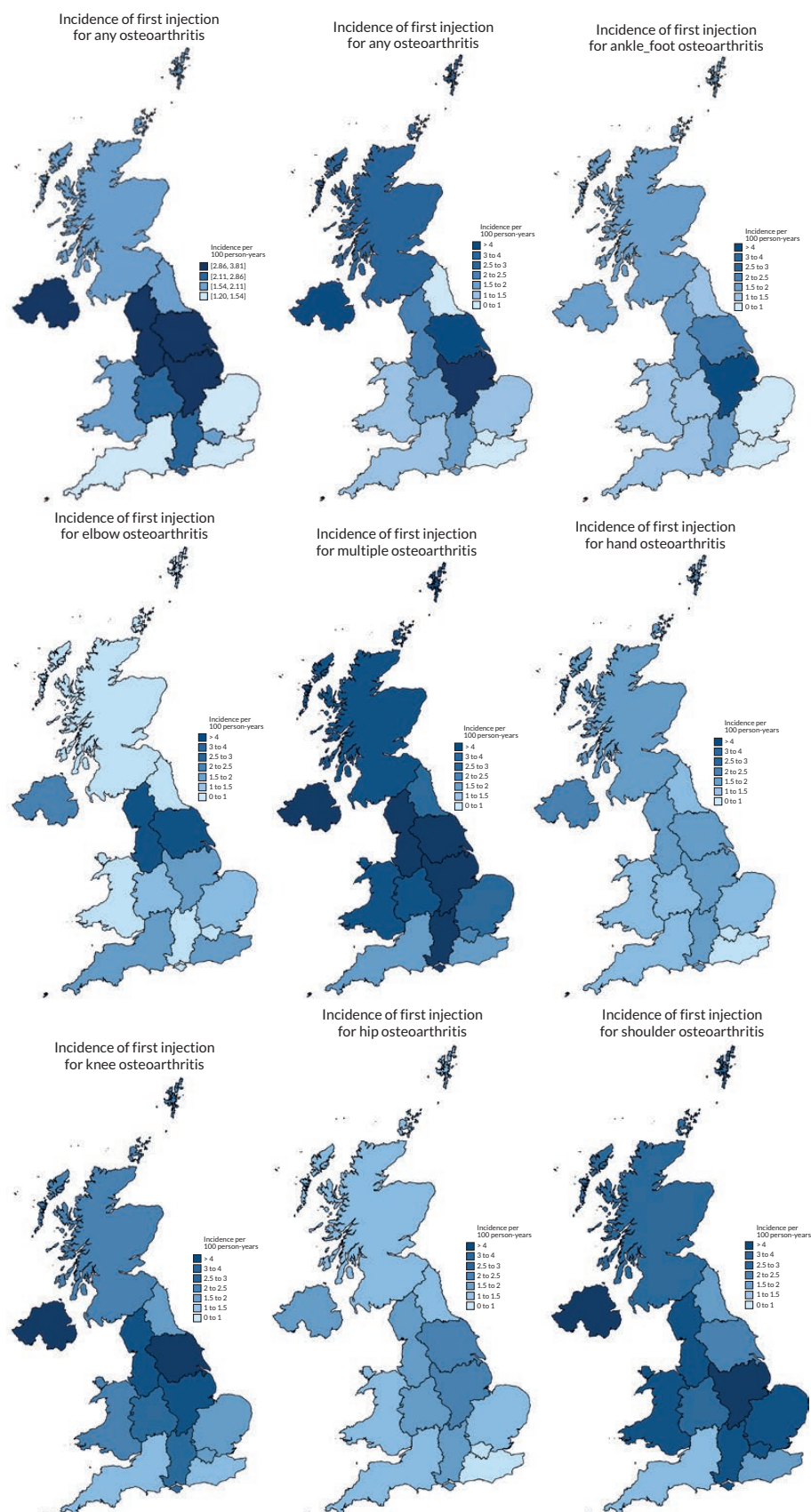


FIGURE 2 Incidence per 100 person-years of injections after OA by joint by geographical region.

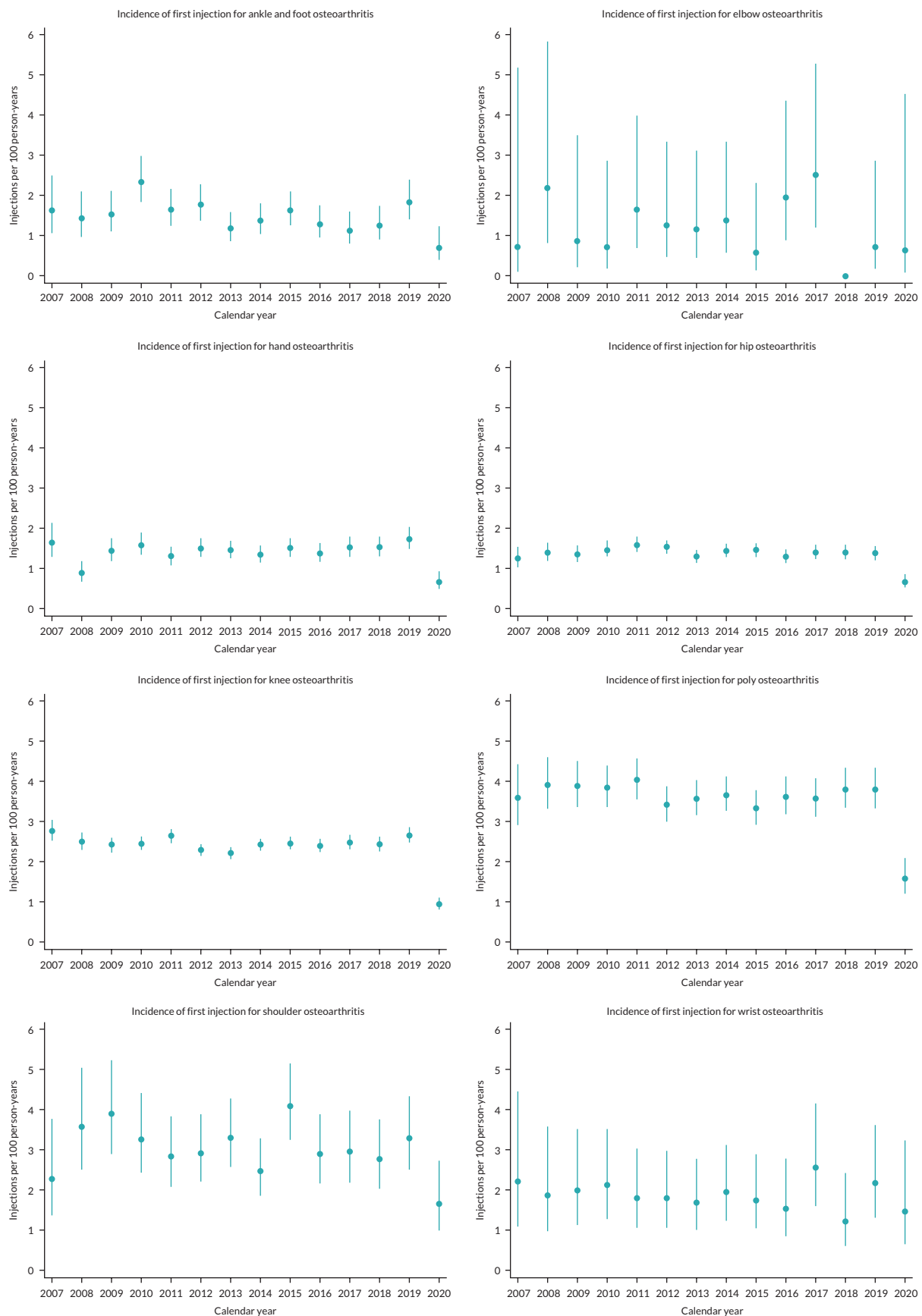


FIGURE 3 Yearly trends of first injection for OA by joint.

We were also unable to identify for certain the joint site injected given the frequency (> 40%) of IACI codes in the dataset which did not specify an anatomical location, although we sought to address this by analysing patients with polyarthritis as a separate cohort. Furthermore, the product codes analysed may have been used for intra-muscular injections, although for main analyses we were able to use Read codes that were specific for intra-articular injection of corticosteroid. Another limitation to the accuracy of estimates of IACI timing in the course of OA progression is that while the identification of OA has been validated in CPRD, timing of diagnosis in relation to disease onset may not be as reliable,²⁹ nor did we distinguish between primary and secondary OA.

Conclusions

In conclusion, this large national UK database study observed that 10.9% of patients diagnosed with OA received at least one IACI on or after their diagnosis. The most injected joints were the shoulder and knee. The use of injections has been unchanged up until 2019, with a decrease in 2020 likely due to COVID-19. However, there was wide heterogeneity in the use of injections between UK geographical regions. This difference in patient access to IACI between regions needs exploration in future work.

Chapter 4 Longer-term effects of IACI: a cohort study using CPRD

Introduction

Intra-articular corticosteroid injection is recommended by NICE for the treatment of uncontrolled pain in people with OA.⁴¹ However, the guidance states there is currently no evidence of therapeutic benefits beyond 3 months after IACI, and that more evidence is needed especially on the effects of IACI in joints other than the knee.^{41,48} Therefore, our aim was to assess the longer-term effects of single or recurrent use of IACI among people with incident ankle/foot, elbow, hand, hip, knee, shoulder or wrist OA.

Methods

Data and participants

Primary care health data were obtained from the UK CPRD GOLD and covered the period between 1 January 2005 and 28 August 2020, as described in [Chapter 2](#). Incident OA patients were identified using joint-specific Read code lists among participating GP practices with at least 1 year of 'up to standard' data uploaded. Separate cohorts were created for each joint studied: ankle/foot, elbow, hand, hip, knee, shoulder and wrist. Exclusion criteria were age < 20 years old, BMI < 15 kg/m² or referral for orthopaedic surgery prior to OA diagnosis date.

Exposure

The exposure of interest was IACI, identified using Read codes. For each joint cohort, we only considered IACI coded as being injected into either that particular joint or of unspecified joint (given the preponderance of such codes in the available data set).

Outcomes

Two broad categories of primary outcomes were investigated. Firstly, incident use of the following analgesics and/or oral corticosteroids: paracetamol, oral NSAIDs, topical NSAIDs, partial opiates, full opiates or oral glucocorticosteroids. Secondly, the following surgical interventions were analysed for only the hip and knee OA cohorts: arthroscopy, debridement, hip replacement (in hip cohort) and knee replacement (in knee cohort). Exploratory analysis indicated other joint cohorts (i.e. not hip or knee) were too small to analyse the impact of IACI on surgical intervention.

Secondary outcomes consisted of outcomes following joint replacement among hip and knee OA patients who underwent these procedures. Composite outcomes were complications [stroke, myocardial infarction (MI), pulmonary embolism, deep vein thrombosis (DVT) and infection] and reoperations (debridement, manipulation under anaesthetic, revision and others). PROMs at 6 months post operation were also analysed, including the OHS and OKS, which comprise questions about pain and joint function over the previous 4-week period and are scored out of 48.^{49–51} The scores have previously been interpreted as follows: excellent (≥ 41 points), good (34–41), fair (27–33) and poor (< 27).^{52,53} The minimum clinically important difference in these scores when comparing two groups (as in a clinical trial) is approximately five points.⁵⁴ In addition to absolute postoperative scores, we also investigated the percentage of potential change (PoP-C) score, which expresses the actual change attained in pre- to postoperative OHS/OKS as a percentage of the potential change possible.⁵⁵ Quality of life at 6 months post operation as measured using EQ-5D-3L was also included, which is an overall weighted index (a highest score being one, representing perfect health) from questions about mobility, self-care, usual activities, pain/discomfort and anxiety/depression.⁵⁶

Covariates

Covariates a-prior identified as potential confounders were measured using the most recent information prior to date of OA diagnosis, using a look-back period of up to 5 years. This look-back length was chosen as longer lengths such as 5 years have previously been associated with better identification of chronic diseases in other settings, although

indefinite look-back is not recommended.^{57,58} Covariates included age, sex, IMD quintile,^{59,60} BMI, smoking status (current, ex-, never), alcoholic drinking status (current, ex-, never), Charlson comorbidity score (0, 1, 2 or ≥ 3) and OA previously diagnosed in other joints (polyarthrititis). Also collected were diagnoses in 5 years prior to OA diagnosis date of the following medical conditions: asthma, cancer, chronic obstructive pulmonary disease (COPD), DVT, fracture, lower respiratory tract infection (LRTI), MI, pulmonary embolism, upper respiratory tract infection (URTI), urinary tract infection (UTI), anaemia, inflammatory arthritis, stroke, diabetes, epilepsy, ischaemic heart disease (IHD), malabsorption, hyperlipidaemia, hypertension, osteoporosis, chronic renal failure, acute renal failure or Parkinson's disease. Prevalent and/or prior drug use defined as any prescription in 5 years prior to OA diagnosis date was also collected for the following medicines: antiarrhythmics, antibiotics, antidepressants, anticonvulsants, anxiolytics, bisphosphonate, calcium/vitamin D, oral glucocorticosteroids, oral NSAIDs, topical NSAIDs, partial opioids, full opioids, paracetamol, proton pump inhibitors, prednisolone, statins, hormone replacement therapy or diuretics. Referral to physiotherapy was similarly derived and included.

Instrumental variable creation and diagnostics

Given the expectation of strong confounding by indication (i.e. characteristics predisposing patients to receiving IACI also predisposing them to experiencing outcome events), main analyses used an instrumental variable (IV) approach to estimate the impact of IACI on study outcomes. While a limitation of traditional methods for confounder adjustment is the limited information collected on confounding variables and the ensuing bias due to residual confounding,⁶¹ under certain assumptions IV analyses can yield unbiased estimates of treatment effect, even in the presence of strong or unmeasured confounding.^{62,63} The method relies on the existence of an 'instrument' which fulfils three strong assumptions:^{63,64} firstly it predicts the exposure, secondly it is associated with the outcome only through the exposure and thirdly it is independent of all measured and unmeasured confounders. When these are met, IV methods can be considered as achieving pseudo-randomisation where model estimates mimic those from a RCT. Various preference-based instruments have been used in previous epidemiological research to estimate treatment effects unaffected by confounding through harnessing 'naturally' occurring preferences for certain medicines, for example among surgeons or groups of healthcare providers.⁶²

The IV we derived and used in analyses was GP practice preference for IACI usage, calculated in a time-dependant manner. The reason for deriving preference at the level of GP practices was to account for the referral of OA patients to specialist clinicians within the same GP practice administering IACIs. For each OA patient the relative frequency of IACI was calculated over the previous 20 consultations (as per protocol) at the same GP practice among all patients with OA at the same anatomical joint. Separate cohorts were created for analysing the separate IVs of preference for single IACI and preference for repeat IACI, both using 'preference for no IACI' as the comparator. If the relative frequency of IACI use was above the national median for that anatomical joint, the patient was considered to belong to a practice preferring IACI at that point in time. If a 'look-back' of 20 patients was not possible given limited sample size, as was the case for the non-knee cohorts, then a smaller look-back (either the previous 5 or 10 rather than 20 patients) was used to derive the IV. In order to minimise the impact of immortal time bias, and given the complexity of accounting for this in the IV framework,⁶⁵ the IV was defined using only IACIs received in the year prior to model index date ([Figure 4](#)). In the main IV analyses, index date was defined as 180 days after OA diagnosis date. In sensitivity analyses, an index date of 365 days after OA diagnosis date was used.

Logistic regression models were fitted to check if the assumption of the IV being predictive of IACI assignment was met. The assumption was considered met for ≥ 2 .⁶⁶ The relationship between the IV and unmeasured confounders could not be assessed, however independence between the IV and measured confounders was assessed (separately for each cohort) using standardised mean differences (SMDs). We considered values exceeding 10% indicative of imbalance,^{67,68} in which case the IV was deemed to have failed to meet a key assumption and was not used in particular analyses where that was the case. We also checked balance in the degree of missing data across IV groups but did not impute missingness as this was considered unnecessary given the assumption of IV status being independent of patient covariates. Furthermore, balance across other potential IVs was also assessed, including calendar year of OA diagnosis and geographical region.⁶⁶

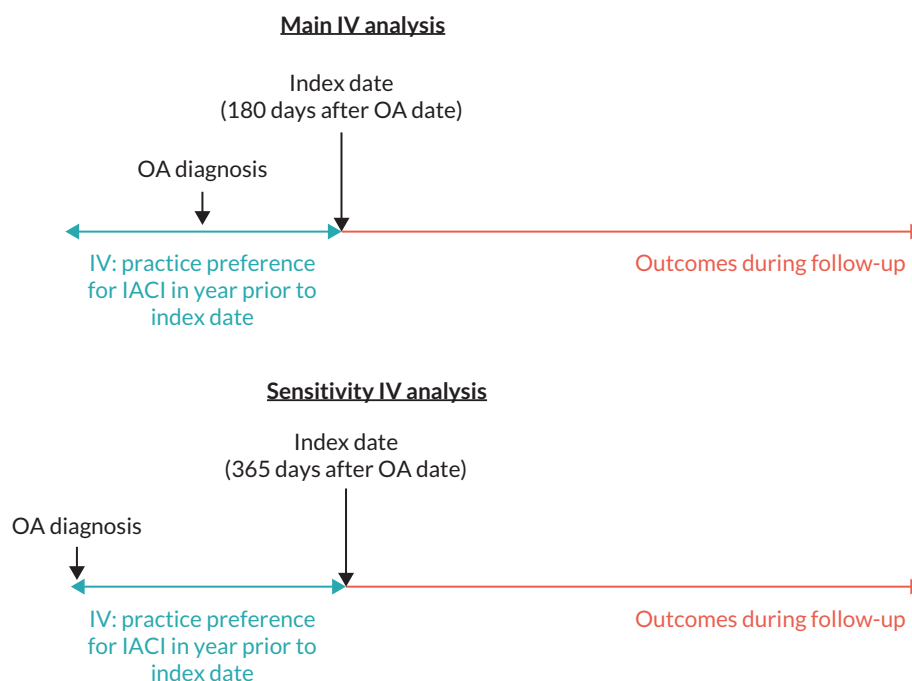


FIGURE 4 Diagram showing IV model.

Instrumental variable analysis of outcomes

In IV analyses, further exclusion was made of patients receiving an IACI more than 1 year prior to model index date, or experiencing the outcome event at any time prior to index date (see [Figure 4](#)). Each primary outcome was investigated using two follow-up times from index date: 12 and 60 months, although surgical interventions were also modelled at 6- and 24-month follow-ups. Given the dichotomous nature of these outcomes, patients were also excluded from a given analysis if the study end date in the CPRD GOLD data (28 August 2020) was within the possible follow-up time, as these patients would otherwise have insufficient follow-up.

In analyses of medication outcomes for each joint studied, cohorts were used which included OA patients irrespective of HES linkage (hereafter referred to as 'prescription cohorts', [Appendix 1, Figures 11 and 12](#)). Given that prescriptions data are captured in primary care, HES data were not required for these analyses. Incident medication outcomes were defined as receipt of at least one prescription of the outcome medication during specified follow-up among treatment-naïve patients at index date, that is those with a prescription of the same medication prior to index date were excluded in analysis of that outcome. Among these same cohorts, a second set of analyses was carried out to estimate the association between IACI use and the dichotomous outcomes of receiving repeat (5 or 15) prescriptions during total follow-up from index date.

In analyses of surgical intervention outcomes, a second set of cohorts were used for each joint studied in which further exclusion was made of patients without linked HES data (hereafter referred to as 'surgery cohorts', [Appendix 1, Figures 11 and 12](#)). HES data were required for these outcomes given that they were based on ICD-10 events coded in a secondary care setting.

In analyses of secondary outcomes after joint replacement, the same IVs were used as derived for primary outcomes. Given that only patients who had undergone joint replacement after OA diagnosis were included in these analyses, covariate balance across IV groups was re-checked. Outcomes were investigated using multiple follow-up time points from joint replacement date (rather than date of OA diagnosis): analyses of complications at 6 months and 1 year, and analyses of reoperation outcomes at 1 and 5 years.

Statistical modelling (single and repeat IACI analysed separately) consisted of two-stage Poisson regression.⁶⁹ In the first stage, the effect of IV on IACI was estimated; the residuals from this equation were then entered into a second model which estimated the effect of IACI exposure on the outcome of interest. Coefficients comparing IACI use versus no-use were expressed as relative risks (RRs) alongside 95% CI. In main analyses these were unadjusted as models were only run where good balance in confounders across IV groups had been demonstrated. However, in sensitivity analyses these models were re-run with adjustment for geographic region and calendar year of OA diagnosis, given these factors may have had a potential confounding role. The number needed to treat (NNT) with IACI to prevent the occurrence of one new outcome event was derived using the RR for each outcome, assuming associations were causal.

Secondary analyses: propensity score-based methods

Because of the strong assumptions of the IV approach, when it is used as a primary analysis, it is recommended that secondary analyses are conducted to allow comparison with alternative methods.⁷⁰ One such alternative is propensity score (PS) methods, which are well-established and widely used in pharmacoepidemiology.⁷¹ They provide a means of condensing a large amount of information on a patient's probability of being exposed to a treatment (IACI in this study) into a single score. This score can then be used to adjust or balance, either at the design or analysis stage, in order to minimise differences between exposed and unexposed patients and reduce confounding.⁷²

Propensity score estimates were created using multiple logistic regression with treatment status (any exposure to IACI during follow-up) as the outcome and all available covariates as measured at time of OA diagnosis included as explanatory variables. All covariates listed above (i.e. over 50 variables including sociodemographic information, clinical characteristics and previous medicines) were included in a multi-level model, with GP practice identifier entered as a random intercept to account for clustering effects. Multiple imputation using chained equations (MICE) was used to impute missing data on BMI, smoking and drinking status, with ten imputed datasets created.⁷³⁻⁷⁶ Missingness was assumed to be 'missing at random', that is dependent on other observed variables but randomly distributed once these dependencies were accounted for.^{73,76} For the prescription cohorts, a missing category was created for IMD rather than this being imputed given that IMD was only captured in the HES dataset (England only) and so the assumption of missing at random was not considered appropriate.⁷⁷ PS estimates were created separately for each imputed dataset.

Two statistical approaches for using the PS to minimise confounding were initially explored: matching and inverse probability weighting.^{72,78} For each method, balance in baseline covariates was assessed between exposure groups in the first of the imputed datasets and the method was not used if characteristics were not sufficiently similar, that is if SMD values were > 0.1 .⁷⁹ These exploratory analyses suggested matching was the best method for minimising differences between exposure groups, given that weighting resulted in insufficient balance across various characteristics. Matching was therefore used for these secondary analyses, with greedy matching implemented using a 2 : 1 ratio of non-IACI users (from the same geographic region and calendar year) to users within a calliper width of 0.2 SDs⁷⁹ of the PS. Separate matching was performed for each outcome so that separate exclusion criteria (e.g. prevalent users of medication excluded only in analyses of that medication) could be applied prior to matching in order to avoid breaking the balance achieved by matching. Balance was assessed within each scenario.

Given the greater flexibility afforded to model time-to-event outcomes in the PS framework, in analyses of primary outcomes patients were followed up from OA diagnosis date and a time-varying exposure approach was taken where follow-up was split according to time-specific exposure status: no IACI, single IACI or repeat IACI. Incidence rates of outcomes with 95% CI were calculated within each exposure period. Association between IACI use and longer-term outcomes were estimated using Cox proportional hazards survival analysis. Given some breach in the proportional hazards assumption was observed in initial models, final models were run using a dynamic cohort where the follow-up time axis was calendar time and the origin date was the study start date (1 January 2005). Patients entered the model on index date (their OA diagnosis date) and contributed follow-up until the first of either outcome event date, censoring date or study end date. Similar approaches have been used previously in the context of drug effectiveness, and are recommended when strong secular trends might otherwise bias a conventional 'time since baseline' time-axis analysis.⁸⁰ These final models satisfied the proportional hazards assumption and were run for all ten imputed datasets, after which estimates were pooled using Rubin's rules.^{75,81}

In analyses of secondary outcomes (only among hip and knee replacement patients), model index date was defined as date of joint replacement. Patients were re-matched on their PS for any IACI exposure during the time period between OA diagnosis date and joint replacement date. Multiple imputation was used to handle missing data in patient covariates and Rubin's rules used to pool estimated impact of injections (no IACI, single IACI or repeat IACI) from Cox models in each imputation. Missingness in PROM outcome data was not imputed, rather patients missing such data were excluded from these analyses. For continuous PROM outcomes, Wilcoxon signed rank tests were used in the matched cohorts to test for equality in medians, given non-normal distribution of these variables.

Sensitivity analyses

Given the inclusion of CPRD Read codes for IACI which did not confirm the anatomical joint injected, to further increase our confidence that the IACI was given in the joint recently diagnosed with OA, we performed sensitivity analyses repeating all statistical models for main outcomes with the additional exclusion of patients diagnosed with OA at more than one joint (either prior to or after index date).

Results

Description of cohorts

Population flow diagrams for the prescription and surgery cohorts used in the IV (see [Appendix 1, Figure 11](#)) and PS (see [Appendix 1, Figure 12](#)) analyses indicate the number of patients removed due to exclusion criteria at each stage of analysis for knee OA (separate diagrams are not included for every joint studied). Wrist and elbow cohorts were not analysed due to small sample size (as reported in [Chapter 3](#)).

For the main IV analyses, of the initially eligible OA patients, the sample size of those retained in the prescription cohorts for analysing single IACI were: ankle/foot = 5180 (48.3%); hand = 16,775 (52.2%); hip = 35,159 (61.1%); knee = 83,188 (72.6%) and shoulder = 3007 (41.6%). Patient characteristics for these patients are included in [Table 5](#). Sample sizes of the prescription cohorts used for analysing repeat IACI were similar to those used for single IACI, although slightly smaller.

Patient characteristics stratified by IACI treatment status and IV group are shown for the prescription cohorts used to analyse single (see [Appendix 1, Table 31](#)) and repeat (see [Appendix 1, Table 32](#)) IACI in IV analyses for knee OA. These stratified tables indicate many differences in characteristics between IACI users and non-users, although importantly these differences were not apparent when comparing IV groups. For example, partial opioid use was twice as high among recurrent users of IACI than non-users, although the difference in partial opioid use between IV groups was negligible (see [Appendix 1, Table 32](#)).

For secondary analyses using PS models, the sample sizes retained in final matched prescription and surgery cohorts are included in [Appendix 1, Tables 33](#) and [34](#), respectively, along with patient characteristics in [Appendix 1, Table 35](#).

Instrumental variable diagnostics

The IV strongly predicted receipt of IACI treatment (footnotes of [Table 6](#) and [Appendix 1, Tables 36](#) and [37](#)), except for in the ankle/foot cohort where the association for single IACI was weak. Generally, the IV for repeated IACI was a discernibly stronger predictor of IACI treatment than the IV for single IACI.

For the prescription cohorts used to analyse single IACI, only hand and knee OA patients had acceptable covariate balance between IV groups (see [Table 6](#)). At least one characteristic was imbalanced for other joints (ankle/foot, hip and shoulder), and so the IV was not used further for patients in these three cohorts. For prescription cohorts used to analyse repeat IACI, sample size in the ankle/foot cohort was too small to allow ascertainment of balance. For the other joint cohorts, sufficient covariate balance was only found for the knee cohort (see [Appendix 1, Table 36](#)) and therefore repeat IACI using the IV framework was only investigated for knee OA.

For the surgery cohorts used to analyse single IACI, acceptable balance was observed between IV groups for both hip and knee OA. For repeat IACI, neither hip or knee osteoarthritis patients had sufficient balance in characteristics across

TABLE 5 Characteristics of OA patients included in the prescription cohorts used in IV analyses of single IACI

Variable	Ankle/foot	Hand	Hip	Knee	Shoulder
	5180	16,775	35,159	83,188	3007
Age in years: mean (SD)	62.2 (13.3)	63.9 (11.2)	67.0 (12.0)	65.8 (12.3)	67.7 (12.8)
Female (%)	55.2	71.0%	58.6%	56.6%	52.8%
Male (%)	44.8	29.0	41.4	43.4	47.2
Least deprived (%)	8.5	14.4	9.5	9.9	7.5
Less deprived (%)	8.9	10.0	7.9	9.2	9.6
Mid deprived (%)	9.7	9.8	7.6	9.7	10.6
More deprived (%)	8.1	5.9	6.0	8.0	8.1
Most deprived (%)	6.4	4.2	4.3	6.3	5.7
Deprivation missing (%)	58.5	55.7	64.6	56.8	58.4
BMI: < 20 kg/m ² (%)	2.0	3.3	2.3	1.3	2.3
BMI 20 < 25 kg/m ² (%)	20.2	27.0	20.9	15.4	20.7
BMI 25 < 30 kg/m ² (%)	34.3	33.7	34.3	31.9	37.4
BMI 30 < 35 kg/m ² (%)	20.1	16.6	19.8	22.5	20.6
BMI 35 < 40 kg/m ² (%)	7.5	6.1	7.3	10.1	7.2
BMI ≥ 40 kg/m ² (%)	3.7	2.8	3.5	6.5	3.1
BMI missing (%)	12.2	10.4	11.8	12.2	8.6
Ex-drinker (%)	3.1	2.4	2.6	2.7	3.2
Never drinker (%)	13.7	14.1	13.9	15.7	17.1
Current drinker (%)	61.7	64.2	63.0	60.2	61.8
Drinking missing (%)	21.6	19.3	20.5	21.4	17.9
Ex-smoker (%)	31.2	30.3	32.2	31.0	36.0
Never smoker (%)	52.8	54.8	51.5	53.6	49.4
Current smoker (%)	13.4	12.4	13.3	11.8	12.1
Smoking missing (%)	2.6	2.5	3.0	3.6	2.5
Charlson = 0 (%)	72.5	74.3	70.6	70.4	64.8
Charlson = 1 (%)	7.6	7.7	8.4	8.4	9.8
Charlson = 2 (%)	10.0	9.6	10.8	11.0	12.9
Charlson ≥ 3 (%)	9.9	8.3	10.2	10.2	12.5
Polyarthritis (%)	16.2	9.9	9.1	4.8	24.0
Asthma (%)	10.8	10.6	9.2	9.7	11.4
Cancer (%)	7.1	6.9	7.9	7.2	9.0
Cerebrovascular disease (%)	2.2	2.0	2.9	2.5	2.5
COPD (%)	5.2	4.8	6.0	4.7	7.7
Diabetes (%)	9.3	8.8	10.8	11.7	13.2
DVT (%)	0.8	0.7	0.9	0.9	1.4

TABLE 5 Characteristics of OA patients included in the prescription cohorts used in IV analyses of single IACI (*continued*)

	Ankle/foot	Hand	Hip	Knee	Shoulder
Variable	5180	16,775	35,159	83,188	3007
Epilepsy (%)	1.3	1.2	1.2	1.4	1.2
Fracture (%)	6.1	4.6	5.4	4.8	6.4
Ischaemic heart disease (%)	3.8	3.2	4.7	4.6	6.4
LRTI (%)	19.2	20.7	18.7	19.5	24.4
Malabsorption (%)	0.3	0.3	0.3	0.2	0.2
MI (%)	1.3	0.8	1.4	1.2	2.2
Hyperlipidaemia (%)	7.4	7.3	7.4	7.8	8.0
Hypertension (%)	16.3	15.8	19.2	20.6	20.6
Osteoporosis (%)	2.9	3.0	3.3	2.6	4.0
Pulmonary embolism (%)	0.3	0.3	0.5	0.5	0.7
Chronic renal failure (%)	9.1	7.3	9.8	9.2	11.1
Acute renal failure (%)	0.4	0.3	0.4	0.4	0.6
URTI (%)	17.5	21.6	14.6	16.6	15.5
UTI (%)	6.2	8.4	7.7	7.4	6.9
Parkinson's disease (%)	1.4	1.1	1.5	1.5	1.7
Antiarrhythmics (%)	3.3	3.2	3.5	3.3	4.0
Antibiotics (%)	15.6	14.0	13.5	14.3	16.5
Antidepressants (%)	19.2	20.4	19.6	18.1	22.3
Anticonvulsants (%)	6.7	5.6	6.9	5.8	8.1
Anxiolytics (%)	9.7	10.7	10.2	9.8	12.4
Bisphosphonates (%)	4.2	4.9	5.8	4.5	7.4
Calcium/vitamin D (%)	7.3	8.1	8.9	7.4	11.5
Oral glucocorticoids (%)	8.2	7.5	8.1	7.2	11.0
NSAIDs oral (%)	33.6	25.8	33.3	34.2	35.0
NSIDs topical (%)	17.0	14.2	14.6	17.7	24.6
Opioids (%)	12.2	8.9	15.1	11.7	17.9
Partial opioids (%)	26.7	21.0	36.9	32.2	36.4
Paracetamol (%)	38.5	31.5	51.8	45.8	52.7
Proton pump inhibitors (%)	34.3	32.6	35.9	34.1	43.0
Prednisolone (%)	8.0	7.3	7.9	7.0	10.7
Statins (%)	30.5	29.2	35.2	33.9	39.9
Hormone replacement therapy (%)	3.0	5.0	2.5	2.6	2.1
Diuretics (%)	19.0	17.1	23.0	24.0	23.1
Physiotherapy (%)	34.1	34.9	31.1	29.4	45.0

TABLE 6 Standardised mean differences comparing patient characteristics between IV groups^a among OA patients included in the prescription cohorts used in IV analyses of single IACI

Variable	Ankle/foot	Hand	Hip	Knee	Shoulder
	IV = 1 (719) ^b	IV = 1 (3987) ^b	IV = 1 (8857) ^b	IV = 1 (33,715) ^b	IV = 1 (909) ^b
	IV = 0 (4461)	IV = 0 (12,788)	IV = 0 (14,326)	IV = 0 (49,473)	IV = 0 (2098)
Age in years	-0.09	-0.01	-0.02	-0.03	-0.15
Female	-0.05	-0.01	-0.01	-0.01	-0.03
Least deprived	0.21	0.07	0.1	0.04	0.15
Less deprived	0.08	-0.08	0.05	-0.04	-0.07
Mid deprived	0.05	-0.06	0.06	-0.06	-0.15
More deprived	0.02	-0.06	0.02	-0.05	-0.2
Most deprived	0.08	-0.04	0.05	0.04	-0.05
Deprivation missing	-0.27	0.07	-0.16	0.04	0.18
BMI: < 20 kg/m ²	-0.02	0.03	0.04	0.01	-0.07
BMI 20 < 25 kg/m ²	-0.03	0.03	0.01	0.02	0.07
BMI 25 < 30 kg/m ²	0.05	-0.01	0.02	0.02	0.06
BMI 30 < 35 kg/m ²	-0.01	-0.01	0.01	0	-0.04
BMI 35 < 40 kg/m ²	0.05	0.01	0	0.01	-0.04
BMI ≥ 40 kg/m ²	-0.05	0.01	-0.01	0	-0.03
BMI missing	-0.02	-0.04	-0.07	-0.06	-0.05
Ex-drinker	-0.02	0.04	0.03	0.02	-0.04
Never drinker	-0.05	0.01	-0.01	0	0.04
Current drinker	0.11	0.01	0.05	0.05	-0.02
Drinking missing	-0.09	-0.04	-0.07	-0.07	0.01
Ex-smoker	0	-0.02	-0.01	0	0.01
Never smoker	0.06	0.04	0.03	0.01	0
Current smoker	-0.07	-0.02	-0.01	0	0.02
Smoking missing	-0.02	-0.02	-0.05	-0.04	-0.08
Charlson = 0	0.06	0	-0.01	0	-0.07
Charlson = 1	-0.04	0.02	0.01	0	0.05
Charlson = 2	-0.01	0	-0.01	0	0.06
Charlson ≥ 3	-0.05	-0.03	0.01	0.01	-0.01
Polyarthritis	-0.07	0.01	0	0.03	0.03
Asthma	-0.04	-0.02	0.02	0.02	0.04
Cancer	-0.02	0	0.02	0.01	-0.04
Cerebrovascular disease	0.01	0.01	-0.02	0.01	0.01
COPD	-0.08	-0.02	-0.02	-0.01	-0.05
Diabetes	-0.03	0	-0.01	-0.01	-0.04

TABLE 6 Standardised mean differences comparing patient characteristics between IV groups^a among OA patients included in the prescription cohorts used in IV analyses of single IACI (*continued*)

Variable	Ankle/foot	Hand	Hip	Knee	Shoulder
	IV = 1 (719) ^b	IV = 1 (3987) ^b	IV = 1 (8857) ^b	IV = 1 (33,715) ^b	IV = 1 (909) ^b
	IV = 0 (4461)	IV = 0 (12,788)	IV = 0 (14,326)	IV = 0 (49,473)	IV = 0 (2098)
DVT	-0.06	0.01	0	0	0.02
Epilepsy	0.02	0.01	-0.01	0	-0.02
Fracture	0.02	0.01	0.01	0.01	-0.02
Ischaemic heart disease	-0.01	0.01	0	0	-0.04
LRTI	-0.08	0.01	0.01	0.01	-0.03
Malabsorption	0.02	0.02	0.01	0.02	-0.03
MI	-0.01	0.02	0.01	0	0.03
Hyperlipidaemia	-0.04	0.06	0.01	0.02	0.11
Hypertension	-0.03	0.07	0.03	0.01	0.09
Osteoporosis	0.02	0.01	0	-0.01	0.03
Pulmonary embolism	-0.02	0.01	0.02	0.01	0.01
Chronic renal failure	-0.05	-0.03	0.01	0	0.1
Acute renal failure	-0.04	-0.02	-0.01	-0.01	0
URTI	0.05	0.01	0.01	-0.02	-0.04
UTI	0.08	0.04	0.03	0.01	0.02
Parkinson's disease	-0.02	0.01	0	0	-0.04
Antiarrhythmics	0.04	0	-0.01	0.01	-0.03
Antibiotics	0.02	-0.01	-0.03	0.02	0
Antidepressants	0.02	0	-0.01	0.01	-0.03
Anticonvulsants	-0.01	-0.02	-0.01	0	-0.04
Anxiolytics	-0.08	0	-0.04	0	0.02
Bisphosphonates	0.02	-0.01	-0.01	-0.01	0.06
Calcium/vitamin D	0.02	-0.01	-0.03	0	0
Oral glucocorticoids	-0.09	-0.03	-0.02	0.02	0.01
NSAIDs oral	-0.01	0.02	0.02	0.01	0.09
NSAIDs topical	0.02	0.03	-0.02	0.04	0.06
Opioids	-0.09	0	0	-0.01	0.01
Partial opioids	-0.04	-0.04	-0.06	-0.01	-0.01
Paracetamol	-0.08	-0.03	-0.04	-0.01	0.03
Proton pump inhibitors	-0.02	-0.01	-0.02	0.02	-0.08
Prednisolone	-0.1	-0.03	-0.02	0.01	0
Statins	-0.05	0.01	-0.03	0	0.07

continued

TABLE 6 Standardised mean differences comparing patient characteristics between IV groups^a among OA patients included in the prescription cohorts used in IV analyses of single IACI (*continued*)

Variable	Ankle/foot	Hand	Hip	Knee	Shoulder
	IV = 1 (719) ^b	IV = 1 (3987) ^b	IV = 1 (8857) ^b	IV = 1 (33,715) ^b	IV = 1 (909) ^b
	IV = 0 (4461)	IV = 0 (12,788)	IV = 0 (14,326)	IV = 0 (49,473)	IV = 0 (2098)
Hormone replacement therapy	0.02	0.02	0	0	0
Diuretics	-0.06	0	-0.03	-0.03	-0.1
Physiotherapy	0.11	0.05	0.06	0.08	0.05

a Using index date of 180 days after OA diagnosis date.

b IV predicted IACI in each joint cohort as follows: odds ratio (OR) = 1.78 (ankle); OR = 3.95 (hand); OR = 2.97 (hip); OR = 5.59 (knee); OR = 3.80 (shoulder).

Note

Greyed background indicates insufficient balance.

IV groups and therefore the impact of repeated IACI on surgical outcomes using the IV framework was not investigated (see [Appendix 1, Table 37](#)).

Instrumental variable analyses of prescription outcomes

In terms of crude associations, actual treatment with single or repeat IACI in the year prior to model index date was broadly associated with greater risk of incident use of pain medications during follow-up for hand and knee OA (see [Appendix 1, Tables 38–40](#)). Conversely, in terms of crude associations between the IV groups and outcomes within the same patient cohorts, there was no increased prescribing of pain medication for those attending GP practices with a preference for IACIs. Instead there were small reductions in risk of subsequent prescribing following single IACI in the hand cohort ([Table 7](#)) and following single or repeat IACI in the knee cohort (see [Table 8](#) and [Appendix 1, Table 41](#)).

Results from the two-step IV regression generally indicated IACI was associated with lower prescribing of pain medication during subsequent follow-up in knee and hand OA ([Figures 5–7](#)).

Among hand OA patients, single IACI was associated (in terms of RRs in [Figure 5](#), expressed as NNT) with a subsequent reduction in incident use of the following medicines within 12 months: oral NSAIDs [NNT = 14 (95% CI 11 to 45)], oral glucocorticosteroids [NNT = 31 (95% CI 27 to 135)], paracetamol [NNT = 10 (95% CI 9 to 114)] and partial opioids [NNT = 5 (95% CI 4 to 12)]. An IACI-associated reduction in partial opioids was also observed at 60 months [NNT = 4 (95% CI 3 to 15)]. These associations persisted following further adjustment for geographic region and calendar year in sensitivity analyses (see [Appendix 1, Figure 13](#)). It was not possible to study repeat IACI in the IV framework for hand OA given lack of covariate balance (see [Appendix 1, Table 36](#)). Similarly, sample size was inadequate to investigate impact of IACI on repeat prescriptions or in models using the sensitivity index date of 365 days after OA diagnosis.

Among knee OA patients, single IACI was associated (in terms of RRs at 60 months in [Figure 6](#), expressed as NNT) with lower incident use of opioids [NNT = 14 (95% CI 9 to 683)], oral glucocorticosteroids [NNT = 18 (95% CI 12 to 70)], paracetamol [NNT = 4 (95% CI 3 to 7)] and partial opioids [NNT = 5 (95% CI 3 to 14)]. Some of these associations were attenuated to include the null upon adjustment of geographic region and calendar year, although results for paracetamol and partial opioids remained unchanged (see [Appendix 1, Figure 13](#)). Estimated impact of single IACI was generally stronger in sensitivity analyses using 365 days after OA diagnosis as model index date (see [Appendix 1, Figure 14](#)). Larger reductions were observed in analyses using repeat pain prescriptions as the outcome (see [Figure 7](#) and [Appendix 1, Figure 15](#)). Overall, larger reductions in pain prescriptions were also observed in IV analyses of repeat IACI than for single IACI (see [Figure 6](#)), although CIs were wider due to smaller sample size. Repeat IACI was associated with a reduction in incident use of the following medicines at 60 months: opioids [NNT = 9 (95% CI 7 to 21)], paracetamol [NNT = 4 (95% CI 3 to 7)], partial opioids [NNT = 3 (95% CI 2 to 5)] and topical NSAIDs [NNT = 6 (95% CI 5 to 14)]. Estimated impact of repeat IACI was similar in sensitivity analyses using 365 days after OA diagnosis as model index

TABLE 7 Incident use of medicines during specified follow-up^a in the prescription cohort used in IV analyses of single IACI for hand OA: by IV status

		GP practice preference for no IACI			GP practice preference for IACI		
Medication	Follow-up (months)	N	n	%	N	n	%
Single injection analysis							
Oral NSAIDs	12	7768	818	10.5	2394	222	9.3
	60	5385	1550	28.8	1553	422	27.2
Opioids	12	11,003	437	4.0	3393	119	3.5
	60	7842	1015	12.9	2237	286	12.8
Oral glucocorticosteroids	12	11,135	439	3.9	3497	116	3.3
	60	7992	1053	13.2	2326	285	12.3
Paracetamol	12	7277	903	12.4	2338	261	11.2
	60	5132	1758	34.3	1566	511	32.6
Partial opioids	12	11,003	2938	26.7	3393	814	24.0
	60	7842	3269	41.7	2237	860	38.4
Topical NSAIDs	12	8508	614	7.2	2682	207	7.7
	60	6277	1436	22.9	1857	414	22.3

a Using index date of 180 days after OA diagnosis date.

TABLE 8 Incident use of medicines during specified follow-up in prescription cohorts used in IV analyses of single or repeat IACI for knee OA: by IV status^a

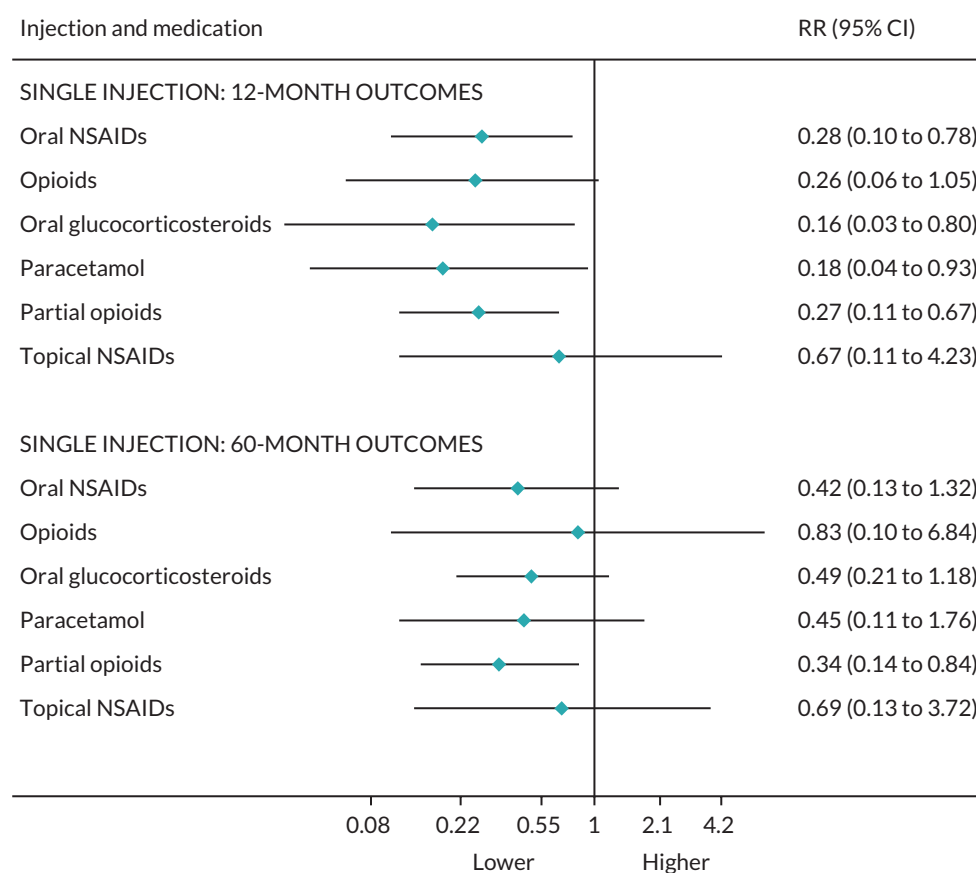
		Preference for no IACI			Preference for IACI		
Medication	Follow-up (months)	N	n	%	N	n	%
Single injection analysis							
Oral NSAIDs	12	25,838	2747	10.6	17,570	1814	10.3
	60	20,345	5669	27.9	12,612	3478	27.6
Opioids	12	39,964	2681	6.7	27,374	1843	6.7
	60	32,386	6616	20.4	20,283	3944	19.4
Oral glucocorticosteroids	12	43,948	1627	3.7	29,734	1086	3.7
	60	35,682	4641	13.0	22,185	2713	12.2
Paracetamol	12	19,078	3153	16.5	13,475	2078	15.4
	60	15,329	6651	43.4	9832	4011	40.8
Partial opioids	12	39,964	16,001	40.0	27,374	10,327	37.7
	60	32,386	17,797	55.0	20,283	10,682	52.7
Topical NSAIDs	12	35,556	2658	7.5	23,670	1812	7.7
	60	29,601	7617	25.7	18,035	4439	24.6

continued

TABLE 8 Incident use of medicines during specified follow-up in prescription cohorts used in IV analyses of single or repeat IACI for knee OA: by IV status^a (continued)

		Preference for no IACI			Preference for IACI		
Medication	Follow-up (months)	N	n	%	N	n	%
Repeat injection analysis							
Oral NSAIDs	12	35,933	3758	10.5	5946	650	10.9
	60	27,645	7684	27.8	4200	1185	28.2
Opioids	12	55,733	3729	6.7	9238	592	6.4
	60	44,187	8879	20.1	6729	1236	18.4
Oral glucocorticosteroids	12	60,884	2230	3.7	10,031	358	3.6
	60	48,449	6154	12.7	7319	879	12.0
Paracetamol	12	26,874	4354	16.2	4678	690	14.7
	60	21,068	9007	42.8	3355	1327	39.6
Partial opioids	12	55,733	21,918	39.3	9238	3326	36.0
	60	44,187	24,029	54.4	6729	3397	50.5
Topical NSAIDs	12	49,205	3684	7.5	7897	604	7.6
	60	40,052	10,221	25.5	5948	1389	23.4

^a Using index date of 180 days after OA diagnosis date.

**FIGURE 5** Forest plot showing estimated effect of single IACI for hand OA on incident use of pain medication within specified follow-up.

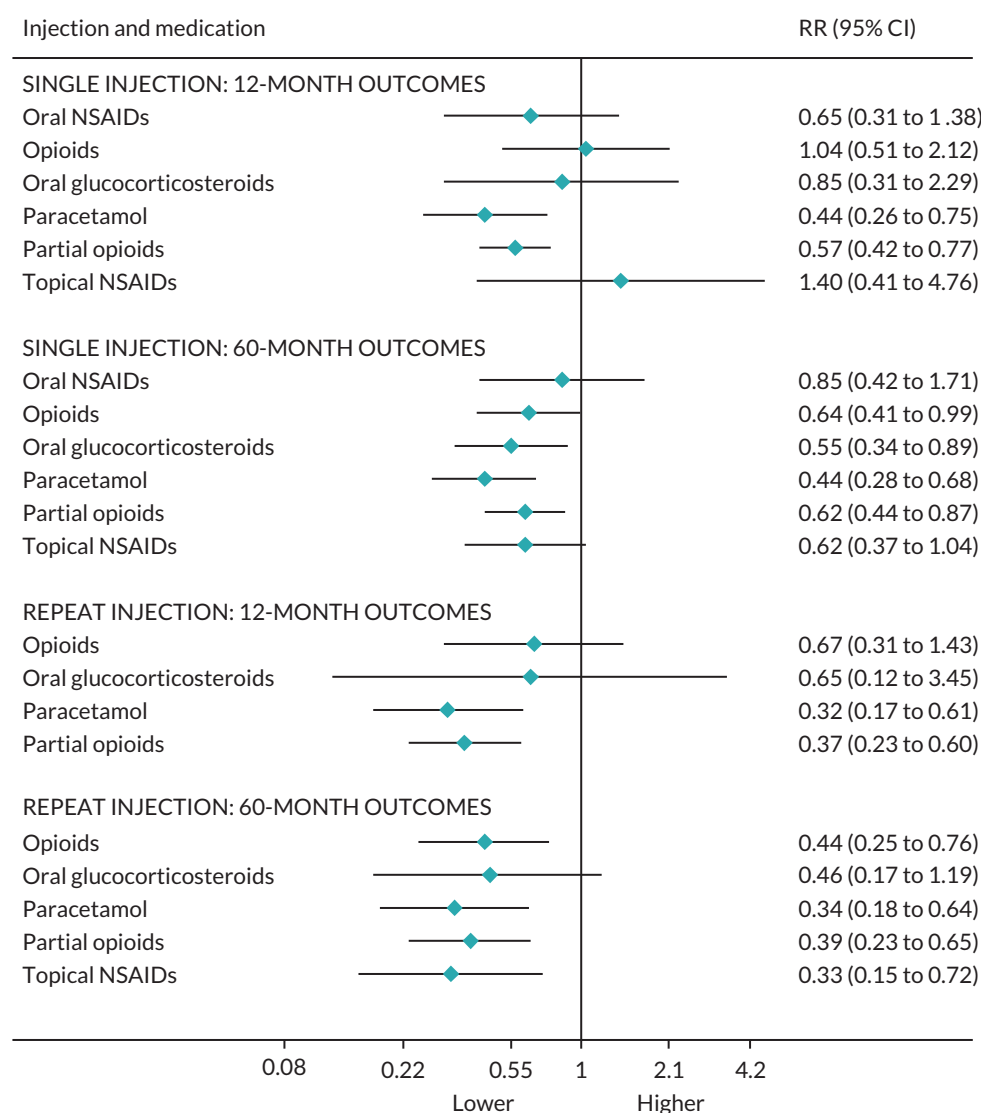


FIGURE 6 Forest plot showing estimated effect of single and repeat IACI use for knee OA on incident use of pain medication during specified follow-up.

date (see [Figure 14](#)) and in models of repeat pain prescriptions adjusted for geographic region and calendar year (see [Figure 15](#)).

Instrumental variable analysis of surgical outcomes

In terms of crude associations, treatment with IACI in the year prior to model index date was broadly associated with greater risk of surgical intervention during follow-up in the hip and knee surgery cohorts used for the IV analyses (see [Appendix 1, Table 42](#)). Conversely, in terms of crude associations between the IV groups and outcomes within these same surgery cohorts, there was no discernible increased risk of arthroscopy or debridement for OA patients attending GP practices with a preference for IACIs ([Table 9](#)). Likewise, there was little difference across IV groups in crude risk of joint replacement in the hip cohort (see [Table 9](#)); however, small reductions in joint replacement risk were observed in the single IACI group in the knee cohort (see [Table 9](#)).

Among hip OA patients, in addition to being unable to investigate repeat IACI due to lack of covariate balance, it was not possible to run two-step IV models of single IACI for arthroscopy or debridement due to insufficient outcome events to achieve model convergence. Single IACI IV models yielded no significant relationship with hip replacement up to 24-month follow-up (see [Figure 8](#) and [Appendix 1, Figure 16](#)), although models for 60-month follow-up would not

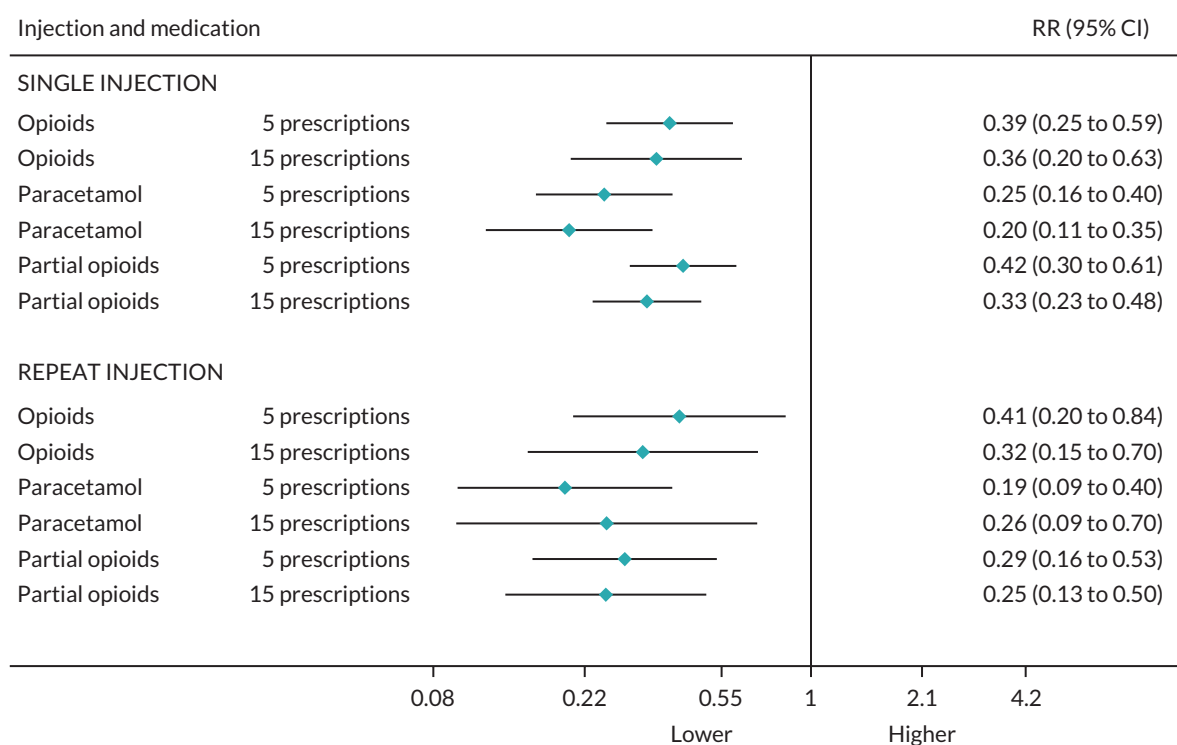


FIGURE 7 Forest plot showing estimated effect of single and repeat IACI use for knee OA on repeat prescriptions during total follow-up.

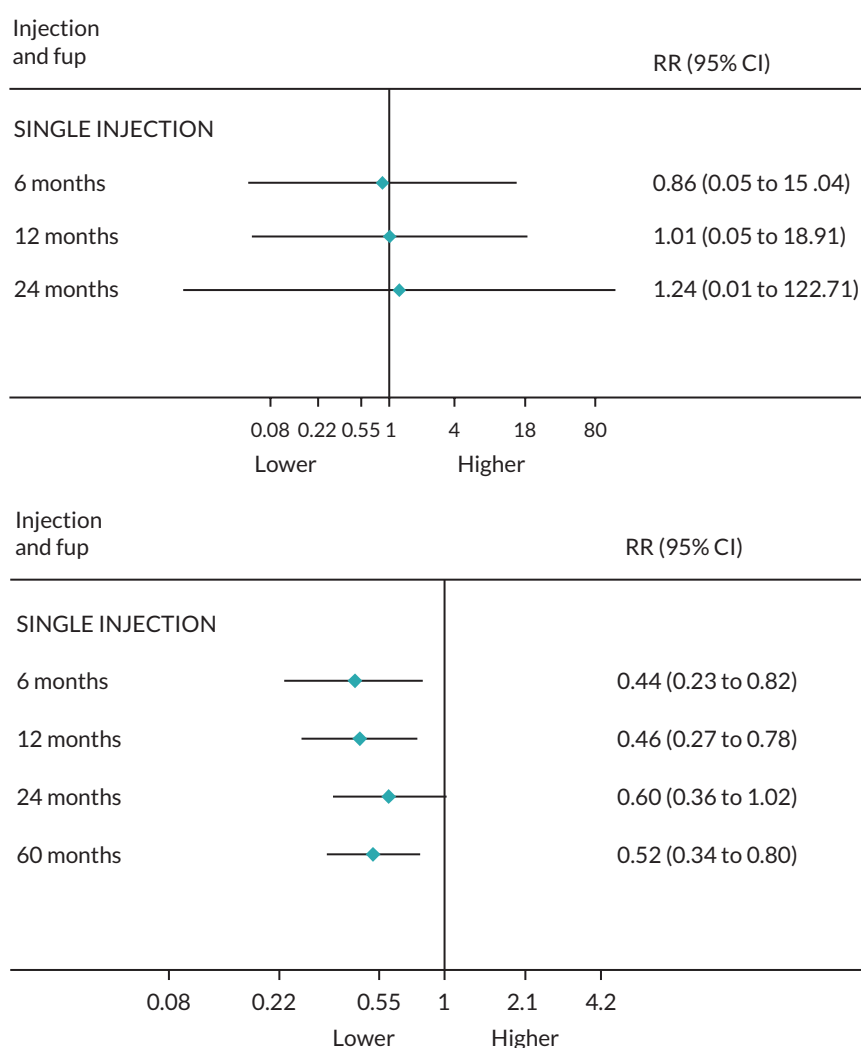
TABLE 9 Surgical intervention during specified follow-up^a among the surgery cohorts used in IV analyses of single IACI for hip or knee OA: by IV status

Procedure	Follow-up (months)	GP practice preference for no IACI			GP practice preference for IACI		
		N	n	%	N	n	%
Hip injection analysis							
Arthroscopy	6	15,944	8	0.1	1690	< 5	0.1
	12	15,763	13	0.1	1658	< 5	0.1
	24	15,421	18	0.1	1591	< 5	0.1
	60	13,652	24	0.2	1356	< 5	0.1
Debridement	6	15,944	< 5	0	1690	0	0
	12	15,763	7	0	1658	0	0
	24	15,421	15	0.1	1591	< 5	0.1
	60	13,652	22	0.2	1356	< 5	0.2
Replacement	6	15,944	1748	11	1690	184	10.9
	12	15,763	2547	16.2	1658	268	16.2
	24	15,421	3441	22.3	1591	357	22.4
	60	13,652	4166	30.5	1356	433	31.9
Knee injection analysis							
Arthroscopy	6	22,782	350	1.5	15,092	269	1.8
	12	22,579	540	2.4	14,918	399	2.7

TABLE 9 Surgical intervention during specified follow-up^a among the surgery cohorts used in IV analyses of single IACI for hip or knee OA: by IV status (*continued*)

Procedure	Follow-up (months)	GP practice preference for no IACI			GP practice preference for IACI		
		N	n	%	N	n	%
Debridement	24	22,185	768	3.5	14,524	546	3.8
	60	20,018	1071	5.4	12,280	671	5.5
	6	22,782	279	1.2	15,092	223	1.5
	12	22,579	453	2	14,918	330	2.2
Replacement	24	22,185	648	2.9	14,524	469	3.2
	60	20,018	913	4.6	12,280	587	4.8
	6	22,782	747	3.3	15,092	435	2.9
	12	22,579	1170	5.2	14,918	687	4.6
	24	22,185	1775	8	14,524	1087	7.5
	60	20,018	2728	13.6	12,280	1540	12.5

a Using index date of 180 days after OA diagnosis date.

**FIGURE 8** Forest plots showing estimated effect of single IACI use for hip (top) and knee (bottom) OA on subsequent risk of joint replacement during specified follow-up (fup).

converge. Likewise, sensitivity analyses using index date of 365 days after OA diagnosis date could not be conducted given the limited sample size.

Among knee OA patients, results from two-step IV regression suggested no clear effect of IACI on subsequent risk of arthroscopy or debridement (see [Figure 8](#)). For these outcomes, models would only converge when using follow-up of 60 months. These estimates [arthroscopy RR = 1.20 (9% CI 0.29 to 4.96) and debridement RR = 2.01 (95% CI 0.16 to 25.48)] suggested some increased risk; however, the CIs were wide and spanned the null. They remained unchanged upon further adjustment for geographic region and calendar year in sensitivity models. A protective effect of single IACI on subsequent joint replacement risk was consistently estimated except at 24-month follow-up where CIs just spanned the null (see [Figure 8](#)). In terms of RRs expressed as NNT with single IACI to prevent one knee replacement at 60-month follow-up, this was NNT = 17 (see 95% CI 12 to 40). Results were largely unchanged in sensitivity analyses adjusted for geographic region and calendar year (see [Appendix 1, Figure 16](#)), and when using a model index date of 365 days after OA diagnosis (see [Appendix 1, Figure 17](#)), although CIs were slightly wider due to a smaller sample size.

Propensity score diagnostics

Propensity score matching achieved good balance in patient covariates between IACI users and non-users (see [Appendix 1, Tables 43 and 44](#)). This was observed in both prescription and surgery cohorts used in PS analyses across all joints studied (ankle/foot, hand, hip, knee and shoulder).

Propensity score analyses of prescription outcomes

[Appendix 1, Table 45](#) contains incidence rates (95% CI) of incident use of pain medicines in the prescription cohorts in PS analyses for each joint – stratified by patient's time-varying exposure of no IACI, single IACI or repeat IACI during specified follow-up. Corresponding hazard ratios (HRs) from time-varying exposure Cox regression models are shown in [Table 10](#), comparing IACI exposure (single and repeat) to non-exposure. Most of these estimates indicated IACI used to be associated with some reduction in incident use of pain medicines within 60 months of follow-up, although many of these had CIs that spanned the null. Incidence of partial opioids was approximately 30–50% lower following a single IACI at any of the joints studied, and rates were generally reduced further following a repeat IACI (for hand, hip and knee patients) although a small non-significant increase was observed following repeat IACI for shoulder OA. Likewise, following single IACI there was higher incident use of oral glucocorticosteroids among hand OA patients, and higher use of opioids following single or repeat IACI use for knee OA.

Propensity score analyses of surgical outcomes

Given the small sample size of the surgery cohort used in PS analyses of IACI for hip OA, the only surgical outcomes modelled among these patients were debridement at 24-month follow-up and hip replacement (see [Table 11](#) and [Appendix 1, Table 46](#)). While these analyses suggested a possible protective effect of IACI on debridement [RR = 0.46 (95% CI 0.06 to 3.80)], the CI was wide and spanned the null. Rates of hip replacement were over twice as high at 24 and 60 months after a single IACI, and while rates were also higher following repeat IACI, there was no 'dose-response' observed (see [Table 11](#)).

Among knee OA patients in the PS-matched surgery cohorts (see [Table 11](#) and [Appendix 1, Table 46](#)), no associations were found between IACI and arthroscopy rates. Rates of debridement were approximately 30% to 40% higher following single IACI, although not following repeat IACI. Knee replacement rates were non-significantly lower during the first 6-month follow-up after single IACI, and during the first 12 months after repeat IACI, but were consistently higher by 24-month follow-up and exceeding HR = 2 at 60 months (see [Table 11](#)).

Analyses of secondary outcomes (outcomes of joint replacement)

Upon re-checking balance across IV groups among only those patients undergoing joint replacement surgery, inadequate balance in both the hip and knee cohort meant outcomes after joint replacement were not investigated using the IV approach.

Covariate balance between the PS-matched cohorts of IACI use (during anytime between OA diagnosis date and joint replacement date) among joint replacement patients was confirmed (results not shown). Subsequent PS analyses of IACI exposure on outcomes of joint replacement suggested there were no significant differences in rates of complications or reoperations associated with IACI use prior to joint replacement ([Table 12](#)).

TABLE 10 Cox regression HRs for incident use of pain medicines during specified follow-up among patients in the prescription cohorts used for PS-matched analyses: by IACI status

			Single injection HR				Repeat injection HR			
Joint	Medication	Follow-up (months)	Estimate	Lower 95% CI	Upper 95% CI	p-value	Estimate	Lower 95% CI	Upper 95% CI	p-value
Ankle/foot	Oral NSAIDs	12	1.22	0.68	2.18	0.51	-	-	-	-
		60	0.84	0.59	1.20	0.33	0.52	0.16	1.70	0.28
	Opioids	12	1.17	0.54	2.50	0.69	-	-	-	-
		60	1.14	0.83	1.58	0.42	1.03	0.46	2.32	0.95
	Oral glucocorticosteroids	12	0.83	0.36	1.93	0.67	-	-	-	-
		60	1.46	1.01	2.11	0.043	0.94	0.35	2.54	0.90
	Paracetamol	12	0.91	0.52	1.62	0.76	1.09	0.12	10.10	0.94
		60	1.05	0.76	1.45	0.76	1.53	0.86	2.74	0.15
	Partial opioids	12	0.59	0.38	0.92	0.019	0.59	0.08	4.35	0.61
		60	0.86	0.66	1.12	0.26	1.00	0.52	1.92	0.99
	Topical NSAIDs	12	0.65	0.30	1.37	0.26	3.97	0.44	36.01	0.22
		60	0.92	0.67	1.26	0.59	0.67	0.24	1.86	0.44
Hand	Oral NSAIDs	12	0.70	0.47	1.05	0.088	-	-	-	-
		60	0.78	0.62	0.99	0.037	0.70	0.44	1.10	0.12
	Opioids	12	1.37	0.82	2.29	0.22	0.89	0.22	3.60	0.87
		60	1.19	0.95	1.50	0.13	1.09	0.75	1.57	0.65
	Oral glucocorticosteroids	12	1.16	0.71	1.89	0.55	0.82	0.20	3.39	0.79
		60	1.15	0.91	1.45	0.25	1.05	0.73	1.52	0.79
	Paracetamol	12	0.72	0.46	1.12	0.15	1.56	0.65	3.76	0.32
		60	0.94	0.76	1.16	0.58	1.08	0.75	1.55	0.68
	Partial opioids	12	0.69	0.51	0.94	0.019	1.06	0.49	2.26	0.89
		60	0.68	0.56	0.81	< 0.001	0.69	0.49	0.96	0.030
continued										

TABLE 10 Cox regression HRs for incident use of pain medicines during specified follow-up among patients in the prescription cohorts used for PS-matched analyses: by IACI status (continued)

Joint	Medication	Follow-up (months)	Single injection HR				Repeat injection HR			
			Estimate	Lower 95% CI	Upper 95% CI	p-value	Estimate	Lower 95% CI	Upper 95% CI	p-value
Hip	Topical NSAIDs	12	0.70	0.44	1.14	0.15	0.41	0.06	3.05	0.38
		60	0.80	0.65	0.98	0.034	0.77	0.54	1.12	0.17
	Oral NSAIDs	12	0.76	0.54	1.07	0.12	2.39	0.85	6.73	0.099
		60	0.87	0.74	1.04	0.12	0.85	0.47	1.53	0.58
	Opioids	12	1.05	0.80	1.37	0.74	0.86	0.23	3.25	0.83
		60	0.99	0.86	1.15	0.91	1.05	0.64	1.70	0.86
	Oral glucocorticosteroids	12	0.93	0.59	1.45	0.73	1.00	0.13	7.76	1.00
		60	0.95	0.79	1.14	0.60	1.31	0.82	2.10	0.26
	Paracetamol	12	0.79	0.57	1.10	0.17	1.45	0.19	11.34	0.72
		60	0.83	0.68	1.01	0.059	1.10	0.51	2.38	0.80
	Partial opioids	12	0.50	0.39	0.63	< 0.001	0.63	0.21	1.91	0.41
		60	0.55	0.48	0.65	< 0.001	0.46	0.25	0.84	0.012
Knee	Topical NSAIDs	12	0.86	0.60	1.23	0.40	0.65	0.09	4.61	0.66
		60	1.02	0.88	1.18	0.81	1.11	0.72	1.69	0.64
	Oral NSAIDs	12	0.93	0.80	1.07	0.32	1.10	0.82	1.48	0.52
		60	0.95	0.87	1.04	0.24	0.83	0.72	0.96	0.011
	Opioids	12	1.08	0.95	1.24	0.25	1.09	0.83	1.45	0.53
		60	1.25	1.16	1.35	< 0.001	1.31	1.17	1.46	< 0.001
	Oral glucocorticosteroids	12	0.89	0.72	1.08	0.24	0.90	0.59	1.39	0.65
		60	0.97	0.88	1.06	0.49	1.10	0.96	1.25	0.18

Joint	Medication	Follow-up (months)	Single injection HR				Repeat injection HR			
			Estimate	Lower 95% CI	Upper 95% CI	p-value	Estimate	Lower 95% CI	Upper 95% CI	p-value
Shoulder	Paracetamol	12	1.02	0.90	1.16	0.78	1.08	0.81	1.44	0.61
		60	0.97	0.89	1.07	0.58	1.07	0.92	1.24	0.38
	Partial opioids	12	0.74	0.67	0.81	< 0.001	0.50	0.39	0.64	< 0.001
		60	0.78	0.72	0.83	< 0.001	0.65	0.58	0.73	< 0.001
	Topical NSAIDs	12	0.91	0.79	1.05	0.21	1.19	0.89	1.58	0.23
		60	0.90	0.84	0.97	0.008	0.90	0.80	1.01	0.077
	Oral NSAIDs	12	0.75	0.43	1.32	0.33	0.48	0.07	3.35	0.46
		60	0.75	0.54	1.04	0.089	0.98	0.53	1.80	0.94
	Opioids	12	1.04	0.65	1.65	0.88	2.11	0.80	5.56	0.13
		60	0.90	0.68	1.20	0.49	1.30	0.78	2.18	0.32
	Oral glucocorticosteroids	12	1.16	0.68	1.99	0.58	1.12	0.27	4.58	0.88
		60	1.10	0.83	1.46	0.49	0.98	0.55	1.75	0.94
	Paracetamol	12	0.55	0.34	0.88	0.014	0.89	0.20	4.01	0.88
		60	0.95	0.72	1.24	0.69	1.23	0.60	2.54	0.57
	Partial opioids	12	0.63	0.46	0.87	0.005	0.83	0.36	1.93	0.67
		60	0.68	0.54	0.86	0.001	1.17	0.73	1.87	0.51
	Topical NSAIDs	12	1.21	0.77	1.88	0.41	1.54	0.38	6.29	0.55
		60	1.17	0.91	1.51	0.21	1.23	0.73	2.07	0.44
Note - Indicates inadequate sample size.										

TABLE 11 Cox regression HRs for surgical intervention during follow-up among patients in the surgery cohorts used for PS-matched analyses: by IACI status

Joint	Surgery	Follow-up (months)	Single IACI HR				Repeat IACI HR			
			Estimate	Lower 95% CI	Upper 95% CI	p-value	Estimate	Lower 95% CI	Upper 95% CI	p-value
Hip	Arthroscopy	6	-	-	-	-	-	-	-	-
		12	-	-	-	-	-	-	-	-
		24	-	-	-	-	-	-	-	-
		60	-	-	-	-	-	-	-	-
	Debridement	6	-	-	-	-	-	-	-	-
		12	-	-	-	-	-	-	-	-
		24	0.46	0.06	3.8	0.47	-	-	-	-
		60	-	-	-	-	-	-	-	-
	Replacement	6	1.05	0.63	1.73	0.86	1.40	0.20	9.74	0.74
		12	1.53	1.17	1.99	< 0.001	1.52	0.72	3.23	0.27
		24	2.22	1.81	2.73	< 0.001	1.43	0.86	2.40	0.17
		60	2.49	2.13	2.91	< 0.001	1.34	0.95	1.89	0.099
Knee	Arthroscopy	6	1.04	0.67	1.62	0.87	0.36	0.05	2.55	0.31
		12	1.18	0.86	1.60	0.30	1.09	0.57	2.08	0.80
		24	1.24	0.99	1.56	0.060	1.06	0.70	1.61	0.78
		60	1.22	1.02	1.47	0.033	1.03	0.76	1.40	0.83
	Debridement	6	1.08	0.69	1.70	0.73	0.83	0.21	3.29	0.79
		12	1.35	0.97	1.88	0.071	0.68	0.28	1.68	0.41
		24	1.39	1.10	1.77	< 0.001	0.91	0.56	1.48	0.71
		60	1.31	1.08	1.59	0.007	1.09	0.79	1.49	0.60

Joint	Surgery	Follow-up (months)	Single IACI HR				Repeat IACI HR			
			Estimate	Lower 95% CI	Upper 95% CI	p-value	Estimate	Lower 95% CI	Upper 95% CI	p-value
	Replacement	6	0.74	0.49	1.12	0.15	0.53	0.13	2.14	0.37
		12	1.07	0.85	1.35	0.57	0.76	0.43	1.36	0.36
		24	1.61	1.37	1.90	< 0.001	1.56	1.19	2.04	< 0.001
		60	2.13	1.90	2.40	< 0.001	2.20	1.88	2.58	< 0.001
Note - Indicates inadequate sample size.										

TABLE 12 Outcomes of knee replacement in the PS-matched knee replacement cohort: by previous IACI exposure

Index joint replacement	Outcome	Follow-up month	No IACI						Single IACI						Repeat IACI					
			N	n	Rate (/1000 PYs)				N	n	Rate (/1000 PYs)				N	n	Rate (/1000 PYs)			
					Estimate	Lower 95% CI	Upper 95% CI	p value ^a			Estimate	Lower 95% CI	Upper 95% CI	p value ^a			Estimate	Lower 95% CI	Upper 95% CI	p value ^a
Hip	Complications ^b	6	714	17	48.7	30.3	78.4	323	9	56.8	29.5	109.1	0.88	37	0	0				
		12	714	21	30.3	19.7	46.4	323	10	31.8	17.1	59.2	0.9	37	0	0				
	Reoperations ^c	12	714	12	17.2	9.8	30.3	323	11	35.5	19.6	64	0.12	37	0	0				
		60	714	23	7.1	4.7	10.6	323	18	12.7	8	20.1	0.14	37	< 5	6.62	0.93	47.02	0.83	
Knee	Complications ^b	6	2122	88	86.2	69.9	106.2	819	21	52.6	34.3	80.6	0.087	249	10	83.6	45	155.4	0.86	
		12	2122	101	49.8	41	60.5	819	30	37.8	26.5	54.1	0.32	249	16	67.3	41.2	109.9	0.27	
	Reoperations ^c	12	2122	54	26.8	20.5	35	819	23	29.2	19.4	44	0.85	249	8	33.6	16.8	67.1	0.78	
		60	2122	84	9.1	7.3	11.3	819	32	9	6.4	12.7	0.36	249	12	11.2	6.4	19.8	0.87	
PYs, person-years.																				
a Derived from Cox model, comparing TVE to IACI to no exposure.																				
b Complications: stroke, MI, PE, DVT and infection.																				
c Reoperations: debridement, MUA, revision and others.																				

Similarly, there were no significant differences in 6-month PROMS. For hip replacement patients not previously receiving IACI: mean OHS = 38.9, mean POP-C = 70.1 and mean EQ5D = 0.81. For knee replacement patients not previously receiving IACI: mean OKS = 35.8, mean POP-C = 57.1 and mean EQ5D = 0.77. These outcomes were either identical or very similar for those receiving single or recurrent IACI (results not shown).

Sensitivity analyses

Results for pain medication and surgical outcomes were largely unchanged in IV and PS sensitivity analyses following additional exclusion of patients with OA diagnosed at multiple joints. Due to the smaller sample size, some CIs increased to incorporate the null and IV models for surgical outcomes in the hip cohort and for knee debridement could not be analysed because of model non-convergence.

Discussion

Key findings

In main analyses of single IACI among hand or knee OA patients, we observed a NNT of approximately five patients to prevent one occurrence of partial opioid initiation over the subsequent 5 years. Findings for knee OA indicated the reduction was larger among recurrent IACI than single IACI users, and that the incidence of repeat prescriptions for paracetamol, partial opioids or full opioids were also reduced. Secondary analyses using PS matching confirmed lower rates of partial opioids at 12-month follow-up after single IACI use across any of the joints studied. These reductions in partial opioid initiation mostly persisted at 5-year follow-up, although recurrent IACI use was only associated with lower rates of partial opioids in the hand, hip and knee cohort.

The effect of IACI on subsequent occurrence of surgical intervention was less clear. In main analyses, a lower 5-year risk of knee replacement was observed following single IACI use (NNT = 17). However, IACI use was associated with higher rates of knee replacement in secondary analyses using PS matching. Likewise, while IV analyses found no effect of single IACI use on hip replacement, PS matching found IACI users had higher subsequent rates of hip replacement. PS matching showed no effect of IACI use on rates of complications, reoperations or PROMs following hip or knee replacement among OA patients who underwent these procedures.

Findings on prescription outcomes in the context of existing literature

The longer-term reduction in incident use of several pain medications associated with IACI use in a number of anatomical joints with OA is a reassuring finding, somewhat in keeping with what is known from prior literature regarding the short-term benefits of IACI on pain reduction. IACI has been a recognised treatment for knee OA for over 50 years.⁸² The Cochrane review on the topic reports 'small to moderate' benefits of IACI on pain reduction (NNT = 8) lasting up to 6 weeks,⁸³ although this same review concludes it is unclear if there are clinically important benefits beyond 6 weeks, and no evidence of an effect at 6 months.⁸³ Likewise, NICE guideline NG226 recommends use of IACI for short-term pain relief when other OA treatments are ineffective or unsuitable, stating there is no evidence of benefit lasting beyond 3 months.⁴¹ These recommendations have been further substantiated by subsequent studies of the knee⁸⁴ and hip,⁸⁵ and a recent systematic review of recurrent use of IACI (irrespective of joint) which found no benefits after 3 months.⁸⁶

However, various limitations to the existing literature have been noted, including high heterogeneity of findings and low overall quality of evidence.^{83,84} It has been recognised there is insufficient follow-up for the adequate study of longer-term outcomes following IACI, which should be addressed in order to help inform existing guidelines.^{86,87} NICE acknowledges the scarcity of evidence for IACIs in joints other than the knee, and explicitly recommends research here is needed.^{41,48} Furthermore, although OARSi guidelines recommend repeated IACI use, and suggest no more than four injections per year,⁸² they acknowledge data are limited on how frequently IACI should be administered, which although pertinent to concerns around safety, is also of relevance to the question of longer-term effectiveness. Given the context of these various limitations to existing literature, our findings add important and novel information to what is already known, as discussed below.

Firstly, the demonstration of lower incidence of pain medications following IACI for hand OA expands the evidence base of IACI effects at non-knee joints. The IV analyses yielded a reduction in risk of initiating oral NSAIDs, oral glucocorticosteroids, paracetamol or partial opioids within 1 year of single IACI for hand OA (see [Figure 5](#)). Although it was not possible to use the IV methodology to study the effects of IACI at other non-knee joints, it is noteworthy that secondary PS analyses identified reductions in partial opioids at 1-year follow-up after single IACI at all joints studied (including ankle/foot, hip and shoulder), and additionally a reduction in incident use of several other medicines including NSAIDs for hand OA (see [Table 10](#)). IACI for hand osteoarthritis has been found in RCTs to reduce pain on movement and joint swelling at 3 months.⁸⁸ Interestingly, the 2018 update to the European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of hand OA revised its previous recommendations which favoured IACI use,⁸⁹ and instead now advises IACI ‘should not generally be used’, given lack of evidence for a beneficial effect.⁹⁰

Secondly, the IACI-associated reduction in initiation of several pain medications that we observed in IV analyses of IACI for hand or knee OA persisted to 12 months or beyond (see [Figures 5 and 6](#)), suggesting that known short-term benefits may have translated to longer-term effects. The strong association between IACI use and repeat pain medication prescriptions among knee OA patients, including full opioids (see [Figure 7](#)) during indefinite follow-up is also an important finding,⁹¹ suggesting clinically meaningful benefits from IACI for OA beyond the short term. NICE states that the primary purpose of providing short-term pain reduction with IACI should be to facilitate therapeutic exercise,⁴¹ which is itself an effective core treatment for OA⁹² providing favourable effects on both pain and disability.⁸² Further work is needed on exploring other mechanisms, although one suggestion is the possible inhibition of processes similar to those involved in persistent chronic pain following acute postoperative pain related to many types of surgery,⁹³ which a single local anaesthetic infiltration has been shown to mitigate against.⁹⁴

Thirdly, in IV analyses of IACI for knee OA, we observed a larger reduction in risk of initiating pain medication following repeat injections than we observed for a single injection (see [Figures 6 and 7](#)). Data are scarce on the relative effect of recurrent versus single IACI for OA.⁸⁶ One high-quality RCT found no effect of repeated IACI on pain reduction over a 2-year period, although pain was only measured 3 months after each injection and therefore any short-term effects were not detected.²² That we observed a ‘dose–response’ in main IV analyses for knee OA patients between IACI use and subsequent longer-term reductions in pain medication prescriptions (an obvious surrogate of pain) suggests a possible cumulative benefit for recurrent (two or more injections) compared to single IACI use. However, there is also likely to be some self-selection present given that patients who respond well to a single IACI are more likely to receive further injections.

Findings on surgical outcomes in the context of existing literature

There is limited literature on the possible effect of IACI on subsequent need and timing of surgical intervention.⁸⁶ Contributing to the 6-month risk reduction in knee replacement (and the non-significant 6-month risk reduction in hip replacement) that we observed in main IV analyses is likely to be a short-term clinician/surgeon reticence to operate on those recently treated with IACI, given concerns around postoperative joint infection.^{87,95} That this short-term reduction in knee replacement persisted up to 5-year follow-up is an interesting finding. NICE guidance recommends joint replacement should be considered when joint symptoms are substantially impacting quality of life and where non-surgical management (including pain relief) is ineffective or unsuitable.⁴¹ It is therefore reasonable to propose that IACI may act to modify a patient’s ‘eligibility’, that is bringing symptoms of pain and function back under control to an extent that either joint symptoms were no longer substantially impacting quality of life or that non-surgical management was no longer deemed ineffective. As suggested above, there is also the possibility short-term pain relief as a result of IACI could yield longer-term effects, providing a ‘window of opportunity’ in which to establish therapeutic exercise and/or to potentially slow or even arrest the progression of chronic pain requiring surgery.

However, our secondary analyses using PS matching did not replicate our IV findings of IACI having a reduced risk of joint replacement, with the PS approach actually estimating an increased risk of joint replacement over the longer term (see [Table 11](#)). Supporting these secondary findings of increased risk are previous RCT data of no effect of repeated IACI on pain reduction over a 2-year period, but instead of greater cartilage loss,²² which has been associated with higher rates of arthroplasty. Joint replacement rates were not explicitly reported in the RCT, although between

group differences in cartilage loss were halved and no longer significant among the subset who completed the trial (presumably without joint replacement). Zeng *et al.* subsequently conducted a time-varying PS-matched analysis that also found continuous use of IACI to be associated with a large increased risk ($HR > 3$) of radiographic OA progression, which persisted, albeit attenuated, in sensitivity analyses considering joint replacement as a competing risk.²¹

While our PS-matched findings of increased risk of joint replacement find some support from previous literature suggesting IACI may contribute to OA progression, our main IV analyses used stronger methodology for dealing with the inherent confounding present in such an investigation of the real-world effectiveness of IACI. The IV approach makes strong assumptions, but where these are upheld, it provides a means of estimating treatment effect in a manner unbiased by either measured or unmeasured confounding, which is particularly useful in studies of intended effects where uncontrolled confounding may otherwise be substantial.⁶² The reversal in risk that we observed upon controlling for confounding via estimation using the IV (crude associations with actual IACI treatment suggested increased risk) is in keeping with the use of preference-based IVs in other contexts.⁹⁶ On the other hand, PS analyses will almost always be limited to some extent by a degree of residual confounding due to limited availability of information on confounding factors. For example, our PS models did not factor in patients' radiographic data, validated measures of OA severity, position within the osteoarthritis care pathway or patient attitudes towards IACI. This is also a likely explanation for why PS-matched analyses yielded estimates of higher rates of initiating some pain medications following repeat IACI use, in which residual confounding was likely to be higher than those for single IACI (see [Table 10](#)).

In considering the difference in findings on joint replacement between IV and PS approaches, it is also worth mentioning the respective analyses included different populations with different baseline characteristics. The IV approach included all eligible patients (after additional exclusions related to deriving the IV, such as the first 10–20 patients in each GP practice to provide a 'burn-in' for calculating preference). The PS-matched cohorts on the other hand excluded the majority of eligible patients (over 85% for the knee cohort, [Appendix 1, Figure 12](#)), leaving a less generalisable study sample reflective of treated patients only due to the matching of users with non-users. For instance, in the prescription cohort for knee OA, prevalence of partial opioid use was 11.7% in the cohort used for IV analyses (see [Table 5](#)) but was 16.0% in the PS-matched cohort (see [Appendix 1, Table 37](#)).

There is little existing data to compare our finding on the association between IACI treatment and outcomes of joint replacement. Previous reports of increased postoperative joint infection associated with prior use of IACI⁹⁵ were not observed in our PS analyses on postoperative complications, reoperations and PROMs. Given that individual complications and reoperations were relatively rare events, we were constrained in analyses to a composite outcome. Likewise, while the number of IACI in the immediate months preceding joint replacement was low (results not shown), an investigation of possible interaction with timing of IACI prior to surgery remains a topic for future study.

Strengths and limitations

Preference-based instruments are widely used in pharmaco-epidemiological research,⁶² and the use of an IV approach as a main analysis in the present study is a major strength given its potential to yield unbiased estimates in the presence of strong and/or unmeasured confounding. The large and generalisable nature (on a national level) of the CPRD GOLD dataset²⁷ is another strength, allowing the study of several different joints and inclusion of a broad range of patient covariates with which to contribute to and assess the validity of IV and PS methodologies. The continuous nature of data upload in CPRD GOLD meant longer-term outcomes could be reliably ascertained, and our use of secondary care HES-PROMS data for surgical outcomes as identified using ICD-10 is arguably more reliable than relying on surgical procedures being accurately coded in primary care data.⁹⁷ We only used IACI codes specific for intra-articular injection of corticosteroid and avoided more general product codes that could have included intra-muscular injections. We also excluded site-specific codes for IACI into unrelated joints in analyses of each individual joint, thus reducing bias.

However, our study is subject to several limitations. While identification of OA has been validated in CPRD, timing of diagnosis in relation to disease onset may not be as reliable,²⁹ although in main IV models, we used several different exposure windows around the time of OA diagnosis. We did not distinguish between primary and secondary OA, nor were we able to perform external validation of code lists used to identify IACI. The IACI codes did not specify joint laterality, so we were unable to distinguish whether recurrent injections were performed at the same or opposite

joint. We also included IACI codes not specifying the joint site injected although results were very similar in sensitivity analyses only including patients with OA diagnosed at one anatomical joint site. We were unable to distinguish IACI administered in secondary care which is more often performed using ultrasound guidance, which may have biased estimates towards the null, and reduced the generalisability of our findings.

Several caveats to the GP preference instrument should also be taken into consideration.⁶³ Practice preference for IACI could in part be driven by an underlying preference and/or local guidelines around surgical intervention rather than IACI per se, for example in end-of-life care or in response to local commissioning guidance which can make injection either restricted or a precursor to referral for surgery, thus introducing an element of reverse causality which we were unable to disentangle using the available data. Likewise, although we only used IVs that we could demonstrate were unrelated to patient confounders, we did not discount IVs on the basis of being associated with other potential instruments such as geographical region or calendar year, although our results were similar in sensitivity analyses adjusted for these factors. The IVs were also only based on preference for IACI around the time of OA diagnosis and are therefore likely to relate to IACI use in a relatively mild osteoarthritis population, whereas our PS-matched models considered and accounted for time-varying exposure to IACI during follow-up.

Conclusions

In this national prospective cohort study, we found single IACI for hand or knee OA was associated with a subsequent reduction in incident use of several pain medications over the longer term. In knee OA patients these reductions were larger following repeat IACI than single IACI. Secondary analyses indicated lower rates of initiating partial opioids at 60-month follow-up after repeat use of IACI for OA in the hand, hip or knee. Our findings suggest a single IACI for knee OA may delay knee replacement with no adverse effect on outcomes. However, the association between IACI and rates of hip and knee replacement were not consistent in secondary analyses, therefore further investigation is recommended in other large cohorts.

Chapter 5 Safety of IACI: a cohort study using CPRD

Introduction

Little is known about the safety of IACI for treating OA. Prior RCTs have not had enough participants to provide robust safety data.^{98,99} A Cochrane systematic review and meta-analysis⁸³ including 27 RCTs with 1767 participants comparing IACI to sham injection determined that those using corticosteroids were 11% less likely to experience adverse events, and less likely to withdraw because of adverse events; however, the CIs were very wide, included the null effect and hence the effect was unclear. The NICE guidelines for the management of OA were based on RCTs that included no more than 500 participants in total with relatively short follow-up periods, which were not powered to detect any potential small differences in safety risks for IACIs.

Therefore, a formal analysis exploring all possible safety outcomes with adequate power to detect small differences in adverse events is needed to determine the risk profile of IACIs. We assessed the safety of IACIs in OA patients from CPRD GOLD data comparing 6-month mortality, bleeding, hemarthrosis, wound infection, diabetes, cerebrovascular disease, MI and IHD between non-injected and injected OA patients.

Methods

Data and participants

Data for participants were obtained from the UK CPRD GOLD, spanning the period from 1 January 2005 to 28 August 2020, as outlined in [Chapter 2](#). In summary, patients acceptable for clinical research with a new diagnosis of OA were identified using joint-specific Read codes (see [Appendix 1, Table 26](#)) among the GP practices that had submitted data which met the up-to-standard for a period of at least 1 year. All patient time was separated into cohorts: ankle/foot, elbow, hand, hip, knee, shoulder and wrist, meaning a patient could be in more than one cohort, but only in one at the same time. We excluded patients aged < 20 years or BMI < 15 kg/m² at OA diagnosis date, or those referred to orthopaedic surgery before the osteoarthritis diagnosis date.

Exposure

The exposure of interest was IACI as identified using Read code lists (see [Appendix 1, Table 28](#)). It was compared to patients with OA without an IACI.

Outcomes

Outcomes of interest were assessed in CPRD using Read codes as the first occurrence of an outcome as identified by a Read code within 6 months of OA diagnosis or after each IACI. Outcomes included mortality, bleeding, hemarthrosis, wound infection, diabetes, cerebrovascular disease, MI and IHD.

Covariates

Covariates were assessed at the time of OA diagnosis. They included age, sex, IMD quintile, geographic region, calendar year, BMI, smoking status (current, ex-, never), alcoholic drinking status (current, ex- or never), Charlson comorbidity score (0, 1, 2 or ≥ 3) and previous OA in another joint. Comorbidities were also assessed in 5 years prior to OA date and included asthma, cancer, COPD, DVT, fracture, LRTI, MI, pulmonary embolism, URTI, UTI, anaemia, inflammatory arthritis, cerebrovascular disease, diabetes, epilepsy, IHD, malabsorption, hyperlipidaemia, hypertension, osteoporosis, chronic renal failure, acute renal failure or Parkinson's disease. Prevalent and/or prior drug use was also assessed as any prescription in 5 years prior to OA diagnosis for antiarrhythmics, antibiotics, antidepressants, anticonvulsants, anxiolytics, bisphosphonates, calcium/vitamin D, oral glucocorticosteroids, oral NSAIDs, topical NSAIDs, partial opioids, full opioids, paracetamol, proton pump inhibitors, prednisolone, statins, hormone replacement therapy or diuretics.

Statistical analyses

Descriptive analysis

For the descriptive analyses, incidence was calculated for each outcome as any first event in 6 months after OA diagnosis or after injections divided per the number of person time years contributed. Follow-up time was censored at the earliest of death, occurrence of a new injection in the same or another joint, or the studied outcome.

Propensity score model

Although the main statistical analysis was supposed to be, as per protocol, IVs the use of this was not possible on safety outcomes, as the short follow-up time prevented the generation of them without introducing bias, and also was prevented by the lack of implementation of this method for survival regression. As PSs seem to have performed well previously for safety outcomes and procedures,⁶⁶ these were used to minimise confounding.

Propensity scores were created regressing all the variables at the time of OA against treatment status (any exposure to IACI during follow-up) as the outcome in a logistic regression model. All covariates listed above (sociodemographic, clinical characteristics and medicine use) were included in a multi-level model, with GP practice identifier entered as a random intercept to account for clustering effects. MICE was used to impute missing data on BMI, smoking and drinking status, with 10 imputed datasets created.¹⁰⁰ We explored matching and inverse probability weighting as per protocol.^{72,78}

Matching was implemented with greedy matching implemented using a 2 : 1 ratio of non-IACI users to IACI users within a calliper width of 0.2 SD⁷⁹ of the PS. Inverse probability weighting using stabilised weights was also applied.¹⁰¹ For each method, we assessed balance in confounders between injected and non-injected patients, and the method was deemed unusable if characteristics were not sufficiently similar, that is if SMD values were > 0.1.⁷⁹

Survival analysis

We divided each follow-up time from OA diagnosis date using a time-varying exposure approach. Follow-up was split into no IACI, single IACI or repeat IACI. We estimated associations between IACI use and 6-month complications and mortality using Cox proportional hazards modelling. Patients entered the model on their OA diagnosis date and contributed follow-up until the first of either outcome event date, censoring date or study end date. All models satisfied the proportional hazards assumption. These models were performed age/sex adjusted and by applying the PS techniques. Models were repeated with a Fine-Gray approach to consider the competing risk of death.¹⁰² All models were run for all 10 imputed datasets, after which estimates were pooled using Rubin's rules.^{75,81}

Self-controlled cohort

Further analyses to minimise unmeasured confounding were done using self-controlled methods.¹⁰³ Here we used the self-controlled cohort method (see [Figure 9](#)), where we kept only the patients exposed to IACI and compared the occurrence of safety events in 6 months after OA compared with the occurrence of events in 6 months following the first IACI for each patient. As the analyses were done conditional on each patient, each person was compared to themselves, thus minimising confounding. Some confounding may still be present if these variables were time-varying, therefore we adjusted for age to minimise this potential effect. RR of complications after IACI compared with after OA diagnosis was calculated for each outcome using a Poisson regression with absorbing factors.

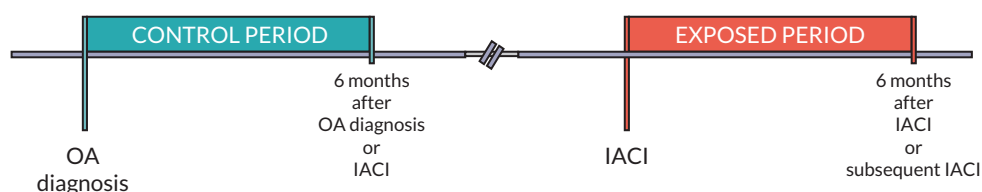


FIGURE 9 Diagram showing self-controlled cohort analysis.

Results

Patients' characteristics

After exclusions, shown in [Appendix 1, Figure 18](#), the total population with OA eligible for inclusion was 197,301 patients, with 8241 (4.2%) receiving an IACI. [Table 13](#) shows the patient characteristics. Injected patients tended to be older, with fewer comorbidities, and higher use of antidepressants and pain medicines.

Six-month complication rates

Mortality rates were 1.2 (95% CI 1.2 to 1.3) deaths per 100 person-years after OA diagnosis, 1.6 (1.3 to 2.1) after first IACI and 1.1 (0.8 to 1.6) after subsequent IACI. There were no cases of bleeding, and all the hemarthroses ($n = 3$) happened after the OA diagnoses in knees, with none happening after IACI. There were little differences in infection rates, with 0.4 (0.4 to 0.5) infections per 100 person-years 6 months after OA diagnosis, 0.3 (0.1 to 0.5) in 6 months following a first IACI, and 0.4 (0.2 to 0.7) in 6 months after subsequent IACI.

Crude rates of new diabetes diagnosis were slightly higher in 6 months after first and subsequent IACI, with rates of 1.5 (1.1 to 2.0) and 1.5 (1.1 to 2.1), respectively, than in 6 months after an OA diagnosis with a rate of 1.0 (0.9 to 1.1). Similar effects were seen with cerebrovascular disease, MI and new cases of IHD. Cerebrovascular disease was observed, with rates of 0.6 (0.5 to 0.6) cases of CVD after OA diagnosis, 0.9 (0.6 to 1.3) after first IACI and 1.1 (0.7 to 1.5) after subsequent IACI; MI rates of 0.3 (0.3 to 0.4) cases of CVD per 100 person-years after OA diagnosis, 0.6 (0.4 to 0.9) after first IACI and 0.5 (0.3 to 0.8) after subsequent IACI; and new cases of IHD, with rates of 0.7 (0.7 to 0.8) cases of IHD per 100 person-years after OA diagnosis, 0.9 (0.7 to 1.3) after first IACI and 0.8 (0.5 to 1.3) after subsequent IACI. [Table 14](#) shows 6-month rates of mortality, infection, diabetes, cerebrovascular disease, MI and IHD by anatomical joint for non-IACI, first IACI and subsequent IACI.

Survival analysis

After calculating PSs, we could not apply inverse probability weights for safety analyses, as it failed to balance more than 9 covariates out of 52 as shown in [Appendix 1, Figure 19](#). After matching using a 1 : 2 ratio, a sample of 8327 IACI patients were matched to 16,654 non-IACI patients. PS matching achieved an excellent balance of all covariates as shown in [Appendix 1, Figure 20](#).

[Table 15](#) shows results for age/sex-adjusted analyses and PS matched analyses when using Cox regression and Fine-Gray regression. Fine-Gray regression gave almost identical results to the Cox regression in all cases. The non-IACI group were the baseline group for these analyses. Mortality rates were similar between non-IACI, and those receiving IACI both in 6 months after the first IACI and after subsequent IACI, with a HR of mortality in the PS-matched analysis of 0.97 (0.48 to 1.98) and 0.64 (0.30 to 1.37) in the successive IACI. For infection, the PS-matched analysis gave a HR of 1.22 (0.26 to 5.78) for the first IACI and 1.63 (0.35 to 7.69) for repeated IACI compared with those not injected. Risk of diabetes was 1.50 (0.63 to 3.60) for the first IACI and similar for subsequent IACI. For cerebrovascular disease the HR was 0.81 (0.32 to 2.10) after the first IACI and 0.97 (0.37 to 2.54) after repeated IACI compared with non-IACI patients. The risk of MI and IHD were increased in both IACI groups compared with those not receiving IACI, however the CIs were very wide and overlapping.

Self-Controlled Cohort Analyses of 7604 patients (we further excluded those who did not have follow-up time after OA diagnosis) suggested there were no significant differences in all outcomes (infection, diabetes, cerebrovascular disease, MI, IHD) in OA patients who did or did not receive IACI ([Table 16](#)).

Discussion

Key findings

In joint-specific analyses, there were no significant differences between crude incidence rates of any adverse events following an injection compared to following OA diagnosis (excluding those who received an IACI). In PS-matched survival analyses, likewise no significant differences were found in rates of any adverse events studied (i.e. all 95% CIs

TABLE 13 Characteristics of patients included in the safety analyses

	Total N = 197,301	No IACI N = 189,060 (95.8%)	IACI N = 8241 (4.2%)
Age (years)	65.5 (12.4)	65.5 (12.4)	66.2 (11.9)
Sex			
Female (%)	58.6	58.6	59.7
Male (%)	41.4	41.4	40.3
IMD			
Least deprived (%)	10.8	10.9	8.4
Less deprived (%)	9.8	9.9	7.3
Mid deprived (%)	9.6	9.7	7.6
More deprived (%)	7.7	7.8	6.6
Most deprived (%)	6.0	6.1	5.8
Deprivation missing (%)	56.1	55.7	64.4
BMI (kg/m ²)	29.0 (5.9)	29.0 (5.9)	30.3 (6.2)
Region			
East Midlands (%)	2.0	2.0	2.1
East of England (%)	6.2	6.3	2.6
London (%)	5.2	5.4	2.1
North East (%)	1.3	1.4	0.5
North West (%)	8.6	8.4	11.5
Northern Ireland (%)	4.8	4.6	9.2
Scotland (%)	22.5	22.2	29.0
South Central (%)	8.7	8.6	10.3
South East Coast (%)	8.6	8.8	4.0
South West (%)	6.2	6.4	2.5
Wales (%)	15.0	15.0	15.1
West Midlands (%)	8.8	8.9	8.6
Yorkshire and The Humber (%)	2.1	2.1	2.5
Alcohol use			
Ex-drinker (%)	2.4	2.4	2.6
Never drinker (%)	14.5	14.5	15.0
Current drinker (%)	59.4	59.4	60.4
Drinking missing (%)	23.6	23.7	22.0
Smoking			
Ex-smoker (%)	30.4	30.4	32.3
Never smoker (%)	51.6	51.6	50.6

continued

TABLE 13 Characteristics of patients included in the safety analyses (*continued*)

	Total	No IACI	IACI
	N = 197,301	N = 189,060 (95.8%)	N = 8241 (4.2%)
Current smoker (%)	12.6	12.6	12.1
Smoking missing (%)	5.4	5.4	5.0
Charlson Comorbidity Index			
Charlson = 0 (%)	72.0	72.2	68.4
Charlson = 1 (%)	8.4	8.4	9.0
Charlson = 2 (%)	10.2	10.1	11.7
Charlson $\geq$ 3 (%)	9.4	9.3	10.9
Comorbidities			
Anaemia (%)	4.5	4.6	4.1
Rheumatoid arthritis (%)	0.9	0.9	0.8
Asthma (%)	9.1	9.1	8.1
Ankylosing arthritis (%)	0.2	0.2	0.1
Cancer (%)	6.9	7.0	5.0
Cardiovascular disease (%)	2.5	2.5	1.9
COPD (%)	4.8	4.8	4.5
Diabetes (%)	10.4	10.5	9.5
DVT (%)	0.8	0.8	0.7
Epilepsy (%)	1.2	1.2	1.2
Fracture (%)	4.7	4.8	3.7
Ischaemic heart disease (%)	4.5	4.5	3.5
LRTIs (%)	18.4	18.6	14.2
Malabsorption disease (%)	0.2	0.2	0.1
MI (%)	1.2	1.2	1.0
Hyperlipidaemia (%)	7.4	7.5	5.0
Hypertension (%)	19.0	19.2	14.4
Osteoporosis (%)	2.7	2.7	2.1
Pulmonary embolism (%)	0.4	0.4	0.3
Renal chronic disease (%)	8.1	8.1	7.6
Acute renal failure (%)	0.3	0.3	0.3
URTI (%)	15.8	16.0	11.1
UTIs (%)	7.1	7.2	5.4
Parkinson's disease (%)	1.3	1.3	1.3
Medications			
Antiarrhythmics (%)	3.3	3.3	3.6
Antidepressants (%)	18.0	17.9	22.0
Anticonvulsants (%)	5.6	5.5	7.6

TABLE 13 Characteristics of patients included in the safety analyses (*continued*)

	Total	No IACI	IACI
	N = 197,301	N = 189,060 (95.8%)	N = 8241 (4.2%)
Anxiolytics (%)	9.9	9.8	13.2
Bisphosphonates (%)	4.8	4.8	5.2
Calcium/vitamin D (%)	7.5	7.4	8.3
Oral glucocorticoids	7.2	7.1	8.4
NSAIDs (%)	33.6	33.2	41.7
NSAIDs topical (%)	14.9	14.6	21.0
Opioids (%)	11.8	11.6	16.7
Partial opioids (%)	31.5	31.2	38.8
Paracetamol (%)	44.5	44.1	53.7
Proton pump inhibitors (%)	32.3	32.0	39.2
Prednisolone (%)	7.0	6.9	8.1
Statins (%)	32.3	32.1	36.7
Diuretics (%)	23.1	23.0	25.9
Physiotherapy (%)	28.3	28.1	32.8

Note

Continuous variables as mean (SD) and % for categorical variables.

TABLE 14 Six-month rates of complications and mortality after OA diagnosis, first IACI and subsequent IACI

Joint	Injection, <i>n</i>	Person- years	Mortality			Infection		
			Cases	Incidence (per 100 person- years)		Cases	Incidence (per 100 person-years)	
Ankle_foot	Non-injected	47	46	0.97	(0.73 to 1.29)	22	0.46	(0.31 to 0.71)
	1 injection	2	< 5			< 5		
	2 + injections	1	< 5			< 5		
Elbow	Non-injected	5	8	1.77	(0.88 to 3.53)	< 5		
	1 injection	0	< 5			< 5		
	2 + injections	0	< 5			< 5		
Hand	Non-injected	145	86	0.59	(0.48 to 0.73)	29	0.20	(0.14 to 0.29)
	1 injection	1	< 5			< 5		
	2 + injections	0	< 5			< 5		
Hip	Non-injected	259	416	1.60	(1.46 to 1.77)	139	0.54	(0.45 to 0.63)
	1 injection	4	< 5			< 5		
	2 + injections	1	< 5			< 5		

continued

TABLE 14 Six-month rates of complications and mortality after OA diagnosis, first IACI and subsequent IACI (*continued*)

Joint	Injection, <i>n</i>	Person-years	Mortality			Infection		
			Cases	Incidence (per 100 person-years)		Cases	Incidence (per 100 person-years)	
Knee	Non-injected	497	556	1.12	(1.03 to 1.22)	202	0.41	(0.35 to 0.47)
	1 injection	27	48	1.79	(1.35 to 2.37)	6	0.22	(0.10 to 0.50)
	2 + injections	24	25	1.06	(0.71 to 1.56)	7	0.30	(0.14 to 0.62)
Shoulder	Non-injected	28	78	2.79	(2.24 to 3.49)	10	0.36	(0.19 to 0.67)
	1 injection	2	5	2.43	(1.01 to 5.84)	< 5		
	2 + injections	1	< 5			< 5		
Wrist	Non-injected	14	21	1.54	(1.00 to 2.36)	6	0.44	(0.20 to 0.98)
	1 injection	0	< 5			< 5		
	2 + injections	0	< 5			< 5		
All	Non-injected	994	1211	1.22	(1.15 to 1.29)	411	0.41	(0.38 to 0.46)
	1 injection	36	59	1.62	(1.26 to 2.10)	10	0.28	(0.15 to 0.51)
	2 + injections	28	30	1.09	(0.76 to 1.56)	10	0.36	(0.20 to 0.68)

Joint	Injection, <i>n</i>	Person-years	Diabetes			Cerebrovascular disease		
			Cases	Incidence (per 100 person-years)		Cases	Incidence (per 100 person-years)	
Ankle_foot	Non-injected	47	48	1.12	(0.84 to 1.49)	21	0.46	(0.30 to 0.70)
	1 injection	2	< 5			< 5		
	2 + injections	1	< 5			< 5		
Elbow	Non-injected	5	< 5			< 5		
	1 injection	0	< 5			< 5		
	2 + injections	0	< 5			< 5		
Hand	Non-injected	145	112	0.85	(0.70 to 1.02)	71	0.50	(0.40 to 0.64)
	1 injection	1	< 5			< 5		
	2 + injections	0	< 5			< 5		
Hip	Non-injected	259	193	0.84	(0.73 to 0.96)	148	0.59	(0.51 to 0.70)
	1 injection	4	< 5			< 5		
	2 + injections	1	< 5			< 5		

TABLE 14 Six-month rates of complications and mortality after OA diagnosis, first IACI and subsequent IACI (*continued*)

Joint	Injection, <i>n</i>	Person-years	Diabetes			Cerebrovascular disease		
			Cases	Incidence (per 100 person-years)		Cases	Incidence (per 100 person-years)	
Knee	Non-injected	497	485	1.11	(1.02 to 1.21)	259	0.54	(0.48 to 0.61)
	1 injection	27	38	1.63	(1.19 to 2.24)	22	0.85	(0.56 to 1.29)
	2 + injections	24	28	1.39	(0.96 to 2.02)	26	1.16	(0.79 to 1.70)
Shoulder	Non-injected	28	29	1.20	(0.83 to 1.73)	23	0.86	(0.57 to 1.30)
	1 injection	2	5	2.87	(1.20 to 6.91)	5	2.56	(1.06 to 6.15)
	2 + injections	1	< 5			< 5		
Wrist	Non-injected	14	11	0.90	(0.50 to 1.62)	9	0.69	(0.36 to 1.32)
	1 injection	0	< 5			< 5		
	2 + injections	0	< 5			< 5		
All	Non-injected	994	880	1.00	(0.93 to 1.06)	533	0.56	(0.51 to 0.60)
	1 injection	36	48	1.52	(1.14 to 2.01)	32	0.91	(0.65 to 1.29)
	2 + injections	28	36	1.54	(1.11 to 2.13)	28	1.07	(0.74 to 1.54)

Joint	Injection, <i>n</i>	Person-years	MI			IHD		
			Cases	Incidence (per 100 person-years)		Cases	Incidence (per 100 person-years)	
Ankle_foot	Non-injected	47	16	0.34	(0.21 to 0.56)	29	0.66	(0.46 to 0.95)
	1 injection	2	< 5			< 5		
	2 + injections	1	< 5			< 5		
Elbow	Non-injected	5	< 5			< 5		
	1 injection	0	< 5			< 5		
	2 + injections	0	< 5			< 5		
Hand	Non-injected	145	31	0.22	(0.15 to 0.31)	71	0.52	(0.41 to 0.66)
	1 injection	1	< 5			< 5		
	2 + injections	0	< 5			< 5		
Hip	Non-injected	259	97	0.38	(0.31 to 0.47)	178	0.75	(0.65 to 0.87)
	1 injection	4	< 5			5	1.41	(0.59 to 3.38)
	2 + injections	1	< 5			< 5		

continued

TABLE 14 Six-month rates of complications and mortality after OA diagnosis, first IACI and subsequent IACI (*continued*)

Joint	Injection, <i>n</i>	Person-years	MI		Incidence (per 100 person-years)	IHD		Incidence (per 100 person-years)
			Cases			Cases		
Knee	Non-injected	497	167	0.34	(0.30 to 0.40)	326	0.71	(0.64 to 0.79)
	1 injection	27	13	0.49	(0.29 to 0.85)	18	0.73	(0.46 to 1.16)
	2 + injections	24	8	0.35	(0.17 to 0.69)	15	0.70	(0.42 to 1.16)
Shoulder	Non-injected	28	15	0.56	(0.34 to 0.92)	28	1.12	(0.77 to 1.62)
	1 injection	2	< 5			< 5		
	2 + injections	1	< 5			< 5		
Wrist	Non-injected	14	< 5	0.38	(0.16 to 0.90)	11	0.88	(0.49 to 1.60)
	1 injection	0	< 5			< 5		
	2 + injections	0	< 5			< 5		
All	Non-injected	994	331	0.34	(0.31 to 0.38)	644	0.7	(0.65 to 0.76)
	1 injection	36	21	0.59	(0.39 to 0.91)	31	0.93	(0.66 to 1.33)
	2 + injections	28	13	0.48	(0.28 to 0.83)	21	0.84	(0.55 to 1.29)

spanned the null). Point estimates for infection (HR = 1.22), diabetes (HR = 1.50), MI (HR = 6.21) and IHD (HR = 2.49) from these analyses did suggest some possible increased risk may have been present for these events, albeit not reaching statistical significance. However, none of these findings were replicated in self-controlled cohort analyses, where rate ratios were very close to one and CIs very clearly overlapped with the null effect.

Interpretation and results in context

In summary, we observed reassuring findings for infection, mortality and cerebrovascular disease, with no consistent excess risk following IACI of any of these outcomes in the performed analyses. In main PS analyses, we observed some increased risk of diabetes, IHD and MI following IACI, but this had wide CIs and was not replicated in self-controlled analyses. The absence of any safety signals using the self-controlled methodology suggests the PS analyses, while achieving good balance in measured covariates across exposure groups, could have been biased by residual unmeasured confounding.

Previous RCTs have been small and not powered for the analysis of adverse events or safety of IACI. A Cochrane systematic review and meta-analysis⁸³ concluded the following: (1) an analysis of two trials with a total of 84 participants and 46 adverse events showed that participants on corticosteroids were 11% less likely to experience adverse events compared with sham injection, however CIs included the null effect and were imprecise; and (2) a separate analysis of two trials with a total of 204 participants and 5 events showed that participants on corticosteroids were also less likely to withdraw because of adverse events, however again CIs were wide and included the null effect.

We reviewed individually each of the RCTs included in the most recent NICE guidelines for the management of OA. We read full reports from all trials with at least 100 participants and including IACIs, which resulted in a total of nine studies.^{22,104–111} All studies were limited to under 500 participants in total, and had relatively short follow-up, limiting

TABLE 15 Hazard ratios of complications: age/sex adjusted, PS matched in Cox regression and PS matched in Fine–Gray regression with the latter accounting for the competing risk of death

	Joint	Injection, n	Mortality	Infection	Diabetes	Cerebrovascular disease	MI	IHD
Cox	Age/sex adjusted	Non-IACI	1	1	1	1	1	1
		1 IACI	1.03 (0.79 to 1.34)	0.67 (0.36 to 1.26)	1.48 (1.11 to 1.98)	1.37 (0.96 to 1.96)	1.54 (0.99 to 2.39)	1.18 (0.83 to 1.70)
		2 + IACI	0.61 (0.43 to 0.88)	0.91 (0.48 to 1.70)	1.49 (1.06 to 2.08)	1.46 (1.00 to 2.13)	1.20 (0.69 to 2.09)	1.02 (0.66 to 1.57)
	PS matched	Non-IACI	1	1	1	1	1	1
		1 IACI	0.97 (0.48 to 1.95)	1.22 (0.26 to 5.78)	1.50 (0.63 to 3.60)	0.81 (0.32 to 2.10)	6.21 (0.94 to 40.92)	2.49 (0.96 to 6.48)
		2 + IACI	0.64 (0.30 to 1.37)	1.63 (0.35 to 7.69)	1.52 (0.62 to 3.69)	0.97 (0.37 to 2.54)	5.08 (0.75 to 34.44)	2.03 (0.75 to 5.50)
Fine–Gray	Age/sex adjusted	Non-IACI		1	1	1	1	1
		1 IACI		0.67 (0.36 to 1.26)	1.48 (1.11 to 1.98)	1.37 (0.96 to 1.96)	1.54 (0.99 to 2.39)	1.18 (0.83 to 1.70)
		2 + IACI		0.91 (0.49 to 1.71)	1.49 (1.07 to 2.08)	1.47 (1.00 to 2.14)	1.20 (0.69 to 2.09)	1.01 (0.66 to 1.57)
	PS matched	Non-IACI		1	1	1	1	1
		1 IACI		1.22 (0.26 to 5.79)	1.50 (0.63 to 3.60)	0.81 (0.32 to 2.10)	6.21 (0.94 to 40.93)	2.49 (0.96 to 6.49)
		2 + IACI		1.64 (0.35 to 7.71)	1.52 (0.62 to 3.70)	0.97 (0.37 to 2.55)	5.09 (0.75 to 34.49)	2.03 (0.75 to 5.51)

TABLE 16 Risk ratios of complications of the conditional Poisson of the self-controlled cohort: age adjusted

Outcome of interest	Risk ratio (95% CI)	
Infection	0.94	(0.24 to 3.64)
Diabetes	1.08	(0.64 to 1.82)
Cerebrovascular disease	0.89	(0.49 to 1.62)
MI	1.05	(0.51 to 2.16)
IHD	0.87	(0.56 to 1.37)

their ability to identify small increases in cardiovascular safety or diabetes risk of the magnitude seen in our data. In any case, none of the reviewed trials reported an increased risk of any of the studied safety events, with the most common adverse events after injection being local and self-limited.

We also performed a literature search for observational studies on the association between IACI and the observed potential safety concerns, including diabetes/hyperglycaemia and cardiovascular disease. We found anecdotal data based on a small number of studies (with around 10–70 patients each) reporting an increase in glucose levels after IACI, mostly among diabetic patients,^{112–115} but no consistent data reporting on an increased risk of diabetes. A narrative literature review based on ten studies showed a similar transient increase in blood glucose levels after local musculoskeletal corticosteroid injections.¹¹⁶ Our study is therefore the largest (involving nearly 200,000 patients) and most robust observational evidence suggesting a possible association between IACI for OA and increased risk of developing diabetes. One potential mechanism underlying such an association could be related to an increase in blood glucose levels after steroid administration, which could trigger hyperglycaemia and a diagnosis of diabetes in primary care or other settings. However, caution is needed in the interpretation of our observed increased risk in diabetes given this was not statistically significant, inconsistent across methods and therefore inconclusive. Given the scarcity of data on this topic and the potential self-limited nature of this effect, we believe that this finding needs replication elsewhere and mechanistic studies on the causality and duration of any such potential excess risk.

Similarly, more data are needed on the cardiovascular safety of IACIs. Our findings of a possible excess risk of IHD, as shown previously in similar research,¹¹⁷ deserve further investigation, although these findings did not replicate in our pre-specified self-controlled sensitivity analyses, raising the possibility of being spurious due to confounding or indication bias.

Strengths and limitations

The strengths of the CPRD GOLD dataset have been mentioned in [Chapters 3](#) and [4](#). These include the nationally representative nature of the dataset,²⁷ its large size (permitting stratified analyses according to anatomical joint), breadth of coverage and longitudinal data collection. In addition, the Read codes used to identify IACI were specific for injection of corticosteroid into the joint. The use of PS matching and self-controlled cohort analysis are further strengths, both approaches being robust statistical methodologies. PS matching is well-established and widely used in pharmacoepidemiology.⁷¹ It has been shown to eliminate bias from differences in variables included in the PS model between exposed and unexposed patients,⁷² although unmeasured confounding will likely have remained given the observational nature of the data used. However, the self-controlled cohort addresses the issue of residual confounding between exposed and unexposed patients inherent in the PS-matched study design by comparing before and after IACI within the same cohort of patients.

There are limitations around the IACI coding, such as the high proportion being non-specific to an anatomical site and a lack of data on ultrasound guidance. Further caveats include the relatively small sample size retained in final PS models which meant we analysed a low number of outcome events, particularly for repeat injections. This was also the case in the self-controlled cohort analyses, which also by design limits the generalisability of findings to the OA patient population who received an IACI.

Conclusion

In conclusion, our findings suggest that the incidence of mortality, infection, bleeding and cardiovascular events were similar in OA patients 6 months after IACI compared with patients not receiving IACI. This remained the case when examining each joint separately, and when using different robust analytical methods. Non-significant differences observed in the risk of diabetes and cardiovascular events may be due to residual confounding and low number of outcomes and they disappeared when using self-controlled methods. Further research is therefore needed on potential safety signals related to IACI use, particularly on the possible risk of developing diabetes and cardiovascular outcomes (MI and IHD).

Chapter 6 Patient and clinician experiences of using intra-articular corticosteroid injections for osteoarthritis

Introduction

The prevalence of symptomatic OA is expected to rise in the future therefore it is likely that IACIs will be used more frequently when treating this condition. To help guide policy, practice recommendations and future research, there is an urgent need for more evidence on patient and clinician experiences, beliefs and motivations for using IACIs, and what factors affect decision-making. We conducted a qualitative interview study to explore patient and clinician experiences and beliefs about IACIs for OA. Topics explored included the benefits and potential disadvantages of IACIs, beliefs about their efficacy, impact on daily living, perceived treatment risks, how they are used in the treatment pathway, as well as views on current evidence and guidelines.

Methods

Study design and setting

We conducted one-to-one, semistructured telephone/videocall interviews with patients and primary care clinicians including general practitioners (GPs) and first contact physiotherapists (FCPs). The interviews were conducted between January 2021 and December 2021. A purposive sampling strategy was used to recruit patients and clinicians from across a range of primary care practices in the Southwest of England. The study received ethical approval from the East Midlands – Leicester Central Research Ethics Committee (REC) in July 2020 (REC ref. 20/EM/0185) and Health Research Authority approval in August 2020. All participants provided informed consent.

Sampling and recruitment

A sample of 40 patients and 30 clinicians was planned as an approximation expected to yield adequate ‘information power’ to address the research questions.¹¹⁸ As there is substantial variation in the sociodemographics of the population, and rural/urban practice setting across Southwest England, the sample size was designed to provide an appropriate cross-section of the wider NHS while achieving sufficient depth.

Primary care practices across the Southwest of England were sent information about the study via the National Institute of Health and Care Research (NIHR) West of England Research Facilitation in Community and Healthcare (WE ReACH) settings team at the West of England Clinical Research Network (CRN). The WE ReACH team provided the research team with the contact details of 15 practices that had completed an expression of interest. Practices were then contacted by the research team. Ten practices responded to the research team invitation and were sent a local information pack and organisational information document (OID) to complete. Primary care practices screened patient information to identify eligible patients and then posted out information packs which included an invitation letter, information leaflet and e-consent form.

Eligible participants were adults aged 45 years or more who received IACIs for OA within the previous 3 years, including those having surgical intervention, and those who had OA but had not received IACIs. Clinicians (GPs and FCPs) from across Southwest England including those who administered IACIs for OA in the preceding 3 years and those who had not were also invited to participate. Exclusion criteria were any individual who lacked capacity to provide informed consent or who could not converse fluently in English.

We used a purposive maximum variation sampling approach¹¹⁹ to gather a diverse range of views and experiences within the sample, using a sampling framework and asking practices to diversify the sample by sex, age groups (45–59,

60–74 and 75+), ethnicity (White, ethnic minorities) and joint injected (knee, hip, shoulder, elbow, thumb or wrist) and including patients who have or had not received joint surgery for OA. Where our sample was lacking in certain characteristics, we used the purposive sampling frame to ask practices to focus on ethnic diversity, and joints other than the knee or shoulder. However, practices reported that ethnicity was not always recorded in patient details, and joints injected other than the knee and shoulder were much less common.

Patients' confidentiality was maintained as the information pack was sent by their own practice (usually a GP research lead or research nurse). Patients and GPs or physiotherapists interested in participating in the study contacted the research team directly by e-mail, text or telephone, for more information and to arrange an interview either by telephone or Microsoft Teams video calling.

Data collection

Prior to the interview, participants provided informed consent. To remove administrative workload to clinicians or technical barriers likely to discourage participants, we offered an option of e-consent forms or verbal consent in keeping with the proportionate approach recommended by the Health Research Authority for low-risk non-interventional studies. Verbal consent was audio-recorded at the beginning of the interview, and a copy of a verbal consent form signed by the researcher sent to the participant following the interview for their records. Data collection took place during the COVID-19 pandemic and following government advice on shielding and physical distancing we felt participants would be at less risk of exposure to COVID-19 by completing electronic or verbal consent forms at home.

All interviews were conducted by the qualitative lead AJM (male, PhD) who is a social scientist with over 14 years' experience in conducting qualitative research on OA pain and management. AJM had no relationship to the participants before this study. All participants provided informed consent to audio-recording of the interviews and publication of anonymised quotations. Interview topic guides were used to provide a flexible structure to the interviews, ensuring participants' responses could be followed up with further questions if new or unexpected findings emerged. Topics included questions on patients' and clinicians' experiences, perspectives and beliefs about the use of IACIs for OA, including efficacy, benefits and disadvantages, factors that affect decision-making, perceived risks of repeated use and clinicians' views on current guidelines and evidence. The topic guides were piloted in the first two interviews and no changes were required. The topic guides were developed in collaboration with clinical team members and patient and public involvement and engagement (PPIE) representatives. PPIE group representatives suggested adding several key questions around ease of access to IACIs; how many GPs in a practice give injections; what conversations patients and clinicians have about IACIs; how many injections patients are told they can have, and how this might affect timing of surgery; and how long patients had to wait to get an injection. These questions were added to the patient and clinician topic guides. Data collection stopped when it was felt that there was sufficient information power within the sample, to meet the broad aims of the study, supported by a purposive sample and strong interview dialogue.¹¹⁸

Data analysis

Interview audio-recordings were transcribed, anonymised and uploaded to NVivo (QSR International, Warrington, UK) data management software.¹²⁰ Transcripts were analysed using a flexible and inductive generic approach to analysis to identify themes and subthemes.^{121–123} Patient and clinician interviews were coded concurrently. The transcripts were initially read alongside a review of the audio-recording before inductive coding was undertaken on a line-by-line basis. Data from each practice were analysed separately to enable comparison. To ensure rigour, a second researcher independently analysed 25% of the transcripts (CP, female, PhD, experienced qualitative health services researcher) with both researchers meeting regularly to discuss developing codes and themes and interpretation of the findings. There were no notable disagreements about the findings. AJM also met regularly with MRW (professor and orthopaedic consultant) to discuss and reflect on the analysis and developing interpretation. The analysis focussed on the experience and perceptions of participants' use of IACIs, and as similarities and relationships between groups of codes were identified, they were aggregated into categories. The coded data were then reviewed, and the categories further refined into more conceptual themes that demonstrate meaning across the data set. Throughout the study a reflexive approach was maintained as AJM kept written field notes to record first impressions of interviews, thoughts or hypotheses and any recurring themes.

Results

We present the results of our analysis in two parts, first describing the sample characteristics and themes based on patient accounts, before then describing those of the clinicians. We have used anonymised exemplary quotes to illustrate meaning within each theme. These can be seen in the thematic map in [Figure 10](#) which illustrates the patient themes (yellow), clinician themes (blue) and areas of overlap.

Patient participant characteristics

Sixteen male and twenty-two female patients participated, aged from 49 to 88 years (average 68.5 years) from six primary care practices. Twenty-eight had received one or more IACI in their knee, although other joints injected included the shoulder, thumb, hip, hand, toe, foot and wrist. Five patients had not received IACIs for OA. Only one patient participant identified as 'mixed race' while all others identified as White. Interviews lasted an average of 37 minutes (range 21–80 minutes) ([Table 17](#)).

Findings from patient interviews

Awareness of IACIs

Participants reported that IACIs were offered by the GP, usually in response to them seeking help for OA pain, and mobility difficulties, especially when other treatments (pain medication, physiotherapy) were unsuccessful. IACIs were also offered at the point that participants were considering joint replacement surgery, by an orthopaedic consultant or the GP to delay/avoid joint surgery. Participants were positive about receiving IACIs at the point of consultation, from the GP. Some patients were referred by their GP to an orthopaedic consultant for their injection. IACIs appeared to be commonly offered in the later stages of OA by GPs, and patients were generally not aware it was an option before this. One patient questioned why they were not offered more 'freely'.

The surgeon I saw said, 'Right, we can, um, do you in 15 days' time, knee replacement' [...] but I thought, 'Blimey, if you're going to chop my knee out, I will need to think about this' [yeah]. And, er, went back to the doctor and he said, 'Have you never had an injection?', and I said, 'No'. He said, 'Well, I'll give you one now', and he gave me the injection and it relieved it.

D5Pa

I'd gone [to the GP] because I just couldn't stand it anymore and she referred me to [hospital] and I saw the consultant ... he suggested that I try an injection which nobody had even mentioned to me previously.

B2Pa

I think they are absolutely brilliant, I always felt quite erm, not surprised but ... I didn't understand why they weren't offered more freely because of how well it worked for me but I guess that's a personal thing.

D3Pa

Variations in access to IACIs

The most common reason that five patients had not received IACIs was that IACIs had never been offered, despite some having joint problems for many years before being offered surgery.

I was a semi-professional [sportsperson] and it was one of these injuries that as a youngster you don't bother to get seen to, you work through it and the after affects then came on but basically again, I was just allocated pain killers for that. And that was quite over a long period of time. [Yeah, okay, and so, have steroid injections ever been discussed with you?] No, they were never discussed with me, no.

E1Pa

The number of IACIs patients allowed within a 12-month period, for each joint affected, varied across the practices. A maximum number of three to four IACIs per year, per joint (1 every 3–4 months) was common. Some participants reported being permitted only two IACIs per year. Some were only offered 'a one-off' treatment, while others were

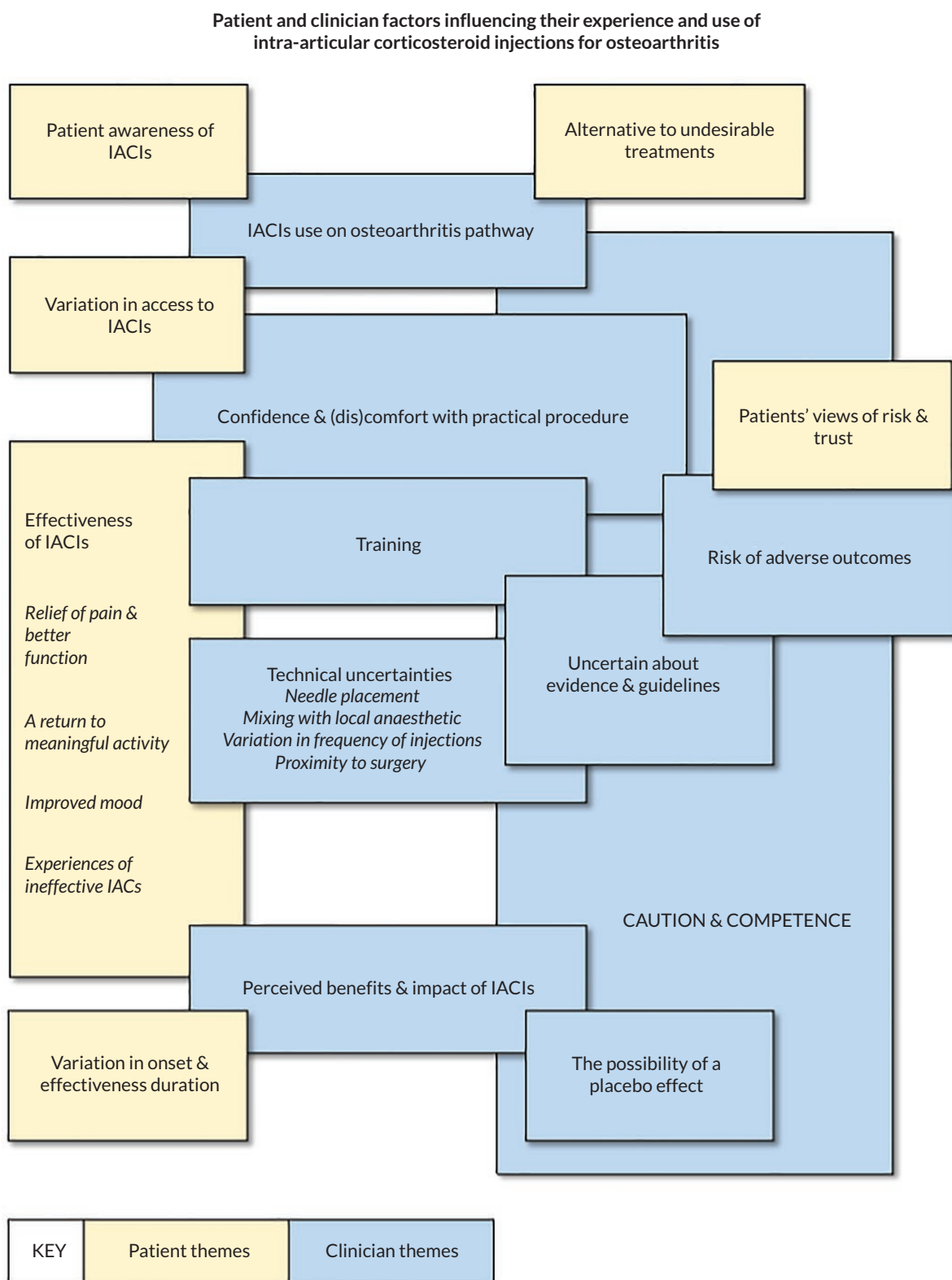
**FIGURE 10** Thematic map.

TABLE 17 Patient participants

Participant ID	Sex (male/female)	Ethnicity (White, ethnic minorities)	Age range at interview (years)	Joint(s) injected (number of times)	Single (×1) IACIs in one or more joint	Multiple (×2 or more) IACIs in one joint	Multiple (×2 or more) IACIs in multiple joints
H1pa	M	Mixed	60–74	Knee (×2)		✓	
H2pa	F	White	60–74	Knee (×3)		✓	
H3pa	M	White	45–59	Knee (×2)		✓	
H4pa	F	White	60–74	Both knees (×1)	✓		
E1pa	M	White	75 +	None	-	-	-
E2pa	M	White	60–74	None	-	-	-
E3pa	M	White	60–74	Shoulder (×1) Both knees more than twice			✓
E4pa	F	White	75 +	Wrist (×2) Thumb (×1)			✓
E5pa	F	White	60–74	Knee (×4)		✓	
E6pa	F	White	75 +	None	-	-	-
E7pa	F	White	45–59	None	-	-	-
F1pa	M	White	60–74	Both shoulders injected (×4 in total)			✓
F3pa	M	White	45–59	Knee (×4)		✓	
F4pa	M	White	60–74	Both knees injected (more than twice)			✓
F6pa	F	White	60–74	Hands and knees injected alternate months (×12)			✓
F7pa	F	White	45–59	Both knees (more than twice)			✓
D2pa	F	White	75 +	Knee (×1)	✓		
D3pa	F	White	60–74	Knee (×2)		✓	
D4pa	F	White	60–74	Both knees (more than twice)			✓
D5pa	M	White	60–74	Knee (×6) Hip (×1)			✓
D6pa	M	White	60–74	Shoulder (×1)	✓		
D7pa	F	White	60–74	Thumb (×1) Shoulder (×1) Knee (×1)	✓		
D8pa	F	White	45–59	Shoulder (20+) Knee (20+)			✓
B1pa	F	White	75 +	Knee (×2)		✓	
B2pa	F	White	45–59	Knee (×1)	✓		
B3pa	M	White	60–74	Thumbs (×1), (×2)			✓

TABLE 17 Patient participants (continued)

Participant ID	Sex (male/female)	Ethnicity (White, ethnic minorities)	Age range at interview (years)	Joint(s) injected (number of times)	Single (×1) IACIs in one or more joint	Multiple (×2 or more) IACIs in one joint	Multiple (×2 or more) IACIs in multiple joints
B4pa	M	White	75 +	Both knees (×2)			✓
B5pa	F	White	75 +	Knee (×1)	✓		
B6pa	F	White	75 +	Knee (×3)		✓	
B7pa	F	White	75 +	Knee (×1)	✓		
B8pa	M	White	75+	Both shoulders (more than twice) Hip (×1) Hand (×3) Knee (more than twice) Foot (×2)			✓
B9pa	M	White	45–59	None	-	-	-
C3pa	F	White	75 +	Both knees (×5–6)			✓
C4pa	M	White	60–74	Both knees (×6)			✓
C5pa	F	White	75+	Knee(×6) Shoulder (×1) Hand (×1)			✓
C6pa	F	White	75 +	Both knees (more than twice)			✓
C7pa	F	White	60–74	Hip (×1) Both shoulders (×1)	✓		
C8pa	M	White	60–74	Knee (×1)	✓		
Total	38 (22 female)		Average 68.5 years Range 49–88 years		9 had single IACIs in one or more joints	8 have had multiple IACIs in one joint	16 have had multiple IACIs in multiple joints

permitted IACIs only once every 2 years. This could be confusing for patients as access often varied depending on which GP they saw in the practice.

You could only have it done every two years, but I think that's changed. Then I went back again when it was painful again after two years, I waited and they sent me to have it done again and said I shouldn't have waited two years, I could have it done whenever I wanted to. So, I think it changes ... Every doctor you see, you get a different story.

H2Pa

For patients with multiple affected joints, some were given a maximum of two in each knee each year. In an extreme example, one patient was permitted only one IACIs every 6 months, to a single joint, effectively requiring them to 'choose' between walking or using their arms.

I can either have it in the shoulder or in the knee and the knee tends to be painful when I walk and because I'm now not walking, as such, if I want to be able to do anything with my arm – so getting dressed, cooking, cleaning – I'm an artist, a craft-person – I can't do anything if that shoulder is painful [...] the only thing they're saying is that, you know, 'The steroid is not going to do you any good by having a large amount of it more regularly or in both joints', so I have to choose.

D8Pa

These experiences indicate considerable variation in access to IACIs; and those limitations imposed by GPs on the maximum number of injections can be challenging for those with OA in multiple joints. Patients from one practice also reported that accessing IACIs became more difficult when more experienced GPs retired. Patients perceived that the new GP was less confident about giving IACIs and reluctant to do so for some patients.

There were two GPs doing it in our surgery and then he retired, one of them and then the other GP did the injections. He took over mine and then he retired, so it was left to another one, who said was going to train up to do it [...] to be honest, I didn't feel that she didn't seem to know much about just, you know. I know that sounds awful and I'm so sorry for saying it, but she didn't seem to know a lot and it did hurt [...] [Are you going to have any more injections?] They won't let me. Um, 'cause the doctor ... said she wasn't keen on it, said [hospital] was going to do it and they, they decided that I'd be better doing these leg exercises.

D4Pa

Patients' views of risk and trust

Most patients recalled that GPs or FCPs had discussed with them the risks associated with IACIs however most could not recall exactly what these were but retained a general awareness that 'you can't have them too often'. Where specific risks were recalled, these were associated with 'degeneration of the joint', 'weakening the bone', although one patient reasoned for the prioritisation of pain relief, as the joint was damaged anyway. Some patients recalled the risk of lowered immunity related to the more recent COVID-19 pandemic, during which practices were advised not to administer IACIs. Most participants acknowledged but did not express concerns about risks and described trust and confidence in the judgement of their GP.

Well, I would like to know, is it true that if you have them more frequently you are running a risk of the bone degeneration increasing long term? Is that true or isn't it? [...] because I do feel very confused. [...] So I have a bit of anxiety about steroids and what they do. So I would really like to know whether frequent steroid injections into the bones will, in the long term, be negative rather than positive, because I'd rather put up with the pain.

H2Pa

There's this fear that they weaken the bone or something around the joint, but I don't know. It's a balance [...] in my head, if you asked me, I would just say, 'Oh, the degeneration of the joint', but then if, if your joint's not great anyway, you think, well, you know, at least that'll relieve it for a while [laughs].

D5Pa

With regards to lowering immune, okay well I guess it's not something I'd want now because we've still got plenty of COVID knocking around. I don't think I'd want my immune system sort of lowered.

E2Pa

I'm very confident in my doctor. I don't think he would have offered it to me if he knew of any bad, you know, results or ...

B1Pa

The effectiveness of IACIs

Relief of pain and better function: patients who had experienced effective IACIs most commonly described either complete removal of their joint pain or that pain was less central to their day-to-day experience. Many also described that swelling around the affected joint had reduced and some reported a reduction in joint stiffness.

Up until I had this injection I was walking with a walking stick all the time. But this injection has allowed me to walk without the, I don't use a walking stick.

B6Pa

Well, it's made me freer [It's made you freer?] Yeah definitely. Before, I had to use a walking stick and the pain was pretty bad really [...] I don't use anything at the moment.

D2Pa

Like when it's near the end I feel like an old bloody man. Like getting out the car, you get your legs out and then you're putting pressure on to stand up and that's when you feel the pain. But when it's done, I'm just out the car, up and take no notice [...] They're brilliant. I love my doctor, I said, 'God blimey, I'm like a new man again now for a few months'.

F4Pa

Well you know, a bit more zest for life. You know, a bit more up and at it. You know, you're not worried about going to do things [...] The best way I can describe it is sort of when I'm bad, if there's a £20 note on the floor I've gotta look two or three times to think about picking it up [laughter]. Is it worth it? When I'm feeling good, whoosh, that'll be away in my pocket [laughter].

C4Pa

A return to meaningful activity: For most participants, relief of OA symptoms and restoration of function increased the positive impact on their lives by enabling them to participate in meaningful or important activities, restoring aspects of a 'normal' life. By returning to physical activities, patients described being enabled to increase their fitness, to lose weight and to improve other comorbidities.

I was dancing more because my knees weren't hurting so much [...] I would say that certainly the injections enabled me to keep my hobby going. So, there was a considerable benefit.

B4Pa

If I have the injection, it does change completely 'cause it makes ... My attitude is if I'm out of pain and I can get more healthier by walking.

D4Pa

The knee was a problem to my ultimate goal which was losing weight and getting away from this diabetic category [...] That was the main driver; it was to go to the gym and practically do something to get myself out of this situation [...] That was the reason for going and getting a steroid injection rather than going for a full knee replacement.

H1Pa

Improvements to mood: With the reduction of long-term OA pain and increased participation in meaningful activities, patients described improvements to mood and emotional health and a restored sense of self. Even patients who did not experience complete pain/symptom relief reported positive benefits for their lives in terms of a reduced mental burden of pain.

[I imagine that's quite a relief?] Oh gosh. Well, it was so miserable. It was so miserable before that now I can just, just about do most things except walk very far.

B1Pa

Well, they've made a lot of difference whereas before it was jolly painful, made me ... I wouldn't say a miserable person but made me hard to get going and the pain sometimes you think oh gosh not again, but when I go for the injections again I feel I can get on, I've got a totally different outlook on life.

C5Pa

Experiences of ineffective IACIs: Of 33 participants who had received IACIs for OA pain, 32 had experienced some benefit or improvement to their symptoms on at least one occasion. However, 12 reported experiencing ineffective IACIs. They often attributed this to poor or incorrect placement of the needle into the joint. Two participants who had experienced both ineffective and extremely painful IACIs reported that they believed their IACIs had been poorly administered by inexperienced GPs who lacked confidence and training.

The two GPs that used to do it, one retired and then the other one took over and he was brilliant and I ... I could go out. I could walk for miles with the dog. But then another, when that doctor retired, another took over and she struggled with it

and she injected my knee and I, I couldn't walk after. I was in agony [...] she said she did do it in the wrong place [...] it got worse after she'd done that, that one knee, and til this day that leg's still the weaker now.

D4Pa

First one was painful, and I could feel the cortisone running down the front of my knee inside my leg so I knew it hadn't gone in the right place and it never worked at all. [The third IACIs] was absolutely perfect [...] he presses around my knee and pushes at the soft point where he thinks it's going to go in the right place, and I somehow know that's the position.

B6Pa

Variation in onset and effect duration

Where IACIs had 'worked' for patients, the interval between IACIs administration and improvement of symptoms varied from immediate to several days or weeks later. Some participants believed the anaesthetic mixed with the IACIs was responsible for the immediate effect. Some patients described limiting their activities after an injection to avoid displacing the steroid from the joint, thus prolonging its effect.

Commonly patients reported experiencing relief of pain and other symptoms for between 2 and 6 months. Some, however, reported that benefits lasted a year or more, with some reporting that they had continued to feel benefit several years after and had not returned to the GP for symptoms in that particular joint.

Some patients reported diminishing benefits from recent IACIs which had lasted less than previous ones, which some attributed to their knee condition worsening.

The pain relief was instantaneous because they put anaesthetic in it so it kills the pain as it goes in.

C8Pa

My advice to anybody that has them – once you've had the injections rest for a couple of days so wherever it's been injected it stays there and still remember that you've got bad legs. Do you see what I mean? Because you have the injection and you think, 'They feel wonderful', but if you start acting like you're okay you're back to square one within a week.

F6Pa

[How long does it last for, the effect?] I would say at least three months and you know – yeah I'd say at least three and sometimes a year.

C4Pa

That first one I had it took me ... through sort of ten months, or so, or more, you know, to the 12 months.

C6Pa

Well, I'd say to be quite honest that they're still lasting ... it's not inflamed in any way (3 years since IACIs)

E4Pa

They don't help as much as they once did but they do give some relief.

C3Pa

I suppose my knees are getting worse, so they're not lasting so long.

F4Pa

An alternative to undesirable treatments

Many participants reflected on how IACIs enabled them to avoid more undesirable treatments such as strong painkillers or joint replacement surgery. When IACIs were effective patients reported they were able to stop or reduce the use of painkillers. Patients also described a preference for IACIs over NSAIDs and opioids, which carried many unpleasant or debilitating side effects.

I take Tramadol, I try not to take too much because it can give you a tendency to get mood swings. So, I'd rather put up with a bit of discomfort [having an IACIs] than keep filling myself up.

B8Pa

The doctor's given me Naproxen [...] I must admit I'd rather be sort of more drug free [...] but when I have the injections, I don't need to take them at all.

D4Pa

If it's between steroid injections and taking the tablets that upset your whole digestive system then, I would go for the injections every time [...] It [codeine] just makes you feel immobile because you don't want to get up and do things.

F7Pa

Joint replacement surgery is often offered to those in whom other treatments are no longer effective. Many patients had been offered surgery without already receiving IACIs, whereas for others surgery was only offered if IACIs failed/ceased to be effective. For patients who were unsure about surgery or wished to delay it, IACIs were a preferred option as long as they were effective and available. Some patients described being listed for surgery as much as 20 years previously – however due to circumstances at the time, never received surgery and were instead offered IACIs, which they continued to receive.

[So, when was the first time that you had your knee injected?] Oh must be 20 years ago I was due to have a knee replacement and I was in the [hospital] all prepped up ready and they decided my bloods are not as they should be, and I didn't have the operation and since then nothing has been done [...] if the injections are gonna help me every few months then I think that's the line I've got to take.

C5Pa

The knee pain was problematic, so the injection was an obvious option in times now where, as my doctor said, 'You need a new knee'. Like I said, he said that five or six years ago but that hasn't happened and the more I've thought about it ... summing up, that's how I got to taking the injections. Personally, I think I've had a good experience with them, and I wouldn't be put off taking another one.

H1Pa

I mean as I say I wouldn't contemplate having surgery at my age if I knew I could have an injection and that injection would last me I don't know, six months.

B1Pa

Obviously, I'd like to sort of put it off for as long as possible and if doing things like physios, exercise and you know, something like these injections sort of keeps you healthy and able to avoid the operation then that's the approach I prefer to take.

B9Pa – not had IACIs

Patient information needs and suggestions for further research

When asked what further information patients would like about IACIs or what questions they wanted future research to focus on, many wished to know more about the long-term side effects of IACIs on bone health, particularly associated with frequent injection use. Some patients wanted to know more about the difference between steroids, and which steroids they had received. The difference between anabolic steroids for muscle growth and IACIs was also unclear to some patients. Other suggestions were to give them more frequently at a lower dose to see if it kept pain fluctuations under better control, and to focus research on making IACIs with a longer-lasting effect.

The first time I ever heard the word 'steroids' was at gymnasiums and people that were doing muscle growth and body builders taking steroids. That always looked like a bit of a dirty word for me anyway.

H1Pa

It would be nice to know whether, if you've had a lot of these steroid injections, whether it was safe, whether it would make a difference.

D2Pa

One thing, if you had steroid injections could they somehow make them last longer? Erm could they lengthen the duration?

B7Pa

Giving them more regularly, maybe a smaller dose. So instead of having a big impact, that maybe keeping the inflammation under control at some level, so that you don't get these hills and valleys of pain over time.

D8Pa

I'd like to know what the effect is on the rest of the body [yeah] that's the research I would like to know erm also, why you can't, I suppose in conjunction with that it's why you can't have more than two, possibly three a year but that's in parallel with what's it doing to the rest of your body isn't it?

C5Pa

Clinician participant characteristics

Ten male and nine female clinicians participated including 16 GPs and 3 FCPs from 10 practices (Table 18). The length of time clinicians had been practicing ranged from 3 to 30 years. The 10 practices represented enabled a sample varied in geographical location and rural and urban environments, serving diverse populations in terms of socioeconomic status, age and ethnicity. Four clinicians did not administer IACIs for OA. Interviews lasted an average of 35 minutes (range 18–49 minutes).

Findings from clinician interviews

Caution and competence

The finding of the clinicians' perception and beliefs about IACIs is encapsulated in the overarching theme of caution and competence. Clinicians felt there was a lack of evidence about the efficacy of IACIs and the absolute risks associated with their use. Coupled with their reported lack of engagement with clinical guidance, which they perceived as insufficient, this led to a general sense that clinicians are cautious about the use of IACIs. Clinicians also reported a lack of regular training and opportunities to gain experience in administering IACIs; insufficient guidance on the technicalities of administering them, and a perception that younger GPs had become more 'risk averse' generally in relation to more practical medical procedures. This also led to a sense that their caution is often associated with how competent they felt in administering IACIs, given these circumstances. This overarching theme of 'caution and competence' can be broken down into a number of subthemes:

Confidence and (dis)comfort with practical procedures

Throughout the interviews with clinicians there appeared to be some who were more confident and comfortable with practical procedures such as administering IACIs with some GPs being more cautious than others. GPs with less years in practice were seen by their older more experienced colleagues (and themselves) to be more risk averse and less confident with administering IACIs particularly when they were uncertain about guidance. An older GP (A1GP) reflected on how previous generations of GPs were more 'hands-on' and willing to 'give something a try', whereas current practice involves 'more litigation and anxiety surrounding risk'. One GP stated they were not a 'stabby kind of doctor' much preferring to chat and prescribe medication which they perceived to be less risky. In contrast one FCP suggested FCPs were well placed to administer injections because of their specialist knowledge of musculoskeletal health. Confidence and (dis)comfort appear here to be associated with the confidence different clinicians had in accomplishing the procedure competently.

There's been other times where you know, I've done procedural things with injections and scalpels and things and I found it quite stressful [...] I prefer to stick with the medicine side of things.

F5GP does not give injections

TABLE 18 Professional participants

Participant ID (practice designated letter, participant number and professional role, i.e. general practitioner or first contact physiotherapist)	Sex (male/female)	Years in current role at time of interview	Joints injected for OA
A1GP	M	30	Shoulders/knees
I1GP	M	26	Toe/ankle/knee/shoulder
J1FCP	F	6–7	Knee/shoulder
J2GP	F	5–6	Does not currently administer IACIs
F2GP	M	6–7	Knees/shoulders
F5GP	M	4–5	Does not administer IACIs
H5GP	M	5	Knees/shoulders
H6GP	F	20	Knees/shoulders
G1GP	F	15	Knees/shoulders/wrists
G2GP	F	6–7	Knees and shoulders
E8GP	M	7	Knees
E9GP	M	10–11	Knees
D1FCP	F	10	Shoulders/wrist/thumb/finger joints/knees/ankles
D9GP	F	3	Knees/shoulders
B10FCP	M	6–7	Prescribes but does not administer
B11GP	F	5	Knees/shoulders
B12GP	M	10	Knees
C1GP	M	12	Knees
C2GP	F	5–6	Does not administer IACIs
Total	19 (9 female)	Range 3–30 years	

I don't dislike doing them but I'm not really a stabby kind of doctor [...] I would much prefer to prescribe and chat to someone than start stabbing them because if there's a problem, you know that's obviously a lot to sort out. So, they will usually have to persuade me.

C1GP 12 yrs in practice

You've got to think about it a bit, so I find that if you do it, they're incredibly satisfying [...] I know a GP who will stick a needle in anything that moves, and I know other GPs that won't go near them. I think GPs are becoming more and more risk averse and particularly to practical procedures. It's quite hard to find a GP now that will do minor ops, for instance, which is a great shame because it provides a good service and a fix for people who otherwise wouldn't get things done, who would have to wait an extraordinarily long time to get things done [...] and, of course, we're brought up now with more litigation and more anxiety surrounding risk.

A1GP 30 yrs in practice

I suspect there's a personality involved in it as well. I do coil fitting, I do minor lumps and bumps and I do joint injections. I am a 'stabby kind of doctor' [laughter] and I don't think of myself as a stabby kind of doctor, but I guess I am. Whereas others are more, 'Let's talk about more medication'.

H6GP 20 yrs in practice

Used in the right person at the right time, it's a very effective modality [...] It definitely has its place but of course with first contact physios like myself now, in primary care who bring the MSK specialism to primary care, you know we're well placed to do these as well [...] well MSK is our thing, our anatomy is really good, you know and again, it's all about skill as well, something you're doing time and time again, then you maintain your skills, and you hopefully become a better injector.

D1FCP 10 years injecting joints

Training

Clinicians' experience of training appeared to be directly related to their confidence in administering IACIs. Training was often provided as an option at various time points during medical training on placements and courses run by a wide variety of providers, or under the mentorship of more experienced colleagues. Often only one or two GPs in a practice would be trained to provide IACIs which limited their availability to patients. More experienced GPs (I1GP) suggested that a lack of confidence and skill among newer GPs could be linked to the current training rotation system where trainee doctors are more used to organising referrals or prescribing medicines, rather than doing procedures themselves. Some GPs believed that training should remain opportunistic as they felt it was a relatively easy procedure to learn; while others felt it should be more standardised or even mandated (made compulsory) to ensure quality assurance and education, and to increase its availability to patients.

It is very ad hoc, yes [...] When I was training [...] you worked in a team, and you have responsibility for those patients through their entire stay [...] whereas now what happens is you work in rotating teams and you don't have the ownership of patients in the same way. You're much more about organising things to be done for those patients rather than doing it yourself, and so that leaves you in place perhaps with less confidence and less skills and less training.

I1GP

I had a very brief orthopaedic job and did some injections then [...] So, I just sort of took it up there, it was all kind of ad hoc apprentice based stuff, there was no real formal training I don't think [...] I think it's such a vital skill that it would be nice if the registrars came a little bit more primed ready to start [...] I definitely think that we should be more widely available not just particular GPs in particular practices, that isn't always that helpful.

E9GP

I think it's like anything practical as a doctor you kind of go through cycles of confidence doing things, and then less confidence. But I think I had two or three knees in a row where I kind of really didn't find it that easy to actually access the joint space and find myself kind of repositioning the needle or doubting myself a bit [...] So it made me doubt myself a bit and think oh goodness me I need a bit more training to be doing this. And so, I was sort of toying with the idea of kind of not really doing it anymore. But since then, there's quite a confident, one of our older partners here he's been doing it for a lot longer, he was reassuring and gave me a bit of a hand and taught me some new tips.

H5GP

Risk of adverse outcomes

When asked about the risks of IACIs, infection appeared to be of most concern to GPs, although they believed the risk was very small. Only two (I1GP, F5GP) mentioned anecdotal evidence of this happening, during their training. In reference to whether IACIs increase the progression of joint degeneration, one GP (E9GP) rationalised that the joint was already *degrading* so it would be difficult to ascertain, and no GPs or FCPs mentioned any evidence of this happening. As no GPs or FCPs had experienced any major adverse events, they were curious about the absolute risks of adverse outcomes associated with IACIs, and there was a sense that these may be overstated.

Well to begin with I was always very kind of conscientious in terms of going through the risk of introducing infection into the joint and to present if you had worsening pain, a fever, swelling or anything like that. But we've never ever – and we

get a lot of injections in this surgery – I've never seen anybody who's had any complications [...] I haven't actually ever seen it in practice. Or heard about it.

F2GP

I guess there is a query as to whether having lots of injections causes osteopenia or whether it causes joint damage. I mean it's pretty damaged joints to start with so I'm not really sure that there's any good evidence that I've seen that which says that they are at risk of faster progression if they have multiple corticosteroid injections.

E9GP

When discussing risks, clinicians focussed more on adverse outcomes, such as infection or joint degeneration and appeared to separate these from the more general risk of not administering the injection with the correct technique, or a risk that it simply would not provide any benefit.

Technical uncertainties

Needle placement: There were some technical aspects of the IACIs procedure where practice varied between clinicians. Needle placement was often a source of uncertainty for clinicians, with some reporting a lack of confidence when injecting different joints, concerned that the needle would not reach the correct spot. Confidence with injecting a particular joint varied between clinicians, even for the same joint. Some clinicians perceived that needle placement was related to the success or effectiveness of the injection (A1GP). One FCP suggested that needle placement mattered less as theoretically the steroid would disperse around the joint capsule.

You can get less certain at times, particularly if the anatomical landmarks aren't clear because somebody's a bit heavier. Particularly shoulders, in fact, are a real issue with that. So yes, not nervous, but just less certain. Reduces your confidence that you're going to get it in the right place.

I1GP

I think with shoulders it's easier because once you're in a shoulder, you know you are in, and you don't get any back pressure and you get the steroid in very easily, it's lovely. Occasionally, you won't get it quite in the right place and it will be a bit trickier to get it in [...] So when you actually get something in and you know you're in, I always think, 'Ah, that's going to work well'.

A1GP

Well they say as long as you're getting the injection into the joint capsule then theoretically the steroid should disperse, spread around the joint and give the same effects. So as long as you're getting it into the joint capsule then I think the approach they said doesn't matter too much.

J1FCP

Mixing with local anaesthetic: Some clinicians used a local anaesthetic mixed in with the steroid, while others did not. Reason for using anaesthetic was to increase the volume of the injected solution to ensure it fills the joint space. Others used it as a diagnostic indicator to determine that the pain was coming from the joint. If no immediate effect was experienced, it is likely the pain was not attributed to OA. Others preferred not to use anaesthetic as they had been told it could leave deposits in the joint itself.

To be honest I'm not entirely sure how useful the local anaesthetic really is. I think in a way it's more to sort of bulk out the steroid a little bit so you can wash it out of the vial more effectively.

F2GP

We only use separate [steroid and anaesthetic] in the surgery because that's historically what we've used and I'm not as keen on [steroid brand] because I've chatted to surgeons and they say it's often difficult for them to then go in and pick it out of the tendon because it leaves a residue for a long period of time.

E9GP

Variation in frequency of injections: How often and how many times clinicians administered IACIs to a patient varied between clinicians, even in the same practice. Some believed once every 3 to 4 months was enough, however the age of the patient was a significant factor in judging how many and how often IACIs were appropriate. An FCP also suggested no more than three per year and suggested that when sleep becomes disturbed, indicating an advanced severity, then IACIs would be less effective. When considering injecting multiple joints in the same person, one GP (D9GP) suggested that one injection would benefit multiple joints throughout the whole body, which is in opposition to the idea that needle placement into the joint capsule is important. Uncertainty is again apparent as they question what their older colleagues may have done in the same situation.

I've never looked back and gone, 'Oh, you've had 15, I'm not giving you anymore'. For me it's more about how many have you had in the last few months or couple of years.

H6GP

I just worry a little bit more about repeated steroid into the same joint over a long period of time. I'm not sure what those affects are really, obviously if we do it, it comes with a risk as well, [...] infection or damaged tendons or surrounding structures [...] But certainly for a fit and young person, you know, with just a bit of degenerative change or pain in a joint, I wouldn't want to be doing that repeatedly, year on year, multiple times over the year. I'd be a bit reticent about doing that.

E8GP

I would say I would do them, maximum, every four months. If people are older and frailer, then I wouldn't be counting up and saying, 'You've reached 20'. For somebody who is 95, I wouldn't be worried about that at all. [...] I rarely have people asking for all of their joints done and I probably wouldn't do them all. I'd say, 'Why don't you just see how this one works in your knee because it will probably benefit your shoulder as well? In a few months, come back and tell me'. Again, like I said, I'm quite cautious and I wonder what my older colleague would have done.

D9GP

I tend to say a maximum of three times a year [...] for all joints, I don't inject any more frequently than that. And I always try and tease them out a little bit longer so definitely talking about not looking at a calendar but going by symptoms and waiting to that point where normally, they can't sleep, so I think once people's sleep is disturbed then pain becomes a real issue and tiredness, and all the things that comes with that.

D1FCP

Proximity to surgery: An area of uncertainty among GPs was the issue of timing between an IACIs injection and referral for orthopaedic consultation. We found practice varied between clinicians. While guidance suggests that IACIs should not be given within 3 months before surgery, GPs reported that they were informed by local orthopaedic surgeons, some of whom agreed with this guidance while GPs reported surgeons in other localities had suggested it made no difference to them. Following COVID-19. One GP had increased the amount of people they were injecting who were on the waiting list for joint replacement, as there was little chance of them having surgery within the three-month timeframe, and otherwise they would be left in pain for much longer.

Increasingly I'm injecting people that are on waiting lists for joints [...] But now we're getting to that stage where it's waiting for so long that I'll say to a patient, look there's a small risk that you're going to get some cancellation and then be told they can't do an operation right now but the chance of that is so slim I think if you're in a lot of pain now we can do this injection and give it a go.

H5GP

Uncertainty about evidence and guidelines

While many clinicians were unfamiliar with the evidence and guidelines for IACIs not having reviewed them 'for a long time', most held the belief that the evidence base was poor, and this influenced their confidence in administering IACIs and their confidence in whether it would work or not. Most were certain that if there were any recommended changes to practice, they would hear about them through colleagues, or professional organisations. One FCP referred directly to the NICE guidelines stating they contained insufficient information to guide practice.

I did a quick internet search myself [...] and there isn't a huge evidence base behind it. I think that informs your confidence in doing a procedure because there's not a pathway, an established evidence base and when you audit your own work, its 50/50 whether it's going to work or not [...] So yes, it's very different to other areas of medicine where there are well worn paths and robust evidence, and you feel confident in what you're doing.

G2GP

I am unsure of it, and I think I'm mixed. I think there's probably some evidence that it helps in the very short-term, but in the long-term I don't think it provides benefit.

F5GP

NICE guidance just said that it's a tool that can be used but there is no real guidance, as there's no guidance as to which drug is the best, or which dosage is the best, you know a lot of the GPs and it seems to be rheumatology as well, put big doses in weight bearing joints, you know 80mgs, and I've always been taught to use the, well I tend to use 40 erm, as per I was taught, but I'm not sure if that's the best dosage to use.

D1FCP

Intra-articular corticosteroid injections use on the osteoarthritis pathway – 'never my go-to ... always an adjunct'

Intra-articular corticosteroid injections are used at various points along the OA pathway although clinicians reported using them most often where core treatments did not work, and as a last resort before surgery. In younger patients, they were sometimes used as a diagnostic tool to assess whether the pain was coming from the joint. In those too early to consider surgery, one physiotherapist used them to help patients to maintain function and continue working. Some clinicians used them to enable patients to take up other core recommended treatments like physiotherapy or exercise.

It's never my go-to it's always that adjunct, later on down the line, so I'll always make sure that within the patient's history that they've at least had attempts at physio and a conservative management.

B10FCP

[Do you ever give it to younger patients?] I will happily give a one-off, if there's an acute problem there, possibly as part of a diagnostic tool. Interested to see if it works. I do heavily counsel the patient, however, this is not a solution to their ongoing problem at that stage.

I1GP

[When would you raise this as an option with a younger patient and when wouldn't you?] I mean I would get their feelings and opinions going forward on what they wanted to achieve [...] It may allow you to, you know, to improve the pain which allows you to do things, to do more exercise, to lose weight, things that have a longer term benefit.

E8GP

Some clinicians used IACIs as an alternative to other analgesia no longer recommended after changes in the guidelines (e.g. opioids), but also for those patients who could not tolerate medications with particularly debilitating or chronic side effects (drowsiness, mood swings, gastrointestinal problems). One physiotherapist (D1FCP) reasoned that with opioids, older patients were also at higher risk of falls, and IACIs presented a safer and more tolerable option. Where patients were unfit for surgery because of comorbidities, age or preference, they were also used more freely by clinicians as they believed no other options were available.

I'd much rather do an injection in the knowledge it's only going to last three months, than have somebody on high dose codeine [...] I mean particularly in the elderly who are at greater risk of falling [...] And the risks of injection, I believe are relatively small. You know side effects are very, very rare.

D1FCP

So, it would be someone who's possibly too frail to consider surgery for, but their pain is uncontrolled or the amount of analgesia they need in order to get their pain under control is too high to tolerate the side effects of it. So, the codeine makes them constipated, or the ibuprofen causes GI upset or worried about their kidneys or whatever.

H6GP

Sometimes for elderly people who've got, you know, as I say are never going to be fit for surgery and have got osteoarthritis in multiple joints, I tend to do it maybe three monthly, say four a year. And I might do that as they require really, I'm much sort of concerned there about, you know, pain relief and functional relief.

E8GP

Perceived benefits and impacts of IACIs – 'I'm able to just kind of keep them going'

Clinicians often described the effects of IACIs as short term, lasting 3 months on average with a 'successful' injection. GPs quoted personal success rates of between 50% and 70%. There was a sense that this is often seen as a limitation, diminishing the perceived value of IACIs. One physiotherapist suggested that this should not be a surprise as corticosteroids only exist in the body for this short period and should not be thought of as a 'cure'. For some GPs, the use of IACIs was 'incredibly satisfying' and meant that they could 'buy time' and 'keep patients going' with good pain relief.

When I've got a patient that's kind of struggling with their pain and they've got sort of moderate [osteoarthritis] on the x-ray then sometimes I'm able to just kind of keep them going for a couple of years but they tend to sort of need referral onwards after a couple of years, but I find that it can buy us a bit of time, and get some good pain relief during that time.

B12GP

Doesn't work all the time I always say, even though I've done this for years, so my success rate's about 70% [...] but when they do work, it's fantastic and very satisfying.

A1GP

In my experience, some of the injections do incredibly well. And some do very poorly. [...] you may see an x-ray with advanced changes, but actually, very little inflammatory type pain, so no pain at night, no pain at rest, just weight bearing pain. I find in my experience that those do not do well [...] So, I never look at x-rays to decide whether I'm going to inject or not. It's very much on the clinical picture. And so if somebody's got active synovitis or a clear inflammatory type pain, so its waking them up at night, can't sit for too long before stiffening up, then I tend to find the injections do really well [...] I tend to find those with night pain do have a good response. And sometimes you know sometimes in the early stage of arthritis, it maybe just that it's settling a flare and they won't come back for a long, long time [...] I think injections, if they're used in the right population, will be shown to be very, very effective [...] It always surprises me when people say that these injections are short term, well it's not a surprise because they only exist in the body for up to 12 weeks. And so for a degenerative condition it's not a cure.

D1FCP

The possibility of a placebo effect

Some clinicians raised the possibility that IACIs provided a placebo effect, and although some felt that any intervention administered for a patient was likely to entail a degree of placebo, others felt that the process of preparing and administering IACIs was particularly powerful. Any potential for placebo effect was not perceived negatively.

It's my personal feeling, like any intervention I think like this, you know, you get some benefit, so how much of it is placebo and how much of it is the effect of the steroid it's difficult to say.

E8GP

And the other thing that sort of you know one sort of struggles with is often with arthritis there is a limit to what you can do conservatively so a steroid injection feels like a really kind of theatrical event for a GP to do for their patient. And you kind of wonder how big a placebo effect and if that kind of has a role in it and then you think well is that a bad thing or not.

H5GP

Clinician information needs and suggestions for further research

When asked what further information clinicians would like about IACIs or what questions they wanted future research to focus on, effectiveness of IACIs in comparison to other therapies and more evidence on the risks of IACIs was

suggested. Clinicians also wanted more information and better guidance on the longer-term use of IACIs, up to 5 years or more, especially if used in younger patients, and what the risks are to surgical outcomes. Clinicians also wanted to know what the optimal dose and optimal drug were to see if the effect can be increased or sustained for a longer period with a smaller dose, and whether using saline or anaesthetic to increase volume improved effectiveness. There was also a request for more evidence on the risks of complications between community-based injections and hospital-based injections to ascertain whether more IACIs could be given in the community by FCPs, or nurse practitioners to offload pressures on GP practices. Finally, clinicians also wanted more guidance on the best techniques for administering IACIs and better information to give to patients.

I guess if there's any way to actually sort of quantify what benefits there might be, either be that sort of symptom relief, that probably would be my main thing, symptom relief.

F2GP

I guess make sure are there any actual genuine harms that are evident? One thing would be direct harms from the steroid injections. You know, how many people do get an infection into the joint or does it cause a worsening of this kind of localised arthritis and does it make surgery more complicated or just a bit of bone sort of softer or less amenable to surgery?

F2GP

Does giving IACIs earlier have a better long-term outcome? 'It's just not something I've ever done. But it's a reasonable thing to do is actually if you do it early and therefore are more able to do physio for which there is reasonably good evidence I believe that it does help, then why would we not? I don't know why would we not. I guess maybe injecting a younger person. Actually no, even that why would you not?'

H6GP

[I]nput from a surgical perspective, just to broaden the base of knowledge that we've got, I suppose the long term implications may be you know five years or more, with these patients, now we are starting to see them happen more regularly and I suppose there will be the sort of guidelines about three injections a year but what are the kind of recommendations for say over a three, four, five year period [yeah] is that still viable, how long can you continue that for before it becomes either a risk or you have to escalate things to surgery?

B10FCP

There's a lot more research needed I think on the optimal dose and the optimal drug [...] I don't know whether by increasing the dose, people may get better pain relief for longer, or if by reducing the dose, they had a similar effect.

D1FCP

I'd like to have some understanding about some research comparing the different preparations with or without anaesthetic. Also, volume is also an important question [...] In terms of system benefits, I think it would be good to compare risks of complications between community-based injections and hospital-based injections because I think there is, you know. I think many more injections could be done in community settings, either by physios or by GPs or by nurse practitioners, and I think the system benefits are we're offloading outpatients and patients are getting a more timely treatment.

I1GP

Which patients get the most benefit from it.

G1GP

It will be a really positive outcome if the outcome were actually the risks have historically been overstated and it has an equal footing with NSAIDs and paracetamol and actually you can do as many as you like, there are no, you know it doesn't adversely affect surgical outcomes for example, that would be a very interesting and positive outcome for me because it empowers us as, you know GPs doesn't it to get on with and do things that involve long waiting lists and physio that no one seems to want to do.

G2GP

I would like to have some clarity on the best techniques for doing them. And I guess that's quite a difficult question to answer. You know if there was a very clear, you know, 'this is the best way to do it', and then just to really give a robust answer about whether this is a good idea to do them or not, are these really helpful in the long term. And some more information to be able to give to our patients about that because at the moment we have these sort of questions, slightly wishy washy conversations that say we can try this, there are some question marks you should be aware of.

H5GP

Areas of convergence

There are a number of converging themes in which the experiences and perspectives of both patients and clinicians support and extend one another. Patients seem to become aware of IACIs only when clinicians raise the possibility of their use on the OA pathway. Variation in access to IACIs experienced by patients seems to be partly dependent on the availability in their practice of trained clinicians and on the clinicians' confidence and comfort with administering IACIs. Patients also thought that the effectiveness of IACIs was related to clinicians' competence and technical factors like needle placement. Patients and clinicians also appeared to question the RRs of IACIs, voicing uncertainty over issues such as accelerated joint degeneration. Patients and clinicians viewed IACIs as relatively low risk in terms of adverse outcomes, but wanted more evidence on the absolute risks of IACIs over the long term and more information and guidance on the optimal number of injections and dosage. Overall, confidence in administering IACIs varied among clinicians.

Discussion

We conducted semistructured interviews with 38 patients and 19 primary care clinicians to investigate their views and experiences of IACIs for OA. We found that patients' awareness and availability of IACIs varied and they thought that this depended on their GPs' views of IACIs and their confidence in administering them. Patients who received IACIs highly valued their potential to reduce pain and improve their quality of life. IACIs enabled patients to continue with activities of daily living, health exercises and leisure interests. While IACIs were not always effective, patients often linked this to the ability of GPs to administer them effectively, and to a reduction in efficacy over time with repeated injections. Patients preferred IACIs as an alternative to other forms of pain medication, and to delay or avoid surgery. Patients were not overly concerned about risks related to IACIs, which they saw as low risk, and patients trusted clinicians who offered IACIs.

Clinicians appeared to be cautious about IACIs and this was related to their confidence in being able to accomplish the procedure competently, which was influenced by multiple factors including personality, training, guidance and lack of evidence. Many valued them as a practical procedure for patients which could provide symptom relief where other strategies did not, or no longer worked. Clinicians thought that the evidence base for IACIs was poor and had little up-to-date knowledge of guidelines. Alongside these views, clinicians' (dis)comfort with procedural medicine affected their confidence in their ability to provide IACIs. This appeared to be more pronounced in GPs with less overall years of practice. One FCP suggested that MSK physiotherapists were well placed as FCPs to deliver IACIs in primary care having more time with patients and to maintain injection skills. GPs described their training in IACIs as ad hoc with some suggesting it should be standardised to ensure quality assurance. This also appeared to be linked to GPs' confidence in their own technique and technical uncertainties around needle placement and injection frequency. There was also variation in beliefs about timing between IACIs injection and referral for orthopaedic consultation. Despite these uncertainties, clinicians appeared to question the evidence around the absolute risks of adverse outcomes associated with IACIs, as none had experienced any in their patients. Clinicians used IACIs at all points along the OA treatment pathway, as an early diagnostic procedure; to enable patients to take up other treatments and to remain active; to alleviate symptoms where other core treatments have failed; and as an alternative to other pain medicines that have burdensome side effects, or to delay or avoid surgery. However, IACIs appeared to be most often used as a 'last resort' before surgery. Clinicians wanted future research to focus on producing evidence and guidance that would give them more confidence in the use of IACIs, including focus on risks of adverse outcomes as well as providing information that could help them to use IACIs appropriately.

Other research on experiences and perspectives of IACIs for OA

There is little evidence on patients' and providers' experience and views about use of IACIs for OA. Two recent studies in America focussed on patient and clinician decisions about the use of various injection therapies for knee OA, including glucocorticoids, hyaluronic acid derivatives and platelet-rich plasma.^{124,125} The studies found that patients were concerned about the effectiveness, safety, availability and cost of injectable therapies; however, these findings are not readily translatable to a UK context as American patients pay all or part of the cost of injection therapies, and the authors do not distinguish between the different injection types.¹²⁴ In a study of US physicians' decision-making for the use of injections, physicians were concerned about the efficacy and risks associated with different injection therapies, the need to manage patient expectations, and the costs.¹²⁵ While the transferability of the findings to a UK context is again limited by differences between healthcare systems, the authors noted that some physicians were more reliant on clinical guidelines and evidence, while others relied more on their clinical experience, which has some resonance with findings from our study.

A major finding from our study is the variability in access to IACIs, related to GPs and their cautiousness and competence in providing them, which in turn is related to ad hoc training and concerns over risks of adverse outcomes and a poor evidence base. Our findings suggest that only a small number of GPs and FCPs within each practice undertake IACIs provision. This becomes problematic when a GP leaves a practice and the skills are lost, often being replaced by more cautious and less confident GPs which further limit patient access. The confidence of GPs who were often less experienced in IACIs is undermined by the lack of evidence and guidelines for IACIs. Evidence from UK and international surveys performed between 1992 and 2022 has found that joint injections are mostly performed by small groups of GPs and that confidence and the number of injections they performed were directly linked to their training and competence, with diagnostic uncertainty and medicolegal concerns also being factors.¹²⁶⁻¹³⁰ Our results suggest that little has changed over 30 years, and many GPs remain uncomfortable with performing procedures, particularly where guidelines and evidence is lacking.

In our study some patients referred to long periods of symptom relief, sometimes spanning years. These periods of relief may provide evidence to support the hypothesis that IACIs work better for patients with inflammation at the time the IACI is performed, while also justifying what Birrell refers to as the 'tear, flare and repair' model of OA, as noted in a recent trial of ultrasound-guided IACIs for hip OA.^{85,131} One FCP and injection specialist from our study suggested 'that quite a lot of studies potentially fail because if they are inviting people who don't have inflammatory type signs, then it's not going to work'. Clinicians in our study had a propensity to use IACIs as a last resort before offering surgery as an option and we can hypothesise that many patients may be towards the end of the inflammatory phase of OA when they are offered IACIs, therefore cutting short the potential benefit of IACIs to serve patients longer as an effective treatment against symptomatic OA. Foster *et al.*'s review echoes this sentiment, highlighting the importance of matching the right patient to the right treatment at the right time.¹³² This raises the question of whether we should be using IACIs earlier on in the OA pathway.

Both patients and clinicians value IACIs for OA because of their potential to improve quality of life, even for short periods, and as a valuable alternative to other less desirable treatments. These findings provide contextual support for more recent trials, which showed that extended-release IACIs can have a 'sustained and profound' analgesic effect in people with knee OA, sometimes maintained up to 6 months later,¹³³⁻¹³⁵ although these are not yet available in the UK. Our results suggest that patients and clinicians would value IACIs with longer durations of benefit.

Recommendations for practice and future research

As NHS surgical waiting times and the potential demand for IACIs increase we suggest that patients need better access to IACIs, from clinicians who are more confident and competent in administering them. More regular training and clearer guidelines around the appropriate use and administration of IACIs are needed – including optimum interval between repeated IACIs, dosage and whether to use local anaesthetic, and better evidence on the absolute risks of infection and the potential for increased cartilage deterioration. Clearer guidance on the safe use of IACIs prior to joint replacement surgery is required particularly as waiting times for surgery increase leaving more people in pain for longer. We also suggest that GPs and FCPs should be made more aware of the potential use for IACIs along all points of the treatment pathway and that, for some patients, they can be a preferred and safer alternative to opioids. In discussing the findings from this study with PPIE representatives, all of whom have OA, many had never been offered IACIs, only surgery, and

were not aware of it as an option, before this study. We suggest that based on our findings and recent evidence there is a lack of GPs who have the skills and confidence to offer and administer IACIs, which precludes any shared decision-making about their therapeutic use for OA. GPs' confidence with injecting certain joints varied among individuals, while the FCP suggested they were better placed to deliver IACIs as they had a better knowledge of musculoskeletal anatomy; we therefore suggest that future research should also focus on identifying who is best placed to deliver IACIs for OA. IACIs should be more available as an option for patients with OA, and more research is needed to identify their therapeutic use and potential benefits at all points along the treatment pathway.

Strengths and limitations

There are no previous studies that we are aware of that have explored patients' and clinicians' experiences of using IACIs in multiple joints for OA. Our data were collected from 10 primary care practices covering diverse populations across Southwest England, and combined with an in-depth thematic analysis this ensured that information power was reached, enabling us to address the research questions.¹¹⁸ We chose not to apply a theoretical framework as our intention was to characterise the experiences relevant to the use and administration of IACIs within primary care for OA, accounting for use on the OA pathway, beliefs about efficacy and risks, views on current evidence and guidelines and factors that affect decision-making. Our pragmatic approach has allowed us to characterise current attitudes of patients and primary care practitioners and enabled us to make recommendations for practice and future research. A common limitation of any research is the self-selecting nature of participation. It was possible that patients who signed up to the study did so because they had positive experiences of IACs. However, as some patients did describe lack of efficacy and limitations of IACs we were able to include a range of experiences. Although the study included some patients and clinicians who had not received or administered IACS, they did not hold negative views of IACs but were simply never offered them in the case of patients, or because GPs colleagues provided them in the practice. We included patients aged 45 years and above, and age was shown to be a decision-making factor for clinicians. However, IACIs may be given to patients below 45 years as shown by the cohort study. Future qualitative research should incorporate the perspectives of younger patients. Only one patient described themselves as of 'mixed race' while all others identified as white. This potentially reduces the diversity of experiences, and while our sampling framework focussed on sampling from under-represented populations, practices fed back that ethnicity were not recorded in patient records. Future research should focus on other ways of identifying under-represented groups and should include resource for an interpreter to potentially remove any language barrier. While the remit of the project was primary care perspectives, we feel that orthopaedic surgeons' views would have increased understanding of perceived value and risks of IACIs for OA, given they would be more experienced with the administration of injections and the subsequent treatment of patients who had or had not received IACIs. Discussion of our findings with the research patient PPIE group assured that our findings were relevant and reflective of wider public experience.

Conclusion

Our findings suggest that over the last 30 years, little has changed in relation to access to IACIs, and this needs improvement. While IACIs are still viewed with caution by some clinicians, many value them as an alternative, and sometimes safer, option to other pain medications, or to surgery, and they are highly valued by patients who benefit from symptomatic relief of OA. More evidence about their safety is needed from well-designed high-quality trials, aimed at evaluating their potential benefit and safety at all points along the OA pathway.

Chapter 7 Delphi study

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Introduction

Osteoarthritis is the most common musculoskeletal condition worldwide and represents a global public health burden.¹ The prevalence of osteoarthritis is expected to rise over the coming years and therefore there will likely be an associated rise in the use of IACIs. Further research on IACIs is needed to provide a robust evidence base that can be used to guide treatment provision and optimise patients' experiences and outcomes following this procedure. It is important to provide a clear direction and framework for this future research, alongside ensuring that the voices, experiences and concerns of key stakeholders, including patients and clinicians, are central to setting the future research agenda. Formal research priority setting can be undertaken to identify and prioritise research areas and questions deemed important to stakeholders.¹³⁷ This can inform funding calls and decisions, thereby facilitating provision of research funding to the areas of highest priority.

Diverse methods can be used in research priority-setting activities, reflecting the different populations and environments in which the work is undertaken. The Delphi technique has been used extensively to identify research priorities in a wide range of healthcare settings, with recent examples including malignant oesophagogastric surgery,¹³⁸ major trauma,¹³⁹ atypical anorexia nervosa¹⁴⁰ and vascular surgery.¹⁴¹ The Delphi technique is a structured process that can be used to gain consensus among experts.¹⁴² It was originally developed by the RAND Corporation in the 1950s for technological forecasting. It is an iterative technique that uses a series of sequential questionnaires completed anonymously by participants with relevant expertise to reach consensus about a particular issue. The Delphi survey technique uses open-ended questions in the first round to elicit information to be used in subsequent rounds. A key feature of the technique is a staged approach. This provides participants with the opportunity to review group feedback and revise their own views. For example, the influence of group dynamics and peer influence are removed as the participants do not interact with one another and remain anonymous to one another.^{142,143} This Delphi study aimed to gain expert consensus on future research priorities for IACIs used in OA and any feasibility considerations associated with these topics.

Participants and methods

Ethical approval was obtained from the North of Scotland Research Ethics Service (21/NS/0070) on 24 May 2021 and Health Research Authority approval on 25 May 2021. All participants provided informed, written consent.

Delphi technique overview

The study involved a 3-round Delphi survey. In Round 1, open-ended questions were used to elicit information to be used in subsequent rounds. Items generated from Round 1 were then ranked from the most important to the least important by participants in Round 2. Those items meeting predefined criteria were carried forward to Round 3. In the final round, participants had the opportunity to review group feedback and revise their own views. The three rounds of questionnaires were administered over an 8-month period between June 2021 and January 2022. Full details of the methods used are provided below.

Recruitment: patient panel

Eligibility criteria for the patient panel included adults in the Southwest of England who had received one or more IACI(s) for OA in the primary care setting, within the last 3 years. Exclusion criteria included patients who lacked capacity to provide informed consent and those who could not complete the questionnaires in English.

Patients were identified through the NIHR West of England CRN, facilitated by the Bristol North Somerset & South Gloucestershire Clinical Commissioning Group (BNSSG CCG) Research and Evidence Team. The NIHR West of England CRN was responsible for engaging research active primary care practices in the study. The research team sent a completed Research Information Sheet for Practices to the WEReACH settings team at the CRN West of England on 25 May 2021. A Service Support Agreement letter was received on 27 July and WE ReACH provided the names of nine GP practices that completed expressions of interest to the research team on 5 August. These practices were contacted by the research team on 9 August, with a reminder sent on 6 September. Three GP practices responded to the research team request and were sent the local information pack and asked to complete an organisation information document (OID) after a site initiation call.

Primary care practices screened patient information and GP Read Codes to identify eligible patients with capacity to consent and then posted out information packs about the study. The study information pack included a letter of invitation, patient information booklet, Round 1 questionnaire with embedded consent form (to minimise the chance of patients returning the questionnaire but not the consent form) and a prepaid envelope. The information booklet described the purpose and aims of the study and provided an explanation of how to participate. The information booklet also encouraged patients to contact the research team if they wanted to discuss the study or ask questions. Patients interested in taking part were asked to return the Round 1 questionnaire with embedded consent form to the research team using the prepaid envelope provided. On receipt of these documents the consent form was countersigned by a researcher. A photocopy of the consent form was sent to the participants for their records with their Round 2 questionnaire. In the Round 1 questionnaire, patients were offered the option of receiving the Round 2 and 3 questionnaires by post or by e-mail.

In addition to the above approach to recruitment, participants from the RUBICON qualitative study (see [Chapter 6](#)), who provided consent to be contacted about further research, were sent study information packs.

Recruitment: commissioner panel

Due to issues with engaging a sufficient number of Commissioners with relevant experience to form a Commissioner panel, Commissioners were merged into the healthcare professional panel. Here we provide details of our attempts to recruit Commissioners.

Eligibility criteria for the Commissioner panel included Commissioners with experience of musculoskeletal services. Exclusion criteria included any conflicts of interests that may bias their responses to the Delphi survey (assessed through a question in the Round 1 questionnaire).

Between May and August 2021, multiple attempts were made to engage with Commissioners about this study. The BNSSG CCG disseminated the study information, both locally and to two CCGs in other areas of the country, and via the R&D Forum's primary care working group. The West of England CRN circulated the study information to CRNs across the UK using the Division five Research Delivery Managers e-mail list, which resulted in teams in Oxford, Thames Valley CRN and North East and North Cumbria CRN circulating the study information to local Commissioners. The Primary Care Rheumatology and Musculoskeletal Medicine Society also circulated the study information to its members via a newsletter and hosted an advert for the study on their website. Despite the multiple efforts, only two Commissioners opted to participate in the study, and therefore the decision was made in a research team management meeting in September 2021 to include the recruited Commissioners in the healthcare professional panel instead of having a separate Commissioners panel.

Recruitment: healthcare professional panel

Eligibility criteria for the healthcare professional panel included primary care physicians, physiotherapists, rheumatologists and orthopaedic surgeons who had experience of commissioning care or providing care in a clinical

capacity for patients receiving IACIs for OA. Exclusion criteria included healthcare professionals with conflicts of interests that may bias their responses to the Delphi survey, which was assessed using a question in the Round 1 questionnaire.

Healthcare professionals were recruited through multiple avenues:

1. Primary care practices that recruited patients also identified and recruited appropriate primary care health professionals working within these organisations. Eligible health professionals were e-mailed the study information by the practice manager/research lead and provided with the link to complete the online Round 1 questionnaire and consent form.
2. Primary care health professionals who participated in the RUBICON qualitative study (see [Chapter 6](#)), and who provided consent to be contacted about further research, were e-mailed study information packs.
3. The Primary Care Rheumatology and Musculoskeletal Medicine Society disseminated information to members via their newsletter and website.
4. Secondary care clinicians were identified from previous research collaborations and e-mailed the study information.

Recruitment: academic panel

Eligibility criteria for the academic panel including academics in the UK who have published research in the English language on treatments or care pathways for OA. Exclusion criteria included academics with conflicts of interests that may bias their responses to the Delphi survey.

A non-systematic literature search using PubMed was conducted in May 2021. Search terms included a combination of corticosteroid, injections and OA. Authors of relevant studies were e-mailed study information. Further potentially eligible academics were identified from reference lists of relevant articles and searching University websites of primary care and musculoskeletal research groups and departments within the UK.

Round 1

In the Round 1 questionnaire, participants were asked to provide some sociodemographic/professional information and then to identify up to five research questions in relation to IACIs for OA. For each topic generated, participants were asked to reflect if there were likely to be any associated feasibility considerations with conducting research on the topic and to provide details in a free-text field. Participants were asked to provide suggestions for feasibility considerations in the Round 1 questionnaire only to minimise participant burden and optimise retention between Delphi Rounds. The questionnaire for professionals and patients had similar content, however the questionnaire sent to patients was written in plain English, and was developed in collaboration with patient representatives.

Round 1 analysis

Responses were collated in Excel and research suggestions were grouped by topic. The topics were then reviewed to develop candidate research questions and associated feasibility considerations. Grouping of topics and development of research questions and feasibility considerations was initially conducted by VW and then reviewed and refined by MRW. The list of candidate research questions was reviewed by patient representatives who worked with the research team to write the research questions in plain English.

Literature searches

A literature search of EMBASE was conducted in November 2021 to evaluate if any of the questions identified in Round 1 had been fully answered by existing research to ensure that only questions with a lack of evidence or treatment uncertainty were included in Round 2 (search terms provided in [Table 19](#)). Records were screened to remove clearly irrelevant records by one reviewer (RD), and potentially relevant records were screened by a reviewer (VW or RD) and either assigned to the relevant research question or classed as non-relevant. The volume of studies identified that addressed each research question was then categorised as 'none/low (< 10 studies)', 'some' (10–30 studies) or 'high' (> 30 studies). Research questions with 'none/low' studies were classified as not fully answered because of a lack of published research. For those candidate research questions with either some or high volume of studies identified, the existing literature was narratively reviewed by one reviewer (VW) and an assessment was made on whether or not the research question had been fully answered.

TABLE 19 Search strategy for literature review

#	Database	Search term
1	EMBASE	(adult*).ti,ab
2	EMBASE	exp ADULT/
3	EMBASE	(1 OR 2)
4	EMBASE	(osteoarthriti*).ti,ab
5	EMBASE	(osteo-arthritis*).ti,ab
6	EMBASE	(joint arthritis*).ti,ab
7	EMBASE	(bon* arthritis*).ti,ab
8	EMBASE	(arthriti*).ti,ab
9	EMBASE	exp ARTHRITIS/OR exp 'DEGENERATIVE DISEASE'/OR exp OSTEOARTHROPATHY/
10	EMBASE	(4 OR 5 OR 6 OR 7 OR 8 OR 9)
11	EMBASE	(inject*).ti,ab
12	EMBASE	(joint inject*).ti,ab
13	EMBASE	(arthrocentesis*).ti,ab
14	EMBASE	(intraarticular*).ti,ab
15	EMBASE	(intra-articular*).ti,ab
16	EMBASE	(intra* articular*).ti,ab
17	EMBASE	exp 'INTRAARTICULAR DRUG ADMINISTRATION'/
18	EMBASE	(11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17)
19	EMBASE	(steroid*).ti,ab
20	EMBASE	(corticosteroid*).ti,ab
21	EMBASE	(cortico-steroid*).ti,ab
22	EMBASE	(cortico*).ti,ab
23	EMBASE	(glucocorticoid*).ti,ab
24	EMBASE	(methylpred*).ti,ab
25	EMBASE	(methyl-pred*).ti,ab
26	EMBASE	(methyl* pred*).ti,ab
27	EMBASE	(triamcinolon*).ti,ab
28	EMBASE	exp CORTICOSTEROID/OR exp GLUCOCORTICOID/
29	EMBASE	exp PREDNISOLONE/
30	EMBASE	exp STEROID/OR exp 'FLUORINATED STEROID'/
31	EMBASE	exp HYDROXYCORTICOSTEROID/
32	EMBASE	(19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31)
33	EMBASE	(18 AND 32)
34	EMBASE	(3 AND 10 AND 33)
35	EMBASE	(rheumat*).ti,ab
36	EMBASE	exp 'RHEUMATIC DISEASE'/
37	EMBASE	(35 OR 36)
38	EMBASE	34 NOT 37

Round 2

Participants who completed a Round 1 questionnaire were invited to participate in Round 2. In the Round 2 questionnaire, participants were asked to rate the importance of each candidate's research question on an ordinal scale from 1 (not important) to 9 (very important). A single e-mail/paper reminder was sent if no response was received within 2 weeks.

Round 2 questionnaire analysis

Median scores for each candidate's research question were calculated. The criteria for retraining research questions were defined a priori in the study protocol and were based on the RAND/UCLA Appropriateness Method.¹⁴⁴ A research question with a median score of 1–3 was defined as representing limited importance, 4–6 as important but not critical and 7–9 as critically important. Those research questions given an importance rating of 7–9 by $\geq 70\%$ of participants were retained and carried forward to Round 3. To ensure the views of the individual panels were represented in the final consensus, research questions with an importance rating of 7–9 by $\geq 90\%$ of members of one panel (i.e. patient, healthcare professional or academic), regardless of the ratings of the other panels, were also carried forward.

Round 3

Participants who responded to Round 2 were invited to participate in Round 3. In this final Round, participants were sent a shortened Round 3 questionnaire which contained the research questions retained from Round 2. Participants were also provided with the median group rating and their own individual rating for each research question retained from Round 2. After reviewing the ratings, participants were given the opportunity to re-rate the importance of each research question. A single e-mail/paper reminder was sent if no response was received within 2 weeks.

Round 3 questionnaire analysis

Those questions given an importance rating of 7–9 by $\geq 70\%$ of participants or by $\geq 90\%$ of members of one panel, were included in the final research priority list.

Sample size

The sample size for a Delphi survey should reflect adequate incorporation of stakeholder diversity in obtaining consensus on a topic, rather than statistical power.¹⁴² There are no recommendations on how many participants should be included in a Delphi survey,¹⁴³ although a minimum of 10 participants on a panel has been suggested.¹⁴² To ensure the views of all key stakeholders were included in our study, we originally aimed to recruit 100 participants onto four panels: 25 patients, 25 healthcare professionals, 25 commissioners and 25 academics. The inclusion of panels in the research design ensured that the views of different key stakeholders were represented in the final consensus.¹⁴³ However, due to difficulties with engaging enough commissioners to form a panel (further details provided in the recruitment section), we revised our recruitment target to 75 participants on three panels: patients ($n = 25$), healthcare professionals (including commissioners; $n = 25$) and academics ($n = 25$).

Results

Participants

A total of 91 participants were recruited and completed Round 1: 41 patients, 25 healthcare professionals and 25 academics. Of these participants, 82 (90%; 38 patients, 23 healthcare professionals and 21 academics) completed the Round 2 questionnaire and 75 (82%; 34 patients, 21 healthcare professionals and 20 academics) completed all three Delphi rounds. Retention rates between Delphi rounds were similar across the different panels. Details of recruited participants and those that completed all three Delphi rounds are provided in [Table 20](#).

Round 1

A total of 310 research topics were generated by the 91 participants who completed the Round 1 questionnaire. Twenty-five of these were deemed to not be a research question or beyond the scope of this study ([Table 21](#)); the remaining 285 research topics were coded, from which 26 research questions were developed ([Table 22](#)). Feasibility considerations that were raised by participants are described in [Table 23](#). These are related to recruitment, long-term follow-up, use of placebo, outcomes assessment, rare occurrence of adverse events and variability of treatment provision and care pathways.

TABLE 20 Participant characteristics

	Recruited	Completed study
Patient panel		
Number	41	34
Median age in years (range)	75 (51–87)	75 (51–87)
Gender (women: men)	27: 14	22: 12
Ethnic group: White	41	34
Healthcare professional panel		
Number	25	21
Gender (women:men)	9:16	8:13
Mean years of experience in profession (SD)	18 (10)	17 (10)
Profession (number)		
GP	10	9
Physiotherapist	7	6
Orthopaedic surgeon	4	3
Rheumatologist	2	2
Commissioner	2	1
Region (number)		
South West of England	13	12
North East of England	6	4
South East of England	3	2
East Midlands	1	1
West Midlands	1	1
London	1	1
Academic panel		
Number	25	20
Gender (women:men)	8:17	8:12
Mean years of experience (SD)	20 (12)	22 (12)
Profession (number)		
Academic orthopaedic surgeon	9	6
Academic physiotherapist	8	7
Academic rheumatologist	2	2
Health services researcher	2	1
Academic general practitioner	1	1
Research nurse	1	1
Health economist	1	1
Statistician	1	1

TABLE 20 Participant characteristics (continued)

	Recruited	Completed study
Region (number)		
South West of England	11	9
West Midlands of England	5	4
South East of England	4	3
Scotland	3	2
North West of England	1	1
East of England	1	1

TABLE 21 Suggestions in Round 1 deemed to not be a research question or beyond the scope of the study

Reasons for exclusion	Number	Examples
Not a research question	16	Description of OA pain or experiences of receiving injections Only give injections if necessary Exercise is beneficial for OA Research into treatments is vital
Beyond scope of this study	9	Lifestyle factors of patients who require corticosteroid injections Evaluation of corticosteroid injections for conditions other than OA for example tennis elbow, trochanteric bursitis, carpal tunnel syndrome Reasons why NICE guidelines are not taken up in practice Investigation of alternative reasons for pain

TABLE 22 Candidate research questions developed from Round 1 questionnaire

	Candidate research questions	Topic code	No. of times suggested by participants	Patient panel	Health professional panel	Academic panel
1	Do intra-articular corticosteroid steroid injections reduce OA symptoms?	Clinical effectiveness	35	14	4	17
2	What are the risks of IACIs for OA?	Risks	33	7	11	15
3	Is it possible to predict which patients are most likely to benefit from IACIs for OA?	Identifying responders	24	6	9	9
4	Are IACIs as good as other non-surgical treatments at reducing OA symptoms?	Alternatives	21	8	7	6
5	How many IACIs is it safe for patients with OA to receive?	Repeat injections – number	18	10	7	1
6	When in the OA treatment pathway should patients be offered IACIs?	Care pathway	16	5	3	8

continued

TABLE 22 Candidate research questions developed from Round 1 questionnaire (*continued*)

	Candidate research questions	Topic code	No. of times suggested by participants	Patient panel	Health professional panel	Academic panel
7	What information should be provided to patients about IACIs for OA?	Information for patients	13	12	1	0
8	How long do the effects of an IACI for OA last?	Duration of benefit	11	6	2	3
9	What IACI technique works the best for OA?	Technique	10	3	5	2
10	Do IACIs help people with OA to do exercises/physiotherapy?	Physiotherapy	10	1	3	6
11	Does the effect of IACIs for OA vary by joint?	Joint	9	6	2	1
12	What is the best dose of IACIs to use for patients with OA?	Dose	9	6	3	0
13	Are IACIs for OA good value for money for the NHS?	Cost-effectiveness	8	0	2	6
14	What are the long-term effects of repeated IACIs for OA?	Repeat injections – safety	8	2	4	2
15	Should IACIs for OA be given in primary care or in a hospital setting?	Primary/secondary care	8	2	5	1
16	What are patients' experiences of having IACIs for OA?	Experience	6	2	3	1
17	Do IACIs for OA delay the need for joint replacement?	Joint replacement	6	3	1	2
18	What follow-up should be offered to patients after IACIs for OA?	Follow-up	6	6	0	0
19	How long after an IACI for OA can a joint replacement operation be performed?	Safety – joint replacement	5	0	1	4
20	Can the duration of benefit from IACIs for OA be increased?	Increased duration of benefit	5	5	0	0
21	Do the benefits of IACIs for OA change with repeated use?	Repeat injections – change in benefit	5	3	1	1
22	What outcomes are important to patients having IACIs for OA?	Outcomes	5	1	1	3
23	What type of corticosteroid works the best for OA?	Steroid type	4	0	3	1
24	What is the best time interval between repeated IACIs for OA?	Repeat injections – time interval	4	2	2	0
25	What are patients' expectations of IACIs for OA?	Expectations	4	0	2	2
26	Is there fair access for patients to IACIs for OA?	Access	2	1	0	1

TABLE 23 Feasibility considerations associated with the candidate research questions from the Round 1 questionnaire

Feasibility consideration	Relevant research question
Corticosteroid injections can be administered in GP practices and in hospitals, and research studies would need to recruit patients from both settings	General
Long-term follow may be difficult if patients with persisting symptoms receive joint replacement	General
Would patients agree to take part in a trial comparing a real corticosteroid injection with a placebo corticosteroid injection?	Do corticosteroid injections reduce OA symptoms?
Would it be ethical to give patients a placebo injection?	Do corticosteroid injections reduce OA symptoms?
Could all the effects of corticosteroid injections be measured within a trial?	Do corticosteroid injections reduce OA symptoms?
There are many different factors that might predict how much people benefit from corticosteroid injections	Is it possible to predict which patients are most likely to benefit from corticosteroid injections?
Adverse effects from corticosteroid injections are rare and so a large study would be required	What are the risks of corticosteroid injections? How many corticosteroid injections is it safe for patients to receive?
Treatment pathways can be variable	When in the OA treatment pathway should patients be offered corticosteroid injections?
The physiotherapy that patients receive can be variable	Do corticosteroid injections help people to do exercises/physiotherapy?
Challenges of recruiting patients from diverse backgrounds	Is there fair access for patients to corticosteroid injections?

Literature review

Searches identified 3200 records, and 273 records were identified as potentially relevant to the research questions. The review of the literature revealed that none of the research questions had been robustly answered by previous research (see [Table 24](#)) and therefore all 26 research questions were included in the Round 2 questionnaire.

Round 2

Of the 26 research questions included in the Round 2 questionnaire, 14 were given a rating of 7–9 by $\geq 70\%$ participants and carried forward to Round 3. Details of the overall ratings and individual panel ratings are provided in [Table 25](#). Within the individual panels, there was a general tendency for the patient panel to give higher importance ratings to research questions than the other 2 panels; 22 research questions were given importance ratings of 7–9 by $\geq 70\%$ participants on the patient panel, this reduced to 13 research questions for the healthcare professional panel and four research questions for the academic panel. Only one research question was rated as 7–9 by $\geq 90\%$ participants on a panel; this was ‘What outcomes are important to patients?’, which was rated as important by 92% of the patient panel. Of the 12 research questions not retained and carried forward to Round 3, 8 were rated as 7–9 by $\geq 70\%$ of the patient panel, 3 by the healthcare professional panel and none by the academic panel.

Round 3

Once participants had re-rated each research question after considering the average panel ratings, all 14 research questions were given a rating of 7–9 by $\geq 70\%$ participants (see [Table 25](#)). There was a trend for the percentage of participants giving an importance rating of 7–9 to increase between Rounds 2 and 3. Across the panels there were seven research questions for which one or two panels had $< 70\%$ of participants assign an importance rating of 7–9; however higher ratings from the other panel(s) resulted in the research question being included in the final research

TABLE 24 Candidate research questions and volume of existing evidence

Research question	Volume of evidence ^a	Fully answered?	Justification
1. Do intra-articular corticosteroid steroid injections reduce OA symptoms?	Green	No	Mostly small randomised and non-randomised studies in knee OA. Conflicting conclusions from systematic reviews and meta-analyses of randomised trials
2. What are the risks of IACIs for OA?		No	Mostly hip or knee OA, often limited in scope of safety outcomes evaluated, focus on risk of infection after subsequent joint replacement surgery
3. Is it possible to predict which patients are most likely to benefit from IACIs for OA?		No	Mostly small randomised and non-randomised studies in knee OA, commonly comparing corticosteroid injections to other intra-articular injections for example platelet-rich plasma or hyaluronic acid
4. Are IACIs as good as other non-surgical treatments at reducing OA symptoms?	Orange	No	Small studies looking at limited number and range of risk factors, mostly in knee OA
5. How many IACIs is it safe for patients with OA to receive?	Red	No	Lack of research
6. When in the OA treatment pathway should patients be offered IACIs?		No	Lack of research
7. What information should be provided to patients about IACIs for OA?		No	Lack of research
8. How long do the effects of an IACI for OA last?		No	Lack of research
9. What IACI technique works the best for OA?		No	Lack of research
10. Do IACIs help people with OA to do exercises/physiotherapy?		No	Lack of research
11. Does the effect of IACIs for OA vary by joint?		No	Lack of research
12. What is the best dose of IACIs to use for patients with OA?		No	Lack of research
13. Are IACIs for OA good value for money for the NHS?		No	Lack of research
14. What are the long-term effects of repeated IACIs for OA?		No	Lack of research
15. Should IACIs for OA be given in primary care or in a hospital setting?		No	Lack of research
16. What are patients' experiences of having IACIs for OA?		No	Lack of research
17. Do IACIs for OA delay the need for joint replacement?		No	Lack of research
18. What follow-up should be offered to patients after IACIs for OA?		No	Lack of research

TABLE 24 Candidate research questions and volume of existing evidence (*continued*)

Research question	Volume of evidence ^a	Fully answered?	Justification
19. How long after an IACI for OA can a joint replacement operation be performed?		No	Lack of research
20. Can the duration of benefit from IACIs for OA be increased?		No	Lack of research
21. Do the benefits of IACIs for OA change with repeated use?		No	Lack of research
22. What outcomes are important to patients having IACIs for OA?		No	Lack of research
23. What type of corticosteroid works the best for OA?		No	Lack of research
24. What is the best time interval between repeated IACIs for OA?		No	Lack of research
25. What are patients' expectations of IACIs for OA?		No	Lack of research
26. Is there fair access for patients to IACIs for OA?		No	Lack of research

^a The volume of studies identified that addressed each research question was categorised as 'none/low' (red, < 10 studies), 'some' (orange, 10–30 studies) and 'high' (green, > 30 studies).

TABLE 25 Delphi Round 2 and 3 results

Research question	% 7–9 rating							
	Overall		Patient panel		Health professional panel		Academic panel	
	R2	R3	R2	R3	R2	R3	R2	R3
What are the long-term effects of repeated IACIs for OA?	80	89	81	91	82	90	76	85
What outcomes are important to patients having IACIs for OA?	80	85	92	94	65	71	76	85
Are IACIs as good as other non-surgical treatments at reducing OA symptoms?	72	84	73	85	74	81	67	85
Can the duration of benefit from IACIs for OA be increased?	73	80	86	91	57	76	67	65
When in the OA treatment pathway should patients be offered IACIs?	77	80	83	94	77	62	67	75
How many IACIs is it safe for patients with OA to receive?	76	80	78	79	86	76	62	85
Do IACIs reduce OA symptoms?	70	79	74	82	70	67	62	85
Are IACIs for OA good value for money for the NHS?	74	77	76	76	74	81	71	75
Is it possible to predict which patients are most likely to benefit from IACIs for OA?	72	77	68	71	83	81	67	85

continued

TABLE 25 Delphi Round 2 and 3 results (continued)

Research question	% 7–9 rating							
	Overall		Patient panel		Health professional panel		Academic panel	
	R2	R3	R2	R3	R2	R3	R2	R3
Do IACIs for OA delay the need for joint replacement?	70	77	83	79	57	76	62	75
What are patients' experiences of having IACIs for OA?	74	74	75	88	70	57	76	70
What is the best dose of IACIs to use for patients with OA?	71	74	85	88	64	67	57	60
What type of corticosteroid works the best for OA?	70	74	89	91	70	57	38	65
Do IACIs help people with OA to do exercises/physiotherapy?	75	72	84	85	70	52	67	70
How long do the effects of IACIs for OA last?	69	-	79	-	61	-	62	-
Do the benefits of IACIs for OA change with repeated use?	69	-	73	-	78	-	52	-
What is the best time interval between repeated IACIs for OA?	64	-	72	-	70	-	43	-
What are the risks of IACIs for OA?	63	-	63	-	70	-	57	-
What are patients' expectations of IACIs for OA?	63	-	81	-	52	-	43	-
Does the effect of IACIs for OA vary by joint?	59	-	70	-	43	-	57	-
What information should be provided to patients about IACIs for OA?	58	-	73	-	43	-	48	-
How long after an IACI for OA can a joint replacement operation be performed?	58	-	57	-	61	-	57	-
What IACI technique works the best for OA?	56	-	86	-	43	-	19	-
What follow-up should be offered to patients after IACIs for OA?	54	-	83	-	35	-	29	-
Is there fair access for patients to IACIs for OA?	53	-	80	-	35	-	29	-
Should IACIs for OA be given in primary care or in a hospital setting?	37	-	51	-	22	-	29	-

Note

R2 = Round 2; R3 = Round 3, - = not retained and carried forward to Round 3.

priority list. The 14 prioritised research questions about IACIs for OA are provided below, ordered by the Round 3 importance rating:

1. What are the long-term effects of repeated IACIs for OA?
2. What outcomes are important to patients having IACIs for OA?
3. Are IACIs as good as other non-surgical treatments at reducing OA symptoms?
4. Can the duration of benefit from IACIs for OA be increased?
5. When in the OA treatment pathway should patients be offered IACIs?

6. How many IACIs are safe for patients with OA to receive?
7. Do IACIs reduce OA symptoms?
8. Are IACIs for OA good value for money for the NHS?
9. Is it possible to predict which patients are most likely to benefit from IACIs for OA?
10. Do IACIs for OA delay the need for joint replacement?
11. What are patients' experiences of having IACIs for OA?
12. What is the best dose of IACIs to use for patients with OA?
13. What type of corticosteroid works the best for OA?
14. Do IACIs help people with OA to do exercises/physiotherapy?

Discussion

This study has established 14 research questions for IACIs for OA which were collectively prioritised as important by a large group of patients, healthcare professionals and academics in the UK through a Delphi survey. The remit of the research priorities is broad, including clinical and cost-effectiveness, measurement of outcomes, comparison to other treatments, provision, safety, identifying responders, maximising benefits and patient experience. Some feasibility considerations have also been identified which should be considered when designing future research, including the use of placebo injections, recruitment of patients from different clinical settings and variability in treatment pathways. The generation of research priorities that are important to key stakeholders can help guide future research, ensuring that it reflects the views of patients and professionals working in the area. These research priorities can be used by funders to inform future funding calls, by journals to develop special issue calls and by researchers to focus research efforts on those areas most important to stakeholders.

There were differing views on the importance of the research questions by healthcare professionals, academics and patients. Similar to other consensus studies involving patients and healthcare professionals,¹⁴⁵ there was a general trend for the patient panel to give higher average importance ratings to the research questions than the other panels. There were also differences in the research questions generated in Round 1 by the different panels; for example, only patient participants suggested questions related to follow-up and increasing the duration of benefit from corticosteroid injections. This emphasises the importance of involving patients in this process; in a patient-centred healthcare system, patient voices must be central to identifying and prioritising areas for research. In our study patients were well represented in the Delphi process, with more patient participants than academic or healthcare professional participants. However, in other studies developing research priorities there has been low or no representation from patients.^{138,139,141} In our study, PPI in the study design and co-working with patient representatives to develop the study documents was invaluable to ensure that the language and approaches used were accessible to patient participants.

This study has a number of strengths and limitations which should be acknowledged when interpreting the results. We used a robust and structured process for gaining consensus, and we applied pre-specified criteria for prioritising the research questions. Participant retention between Delphi rounds was high (82% of recruited participants completed all three rounds) and retention was similar between the three panels, reflecting ongoing engagement by all members of all participant panels in the process. However, we acknowledge that other methods can be used to develop research priorities. For example, The James Lind Alliance Priority Setting Partnerships are collaborative initiatives that identify and prioritise evidence uncertainties in specific conditions or healthcare settings that could be answered by research, for example early hip and knee OA¹⁴⁶ and problematic knee replacement.¹⁴⁷ However, Priority Setting Partnerships can be costly, complex and have a long duration; the Delphi approach offered a cost-effective approach to the timely generation of research priorities.

Participants in our study reflected the key stakeholders relevant to the topic, ensuring that the research priorities are relevant to those receiving, administering, commissioning and researching corticosteroid injections. The multidisciplinary composition of both the healthcare professional and academic panels ensured the inclusion of diversity of views in the consensus process. However, our patient panel lacked ethnic diversity; this may be a reflection that our recruitment was limited to a small number of GP surgeries in the South West of England and did not explore other avenues to reach underserved communities, for example through engagement with faith organisations or local

community groups.^{148,149} Given the geographical variable in IACI provision, limiting patient recruitment to the South West of England may have limited the generalisability of our findings. Also, our focus was on developing research priorities relevant to the NHS and therefore our priority list does not reflect the views of people from outside the UK. We had broad inclusion criteria for the academic panel and therefore participants may have had limited expertise in the field of IACIs. Finally, our process for determining if the candidate research questions had been fully answered by previous research was limited as it was not conducted in duplicate and there was no formal assessment of study quality.

In conclusion, the generation of these 14 key research priorities on IACIs for OA can be used by funding bodies and researchers to shape the research landscape and ensure that future research reflects the priorities of key stakeholders. By informing the research agenda, they will promote the development of research that is directed towards the key unanswered questions that could lead to improved care and outcomes for patients receiving IACIs for OA.

Chapter 8 Conclusions

At the time of the NIHR HTA issuing this commissioned research brief, NICE guidelines recommended the use of IACIs as an adjunct to core treatments for the relief of moderate-to-severe uncontrolled pain in people with OA.⁹ Evidence for this recommendation was based on limited data indicating a short-term benefit of repeated IACIs for pain relief in knee OA.^{10–13} However, the benefits and risks of single and recurrent use of IACIs in different joints affected by OA remained unknown. Furthermore, there is concern that IACI use could become more common in future years for a number of reasons including the predicted increasing prevalence of OA, to bridge longer waiting times before undergoing joint replacement, or as an alternative treatment for people who do not wish to undergo surgery or in those where surgery is not an option due to significant comorbidities without evidence of effectiveness, safety and acceptability to support this change. The NIHR HTA therefore commissioned this research to explore the current practice of IACIs for OA in primary care, to establish the long-term effects of single and recurrent IACIs as well as the safety aspects of IACIs, to assess patient and clinician views and experiences of IACIs, and to assess priorities and associated feasibility for future research in this area.

Observational work: usage

A large observational cohort of over 220,000 patients with OA was available to explore the use of IACIs in primary care on a national scale across multiple anatomical joints over a 15-year time period (see [Chapter 3](#)). This work represents a substantial addition to the literature given that most previous work on this topic involves very small cohorts over short time periods and focuses on the knee joint only, whereas we looked at all major joints (shoulder, elbow, wrist, hand, hip, knee and ankle/foot).²⁶ Excluding the reduction in IACI use likely related to COVID-19,¹⁵⁰ the use of IACI was remarkably stable on a national scale over more than a decade. This broadly suggests that IACIs were being offered at the same rates by individual clinicians within a geographical area over this period, and that there were no major changes in the evidence base during the study period which caused clinicians to markedly change their individual practice. This notion is supported by the findings of the qualitative work (see [Chapter 6](#)).

However, interestingly we observed wide heterogeneity in providing IACIs between UK regions, which was also seen to some extent within a region at the GP practice level in the qualitative interviews undertaken (see [Chapter 6](#)). There are a number of possible explanations for this, such as primary and secondary care healthcare services being set-up differently between geographical regions across the country with different clinical guidelines in place, which may affect patient access to IACIs specifically within primary care. However, the geographical variation observed in IACI use may be due to modifiable factors. These could include lack of clinician training or confidence to administer IACIs, limited awareness of IACIs as a treatment option for OA, uncertainty about when IACIs can be used in the patient pathway, and/or uncertainty about the efficacy of IACI for managing OA in various joints.^{83,151,152} These factors were identified during our qualitative interviews with clinicians (see [Chapter 6](#)), as well as variation in the confidence of clinicians in delivering IACI, and therefore could mean patients are being denied access to a potentially efficacious treatment for their OA if they live in low injection use regions or attend GP practices with low rates of utilisation. If modifiable factors are responsible for the geographical variation in IACI use observed, then steps should be taken in the future to understand these factors and issues better to then allow equitable treatment access to patients with OA in the UK.

Observational work: longer-term effects

The effectiveness of IACIs in OA was consistently highlighted as an important area for future research by patients, clinicians and academics during our qualitative and Delphi studies (see [Chapters 6](#) and [7](#)). However, the evidence in this area is heterogeneous, as it has focussed on small patient cohorts with predominantly knee OA and short-term follow-up, with variable comparator groups (e.g. other injection compound, placebo or best practice). A Cochrane review suggested any benefits of IACIs last for up to 6 weeks, with no evidence of an effect seen at 6 months.⁸³ NICE more recently suggested there is no evidence of IACIs having benefit lasting beyond 3 months.¹⁵³ Similarly a recent meta-analysis of ten RCTs focussing on recurrent IACIs for OA (either knee or hand trapeziometacarpal) concluded that they

provided inferior (or non-superior) symptom relief compared with other injectables (including placebo) at 3 months and beyond.⁸⁶ A three-arm RCT on hip OA reported a greater improvement in 6-month hip pain intensity scores in patients having an ultrasound IACI which included local anaesthetic in addition to best current treatment (advice and education) compared with those receiving best current treatment alone; however, there was no significant difference in 6-month hip pain scores in patients receiving ultrasound IACI with local anaesthetic and best current treatment compared with those receiving an ultrasound injection of local anaesthetic alone with best current treatment.⁸⁵ Evidence on the effectiveness of IACIs for OA in the longer-term (beyond 3–6 months), especially for non-knee joints, is lacking.

In a large nationwide observational cohort, we were able to examine the longer-term effects (at up to 5-year follow-up) of both single and recurrent IACIs in multiple joints affected by OA (see [Chapter 4](#)). This work is therefore helpful in dealing with a number of the deficiencies already highlighted with the current evidence base. Furthermore, the use of IV analysis to answer this important clinical question (and PS matching as a secondary analysis) is novel and has not been previously performed as far as we are aware, with these robust and recognised statistical approaches allowing the possibility of getting as close to causation as possible without doing a large expensive RCT. It is becoming increasingly recognised that well-designed observational studies can replicate the findings from real RCTs in a number of cases.^{62,154,155} With this in mind, we consistently observed a reduction in usage of certain pain medications over the longer term after IACIs for OA in most joints. Given the potential serious side effects associated with stronger regular pain medications, such as opiates,¹⁵⁶ this is a clinically relevant finding which is important to consider during the shared decision-making process between patient and clinician when considering the use of IACIs for OA. Specifically in knee osteoarthritis there was a dose-response effect observed, with those receiving repeat IACIs having a greater reduction in pain medication prescriptions compared with those patients having a single IACI. This is also an important finding when considering the increasing use of IACIs in managing symptoms in patients on long surgical waiting lists, and provides support that repeat IACIs are safe in this context. Our findings are in contrast to a recent meta-analysis showing no clinically significant benefit of recurrent IACIs for OA at 3 months and beyond,⁸⁶ which may highlight that longer follow-up periods are needed to assess if patients truly obtain benefit from IACIs.

Observational work: safety

Safety of IACIs in OA was also highlighted as an important future research area by patients, clinicians and academics in our qualitative and Delphi studies (see [Chapters 6](#) and [7](#)). Safety is always an important consideration with any medical intervention, and with IACIs the evidence on safety is limited. This may be because in general the risks of IACIs are considered to be low, and previous studies have included small, often single-centre, patient cohorts (usually involving the knee only) with short follow-up periods and limited statistical power to meaningfully assess any risks or safety concerns specific to IACIs. This has limited the ability of previous meta-analyses to identify any statistically significant findings relating to adverse events compared with sham injection or no treatment.^{83,86}

The safety work done within the observational cohort here had a number of advantages including being a large nationwide cohort (over 197,000 patients with over 8000 injected), involving all major joints, with a control group of OA patients not receiving IACI, and having a 6-month follow-up period (see [Chapter 5](#)). Furthermore, the use of sophisticated statistical methods, such as PS matching and a self-controlled cohort, allowed the minimisation of unmeasured confounding. Therefore this work on safety of IACIs is also a substantial contribution to the current literature. Reassuringly we observed no consistent statistically significant differences in the 6-month risk of mortality, infection, diabetes, cerebrovascular disease, IHD and MI between those receiving and not receiving IACI for OA. However in certain analyses the incidences of diabetes, IHD and MI were numerically higher in the IACI group and approached borderline statistical significance, which requires further investigation.

Our findings on safety of IACIs are important for patients and clinicians to be aware of during shared decision-making when considering the potential benefits and risks of IACIs compared with more invasive procedures, like joint replacement, at various points along the OA patient pathway. As this was a large observational study in primary care there was no access to radiographs, which is a recognised limitation when considering the risk of potential adverse outcomes within the affected joint highlighted in some previous small studies, such as joint degeneration or radiological OA progression with bone and cartilage damage.^{20–22,152} However reassuringly from a safety perspective when using the

more robust IV analysis in our large cohort we did not observe an increased risk of joint replacement in patients with hip or knee OA receiving single IACIs (see [Chapter 4](#)), and no increased risk of adverse events or effect on patient-reported outcomes for those that went on to receive joint replacement.

Qualitative and Delphi work

The qualitative and Delphi studies (see [Chapters 6](#) and [7](#)) used robust methodology and included a large number of views, experiences and areas for future research on IACIs from patients, clinicians and academics. The qualitative interviews highlighted that clinicians were more cautious about administering IACIs compared with patients' perceptions when considering whether they would be willing to receive IACIs. This is likely related to the differences in the weighting of various factors considered in the decision-making process by patients compared with clinicians. Patients often consider IACI to be a low-risk alternative to more invasive procedures such as surgical joint replacement, which can be associated with substantial risk and prolonged recovery times. In addition patients preferred IACIs over taking other forms of pain medications, like opioids, which can have marked side effects and even dependence especially with prolonged use.¹⁵⁶

By contrast, the more cautious approach of clinicians to offer IACIs to patients was related to two broad factors. The first was concern that the evidence base regarding the effectiveness of IACIs was unclear, therefore clinicians were unsure whether or not to offer IACIs, and if offering them they were unsure when in the treatment pathway to offer IACI. This is supported by the weak and limited robust literature showing any clear benefit of IACIs in patients with OA,^{83,86} as discussed earlier. The second factor supporting the more cautious approach of clinicians related to their individual competence and confidence in administering IACIs. Clinicians in primary care highlighted they only received ad hoc training to perform IACIs, and as such had concerns about the technical aspects of administering IACIs including correct needle placement, which was considered vital to delivering any drug directly into a bodily joint by most participants. This is supported by previous work conducted with primary care clinicians highlighting low confidence in performing IACIs, which itself stemmed from a lack of training in the procedure both at medical school and as a qualified clinician.¹⁵¹ A previous survey of primary care clinicians reported that 95% considered themselves as inadequately trained to perform IACIs, with 89% of those surveyed referring patients to speciality clinics to receive IACIs.¹²⁸ This highlights the importance of adequate training of primary care clinicians to perform IACIs with regular quality assurance to help provide equitable patient access to IACIs across the UK, with this lack of current equitable access identified in our observational work (see [Chapter 3](#)).

In terms of identifying areas for future research related to IACIs, there were some common themes between the qualitative interviews with patients and clinicians (see [Chapter 6](#)) and the Delphi study (see [Chapter 7](#)). This overlap is predominantly related to the clinical effectiveness and safety of IACIs. Furthermore, a recent priority-setting partnership exercise involving 16 members (patients, carers, allied professionals and clinicians) supports our findings by also highlighting the clinical effectiveness of IACIs for foot and ankle arthritis as a key future research question given the lack of current evidence.¹⁵⁷ Our Delphi study identified 14 priority research questions relating to IACIs in OA. These covered long-term effects, clinical and cost-effectiveness, measurement of outcomes, comparison to other treatments, provision, safety, identifying responders, maximising benefits, patient experience, delaying the need for joint replacement and dosage. As the work packages for our research were conducted in parallel, we have already made contributions to the evidence base in a number of the areas identified in the Delphi, including long-term effects, clinical effectiveness, measurement of outcomes, comparison to no treatment, provision, safety and patient experience (see [Chapters 3–7](#)).

Patient and public involvement

There has been PPI at all stages of this research. Before applying to the NIHR HTA for funding we discussed the study with our PPI group, the Patient Experience Partnership in Research (PEP-R) group, an established forum of eight service users with musculoskeletal conditions. They agreed it was important to look at the results of treatment with IACIs for OA. Group members had experience of receiving injections for osteoarthritis, with common sites including the knee

and hand. Some group members had experienced problems with receiving injections as not all GPs in their practice performed them and some only injected certain joints. They felt it was important to establish whether injections helped with pain and how safe they were to use, including whether there should be a limit to the number received and over what period of time. The PEP-R group also felt it was important to look at whether injections led to a delay in other procedures such as joint replacement. The PEP-R group members provided very useful feedback and input for the plain language summary and as well as ongoing study support throughout. The co-applicants and chief investigator have reported back to the wider PPI group on a number of occasions during this study to gain wider opinion and insight into the development and delivery of the work, which has been appropriately guided by the group.

Our PPI co-applicant has provided substantial input into the final research proposal and expressed satisfaction with the extent of the work proposed, the methods used and the variety of different ways we analysed the data to ensure that the findings are as robust as possible. She advised on the preferred mechanism for her involvement in the study (such as type of input and frequency) and we have followed these requests. Our PPI co-applicant, as per her request, has joined the Project Management Committee supported by our patient involvement co-ordinator. In this role she has attended regular meetings and been included in relevant communications. She has played an integral part in steering the research with activities such as developing documentation for patient participants, interpreting the research results and advising on dissemination strategies and material.

There have also been formal patient participation with the research undertaken for the qualitative study (semistructured interviews involving 38 patients) and the Delphi study (involving 41 patients with 34 completing the Delphi) as described earlier within this report (see [Chapters 6](#) and [7](#), respectively). This substantial patient participation and involvement has ensured that the thoughts and considerations of patients have been incorporated into the final outcome of this body of research, which will likely benefit future patients with OA who may require or consider having IACIs.

Equality, diversity and inclusion

The observational work included over 200,000 patients and was based on a nationwide primary care dataset (CPRD), which has previously been shown to be representative of the UK in terms of age, sex and ethnicity.²⁷ To ensure our research findings were generalisable and relevant to as many people as possible our cohort study also considered deprivation status when performing our analyses, with sociodemographic factors adjusted and/or matched for in the analyses performed. As OA is a disease of joints in an older population, our work is limited by not being able to include younger patients.

In the qualitative interview study, we tried to ensure that we captured the variation in the sociodemographics of the population by including primary care practices from rural and urban settings across Southwest England. We asked practices to use a sampling framework to ensure that when they identified patients to send the invitation pack to, they accounted for age, gender and ethnicity. However, we could not control for which patients responded. Of the 38 patients we interviewed 37 described themselves as White British, while one described themselves as mixed race. Sixteen male and 22 female patients participated, aged from 49 to 88 years (average 68.5 years) from six primary care practices. The balance of gender is reflective of the prevalence of OA in the general population. However, the lack of ethnic diversity in the sample is perhaps in part due to our focus on practices in the Southwest, and lack of engagement with multi-ethnic partner organisations and local community groups. In future we could work with these groups to raise awareness of the research and study aims, to make our research more accessible to underserved communities. We achieved a balance in gender across the sample of clinicians and a range of levels of expertise and years in practice and clinicians were recruited from 10 practices which varied in geographical location and rural and urban environments, serving diverse populations in terms of socioeconomic status, age and ethnicity.

As the study was conducted during the COVID-19 pandemic we considered government advice on shielding and physical distancing at the time and ensured that we used verbal or electronic consent processes to ensure participants comfort and safety as these did not require a written document requiring signature and return postage. All interviews

took place via telephone or Microsoft Teams. We included PPIE representatives in the development of the interview topic guides and patient-facing documents (study invitations and information leaflets).

For patient participants in the Delphi study, we recruited predominately older people and we had more female participants than male participants, which reflects the prevalence of OA. However, our patient participant population was not inclusive as all participants were White. The lack of ethnic diversity in our patient panel may be a reflection of our recruitment processes, including recruiting participants from a small number of GP surgeries in the Southwest of England. We did not explore other avenues to reach underserved communities, for example through engagement with faith organisations or local community groups. In future, we will explore additional avenues for recruitment and also the provision of information in different formats, such as easy-read patient information leaflets and videos with subtitles/voiceover, to make our research more inclusive. In a separate programme of work, we have been working with local community organisations in Bristol to co-produce a list of musculoskeletal research priorities for people from ethnic minority backgrounds. This work is ongoing, but the effectiveness of IACIs for OA has been raised by the community organisations as an important topic.

Our research team brought together a team representing a variety of research methodologies to best answer the questions proposed in the NIHR commissioned call. Senior team members were drawn from existing collaborations across the Universities of Bristol and Oxford. There was a range of experience and expertise across the team with mentorship and support provided for junior members of the team both in terms of delivering the research programme and in further career development opportunities following on from this body of work. Our research team included a patient representative recruited from our existing PPIE group (PEP-R) with the wider PPIE group of patients with lived experience of painful musculoskeletal conditions supporting the research programme through all stages from conceptualisation, to prioritisation through to reporting. Their insight was extremely valuable and instrumental in developing and delivering this research.

Future research recommendations

The work undertaken using routinely collected UK observational healthcare data (see [Chapters 3–5](#)) has highlighted a number of areas that could be explored in future research. The reasons for geographical heterogeneity in patient access to IACIs identified in the temporal trend work should be explored in future studies as it is possible that patients are currently being denied access to a potentially efficacious treatment for their OA if they live in low injection use regions.

In the work undertaken to assess the longer-term effects of IACIs, some subgroup analyses were small therefore future work in larger observational cohorts would be beneficial, although the limited availability of larger comprehensive datasets than studied here is acknowledged. This includes performing IV analysis in other joints (such as the shoulder, elbow, wrist, hip and ankle/foot) which would require even larger samples, more data on recurrent versus single IACIs, and comparison of IV versus PS matching to assess longer-term effects given the contrasting findings seen here when assessing the rates of surgery after IACI in hip and knee OA patients with these two analytical approaches. It would also be useful to assess similar research questions relating to IACIs for OA within a secondary care setting, as our observational dataset included only IACIs performed within primary care. Repeating the safety work on IACIs in other large healthcare datasets around the world would be beneficial to validate our findings, especially with regard to the risk of diabetes and cardiovascular outcomes (IHD and MI) after IACI.

The qualitative interviews with patients and clinicians (see [Chapter 6](#)) identified many of the same areas for future research (see below) identified in the Delphi study (see [Chapter 7](#)). The first specific area for future research identified from the qualitative work was when within the OA patient pathway is it best to offer IACIs to patients. In combination with the observational data presented, we feel that this would be suitable for testing in a RCT of delivery of IACIs at different stages of the patient pathway for patients with knee OA. Recognising the nature of osteoarthritis and different elements of care and treatment, this would likely be best achieved as part of an intervention package at different stages of the patient pathway. The second area identified was how we can educate and train GPs to be more knowledgeable and confident about administering IACIs within primary care so patients have equitable access to this treatment

across the UK. This would likely take the form of further qualitative work to understand the training needs and how to integrate this into existing training or practice with a focus on improved adoption. This could then be formally tested in an appropriate trial design such as a cluster randomised trial based on regions and primary care networks. It would also be helpful to know the role of IACIs in managing patients on long joint replacement waiting lists, which is becoming increasingly prevalent following COVID-19 and the potential utility of longer-acting steroid injections in comparison to existing common IACI agents.

The Delphi study (see [Chapter 7](#)) which included 75 participants completing all 3 questionnaire rounds identified a priority list of 14 research questions relating to the use of IACIs for OA (summarised in [Round 3](#)). The 14 priority research questions covered long-term effects, clinical and cost-effectiveness, measurement of outcomes, comparison to other treatments, provision, safety, identifying responders, maximising benefits, patient experience, delaying the need for joint replacement and dosage; a number of which have been answered by this research as described already. The Delphi work therefore provides clear avenues and targets for future clinical research into IACIs for OA, which are considered important to patients, clinicians and academic researchers. In combination with the further studies suggested above, the unanswered questions such as comparison of the effectiveness of IACIs to other non-surgical treatments, when in the OA pathway patients should be offered IACI, value for money of IACI, what dose of IACI and what type of IACI are most effective and whether IACI helps people carry out therapy exercises would now be suitable for testing within RCTs that could be efficiently designed to tackle multiple questions.

Additional information

CRediT contribution statement

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data is used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

For the observational work, the use of anonymised linked healthcare data was approved by the Clinical Practice Research Datalink Independent Scientific Advisory Committee, ref: 20_067RA on 16 October 2020. For the qualitative work, ethical approval was obtained from East Midlands – Leicester Central Research Ethics Committee (REC ref. 20/EM/0185) on 20 July 2020, and Health Research Authority approval was also obtained on 14 August 2020. For the Delphi study, ethical approval was obtained from the North of Scotland Research Ethics Service (21/NS/0070) on 24 May 2021 and Health Research Authority approval was also obtained on 25 May 2021.

Information governance statement

The University of Bristol is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under Data Protection legislation, for the CPRD-linked data analysis the University of Bristol and the University of Oxford are the Data Processors; the Department for Health and Social Care (DHSC) is the Data Controller, and we process personal data in accordance with their instructions. For the qualitative work and the Delphi study, the University of Bristol is the Data Controller. You can find out more about how we handle personal data, including how to exercise your individual rights here and how the DHSC handles personal data, including how to exercise your individual rights here.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at <https://doi.org/10.3310/LFAJ9337>.

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Michael Richard Whitehouse – Institution has received research funding from the NIHR, NIHR Bristol Biomedical Research Centre, Healthcare Quality Improvement Partnership (HQIP) and Ceramtec. Receives royalties from Taylor

Francis. Institution receives payment for teaching from Heraeus. Chair and/or member of various NIHR research Trial Steering Committees and Data Monitoring Committees. Member of the British Hip Society Research Committee (unpaid), the British Orthopaedic Association Research Committee (unpaid) and previous member of the NIHR CRN (Trauma and Emergencies CRN Speciality Lead for the West of England with support paid to institution).

Andrew Judge – Institution has received research funding from the NIHR, HDR UK, Versus Arthritis, Healthcare Quality Improvement Partnership (HQIP), Royal College of Physicians (RCP) and Tommy's Health Foundation. Chair of Data Monitoring Committee for an NIHR HTA (unpaid). Chair of Trial Steering Committee for an NIHR HTA (unpaid). Data Monitoring Committee Member for an NIHR HTA (unpaid). Steering Committee Member for Nuffield Foundation (unpaid). Subpanel member of the NIHR Programme Grants for Applied Research (PGfAR) programme (unpaid). Versus Arthritis Health Subcommittee member (unpaid). Co-chair Versus Arthritis Research Expert group (unpaid). Nuffield Foundation Oliver Bird Fund Expert Panel Member (received payments).

Albert Prats Uribe – Institution has received research funding from the European Medicines Agency.

Gulraj Matharu – Institution has received research funding from the NIHR (HTA and as an NIHR Clinical Lecturer) and the Academy of Medical Sciences.

Vikki Wylde – Institution has received research funding from the NIHR. Chair of Trial Steering Committees for NIHR (unpaid).

Edith Anderson – Payments made from NIHR to reimburse time as a patient representative on this grant.

Ashley W Blom – Institution has received research funding from the NIHR. Receives royalties from Taylor Francis. Chair and/or member of various NIHR research Trial Steering Committees and Data Monitoring Committees. Member of University of Sheffield Executive Board NED Sheffield Teaching Hospitals.

Rachael Goberman-Hill – Received payments from UK Research and Innovation as a Co-Chair on the UK Committee on Research Integrity.

Karen Barker – Receives payment for medicolegal reports relating to professional physiotherapy practice.

Daniel Prieto-Alhambra – Institution has received research funding from the European Medicines Agency, Innovative Medicines Initiative, Amgen, Chiesi-Taylor, Lilly, Janssen, Novartis and UCB Biopharma. Received consultancy fees from AstraZeneca and UCB Biopharma. Amgen, Astellas, Janssen, Synapse Management Partners and UCB Biopharma have funded or supported training programmes organised by DPA's department. Membership of NIHR HTA Clinical Evaluation and Trials Committee (November 2017 to November 2021).

The rest of the authors have nothing to declare.

Publications

Wylde V, Moore AJ, Anderson E, Donovan R, Blom AW, Judge A, Whitehouse MR. Research priorities for intra-articular corticosteroid injections for osteoarthritis: a Delphi study. *Osteoarthritis Cartilage* 2022;**4**(3):100291.

Donovan RL, Edwards TA, Judge A, Blom AW, Kunutsor SK, Whitehouse MR. Effects of recurrent intra-articular corticosteroid injections for osteoarthritis at 3 months and beyond: a systematic review and meta-analysis in comparison to other injectables. *Osteoarthritis Cartilage* 2022;**30**(12):1658–69.

Abstracts accepted for meeting presentation

Hawley S, Prats-Urbe A, Matharu G, Delmestri A, Prieto-Alhambra D, Judge A, Whitehouse MR. Long-term effects of intra-articular corticosteroid injections among knee osteoarthritis patients: an instrumental variable and propensity score analysis (Podium Presentation). International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE) Halifax, Canada. August 2023.

Prats-Urbe A, Hawley S, Matharu G, Delmestri A, Judge A, Whitehouse MR, Prieto-Alhambra D. Use of intra-articular corticosteroid injections among osteoarthritis patients in UK general practice (Poster Presentation). International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE) Halifax, Canada. August 2023.

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Appendix 1 Supplementary tables and figures

Chapter 2 Data sources used in *Chapters 3–5*

TABLE 26 Read codes used to define osteoarthritis cohorts

Joint	Read code	Read term
Ankle/foot	N052700	Localised, secondary osteoarthritis of the ankle and foot
	N05z712	Foot osteoarthritis NOS
	N053700	Localised osteoarthritis, unspecified, of the ankle and foot
	N05z713	Toe osteoarthritis NOS
	N05zS00	Osteoarthritis NOS, of 1st MTP joint
	N05zN00	Osteoarthritis NOS, of ankle
	N05zT00	Osteoarthritis NOS, of lesser MTP joint
	N05z700	Osteoarthritis NOS, of ankle and foot
	N051700	Localised, primary osteoarthritis of the ankle and foot
	N05zU00	Osteoarthritis NOS, of IP joint of toe
	N051E00	Localised, primary osteoarthritis of toe
	N05zP00	Osteoarthritis NOS, of subtalar joint
	N05z711	Ankle osteoarthritis NOS
	N05zR00	Osteoarthritis NOS, of other tarsal joint
	N05zQ00	Osteoarthritis NOS, of talonavicular joint
	N054700	Oligoarticular osteoarthritis, unspecified, of ankle/foot
	N05zM00	Osteoarthritis NOS, of tibio-fibular joint
Elbow	N05z211	Elbow osteoarthritis NOS
	N051F00	Localised, primary osteoarthritis of elbow
	N05zC00	Osteoarthritis NOS, of elbow
	N052300	Localised, secondary osteoarthritis of the forearm
	N05z300	Osteoarthritis NOS, of the forearm
	N051300	Localised, primary osteoarthritis of the forearm
	N053300	Localised osteoarthritis, unspecified, of the forearm
	N052200	Localised, secondary osteoarthritis of the upper arm
	N051200	Localised, primary osteoarthritis of the upper arm
	N05z200	Osteoarthritis NOS, of the upper arm
Hand	N053200	Localised osteoarthritis, unspecified, of the upper arm
	N052400	Localised, secondary osteoarthritis of the hand
	Nyu2A00	[X]Other post-traumatic arthrosis/1st carpometacarpal joint
	Nyu2B00	[X]Other 2ndry arthrosis/1st carpometacarpal joints, bilaterl
	N05z400	Osteoarthritis NOS, of the hand

TABLE 26 Read codes used to define osteoarthritis cohorts (continued)

Joint	Read code	Read term
Hip	N05z412	Thumb osteoarthritis NOS
	N050111	Heberdens' nodes
	N05z411	Finger osteoarthritis NOS
	N05zF00	Osteoarthritis NOS, of MCP joint
	N05zH00	Osteoarthritis NOS, of DIP joint of finger
	N05zG00	Osteoarthritis NOS, of PIP joint of finger
	N053400	Localised osteoarthritis, unspecified, of the hand
	2G26.00	O/E – hands – Heberden's nodes
	N053900	Arthrosis of first carpometacarpal joint, unspecified
	N051400	Localised, primary osteoarthritis of the hand
	N050700	Heberden's nodes with arthropathy
	N050112	Bouchards' nodes
	N051C00	Primary arthrosis of first carpometacarpal joints, bilateral
	N050100	Generalised osteoarthritis of the hand
	N050300	Bouchard's nodes with arthropathy
	N054400	Oligoarticular osteoarthritis, unspecified, of hand
	N052B00	Post-traumatic arthrosis of first carpometacarpal jt bilat
	Nyu2900	[X]Other primary arthrosis of first carpometacarpal joint
	N051A00	Coxarthrosis resulting from dysplasia, bilateral
	Nyu2200	[X]Other dysplastic coxarthrosis
	Nyu2E11	[X] Unilateral secondary coxarthrosis
	Nyu2400	[X]Other secondary coxarthrosis, bilateral
	Nyu2E00	[X]Other secondary coxarthrosis
	N052900	Post-traumatic coxarthrosis, bilateral
	Nyu2300	[X]Other post-traumatic coxarthrosis
	N053512	Hip osteoarthritis NOS
	N05z511	Hip osteoarthritis NOS
	N05zJ00	Osteoarthritis NOS, of hip
	Nyu2100	[X]Other primary coxarthrosis
	N051900	Primary coxarthrosis, bilateral
	N05zK00	Osteoarthritis NOS, of sacro-iliac joint
	N053511	Otto's pelvis
	N052500	Localised, secondary osteoarthritis of pelvic region/thigh
	N05z500	Osteoarthritis NOS, pelvic region/thigh
	N051500	Localised, primary osteoarthritis of the pelvic region/thigh
continued		

TABLE 26 Read codes used to define osteoarthritis cohorts (*continued*)

Joint	Read code	Read term
Knee	N053500	Localised osteoarthritis, unspecified, pelvic region/thigh
	Nyu2811	[X] Unilateral secondary gonarthrosis
	Nyu2800	[X] Other secondary gonarthrosis
	Nyu2700	[X] Other secondary gonarthrosis, bilateral
	N052A00	Post-traumatic gonarthrosis, bilateral
	N052C00	Post-traumatic gonarthrosis, unilateral
	N05z611	Knee osteoarthritis NOS
	N053611	Patellofemoral osteoarthritis
	N05zL00	Osteoarthritis NOS, of knee
	N072100	Degenerative lesion of articular cartilage of knee
	Nyu2511	[X] Unilateral primary gonarthrosis
	N051B00	Primary gonarthrosis, bilateral
	Nyu2500	[X] Other primary gonarthrosis
	N052600	Localised, secondary osteoarthritis of the lower leg
	N05z600	Osteoarthritis NOS, of the lower leg
	N051600	Localised, primary osteoarthritis of the lower leg
	N053600	Localised osteoarthritis, unspecified, of the lower leg
	N054600	Oligoarticular osteoarthritis, unspecified, of lower leg
	N05zM00	Osteoarthritis NOS, of tibio-fibular joint
Shoulder	N052100	Localised, secondary osteoarthritis of the shoulder region
	N05z100	Osteoarthritis NOS, of shoulder region
	N05z900	Osteoarthritis NOS, of shoulder
	N053100	Localised osteoarthritis, unspecified, of shoulder region
	N051100	Localised, primary osteoarthritis of the shoulder region
	N054100	Oligoarticular osteoarthritis, unspecified, of shoulder
	N052200	Localised, secondary osteoarthritis of the upper arm
	N051200	Localised, primary osteoarthritis of the upper arm
	N05z200	Osteoarthritis NOS, of the upper arm
	N053200	Localised osteoarthritis, unspecified, of the upper arm
Wrist	N052300	Localised, secondary osteoarthritis of the forearm
	N05z300	Osteoarthritis NOS, of the forearm
	N051300	Localised, primary osteoarthritis of the forearm
	N053300	Localised osteoarthritis, unspecified, of the forearm
	N05zE00	Osteoarthritis NOS, of wrist
	N05z311	Wrist osteoarthritis NOS
	N051D00	Localised, primary osteoarthritis of the wrist
	N05zD00	Osteoarthritis NOS, of distal radio-ulnar joint

Chapter 3 Current practice of use of IACI

TABLE 27 N, women % and mean age at first OA by combination of sites

Osteoarthritis site/s			N	Women, %	Mean age at first OA diagnosis
Knee			10,6890	56.0	65.6
Hip			50,970	57.7	66.7
Hand			27,820	72.4	62.8
Ankle_foot			8550	52.5	61.2
Shoulder			5490	52.7	67.9
Wrist			2351	59.4	66.0
Elbow			824	30.0	61.8
Hip	knee		6860	61.7	68.0
Hand	knee		2969	69.8	64.7
Ankle_foot	knee		1293	58.3	64.3
Hand	hip		1137	73.6	65.6
Knee	shoulder		971	59.4	69.0
Hip	shoulder		464	61.6	69.6
Ankle_foot	hand		424	72.9	61.7
Ankle_foot	hip		405	59.0	64.7
Knee	wrist		350	54.3	67.0
Hand	wrist		225	66.7	66.0
Hand	shoulder		196	71.9	67.8
Hip	wrist		147	61.9	69.1
Elbow	knee		112	36.6	62.6
Ankle_foot	shoulder		81	55.6	66.9
Elbow	wrist		73	54.8	59.7
Elbow	hip		43	48.8	63.9
Ankle_foot	wrist		40	55.0	67.1
Elbow	shoulder		38	47.4	64.7
Elbow	hand		30	36.7	61.0
Shoulder	wrist		25	72.0	67.8
Ankle_foot	elbow		10	20.0	58.4
Hand	hip	knee	285	77.9	66.8
Hip	knee	shoulder	194	64.9	69.9
Ankle_foot	hip	knee	168	63.1	66.6
Ankle_foot	hand	knee	110	67.3	63.4
Hand	knee	shoulder	74	75.7	68.4

continued

TABLE 27 N, Women % and Mean age at first OA by combination of sites (*continued*)

Osteoarthritis site/s				N	Women, %	Mean age at first OA diagnosis
Hand	knee	wrist		46	58.7	65.2
Ankle_foot	hand	hip		43	67.4	64.8
Ankle_foot	knee	shoulder		36	50.0	67.2
Hip	knee	wrist		33	60.6	66.6
Hand	hip	shoulder		28	64.3	67.8
Ankle_foot	hip	shoulder		25	60.0	68.2
Hand	hip	wrist		19	63.2	68.1
Ankle_foot	elbow	knee		15	26.7	63.5
Ankle_foot	knee	wrist		14	50.0	71.1
Elbow	knee	wrist		14	78.6	64.1
Ankle_foot	hand	shoulder		12	58.3	61.3
Elbow	hip	knee		12	16.7	69.1
Ankle_foot	hand	wrist		11	72.7	67.8
Knee	shoulder	wrist		10	60.0	71.3
Ankle_foot	hand	hip	knee	28	75.0	64.8
Ankle_foot	hip	knee	shoulder	25	60.0	67.8
Hand	hip	knee	shoulder	25	68.0	65.6

TABLE 28 Read codes of IACI site and osteoarthritis diagnosed joint

Read code	Osteoarthritis diagnosed joint								
Injection site	Ankle_foot	Elbow	Hand	Hip	Knee	Shoulder	Wrist	Multiple	Total
Ankle_foot	213	< 5	23	41	120	9	< 5	135	545
Elbow	7	< 5	37	42	95	6	< 5	35	230
Hand	26	< 5	477	84	223	13	23	179	1025
Hip	22	< 5	73	1306	338	14	10	375	2140
Knee	252	21	652	1132	20,054	144	64	3870	26,189
Shoulder	430	31	1535	2476	5341	1387	139	2224	13,563
Wrist	12	< 5	127	59	112	8	87	119	527
Unspecific	1096	93	4060	5622	18,124	993	327	4531	34,846
Total	2058	157	6984	10,762	44,407	2574	655	11,468	79,065

Note

Cells in bold highlight concordance between recorded injection site according to the Read code and the registered osteoarthritis site.

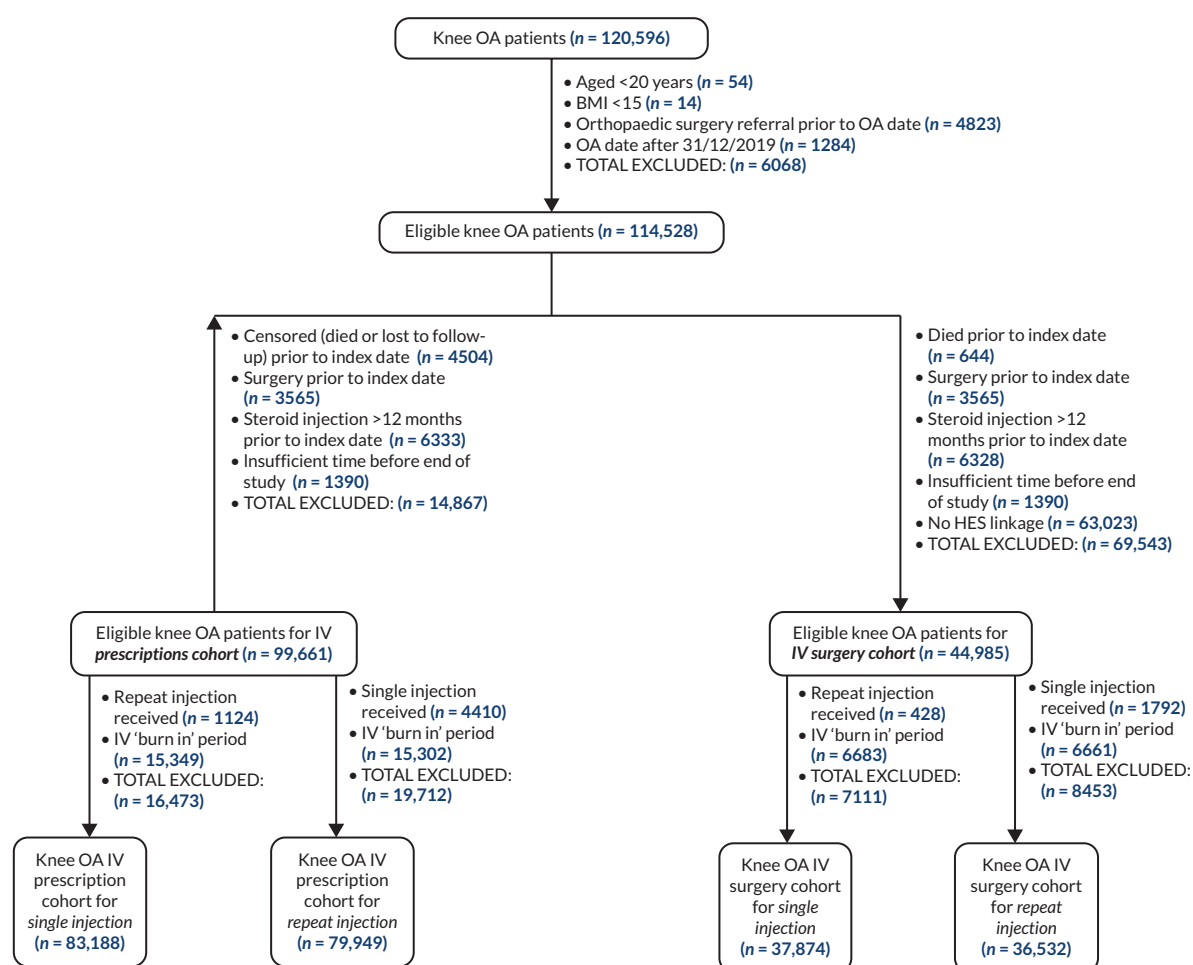
TABLE 29 Number of injections, patients and time from OA diagnosis to injection for injections before osteoarthritis diagnosis

OA site	Injections	Injected patients	OA patients	Injections per OA patient	Injections per injected patient	% OA patients injected	Injection time since OA (years)						
							Min	Mean	p5	p25	p50	p75	Max
Ankle foot	845	504	8550	0.10	1.7	5.89	-22.5	-4.4	-13.4	-6.1	-3.2	-1.2	0.0
Elbow	81	49	824	0.10	1.7	5.95	-15.9	-4.7	-12.3	-7.1	-3.2	-1.6	-0.1
Hand	3011	1701	27,820	0.11	1.8	6.11	-25.9	-4.7	-13.2	-6.8	-3.5	-1.5	0.0
Hip	5075	2936	50,970	0.10	1.7	5.76	-25.5	-4.7	-13.4	-6.9	-3.4	-1.3	0.0
Knee	15,958	8537	106,890	0.15	1.9	7.99	-27.5	-3.8	-12.1	-5.5	-2.5	-0.9	0.0
Multiple	4175	2107	17,230	0.24	2.0	12.23	-25.4	-4.1	-12.0	-6.2	-2.9	-1.1	0.0
Shoulder	1236	703	5490	0.23	1.8	12.81	-22.1	-3.7	-12.9	-5.3	-2.0	-0.6	0.0
Wrist	308	182	2351	0.13	1.7	7.74	-18.6	-4.5	-12.6	-6.8	-3.4	-1.1	0.0

TABLE 30 Prevalence and cumulative incidence of first injection after osteoarthritis

	Ankle foot, %	Elbow, %	Hand, %	Hip, %	Knee, %	Shoulder, %	Wrist, %	Multiple, %
Prevalence (years)								
1	1.22	1.09	0.89	1.15	2.03	4.50	1.49	2.54
2	1.84	2.18	1.78	1.90	3.25	6.30	2.47	4.31
3	2.53	2.91	2.48	2.57	4.08	7.34	3.23	5.60
4	3.13	3.28	3.10	3.07	4.78	8.29	3.96	6.77
5	3.68	3.52	3.64	3.51	5.38	9.13	4.55	7.80
Incidence (years)								
1	2.80	1.58	2.25	2.08	4.90	6.99	3.28	5.77
2	3.54	2.31	3.11	2.98	6.10	8.07	4.13	7.63
3	4.26	3.16	3.71	3.64	6.96	8.65	4.81	8.97
4	4.88	3.76	4.23	4.08	7.61	9.05	5.36	10.20
5	5.27	4.25	4.66	4.47	8.13	9.36	5.66	11.09

Chapter 4 Long-term effects of IACI

**FIGURE 11** Population flow diagram for prescription and surgery cohorts used in IV analyses of single and repeat IACI for knee osteoarthritis (outcomes at 6-month follow-up).

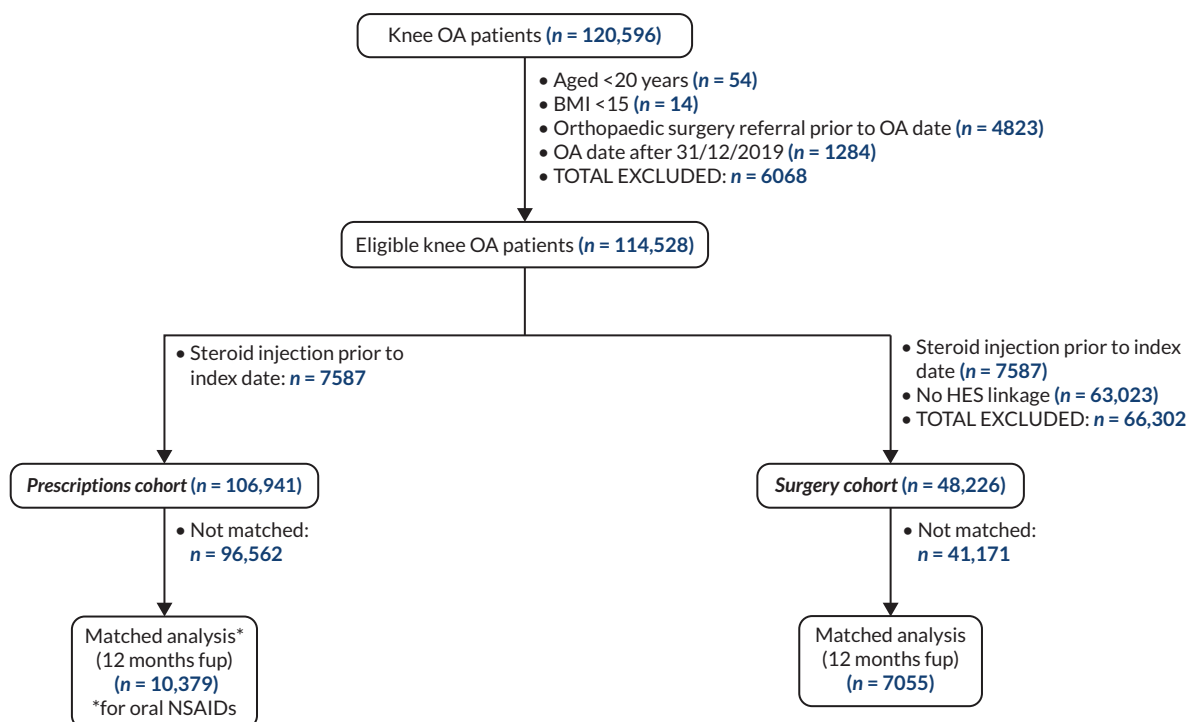


FIGURE 12 Population flow diagram for prescription and surgery cohorts used in PS analyses of IACI for knee osteoarthritis (outcomes at 6-month follow-up).

TABLE 31 Description of covariates among knee OA patients included in the prescription cohorts used in IV analyses of single IACI: stratified by IACI exposure and IV group

Variable	By IACI exposure during IV window			By IV group		
	Total	No IACI	IACI	Total	No IACI	IACI
	N = 83,188	N = 79,322	N = 3866	N = 83,188	N = 49,473	N = 33,715
Age in years: mean (SD)	65.8 (12.3)	65.7 (12.3)	67.7 (11.8)	65.8 (12.3)	65.9 (12.3)	65.6 (12.3)
Female (%)	56.6	56.5	59.4	56.6	56.9	56.2
Least deprived (%)	9.8	9.8	9.9	9.8	9.2	10.5
Less deprived (%)	9.1	9.2	7.5	9.1	9.6	8.5
Mid deprived (%)	9.6	9.7	7.8	9.6	10.3	8.6
More deprived (%)	7.9	8.0	6.5	7.9	8.6	7.1
Most deprived (%)	6.3	6.3	6.5	6.3	5.9	6.7
Deprivation missing (%)	57.3	57.1	61.8	57.3	56.4	58.6
BMI: < 20 kg/m ² (%)	1.3	1.3	1.1	1.3	1.3	1.4
BMI 20 < 25 kg/m ² (%)	15.4	15.4	13.8	15.4	15.0	15.8
BMI 25 < 30 kg/m ² (%)	31.9	31.9	32.0	31.9	31.5	32.4
BMI 30 < 35 kg/m ² (%)	22.6	22.4	25.5	22.6	22.6	22.5
BMI 35 < 40 kg/m ² (%)	10.2	10.1	12.2	10.2	10.1	10.3
BMI ≥ 40 kg/m ² (%)	6.5	6.5	7.3	6.5	6.4	6.6
BMI missing (%)	12.1	12.4	8.1	12.1	13.0	11.0
Ex-drinker (%)	2.7	2.7	2.9	2.7	2.6	2.9
Never drinker (%)	15.7	15.7	17.2	15.7	15.7	15.8
Current drinker (%)	60.3	60.2	62.2	60.3	59.2	61.7
Drinking missing (%)	21.3	21.5	17.6	21.3	22.6	19.6
Ex-smoker (%)	31.0	30.9	32.8	31.0	31.0	31.0
Never smoker (%)	53.6	53.6	53.7	53.6	53.3	54.0
Current smoker (%)	11.8	11.8	11.0	11.8	11.7	11.8
Smoking missing (%)	3.6	3.7	2.4	3.6	3.9	3.2
Charlson = 0 (%)	70.5	70.7	65.6	70.5	70.5	70.4
Charlson = 1 (%)	8.4	8.4	9.0	8.4	8.5	8.4
Charlson = 2 (%)	11.0	10.9	12.9	11.0	11.0	10.9
Charlson ≥ 3 (%)	10.1	10.0	12.5	10.1	10.0	10.3
Polyarthritis (%)	4.3	4.3	5.4	4.3	4.2	4.6
Asthma (%)	9.7	9.6	11.5	9.7	9.5	10.0
Cancer (%)	7.2	7.2	7.2	7.2	7.2	7.3
Cerebrovascular disease (%)	2.5	2.5	2.7	2.5	2.5	2.6
COPD (%)	4.7	4.6	5.7	4.7	4.7	4.6
Diabetes (%)	11.8	11.7	13.0	11.8	11.9	11.6

TABLE 31 Description of covariates among knee OA patients included in the prescription cohorts used in IV analyses of single IACI: stratified by IACI exposure and IV group (*continued*)

Variable	By IACI exposure during IV window			By IV group		
	Total	No IACI	IACI	Total	No IACI	IACI
	N = 83,188	N = 79,322	N = 3866	N = 83,188	N = 49,473	N = 33,715
DVT (%)	0.9	0.9	1.1	0.9	0.9	0.9
Epilepsy (%)	1.4	1.3	1.5	1.4	1.4	1.3
Fracture (%)	4.8	4.8	6.0	4.8	4.7	5.0
Ischaemic heart disease (%)	4.6	4.5	5.8	4.6	4.6	4.5
LRTI (%)	19.5	19.4	22.8	19.5	19.3	19.9
Malabsorption (%)	0.2	0.2	0.2	0.2	0.1	0.2
MI (%)	1.2	1.2	1.5	1.2	1.2	1.2
Hyperlipidaemia (%)	7.7	7.7	8.8	7.7	7.5	8.0
Hypertension (%)	20.6	20.4	23.7	20.6	20.5	20.7
Osteoporosis (%)	2.6	2.5	3.3	2.6	2.7	2.5
Pulmonary embolism (%)	0.5	0.4	0.6	0.5	0.4	0.5
Chronic renal failure (%)	9.1	9.0	12.6	9.1	9.1	9.2
Acute renal failure (%)	9.1	9.0	12.6	9.1	9.1	9.2
URTI (%)	16.6	16.5	17.0	16.6	16.9	16.2
UTI (%)	7.4	7.3	9.6	7.4	7.4	7.5
Parkinson's disease (%)	1.5	1.4	2.2	1.5	1.5	1.5
Antiarrhythmics (%)	3.3	3.3	3.8	3.3	3.2	3.4
Antibiotics (%)	14.3	14.2	15.6	14.3	14.0	14.7
Antidepressants (%)	37.6	37.3	41.4	37.6	37.6	37.5
Anticonvulsants (%)	18.2	17.9	23.7	18.2	18.1	18.4
Anxiolytics (%)	5.9	5.7	9.5	5.9	5.9	5.9
Bisphosphonates (%)	9.8	9.6	13.4	9.8	9.8	9.9
Calcium/vitamin D (%)	4.5	4.4	5.9	4.5	4.6	4.3
Oral glucocorticoids (%)	7.4	7.3	9.2	7.4	7.4	7.3
NSAIDs oral (%)	7.3	7.1	9.7	7.3	7.1	7.5
NSAIDs topical (%)	34.2	33.8	40.6	34.2	34.1	34.3
Opioids (%)	17.8	17.3	25.6	17.8	17.2	18.6
Partial opioids (%)	11.7	11.4	17.7	11.7	11.8	11.6
Paracetamols (%)	32.3	31.8	41.9	32.3	32.5	31.9
Proton pump inhibitor (%)	45.9	45.2	57.9	45.9	46.1	45.6
Prednisolone (%)	34.4%	33.9	43.5	34.4	34.0	34.8
Statins (%)	7.1%	7.0	9.3	7.1	6.9	7.3

continued

TABLE 31 Description of covariates among knee OA patients included in the prescription cohorts used in IV analyses of single IACI: stratified by IACI exposure and IV group (*continued*)

Variable	By IACI exposure during IV window			By IV group		
	Total	No IACI	IACI	Total	No IACI	IACI
	N = 83,188	N = 79,322	N = 3866	N = 83,188	N = 49,473	N = 33,715
Hormone replacement therapy (%)	34.0	33.7	39.4	34.0	34.0	34.0
Diuretics (%)	24.0	23.8	26.7	24.0	24.6	23.2
Physiotherapy (%)	29.5	29.1	37.1	29.5	28.0	31.6

a Using index date of 180 days after OA diagnosis date.

TABLE 32 Description of covariates among knee osteoarthritis patients included in the prescription cohorts^a used in IV analyses of repeat IACI: stratified by IACI exposure and IV group

Variable	By IACI exposure during IV window			By IV group		
	Total	No IACI	IACI	Total	No IACI	IACI
	N = 79,949	N = 78,988	N = 961	N = 79,949	N = 68,634	N = 11,315
Age in years: mean (SD)	65.7 (12.3)	65.7 (12.3)	68.4 (11.7)	65.7 (12.3)	65.8 (12.3)	65.2 (12.3)
Female (%)	56.5	56.5	59.9	56.5	56.5	56.4
Least deprived (%)	9.9	9.9	9.5	9.9	9.9	9.7
Less deprived (%)	9.3	9.3	6.6	9.3	9.4	8.4
Mid deprived (%)	9.8	9.8	7.4	9.8	10.2	7.4
More deprived (%)	8.1	8.1	7.2	8.1	8.3	7.0
Most deprived (%)	6.3	6.3	7.3	6.3	6.1	7.5
Deprivation missing (%)	56.7	56.6	62.1	56.7	56.2	60.0
BMI: < 20 kg/m ² (%)	1.3	1.3	1.8	1.3	1.3	1.4
BMI 20 < 25 kg/m ² (%)	15.4	15.5	14.2	15.4	15.3	16.1
BMI 25 < 30 kg/m ² (%)	31.9	31.9	30.1	31.9	31.7	33.3
BMI 30 < 35 kg/m ² (%)	22.4	22.4	24.8	22.4	22.5	22.3
BMI 35 < 40 kg/m ² (%)	10.1	10.1	13.6	10.1	10.1	10.3
BMI ≥ 40 kg/m ² (%)	6.5	6.4	8.0	6.5	6.4	6.7
BMI missing (%)	12.3	12.4	7.6	12.3	12.7	10.1
Ex-drinker (%)	2.7	2.6	3.6	2.7	2.6	2.9
Never drinker (%)	15.7	15.7	18.4	15.7	15.6	16.0
Current drinker (%)	60.2	60.1	62.0	60.2	59.7	62.9
Drinking missing (%)	21.5	21.6	15.9	21.5	22.0	18.2
Ex-smoker (%)	30.9	30.9	34.9	30.9	31.0	30.3
Never smoker (%)	53.6	53.6	52.1	53.6	53.4	54.7
Current smoker (%)	11.8	11.8	10.1	11.8	11.8	12.0

TABLE 32 Description of covariates among knee osteoarthritis patients included in the prescription cohorts^a used in IV analyses of repeat IACI: stratified by IACI exposure and IV group (*continued*)

Variable	By IACI exposure during IV window			By IV group		
	Total	No IACI	IACI	Total	No IACI	IACI
	N = 79,949	N = 78,988	N = 961	N = 79,949	N = 68,634	N = 11,315
Smoking missing (%)	3.7	3.7	2.9	3.7	3.8	3.0
Charlson = 0 (%)	70.6	70.7	64.4	70.6	70.5	71.0
Charlson = 1 (%)	8.4	8.4	11.0	8.4	8.5	8.1
Charlson = 2 (%)	10.9	10.9	12.3	10.9	10.9	11.0
Charlson ≥ 3 (%)	10.1	10.0	12.3	10.1	10.1	10.0
Polyarthritis (%)	4.8	4.8	5.6	4.8	4.7	5.2
Asthma (%)	9.6	9.6	12.5	9.6	9.6	9.7
Cancer (%)	7.2	7.2	7.4	7.2	7.3	6.9
Cerebrovascular disease (%)	2.5	2.5	4.2	2.5	2.5	2.6
Chronic obstructive pulmonary disease (%)	4.7	4.6	6.9	4.7	4.7	4.4
Diabetes (%)	11.7	11.7	14.0	11.7	11.8	11.2
DVT (%)	0.9	0.9	1.7	0.9	0.9	0.8
Epilepsy (%)	1.4	1.4	2.1	1.4	1.4	1.4
Fracture (%)	4.8	4.8	6.2	4.8	4.8	4.7
Ischaemic heart disease (%)	4.5	4.5	6.0	4.5	4.6	4.4
LRTI (%)	19.5	19.4	24.0	19.5	19.4	19.5
Malabsorption (%)	0.2	0.2	0.1	0.2	0.2	0.2
MI (%)	1.2	1.2	2.1	1.2	1.2	1.2
Hyperlipidaemia (%)	7.7	7.7	8.0	7.7	7.7	7.8
Hypertension (%)	20.4	20.4	20.9	20.4	20.5	20.3
Osteoporosis (%)	2.6	2.6	3.9	2.6	2.6	2.4
Pulmonary embolism (%)	0.4	0.4	0.6	0.4	0.5	0.4
Chronic renal failure (%)	9.1	9.0	11.7	9.1	9.1	8.9
Acute renal failure (%)	0.4	0.4	0.3	0.4	0.4	0.2
URTI (%)	16.6	16.6	18.5	16.6	16.8	15.7
UTI (%)	7.4	7.4	12.1	7.4	7.3	7.8
Parkinson's disease (%)	1.4	1.4	1.9	1.4	1.4	1.4
Antiarrhythmics (%)	3.3	3.3	2.8	3.3	3.2	3.5
Antibiotics (%)	14.3	14.3	17.3	14.3	14.3	14.4
Antidepressants (%)	18.0	17.9	25.2	18.0	18.0	17.6
Anticonvulsants (%)	5.7	5.7	11.7	5.7	5.7	5.9
Anxiolytics	9.7	9.6	15.0	9.7	9.6	10.1

continued

TABLE 32 Description of covariates among knee osteoarthritis patients included in the prescription cohorts^a used in IV analyses of repeat IACI: stratified by IACI exposure and IV group (*continued*)

Variable	By IACI exposure during IV window			By IV group		
	Total	No IACI	IACI	Total	No IACI	IACI
	N = 79,949	N = 78,988	N = 961	N = 79,949	N = 68,634	N = 11,315
Bisphosphonates (%)	4.4	4.4	6.3	4.4	4.5	4.1
Calcium/vitamin D (%)	7.3	7.3	9.6	7.3	7.3	7.0
Oral glucocorticoids (%)	7.1	7.1	11.4	7.1	7.2	7.0
NSAIDs oral (%)	34.0	33.9	42.1	34.0	34.0	34.0
NSAIDs topical (%)	17.4	17.3	28.7	17.4	17.3	18.6
Opioids (%)	11.5	11.4	20.7	11.5	11.6	11.4
Partial opioids (%)	32.0	31.8	46.0	32.0	32.2	30.6
Paracetamols (%)	45.5	45.3	63.7	45.5	45.7	44.0
Proton pump inhibitor (%)	33.9	33.7	46.3	33.9	33.9	34.0
Prednisolone (%)	7.0	6.9	10.9	7.0	7.0	6.8
Statins (%)	33.8	33.7	40.9	33.8	33.9	32.8
Hormone replacement therapy (%)	2.6	2.6	2.9	2.6	2.6	2.6
Diuretics (%)	23.9	23.9	27.0	23.9	24.2	22.6
Physiotherapy (%)	29.2	29.1	40.2	29.2	29.0	30.6

^a Using index date of 180 days after OA diagnosis date.

TABLE 33 Final sample sizes of prescription cohorts^a used in final PS-matched analyses of IACI use on medication outcomes: by joint, outcome and follow-up

Joint (eligible patients)	Medication	Follow-up (months)	IACI during fup	No IACI during fup
Ankle (N = 10,225)	NSAIDs	12	139	275
		60	251	499
	Opioids	12	215	426
		60	390	773
	Oral glucocorticosteroids	12	243	484
		60	443	876
	Paracetamol	12	137	274
		60	254	507
	Partial opioids	12	215	426
		60	390	773
	Topical NSAIDs	12	215	421
		60	383	759

TABLE 33 Final sample sizes of prescription cohorts^a used in final PS-matched analyses of IACI use on medication outcomes: by joint, outcome and follow-up (*continued*)

Joint (eligible patients)	Medication	Follow-up (months)	IACI during fup	No IACI during fup
Hand (N = 30,672)	NSAIDs	12	412	823
		60	787	1573
	Opioids	12	553	1104
		60	1054	2103
	Oral glucocorticosteroids	12	609	1219
		60	1149	2295
	Paracetamol	12	359	718
		60	699	1396
	Partial opioids	12	553	1104
		60	1055	2103
	Topical NSAIDs	12	520	1038
		60	1004	2005
Hip (N = 55,159)	NSAIDs	12	618	1235
		60	1250	2498
	Opioids	12	817	1631
		60	1686	3370
	Oral glucocorticosteroids	12	989	1976
		60	1995	3986
	Paracetamol	12	410	820
		60	866	1729
	Partial opioids	12	817	1631
		60	1686	3370
	Topical NSAIDs	12	895	1790
		60	1843	3682
Knee (N = 106,941)	NSAIDs	12	3460	6919
		60	5447	10,887
	Opioids	12	4806	9611
		60	7677	15,344
	Oral glucocorticosteroids	12	5767	11,529
		60	8371	16,735
	Paracetamol	12	2562	5119
		60	4181	8348
continued				

TABLE 33 Final sample sizes of prescription cohorts^a used in final PS-matched analyses of IACI use on medication outcomes: by joint, outcome and follow-up (*continued*)

Joint (eligible patients)	Medication	Follow-up (months)	IACI during fup	No IACI during fup
Shoulder (N = 6292)	Partial opioids	12	5240	10,478
		60	7677	15,344
	Topical NSAIDs	12	4452	8901
		60	7169	14,326
	NSAIDs	12	308	600
		60	427	831
	Opioids	12	417	818
		60	574	1126
	Oral glucocorticosteroids	12	471	933
		60	656	1288
	Paracetamol	12	212	416
		60	302	581
	Partial opioids	12	417	818
		60	574	1126
	Topical NSAIDs	12	408	799
		60	560	1098

fup, follow-up.

a Using index date of OA diagnosis date.

TABLE 34 Final sample sizes of surgery cohorts^a used in final PS-matched analyses of IACI use on surgical outcomes: by joint, outcome and follow-up

Joint (eligible patients)	Outcome	Follow-up (months)	IACI during fup	No IAC during fup
Hip (N = 22,627)	Arthroscopy, Debridement and Joint replacement	6	376	752
		12	520	1038
		24	709	1416
		60	1024	2041
Knee (N = 48,226)	Arthroscopy, Debridement and Joint replacement	6	1925	3847
		12	2353	4702
		24	2892	5781
		60	3820	7632

fup, follow-up.

a Using index date of OA diagnosis date.

TABLE 35 Description of patient characteristics in the PS-matched cohorts (for analysis of outcomes at 60-month follow-up)

Variable	Prescription cohorts ^a					Surgery cohorts	
	Ankle	Hand	Hip	Knee	Shoulder	Hip	Knee
	N = 1411	N = 3694	N = 6619	N = 27,570	N = 2212	N = 3065	N = 11,452
Age in years: mean (SD)	61.1 (12.8)	62.9 (11.0)	65.9 (12.1)	66.9 (12.0)	67.2 (13.0)	65.8 (12.0)	66.9 (12.2)
Female (%)	54.7	74.3	64.4	60.3	54.3	64.2	62.1
BMI kg/m ² : mean (SD)	29.3 (5.7)	28.2 (5.8)	29.2 (5.8)	30.6 (6.4)	28.6 (5.5)	28.9 (5.8)	30.0 (6.2)
Least deprived (%)	11.5	14.3	11.0	9.5	8.8	23.2	23.7
Less deprived (%)	8.9	9.5	10.6	7.9	7.8	23.1	19.8
Mid deprived (%)	11.2	7.5	9.5	8.2	10.8	21.6	20.5
More deprived (%)	7.4	5.3	8.2	6.8	5.6	17.2	17.6
Most deprived (%)	6.7	4.5	7.3	7.4	5.7	14.9	18.3
Deprivation missing (%)	54.2	59.0	53.4	60.2	61.4	-	-
Ex-drinker (%)	4.0	1.8	3.2	3.4	2.4	3.8	3.2
Never drinker (%)	19.1	17.7	16.5	20.5	22.2	16.7	19.4
Current drinker (%)	77.0	80.5	80.3	76.1	75.4	79.5	77.3
Ex-smoker (%)	35.0	33.1	33.6	33.4	37.8	33.7	32.1
Never smoker (%)	52.4	54.2	52.0	54.3	48.2	51.2	56.1
Current smoker (%)	12.5	12.7	14.4	12.3	14.0	15.1	11.8
Charlson = 0 (%)	74.6	76.2	67.7	67.7	63.7	65.8	67.2
Charlson = 1 (%)	6.2	7.1	10.5	9.3	10.8	11.0	9.1
Charlson = 2 (%)	10.6	8.4	10.9	12.2	13.0	12.1	12.2
Charlson ≥ 3 (%)	8.5	8.3	10.8	10.8	12.5	11.0	11.5
Polyarthritis (%)	12.1	8.0	8.4	4.8	18.4	9.5	4.0
Asthma (%)	8.6	12.0	10.4	11.0	10.5	10.3	10.8
Cancer (%)	7.0	5.6	7.9	7.1	6.6	7.9	8.4
Cerebrovascular disease (%)	2.1	2.6	3.0	2.9	3.4	3.1	2.6
COPD (%)	5.6	4.7	6.0	5.1	7.7	6.5	4.9
Diabetes (%)	8.5	7.6	11.3	12.1	12.7	11.1	11.8
DVT (%)	0.8	0.9	0.8	1.1	0.9	1.0	1.2
Epilepsy (%)	0.7	1.4	1.4	1.5	1.3	1.7	1.5
Fracture (%)	5.6	5.4	5.8	5.4	6.1	5.5	5.1
Ischaemic heart disease (%)	4.6	4.3	5.8	5.5	7.4	5.6	6.4
LRTI (%)	18.9	21.2	21.1	22.0	23.6	23.3	25.0
Malabsorption (%)	0.3	0.3	0.2	0.2	0.1	0.1	0.2
MI (%)	0.9	0.9	1.4	1.4	1.6	1.3	1.4
Hyperlipidaemia (%)	7.9	7.8	8.2	8.9	9.4	8.0	10.5
Hypertension (%)	20.6	17.9	21.0	22.3	21.7	20.4	23.4

continued

TABLE 35 Description of patient characteristics in the PS-matched cohorts (for analysis of outcomes at 60-month follow-up) (*continued*)

Variable	Prescription cohorts ^a					Surgery cohorts	
	Ankle	Hand	Hip	Knee	Shoulder	Hip	Knee
	N = 1411	N = 3694	N = 6619	N = 27,570	N = 2212	N = 3065	N = 11,452
Osteoporosis (%)	1.3	2.6	4.7	3.2	3.4	5.1	3.2
Pulmonary embolism (%)	0.3	0.6	0.4	0.5	0.9	0.3	0.6
Chronic renal failure (%)	9.1	5.8	10.2	10.5	11.4	11.3	11.2
Acute renal failure (%)	9.1	5.8	10.2	10.5	11.4	11.3	11.2
URTI (%)	17.2	24.7	18.4	17.3	17.5	21.2	20.2
UTI (%)	5.0	10.6	9.5	8.8	9.0	10.8	10.3
Parkinson's disease (%)	1.6	1.2	1.2	2.0	1.6	0.7	1.9
Antiarrhythmics (%)	4.5	2.6	4.3	3.7	4.2	3.6	4.1
Antibiotic (%)	14.5	14.2	13.1	15.6	16.4	13.6	15.0
Antidepressant (%)	39.3	44.2	40.0	41.4	42.4	38.5	41.7
Anticonvulsants (%)	22.7	29.1	26.0	21.7	20.8	23.7	21.6
Anxiolytics (%)	7.0	7.0	8.8	7.5	8.5	7.4	7.1
Bisphosphonate (%)	9.2	13.8	12.5	12.8	14.3	11.2	11.0
Calcium/vitamin D (%)	2.8	5.2	6.9	5.4	8.6	6.6	5.5
Oral glucocorticoid (%)	6.5	8.4	9.6	8.4	10.8	10.0	8.3
NSAID oral (%)	6.1	6.6	9.4	8.8	10.8	10.5	8.1
NSAID topical (%)	46.9	36.1	43.3	40.6	41.8	43.2	40.1
Opioid (%)	19.0	18.5	16.1	21.8	22.8	14.0	17.6
Partial opioid (%)	18.1	14.1	23.4	16.0	20.0	21.9	14.4
Paracetamol (%)	33.7	30.5	46.3	39.9	39.9	43.6	36.7
Proton pump inhibitor (%)	46.3	42.8	61.3	54.4	57.6	56.6	52.1
Prednisolone (%)	34.3	39.8	39.1	40.1	40.3	38.2	37.6
Statins (%)	6.2	6.3	9.2	8.5	10.4	10.3	7.8
Hormone replacement therapy (%)	27.3	28.2	38.5	37.4	41.7	36.6	35.4
Diuretic (%)	19.1	19.2	27.5	26.7	26.3	25.4	26.4
Physiotherapy (%)	36.1	36.1	37.5	34.2	41.7	42.1	36.6

^a Prior to re-matching after exclusion of prevalent medication use.

TABLE 36 SMD comparing patient characteristics between IV groups^a among patients included in the prescription cohorts used in IV analyses of repeat IACI

Variable		Ankle	Hand	Hip	Knee	Shoulder
		IV = 1 (115) ^a IV = 0 (4949)	IV = 1 (955) ^b IV = 0 (15,442)	IV = 1 (1248) ^b IV = 0 (33,164)	IV = 1 (11,315) ^b IV = 0 (68,634)	IV = 1 (511) ^b IV = 0 (2105)
Age	-		0.004	-0.01	-0.05	-0.01
Female	-		0.054	0	0.00	-0.04
Least deprived	-		0.128	0.1	-0.01	0.19
Less deprived	-		0.004	0.03	-0.04	0.1
Mid deprived	-		-0.113	-0.01	-0.10	-0.04
More deprived	-		-0.094	-0.07	-0.05	-0.22
Most deprived	-		-0.014	0.17	0.06	-0.09
Deprivation missing	-		0.012	-0.12	0.08	0
BMI: < 20 kg/m ²	-		0.042	-0.01	0.00	-0.01
BMI 20 < 25 kg/m ²	-		0.046	-0.1	0.02	0.11
BMI 25 < 30 kg/m ²	-		0.009	0.05	0.03	0.14
BMI 30 < 35 kg/m ²	-		-0.088	0.07	-0.01	-0.03
BMI 35 < 40 kg/m ²	-		0.031	0.04	0.01	-0.15
BMI ≥ 40 kg/m ²	-		-0.032	-0.06	0.01	0.05
BMI missing	-		-0.012	-0.04	-0.08	-0.3
Ex-drinker	-		-0.009	-0.07	0.02	0.04
Never drinker	-		-0.004	0.07	0.01	0.03
Current drinker	-		0.008	0.08	0.06	0.07
Drinking missing	-		-0.003	-0.14	-0.10	-0.14
Ex-smoker	-		-0.042	-0.03	-0.02	0.06
Never smoker	-		0.066	0.01	0.02	0.01
Current smoker	-		-0.037	0.04	0.01	-0.08
Smoking missing	-		-0.011	-0.04	-0.04	-0.06
Charlson = 0	-		0.045	-0.01	0.01	-0.03
Charlson = 1	-		-0.028	0.01	-0.02	-0.04
Charlson = 2	-		0.005	0.02	0.00	0
Charlson ≥ 3	-		-0.049	-0.02	0.00	0.08
Polyarthritis	-		-0.048	-0.08	0.02	0.03
Asthma	-		-0.054	-0.03	0.00	-0.04
Cancer	-		-0.004	0.02	-0.01	0.01
Cerebrovascular disease	-		-0.021	0.02	0.00	0.03

continued

TABLE 36 SMD comparing patient characteristics between IV groups^a among patients included in the prescription cohorts used in IV analyses of repeat IACI (*continued*)

Variable	Ankle	Hand	Hip	Knee	Shoulder
	IV = 1 (115) ^a IV = 0 (4949)	IV = 1 (955) ^b IV = 0 (15,442)	IV = 1 (1248) ^b IV = 0 (33,164)	IV = 1 (11,315) ^b IV = 0 (68,634)	IV = 1 (511) ^b IV = 0 (2105)
COPD	-	-0.022	-0.08	-0.01	-0.1
Diabetes	-	-0.068	0.02	-0.02	-0.09
DVT	-	-0.01	-0.01	-0.01	0.05
Epilepsy	-	0.026	-0.08	0.01	-0.03
Fracture	-	-0.04	-0.09	-0.01	0.04
Ischaemic heart disease	-	0.051	-0.02	-0.01	0.08
LRTI	-	-0.056	-0.08	0.00	-0.03
Malabsorption	-	0.03	0.03	0.01	-
MI	-	0.028	-0.02	0.01	0.18
Hyperlipidaemia	-	0.042	0.01	0.00	0.15
Hypertension	-	0	0.03	0.00	0.08
Osteoporosis	-	-0.025	-0.02	-0.01	0.07
Pulmonary embolism	-	0.002	0.03	0.00	-0.03
Chronic renal failure	-	-0.045	-0.07	-0.01	0.04
Acute renal failure	-	-0.028	-0.02	-0.03	0.12
URTI	-	0.051	0	-0.03	0.07
UTI	-	0.067	0.02	0.02	-0.03
Parkinson's disease	-	0.019	-0.04	-0.01	-0.03
Antiarrhythmics	-	0.012	-0.04	0.02	0
Antibiotic	-	-0.019	0.03	0.01	0.02
Antidepressant	-	-0.05	0.01	-0.01	-0.03
Anticonvulsants	-	0.033	-0.02	0.01	-0.13
Anxiolytics	-	-0.044	-0.04	0.02	0.11
Bisphosphonate	-	-0.043	0	-0.02	0.03
Calcium/vitamin D	-	-0.064	-0.01	-0.01	-0.02
Oral glucocorticoid	-	-0.023	0.01	-0.01	0.08
NSAID oral	-	-0.018	0.07	0.00	-0.11
NSAID topical	-	0.047	0.02	0.03	0.04
Opioid	-	-0.08	0.03	-0.01	-0.1
Partial opioid	-	-0.048	0.01	-0.04	0
Paracetamol	-	0.017	0.03	-0.03	0.02
Proton pump inhibitor	-	-0.056	0.06	0.00	-0.1

TABLE 36 SMD comparing patient characteristics between IV groups^a among patients included in the prescription cohorts used in IV analyses of repeat IACI (*continued*)

Variable	Ankle	Hand	Hip	Knee	Shoulder
	IV = 1 (115) ^a IV = 0 (4949)	IV = 1 (955) ^b IV = 0 (15,442)	IV = 1 (1248) ^b IV = 0 (33,164)	IV = 1 (11,315) ^b IV = 0 (68,634)	IV = 1 (511) ^b IV = 0 (2105)
Prednisolone	-	-0.019	0.02	-0.01	0.07
Statins	-	-0.065	-0.02	-0.02	0.04
Hormone replacement therapy	-	0.015	-0.04	0.00	-0.05
Diuretic	-	-0.005	0	-0.04	-0.1
Physiotherapy	-	0.052	0.02	0.04	-0.11

a Using index date of 180 days after OA diagnosis date.

b Instrumental variable predicted IACI exposure as follows: ankle insufficient sample size; hand odds ratio (OR) 12.0; hip OR 7.12; knee OR 8.99; shoulder OR 3.5.

Note

Greyed background indicates insufficient balance. Ankle cohort too small for analysis.

TABLE 37 Standardised mean difference comparing patient characteristics between IV groups^a among patients included in the surgery cohorts used in IV analyses of single or repeat IACI

Variable	Hip		Knee	
	Single	Repeat	Single	Repeat
	IV = 1 (1690) ^b IV = 0 (15,944)	IV = 1 (190) ^b IV = 0 (17,093)	IV = 1 (15,092) ^b IV = 0 (22,782)	IV = 1 (4866) ^b IV = 0 (31,666)
Age	-0.04	-0.09	-0.06	-0.07
Female	0	-0.04	0	0.02
Least deprived	0.06	0.12	0.10	0.01
Less deprived	-0.02	-0.05	-0.04	0.01
Mid deprived	0.01	-0.11	-0.07	-0.12
More deprived	-0.06	-0.19	-0.06	-0.04
Most deprived	0.01	0.2	0.08	0.15
BMI: <20 kg/m ²	0.05	-0.05	0.01	-0.04
BMI 20 < 25 kg/m ²	0	-0.11	0.02	0.02
BMI 25 < 30 kg/m ²	0	0	0.02	0
BMI 30 < 35 kg/m ²	-0.01	0.14	0	0
BMI 35 < 40 kg/m ²	0.02	0.03	0.03	0.05
BMI ≥ 40 kg/m ²	-0.03	-0.1	0.01	0.02

continued

TABLE 37 Standardised mean difference comparing patient characteristics between IV groups^a among patients included in the surgery cohorts used in IV analyses of single or repeat IACI (*continued*)

Variable	Hip		Knee	
	Single	Repeat	Single	Repeat
	IV = 1 (1690) ^b	IV = 1 (190) ^b	IV = 1 (15,092) ^b	IV = 1 (4866) ^b
	IV = 0 (15,944)	IV = 0 (17,093)	IV = 0 (22,782)	IV = 0 (31,666)
BMI missing	-0.02	0	-0.09	-0.1
Ex-drinker	0.01	-0.02	0.02	0.01
Never drinker	0.02	-0.06	0.01	0
Current drinker	0.03	0.14	0.06	0.07
Drinking missing	-0.06	-0.12	-0.08	-0.1
Ex-smoker	-0.04	0.04	0	0.01
Never smoker	0.05	-0.05	0.02	0.02
Current smoker	0.01	0.03	0.02	0.01
Smoking missing	-0.05	-0.02	-0.09	-0.09
Charlson = 0	0	0.07	0.01	0.02
Charlson = 1	0	-0.05	-0.01	-0.03
Charlson = 2	0	-0.05	-0.02	-0.02
Charlson ≥ 3	0	-0.01	0.02	0.01
Polyarthritis	0.01	-0.07	0.03	0.01
Asthma	0.04	-0.03	0.01	0.02
Cancer	0.01	0.06	0.01	-0.03
Cerebrovascular disease	-0.02	0.11	0.02	0.02
COPD	0	-0.18	0.01	0
Diabetes	-0.02	0.02	-0.01	-0.04
DVT	-0.03	-0.04	0.01	0
Epilepsy	-0.01	-0.1	-0.02	0
Fracture	0.01	-0.13	0	-0.02
Ischaemic heart disease	-0.01	-0.03	0.01	-0.02
LRTI	0.03	-0.1	0.02	0.03
Malabsorption	0.02	0.02	0.02	-0.02
MI	0.02	-0.04	-0.01	-0.01
Hyperlipidaemia	0.01	0.07	0	-0.03
Hypertension	0.01	0.02	0	-0.01

TABLE 37 Standardised mean difference comparing patient characteristics between IV groups^a among patients included in the surgery cohorts used in IV analyses of single or repeat IACI (*continued*)

Variable	Hip		Knee	
	Single	Repeat	Single	Repeat
	IV = 1 (1690) ^b	IV = 1 (190) ^b	IV = 1 (15,092) ^b	IV = 1 (4866) ^b
	IV = 0 (15,944)	IV = 0 (17,093)	IV = 0 (22,782)	IV = 0 (31,666)
Osteoporosis	0.01	0.03	-0.03	-0.01
Pulmonary embolism	-0.02	0.01	0.02	0.02
Chronic renal failure	-0.02	-0.19	0.01	0.05
Acute renal failure	-0.01	0.08	0.02	-0.05
URTI	0.06	0.05	-0.01	-0.05
UTI	0.05	0.1	0.02	0.03
Parkinson's disease	0.03	-0.11	0.02	0.02
Antiarrhythmics	-0.01	-0.05	0.03	0.01
Antibiotic	-0.01	0	0.02	0.02
Antidepressant	0.03	0	0.03	-0.01
Anticonvulsants	0.03	-0.05	0.02	0.01
Anxiolytics	-0.08	-0.09	-0.01	-0.03
Bisphosphonate	0	0	-0.03	-0.03
Calcium/vitamin D	-0.03	-0.01	0	-0.01
Oral glucocorticoid	-0.03	0	0.02	0.02
NSAID oral	0.01	0.06	0.01	-0.02
NSAID topical	0.02	0.15	0.04	0.05
Opioid	0	0.01	0.01	-0.01
Partial opioid	-0.02	-0.01	0	-0.06
Paracetamol	-0.04	-0.06	0	-0.05
Proton pump inhibitor	-0.01	0.06	0.03	0.01
Prednisolone	-0.02	0.01	0.01	0.01
Statins	0	-0.04	0.02	-0.01
Hormone replacement therapy	-0.01	0.03	-0.02	-0.01
Diuretic	-0.03	-0.09	-0.04	-0.03
Physiotherapy	0.06	0.12	0.08	-0.01

a Using index date of 180 days after OA diagnosis date.

b Instrumental variable predicted IACI exposure as follows: hip single injection odds ratio (OR) 2.72; hip repeat injection OR 3.40; knee single injection OR 5.39; knee repeat injection OR 7.35.

Note

Greyed background indicates insufficient balance.

TABLE 38 Incident use of pain medicines during specified follow-up in the prescription cohort used in IV analyses of IACI for hand OA: by actual IACI exposure status in year prior to index date^a

		No IACI			IACI		
Medication	Follow-up (months)	N	n	%	N	n	%
Single injection analysis							
Oral NSAIDs	12	9982	1014	10.2	180	26	14.4
	60	6811	1940	28.5	127	32	25.2
Opioids	12	14,124	544	3.9	272	12	4.4
	60	9895	1268	12.8	184	33	17.9
Oral glucocorticosteroids	12	14,350	543	3.8	282	12	4.3
	60	10,125	1299	12.8	193	39	20.2
Paracetamol	12	9450	1143	12.1	165	21	12.7
	60	6589	2230	33.8	109	39	35.8
Partial opioids	12	14,124	3666	26.0	272	86	31.6
	60	9895	4045	40.9	184	84	45.7
Topical NSAIDs	12	10,971	806	7.3	219	15	6.8
	60	7979	1806	22.6	155	44	28.4

^a Using index date of 180 days after OA diagnosis date.

TABLE 39 Incident use of pain medicines among knee osteoarthritis patients during specified follow-up in the prescription cohort used in IV analyses of single or repeat IACI: by actual IACI exposure status in year prior to index date^a

		No IACI			IACI		
Medication	Follow-up (months)	N	n	%	N	n	%
Single injection analysis							
Oral NSAIDs	12	41,610	4373	10.5	1798	188	10.5
	60	31,678	8816	27.8	1279	331	25.9
Opioids	12	64,567	4249	6.6	2771	275	9.9
	60	50,678	10,021	19.8	1991	539	27.1
Oral glucocorticosteroids	12	70,406	2568	3.6	3276	145	4.4
	60	55,463	6990	12.6	2404	364	15.1
Paracetamol	12	31,470	5016	15.9	1083	215	19.9
	60	24,390	10,310	42.3	771	352	45.7
Partial opioids	12	64,567	25,011	38.7	2771	1317	47.5
	60	50,678	27,261	53.8	1991	1218	61.2
Topical NSAIDs	12	56,793	4245	7.5	2433	225	9.2
	60	45,814	11,544	25.2	1822	512	28.1

TABLE 39 Incident use of pain medicines among knee osteoarthritis patients during specified follow-up in the prescription cohort used in IV analyses of single or repeat IACI: by actual IACI exposure status in year prior to index date (*continued*)

		No IACI			IACI		
Medication	Follow-up (months)	N	n	%	N	n	%
Repeat injection analysis							
Oral NSAIDs	12	41,436	4351	10.5	443	57	12.9
	60	31,530	8776	27.8	315	93	29.5
Opioids	12	64,288	4234	6.6	683	87	12.7
	60	50,420	9969	19.8	496	146	29.4
Oral glucocorticosteroids	12	70,104	2554	3.6	811	34	4.2
	60	55,182	6949	12.6	586	84	14.3
Paracetamol	12	31,317	4993	15.9	235	51	21.7
	60	24,254	10,249	42.3	169	85	50.3
Partial opioids	12	64,288	24,901	38.7	683	343	50.2
	60	50,420	27,112	53.8	496	314	63.3
Topical NSAIDs	12	56,532	4231	7.5	570	57	10.0
	60	45,571	11,493	25.2	429	117	27.3

a Using index date of 180 days after OA diagnosis date.

TABLE 40 Incident use of repeat pain prescriptions among knee osteoarthritis patients during total follow-up in the prescription cohorts used in IV analyses of single or repeat IACI: by actual IACI exposure status in year prior to index date^a

Medication	Number of prescriptions	No injection			Injection		
		N	n	%	N	n	%
Single injection analysis							
Oral NSAIDs	5	42,777	2592	6.1	1875	99	5.3
	15	42,777	771	1.8	1875	42	2.2
Opioids	5	66,129	5133	7.8	2871	308	10.7
	15	66,129	2503	3.8	2871	135	4.7
Oral glucocorticosteroids	5	72,047	2842	3.9	3400	140	4.1
	15	72,047	1076	1.5	3400	52	1.5
Paracetamol	5	32,348	5259	16.3	1126	205	18.2
	15	32,348	2488	7.7	1126	96	8.5
Partial opioids	5	66,129	17,296	26.2	2871	873	30.4
	15	66,129	9470	14.3	2871	505	17.6

continued

TABLE 40 Incident use of repeat pain prescriptions among knee osteoarthritis patients during total follow-up in the prescription cohorts used in IV analyses of single or repeat IACI: by actual IACI exposure status in year prior to index date^a (*continued*)

Medication	Number of prescriptions	No injection			Injection		
		N	n	%	N	n	%
Topical NSAIDs	5	58,012	3838	6.6	2525	161	6.4
	15	58,012	1389	2.4	2525	73	2.9
Repeat injection analysis							
Oral NSAIDs	5	42,609	2572	6.0	453	36	7.9
	15	42,609	765	1.8	453	10	2.2
Opioids	5	65,850	5107	7.8	697	112	16.1
	15	65,850	2487	3.8	697	49	7.0
Oral glucocorticosteroids	5	71,746	2820	3.9	826	30	3.6
	15	71,746	1067	1.5	826	7	0.8
Paracetamol	5	19,575	3401	17.4	13,899	2063	14.8
	15	19,575	1645	8.4	13,899	939	6.8
Partial opioids	5	65,850	17,213	26.1	697	238	34.1
	15	65,850	9431	14.3	697	141	20.2
Topical NSAIDs	5	57,752	3820	6.6	581	45	7.7
	15	57,752	1383	2.4	581	19	3.3

^a Using index date of 180 days after OA diagnosis date.

TABLE 41 Incident use of repeat pain prescriptions among knee osteoarthritis patients during total follow-up in the prescription cohorts used in IV analyses of single or repeat IACI: by IV status^a

Medication	Number of prescriptions	Preference for no IACI			Preference for IACI		
		N	n	%	N	n	%
Single injection analysis							
Oral NSAIDs	5	26,497	1654	6.2	18,155	1037	5.7
	15	26,497	489	1.8	18,155	324	1.8
Opioids	5	40,844	3399	8.3	28,156	2042	7.3
	15	40,844	1652	4.0	28,156	986	3.5
Oral glucocorticosteroids	5	44,896	1892	4.2	30,551	1090	3.6
	15	44,896	708	1.6	30,551	420	1.4
Paracetamol	5	32,194	5218	16.2	238	54	22.7
	15	32,194	2471	7.7	238	31	13.0

TABLE 41 Incident use of repeat pain prescriptions among knee osteoarthritis patients during total follow-up in the prescription cohorts used in IV analyses of single or repeat IACI: by IV status^a (*continued*)

Medication	Number of prescriptions	Preference for no IACI			Preference for IACI		
		N	n	%	N	n	%
Partial opioids	5	40,844	11,185	27.4	28,156	6984	24.8
	15	40,844	6278	15.4	28,156	3697	13.1
Topical NSAIDs	5	36,254	2566	7.1	24,283	1433	5.9
	15	36,254	952	2.6	24,283	510	2.1
Repeat injection analysis							
Oral NSAIDs	5	36,922	2264	6.1	6140	344	5.6
	15	36,922	661	1.8	6140	114	1.9
Opioids	5	57,043	4550	8.0	9504	669	7.0
	15	57,043	2230	3.9	9504	306	3.2
Oral glucocorticosteroids	5	62,267	2507	4.0	10,305	343	3.3
	15	62,267	939	1.5	10,305	135	1.3
Paracetamol	5	27,598	4599	16.7	4834	673	13.9
	15	27,598	2174	7.9	4834	328	6.8
Partial opioids	5	57,043	15,204	26.7	9504	2247	23.6
	15	57,043	8387	14.7	9504	1185	12.5
Topical NSAIDs	5	50,229	3389	6.7	8104	476	5.9
	15	50,229	1235	2.5	8104	167	2.1

a Using index date of 180 days after OA diagnosis date.



FIGURE 13 Forest plots showing estimated effect of IACI use on pain medication initiation within specified follow-up among hand and knee OA patients: adjusted for geographic region and calendar year.

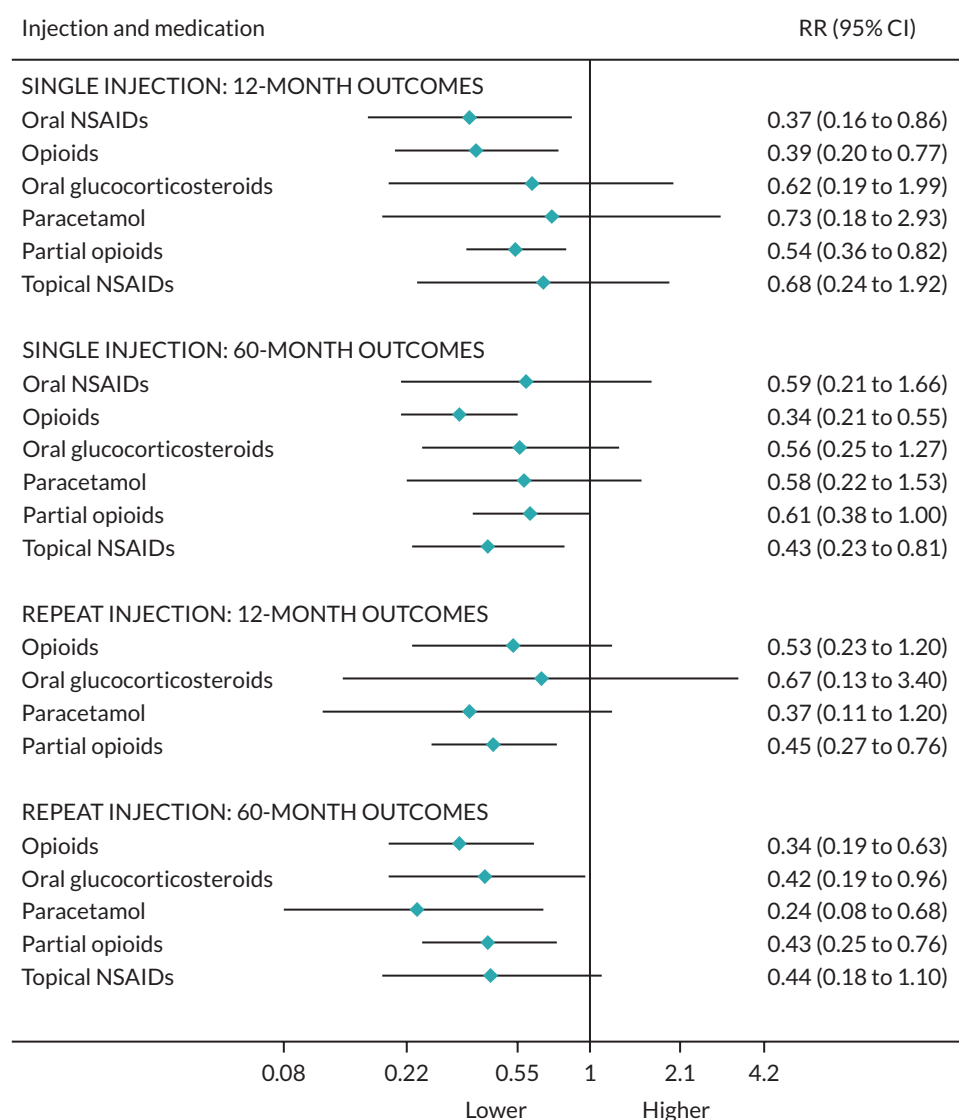


FIGURE 14 Forest plot showing estimated effect of IACI use on pain medication initiation within specified follow-up among knee OA patients: using sensitivity definition of 365 days after osteoarthritis diagnosis as index date.

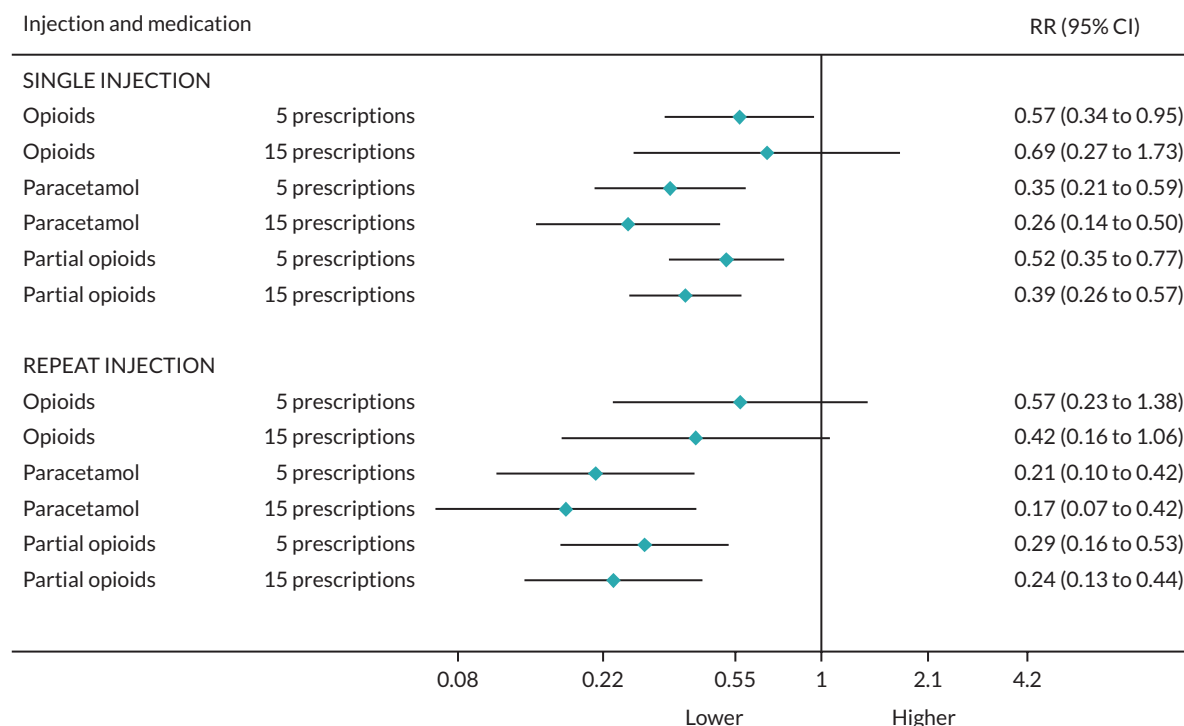


FIGURE 15 Forest plots showing estimated effect of IACI on incident use of repeat pain prescriptions during total follow-up among knee OA patients: adjusted for geographic region and calendar year.

TABLE 42 Surgical interventions during specified follow-up among hip and knee osteoarthritis patients in the surgery cohorts used in IV analyses of single IACI: by actual IACI exposure status in year prior to index date^a

		GP practice preference for no IACI			GP practice preference for IACI		
Procedure	Follow-up (months)	N	n	%	N	n	%
Hip injection analysis							
Arthroscopy	6	17,256	9	0.1	378	0	0
	12	17,047	15	0.1	374	0	0
	24	16,652	20	0.1	360	0	0
	60	14,698	25	0.2	310	< 5	0.3
Debridement	6	17,256	< 5	0	378	0	0
	12	17,047	7	0	374	0	0
	24	16,652	16	0.1	360	0	0
	60	14,698	23	0.2	310	< 5	0.6
Replacement	6	17,256	1863	10.8	378	69	18.3
	12	17,047	2710	15.9	374	105	28.1
	24	16,652	3663	22	360	135	37.5
	60	14,698	4457	30.3	310	142	45.8

TABLE 42 Surgical interventions during specified follow-up among hip and knee osteoarthritis patients in the surgery cohorts used in IV analyses of single IACI: by actual IACI exposure status in year prior to index date^a (*continued*)

		GP practice preference for no IACI			GP practice preference for IACI		
Procedure	Follow-up (months)	N	n	%	N	n	%
Knee injection analysis							
Arthroscopy	6	36,294	578	1.6	1580	41	2.6
	12	35,944	878	2.4	1553	61	3.9
	24	35,192	1225	3.5	1517	89	5.9
	60	31,000	1647	5.3	1298	95	7.3
Debridement	6	36,294	471	1.3	1580	31	2
	12	35,944	733	2	1553	50	3.2
	24	35,192	1043	3	1517	74	4.9
	60	31,000	1413	4.6	1298	87	6.7
Replacement	6	36,294	1102	3	1580	80	5.1
	12	35,944	1726	4.8	1553	131	8.4
	24	35,192	2652	7.5	1517	210	13.8
	60	31,000	3984	12.9	1298	284	21.9

^a Using index date of 180 days after osteoarthritis diagnosis date.

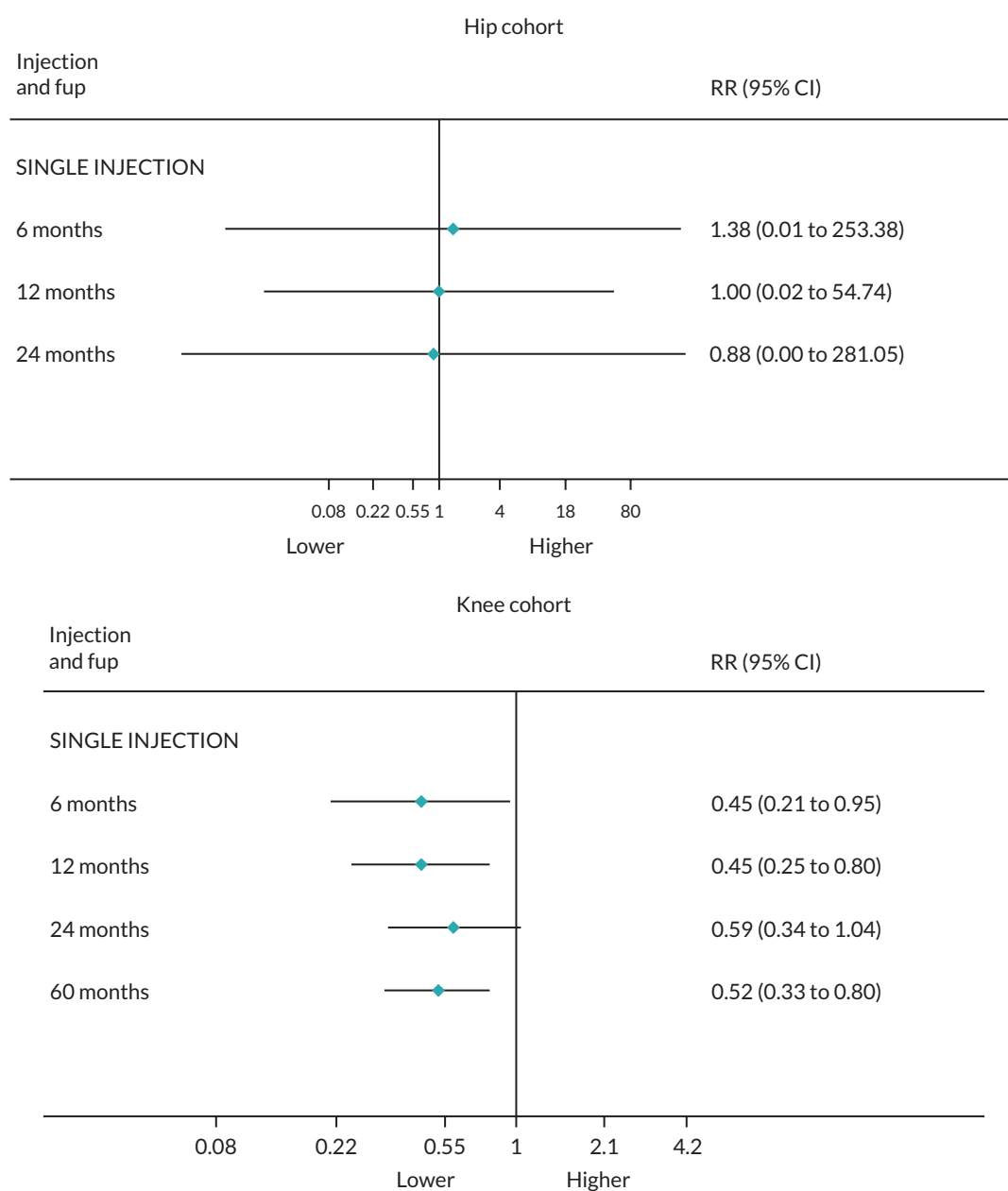


FIGURE 16 Forest plot showing estimated effect of IACI on hip (top) and knee (bottom) replacement during specified follow-up (fup): adjusted for geographic region and calendar year.

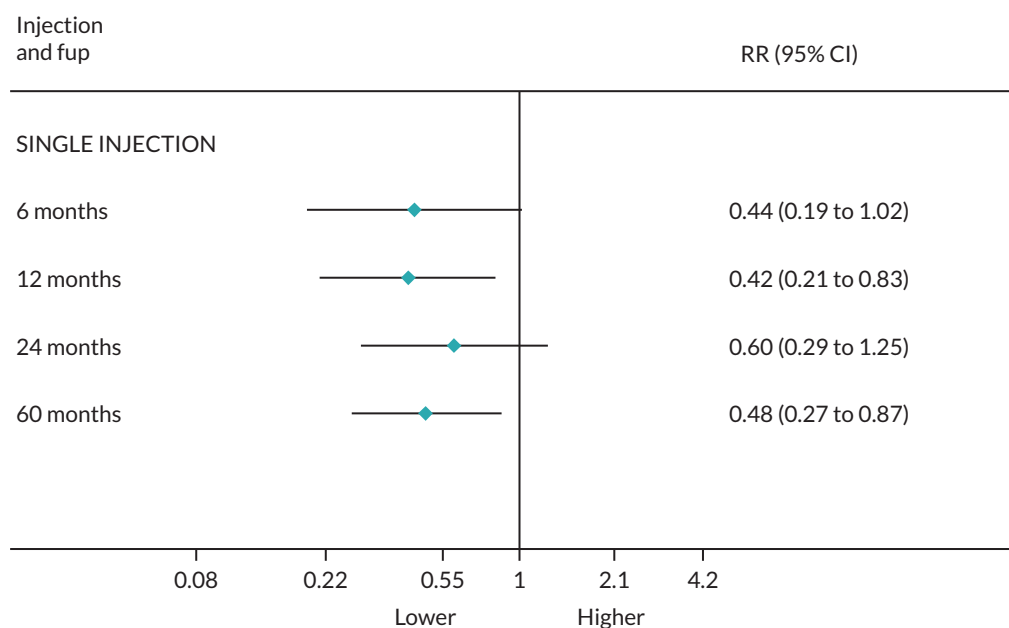


FIGURE 17 Forest plot showing estimated effect of IACI on knee replacement during specified follow-up (fup) among knee osteoarthritis patients: using sensitivity definition of 365 days after OA diagnosis as index date.

TABLE 43 Standardised mean difference comparing covariate balance between IACI users matched to non-users in prescription cohorts used in PS-matched analyses

Variable	Ankle	Hand	Hip	Knee	Shoulder
Age (years)	0.08	0.03	0.01	0.02	0.02
Female	0.06	0.00	-0.01	0.01	-0.01
BMI (kg/m ²)	-0.02	0.03	0.01	-0.01	0.04
Least deprived	-0.01	0.02	0.01	0.02	-0.01
Less deprived	0.01	0.01	0.01	0.02	0.00
Mid deprived	0.04	0.00	0.02	0.04	0.00
More deprived	0.01	-0.01	-0.02	0.03	0.01
Most deprived	-0.03	0.00	-0.03	-0.01	-0.04
Deprivation missing	-0.01	-0.02	0.00	-0.06	0.02
Ex-drinker	0.02	0.07	0.00	-0.02	0.00
Never drinker	0.07	0.03	0.01	0.00	-0.01
Current drinker	-0.07	-0.05	0.00	0.01	0.01
Ex-smoker	0.03	0.00	0.02	-0.01	0.03
Never smoker	0.00	0.00	-0.01	0.02	-0.04
Current smoker	-0.05	-0.01	-0.01	-0.02	0.01
Charlson = 0	0.00	-0.03	-0.01	-0.01	-0.02
Charlson = 1	0.00	0.02	0.00	0.00	0.05
Charlson = 2	0.00	0.01	0.01	0.01	0.01

continued

TABLE 43 Standardised mean difference comparing covariate balance between IACI users matched to non-users in prescription cohorts used in PS-matched analyses (*continued*)

Variable	Ankle	Hand	Hip	Knee	Shoulder
Charlson ≥ 3	-0.01	0.03	0.00	0.01	-0.03
Polyarthritis	0.07	0.03	0.01	0.00	-0.01
Asthma	0.03	-0.01	0.01	0.01	0.05
Cancer	-0.02	0.00	-0.01	0.02	0.03
Cerebrovascular disease	-0.03	-0.02	-0.01	-0.01	-0.02
COPD	-0.02	-0.03	0.02	0.00	0.02
Diabetes	-0.04	0.05	0.00	0.01	0.04
DVT					
Epilepsy	0.02	0.01	-0.01	0.00	-0.01
Fracture	-0.02	0.01	-0.01	0.00	0.00
Ischaemic heart disease	0.00	0.02	-0.03	0.00	-0.02
LRTI	0.01	0.04	0.00	0.00	0.05
Malabsorption	-0.02	0.02	0.00	-0.01	0.00
MI	0.02	0.00	0.00	0.00	0.01
Hyperlipidaemia	0.03	0.02	0.01	0.00	0.00
Hypertension	-0.02	0.00	-0.02	0.01	0.01
Osteoporosis	0.02	0.02	-0.04	-0.01	0.02
Pulmonary embolism	-0.02	-0.01	-0.02	-0.01	-0.04
Chronic renal failure	0.00	-0.01	0.00	0.00	-0.03
Acute renal failure		0.00	0.02	0.01	0.01
URTI	-0.03	-0.03	0.02	0.00	-0.04
UTI	0.03	-0.01	0.00	0.01	0.01
Parkinson's disease	0.01	0.03	0.02	0.00	0.00
Antiarrhythmics	-0.04	0.04	-0.02	0.00	0.03
Antibiotic	-0.01	0.00	0.01	0.00	0.01
Antidepressant	-0.03	-0.03	-0.03	0.01	0.04
Anticonvulsants	-0.03	0.00	0.02	0.02	0.01
Anxiolytics	-0.05	0.03	0.01	0.01	-0.02
Bisphosphonate	0.04	0.03	-0.05	-0.01	0.02
Calcium/vitamin D	-0.01	0.02	-0.02	0.00	0.04
Oral glucocorticoid	0.03	0.01	0.01	0.01	0.03
NSAID oral	-0.03	-0.01	0.00	0.00	-0.03
NSAID topical	-0.03	0.00	0.01	0.00	0.00
Opioid	-0.02	0.00	0.00	0.02	0.03

TABLE 43 Standardised mean difference comparing covariate balance between IACI users matched to non-users in prescription cohorts used in PS-matched analyses (*continued*)

Variable	Ankle	Hand	Hip	Knee	Shoulder
Partial opioid	-0.01	0.01	-0.03	-0.01	-0.04
Paracetamol	-0.04	0.00	-0.02	0.00	-0.02
Proton pump inhibitor	0.05	0.03	0.04	0.00	0.05
Prednisolone	0.02	0.01	0.01	0.00	0.03
Statins	-0.01	0.03	-0.01	0.00	0.02
Hormone replacement therapy	0.08	-0.01	0.02	0.01	0.00
Diuretic	0.00	-0.01	-0.02	0.02	-0.02
Physiotherapy	0.03	0.04	0.03	0.00	0.02

TABLE 44 Standardised mean difference comparing covariate balance between IACI users matched to non-users in surgery cohorts used in PS-matched analyses

Variable	Hip	Knee
Age	0.01	0.02
Female	0.03	0.00
BMI	-0.01	0.00
Least deprived	0.03	0.00
Less deprived	0.00	0.01
Mid deprived	-0.02	0.03
More deprived	-0.01	-0.01
Most deprived	0.00	-0.03
Ex-drinker	0.01	0.00
Never drinker	-0.01	0.00
Current drinker	0.01	0.00
Ex-smoker	-0.02	0.00
Never smoker	0.05	0.01
Current smoker	-0.04	-0.01
Charlson = 0	-0.01	-0.02
Charlson = 1	0.02	-0.01
Charlson = 2	-0.01	0.01
Charlson ≥ 3	0.01	0.02
Polyarthritis	-0.01	0.02
Asthma	0.06	0.01
Cancer	-0.01	0.00
Cerebrovascular disease	0.00	0.00
COPD	-0.01	0.00

continued

TABLE 44 Standardised mean difference comparing covariate balance between IACI users matched to non-users in surgery cohorts used in PS-matched analyses (*continued*)

Variable	Hip	Knee
Diabetes	0.00	0.01
DVT		
Epilepsy	-0.02	-0.01
Fracture	-0.02	0.00
Ischaemic heart disease	-0.01	0.00
LRTI	0.00	-0.03
Malabsorption	0.04	0.02
MI	0.00	0.00
Hyperlipidaemia	0.04	-0.03
Hypertension	0.01	-0.01
Osteoporosis	0.00	0.00
Pulmonary embolism	-0.01	-0.01
Chronic renal failure	0.01	0.02
Acute renal failure		0.00
URTI	0.01	-0.02
UTI	0.01	0.01
Parkinson's disease	0.01	0.01
Antiarrhythmics	0.02	-0.02
Antibiotic	0.01	0.00
Antidepressant	0.02	0.00
Anticonvulsants	0.01	0.02
Anxiolytics	0.04	0.02
Bisphosphonate	0.00	0.00
Calcium/vitamin D	0.01	0.02
Oral glucocorticoid	0.02	0.02
NSAID oral	-0.04	-0.02
NSAID topical	0.04	0.01
Opioid	0.00	0.02
Partial opioid	-0.02	-0.02
Paracetamol	-0.01	-0.01
Proton pump inhibitor	-0.01	0.01
Prednisolone	0.02	0.01
Statins	-0.01	0.00
Hormone replacement therapy	0.00	0.01
Diuretic	-0.02	0.01
Physiotherapy	0.01	0.01

TABLE 45 Rates of incident use of pain medication during specified follow-up from osteoarthritis diagnosis date among patients in the PS-matched prescription cohorts: by exposure status after TVE splitting follow-up (first imputation only)

			No injection					Single injection					Repeat injection					
			Incidence (/1000 PYs)					Incidence (/1000 PYs)					Incidence (/1000 PYs)					
			N	n	Estimate	Lower 95% CI	Upper 95% CI	N	n	Estimate	Lower 95% CI	Upper 95% CI	N	n	Estimate	Lower 95% CI	Upper 95% CI	
Joint	Medication	Follow-up (months)																
Ankle	Oral NSAIDs	12	225	31	201.5	141.7	286.6	114	20	259.5	167.4	402.3	7	0	-	-	-	
		60	417	151	186.3	158.8	218.5	171	48	140.2	105.7	186.1	19	< 5	93.6	30.2	290.2	
	Opioids	12	371	18	65.0	40.9	103.2	187	11	84.5	46.8	152.5	15	0	-	-	-	
		60	646	109	66.4	55.0	80.1	297	50	72.5	54.9	95.6	54	6	61.6	27.7	137.1	
	Oral glucocorticosteroids	12	418	21	66.3	43.2	101.7	213	8	54.2	27.1	108.3	14	0	-	-	-	
		60	762	76	38.4	30.7	48.1	366	48	55.7	42.0	74.0	61	< 5	35.4	13.3	94.2	
	Paracetamol	12	215	33	231.2	164.4	325.2	113	16	217.4	133.2	354.8	9	< 5	-	-	-	
		60	419	166	192.9	165.6	224.5	166	59	194.1	150.4	250.5	22	11	291.2	161.3	525.8	
	Partial opioids	12	346	84	389.9	314.9	482.9	165	26	242.9	165.4	356.7	12	< 5	345.4	48.7	2452.3	
		60	612	264	242.0	214.5	273.0	232	80	188.9	151.7	235.2	34	11	218.3	120.9	394.2	
Topical NSAIDs	12	335	28	114.2	78.9	165.5	177	9	71.9	37.4	138.2	11	< 5	369.2	52.0	2621.1		
	60	617	138	93.1	78.8	110.0	282	57	86.7	66.8	112.3	36	< 5	66.9	25.1	178.2		
Hand	Oral NSAIDs	12	730	108	224.5	185.9	271.0	308	29	157.2	109.2	226.2	36	0	-	-	-	
		60	1405	430	150.1	136.6	165.0	455	91	113.0	92.1	138.8	109	19	97.7	62.3	153.2	
	Opioids	12	1019	45	63.8	47.6	85.5	466	24	87.0	58.3	129.8	73	< 5	61.1	15.3	244.4	
		60	1984	292	60.7	54.2	68.1	806	106	72.4	59.9	87.6	220	31	66.3	46.7	94.3	
	Oral glucocorticosteroids	12	1131	53	68.2	52.1	89.2	522	25	81.7	55.2	121.0	87	< 5	52.3	13.1	208.9	
		60	2162	265	50.1	44.4	56.5	934	100	58.7	48.3	71.4	262	31	54.2	38.1	77.1	
	Paracetamol	12	572	83	225.6	181.9	279.8	267	26	165.0	112.4	242.4	35	5	338.6	140.9	813.4	
		60	1201	415	172.9	157.0	190.3	417	110	161.8	134.2	195.1	102	33	177.9	126.5	250.3	
	Partial opioid	12	961	200	351.5	306.0	403.7	393	54	244.3	187.1	319.0	51	7	337.4	160.8	707.7	
		60	1867	745	234.8	218.5	252.2	605	151	151.9	129.5	178.2	144	40	150.0	110.0	204.4	
continued																		

Joint	Medication	Follow-up (months)	No injection					Single injection					Repeat injection				
			N	n	Incidence (/1000 PYs)			N	n	Incidence (/1000 PYs)			N	n	Incidence (/1000 PYs)		
					Estimate	Lower 95% CI	Upper 95% CI			Estimate	Lower 95% CI	Upper 95% CI			Estimate	Lower 95% CI	Upper 95% CI
Hip	Topical NSAID	12	822	70	126.3	99.9	159.6	379	22	95.3	62.8	144.8	50	< 5	49.2	6.9	349.5
		60	1606	414	113.9	103.4	125.4	618	109	93.3	77.3	112.5	161	31	92.1	64.8	131.0
	Oral NSAID	12	1217	178	223.7	193.2	259.1	477	46	171.7	128.6	229.2	25	< 5	472.3	152.3	1464.5
		60	2323	653	135.5	125.5	146.3	813	191	116.4	101.0	134.2	72	12	105.3	59.8	185.3
	Opioid	12	1529	212	211.0	184.4	241.4	619	79	229.7	184.2	286.4	33	< 5	190.5	47.6	761.8
		60	3110	849	126.7	118.5	135.5	1119	279	123.2	109.5	138.5	97	19	124.0	79.1	194.3
	Oral glucocorticosteroid	12	1892	86	64.3	52.1	79.5	852	28	56.2	38.8	81.4	45	< 5	70.2	9.9	498.6
		60	3806	423	44.1	40.1	48.5	1630	165	42.8	36.8	49.9	164	18	59.1	37.3	93.9
	Paracetamol	12	635	166	444.8	382.0	517.9	237	46	348.2	260.8	464.8	8	< 5	850.9	119.9	6040.3
		60	1328	624	293.2	271.1	317.1	390	160	233.2	199.7	272.3	22	9	300.4	156.3	577.4
	Partial opioid	12	1371	511	754.6	691.9	822.9	451	85	358.4	289.8	443.3	22	< 5	445.8	143.8	1382.3
		60	2771	1428	354.1	336.2	372.9	749	257	183.5	162.4	207.4	56	12	141.2	80.2	248.7
Knee	Topical NSAID	12	1706	124	104.6	87.7	124.7	733	39	91.4	66.8	125.1	46	< 5	66.7	9.4	473.5
		60	3445	694	86.0	79.8	92.6	1368	266	87.6	77.7	98.8	125	23	96.6	64.2	145.3
	Oral NSAID	12	6170	695	176.0	163.4	189.6	2636	259	164.5	145.6	185.8	520	47	196.8	147.8	261.9
		60	9881	2430	124.0	119.2	129.0	3618	665	114.1	105.8	123.2	1094	213	96.9	84.7	110.8
	Opioid	12	9028	730	123.5	114.9	132.8	4037	327	134.6	120.8	150.0	805	53	137.9	105.4	180.5
		60	14,900	2791	84.7	81.6	87.9	5941	1048	103.8	97.7	110.2	1799	399	107.0	97.0	118.1
	Oral glucocorticosteroid	12	9973	359	53.4	48.1	59.2	4621	137	47.6	40.3	56.3	948	22	49.2	32.4	74.7
		60	16,410	1748	44.4	42.4	46.5	7044	577	42.9	39.5	46.6	2269	249	48.6	42.9	55.0
	Paracetamol	12	4034	869	367.5	343.9	392.8	1685	350	369.9	333.2	410.8	277	49	390.2	294.9	516.3
		60	6778	2789	245.9	236.9	255.2	2220	758	236.3	220.1	253.7	559	231	250.8	220.5	285.4

TABLE 45 Rates of incident use of pain medication during specified follow-up from osteoarthritis diagnosis date among patients in the PS-matched prescription cohorts: by exposure status after TVE splitting follow-up (first imputation only) (*continued*)

Joint	Medication	Follow-up (months)	No injection					Single injection					Repeat injection				
			N	n	Incidence (/1000 PYs)			N	n	Incidence (/1000 PYs)			N	n	Incidence (/1000 PYs)		
					Estimate	Lower 95% CI	Upper 95% CI			Estimate	Lower 95% CI	Upper 95% CI			Estimate	Lower 95% CI	Upper 95% CI
Shoulder	Partial opioid	12	9044	2237	454.3	435.9	473.5	3592	671	333.7	309.4	360.0	642	66	224.6	176.4	285.9
		60	13,439	6128	298.9	291.5	306.4	4040	1318	224.4	212.6	236.8	1028	350	184.6	166.3	205.0
	Topical NSAID	12	7792	717	142.0	132.0	152.8	3551	282	132.3	117.7	148.7	683	53	169.2	129.3	221.5
		60	12,947	3066	109.8	106.0	113.8	5109	924	99.8	93.6	106.4	1465	313	100.4	89.9	112.1
	Oral NSAID	12	557	46	124.1	92.9	165.6	250	17	102.8	63.9	165.3	31	< 5	66.6	9.4	473.2
		60	821	167	104.7	90.0	121.8	315	50	77.4	58.7	102.1	63	12	94.6	53.7	166.5
	Opioid	12	763	57	110.9	85.5	143.8	343	27	118.3	81.2	172.6	39	< 5	214.9	80.7	572.6
		60	1142	207	81.8	71.4	93.8	442	70	72.6	57.5	91.8	83	17	108.0	67.1	173.7
	Oral glucocorticosteroid	12	885	42	68.4	50.6	92.6	408	22	80.1	52.7	121.6	48	< 5	85.7	21.4	342.5
		60	1280	155	52.7	45.0	61.6	550	72	56.2	44.6	70.8	107	11	48.1	26.6	86.8
	Paracetamol	12	342	77	377.0	301.5	471.3	141	20	215.2	138.8	333.6	11	< 5	383.4	95.9	1533.0
		60	519	210	241.5	210.9	276.5	176	70	220.3	174.3	278.5	15	7	288.0	137.3	604.1
	Partial opioid	12	708	196	495.7	431.0	570.2	270	54	327.6	250.9	427.8	26	5	420.7	175.1	1010.8
		60	1051	452	283.4	258.5	310.8	317	112	190.4	158.2	229.2	42	20	328.6	212.0	509.3
	Topical NSAID	12	661	53	121.5	92.8	159.0	317	27	130.7	89.6	190.6	34	< 5	125.0	31.3	499.7
		60	1013	205	92.7	80.8	106.3	401	93	106.8	87.2	130.9	76	17	114.3	71.1	183.9

PYs, person-years.

TABLE 46 Incidence rates of surgical intervention during specified follow-up from osteoarthritis diagnosis date among patients in the PS-matched surgery cohorts: by exposure status after TVE splitting follow-up (first imputation only)

			No injection						Single injection						Repeat injection					
			Incidence (/1000 PYs)						Incidence (/1000 PYs)						Incidence (/1000 PYs)					
			N	n	Estimate	Lower 95% CI	Upper 95% CI	N	n	Estimate	Lower 95% CI	Upper 95% CI	N	n	Estimate	Lower 95% CI	Upper 95% CI			
Hip	Arthroscopy	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
		12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
		24	1383	0	0	-	-	625	< 5	2.4	0.6	9.7	52	< 5	-	-	-			
		60	1931	0	0	-	-	902	5	1.6	0.7	3.9	85	< 5	4.5	0.6	31.9			
	Debridement	6	744	< 5	10.2	3.3	31.6	331	< 5	-	-	-	7	< 5	-	-	-			
		12	1031	< 5	1.3	0.2	9.1	455	< 5	-	-	-	30	< 5	-	-	-			
		24	1383	5	2.5	1	6	625	< 5	1.2	0.2	8.6	52	< 5	-	-	-			
		60	1932	0	-	-	-	902	< 5	1.3	0.5	3.5	85	< 5	-	-	-			
	Replacement	6	737	60	215.2	167.1	277.2	331	21	218.9	142.7	335.7	7	0	0	-	-			
		12	1024	159	232	198.6	271	454	94	365.3	298.5	447.2	30	< 5	262.2	65.6	1048.4			
		24	1380	231	134.9	118.6	153.5	624	187	302.5	262.1	349.1	52	10	262.6	141.3	488.1			
		60	1923	458	91.8	83.8	100.7	900	374	212.3	191.8	234.9	85	20	118.7	76.6	183.9			
Knee	Arthroscopy	6	3648	64	47.7	37.3	61.0	1739	30	50.4	35.2	72.1	233	1	18.1	2.5	128.2			
		12	4599	141	43.5	36.9	51.3	2096	65	48.4	37.9	61.7	421	10	46.1	24.8	85.8			
		24	5699	252	32.9	29.0	37.2	2543	117	39.4	32.9	47.2	651	25	34.2	23.1	50.6			
		60	7712	436	18.2	16.5	20.0	3280	175	20.8	18.0	24.2	971	50	17.3	13.1	22.9			
	Debridement	6	3654	59	43.8	34.0	56.6	1743	29	48.6	33.8	70.0	233	2	36.1	9.0	144.5			
		12	4605	108	33.1	27.4	40.0	2112	60	44.4	34.5	57.2	424	5	22.9	9.5	55.0			

TABLE 46 Incidence rates of surgical intervention during specified follow-up from osteoarthritis diagnosis date among patients in the PS-matched surgery cohorts: by exposure status after TVE splitting follow-up (first imputation only) *(continued)*

Joint	Medication	Follow-up (months)	No injection					Single injection					Repeat injection				
			N	n	Incidence (/1000 PYs)			N	n	Incidence (/1000 PYs)			N	n	Incidence (/1000 PYs)		
					Estimate	Lower 95% CI	Upper 95% CI			Estimate	Lower 95% CI	Upper 95% CI			Estimate	Lower 95% CI	Upper 95% CI
		24	5707	203	26.3	22.9	30.1	2564	109	36.4	30.1	43.9	658	18	24.2	15.3	38.5
		60	7719	354	14.6	13.2	16.2	3316	161	18.9	16.2	22.1	986	46	15.6	11.7	20.8
	Replacement	6	3654	93	69.5	56.7	85.2	1754	32	53.5	37.8	75.6	235	2	36.0	9.0	143.8
		12	4612	233	72.7	63.9	82.7	2141	104	77.2	63.7	93.6	432	12	54.5	30.9	95.9
		24	5719	406	54.4	49.4	60.0	2623	253	87.1	77.0	98.5	679	62	85.0	66.2	109.0
		60	7727	767	33.7	31.4	36.2	3431	548	71.7	66.0	78.0	1033	203	74.4	64.9	85.4
PYs, person-years.																	

Chapter 5 Safety of IACI

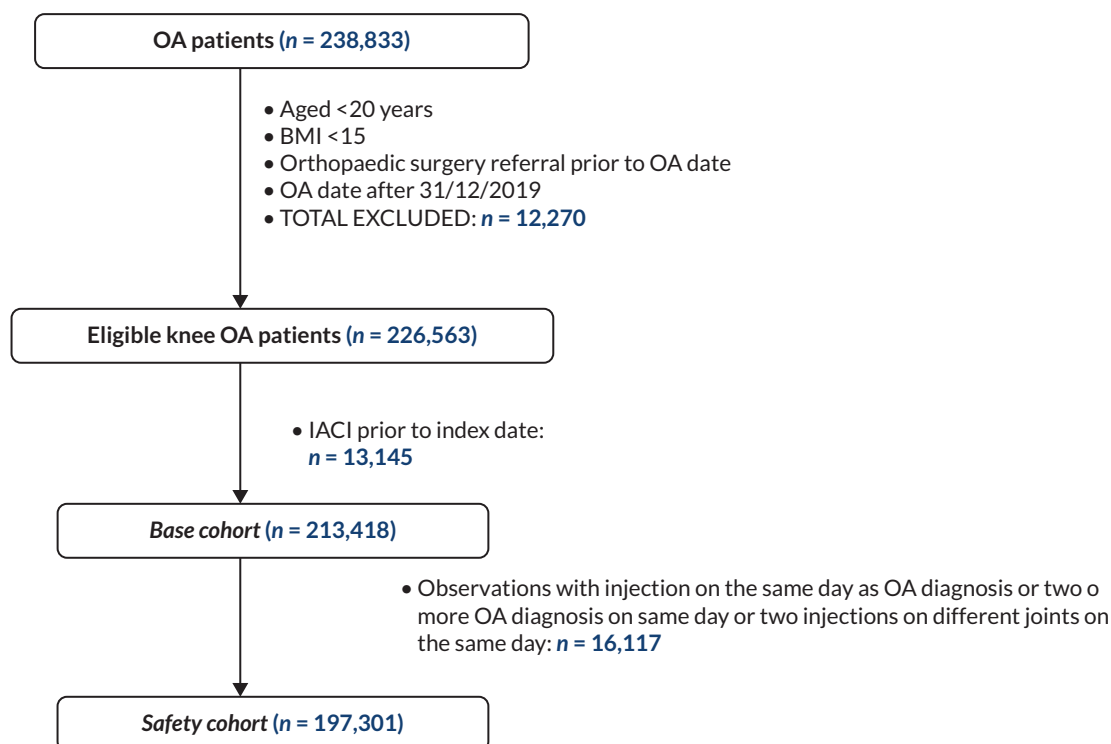


FIGURE 18 Flowchart of included patients for safety analyses.

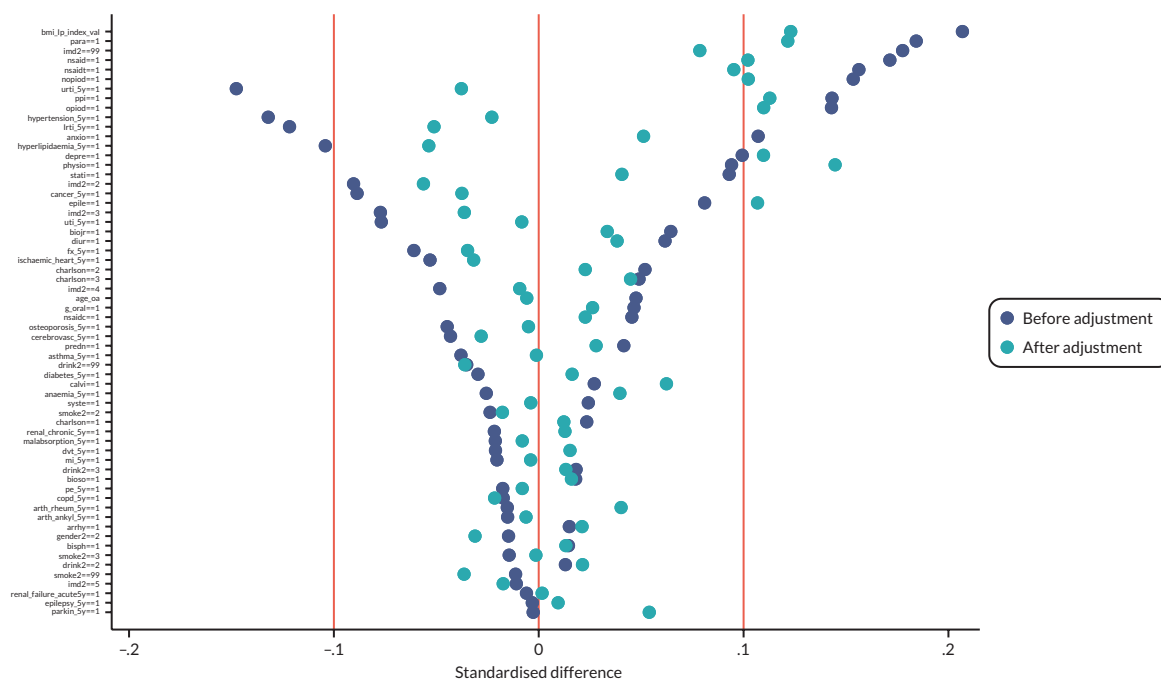


FIGURE 19 Balance of known confounders after applying inverse probability weighting.

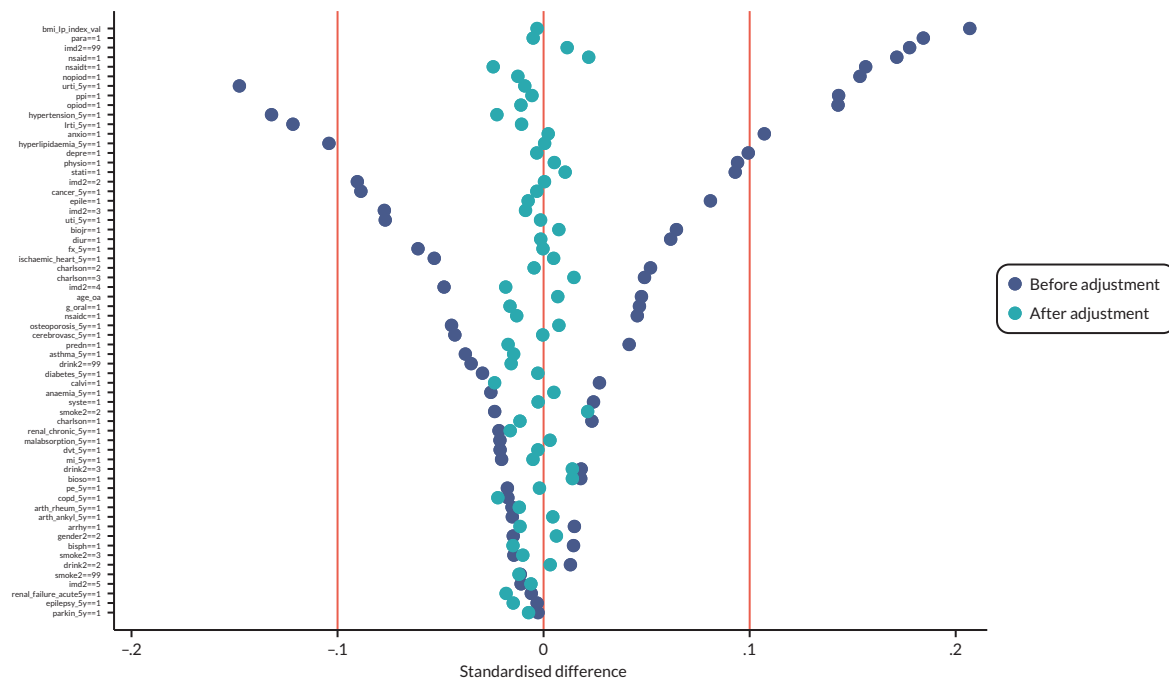


FIGURE 20 Balance of known confounders after PS matching.

EME
HSDR
HTA
PGfAR
PHR

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