RUbICOn Protocol

1. Full title of project

RecUrrent Intra-articular Corticosteroid injections in Osteoarthritis: the RUbICOn study

2. Funding

This study is funded by the National Institute for Health Research (NIHR) HTA programme (project reference NIHR129011)

3. Summary of Research (abstract)

Aim 1: To establish the current practice of use of intra-articular corticosteroid injection for the treatment of joint pain due to osteoarthritis.
Aim 2: To establish the long-term effects of the use of recurrent intra-articular injection of corticosteroid.
Aim 3: To explore the views and experiences of patients and clinicians of the use of intra-articular injection of corticosteroid.
Aim 4: To assess priorities and associated feasibility considerations for future primary research.

Settings: Three large prospective routinely collected datasets: Clinical Practice Research Datalink (CPRD) with linkage to Hospital Episode Statistics (HES) and National Patient Reported Outcomes Measures (PROMs) data.
Qualitative interviews with patients and primary healthcare professionals and a Delphi survey of these groups, researchers and commissioners.

Population: CPRD: Feasibility estimates indicate approximately 25,000 patients with knee osteoarthritis and 9,000 with hip osteoarthritis have received intra-articular injection of corticosteroid (IACI) with >100,000 control cases available.

Sample size: For the knee (most common IACI site), using a 2-sided log rank test for equality of survival curves, 90% power and 5% level of significance, where outcome is time to arthroplasty and an anticipated arthroplasty rate of 7% over 4-years we can detect a hazard ratio of 0.85 (equivalent to a 7% arthroplasty rate in non-IACI users and 6% in IACI users) with a total sample size of 24,613 (12,300 in each group).

Qualitative interviews: 40 patients and 30 General Practitioners (GPs).

Delphi survey: 25 patients, 25 healthcare professionals, 25 researchers, 25 commissioners.

Methods:
WP1: Data linkage of CPRD-HES-PROMs datasets. Current practice will be described by analysis of population and patient level data including secular trends. Safety (pain, bleeding, infection, diabetes, cardiovascular) and association of the use of IACI with outcomes (drug utilisation, timing to surgical intervention, subsequent outcome of arthroplasty, PROMs). To

address the issue of confounding, we will perform instrumental variable regression as our primary analysis. Propensity score matching and inverse probability weighting we will be utilised as alternative complementary approaches for secondary analyses.

WP2: Semi-structured in-depth interviews will be performed. Healthcare behaviour theories will be used to inform the analysis.

WP3: 3-round modified Delphi study with patients, healthcare professionals, researchers and commissioners to identify future primary research priorities and associated feasibility considerations.

Timelines:
Month 1: CPRD-HES-PROMs data extraction, linkage and management; commence qualitative interview documentation development
Month 4: commence utilisation and safety analysis
Month 5: commence patient and clinician recruitment and qualitative interviews
Month 9: interim statistical results meeting, commence outcomes analysis
Month 15: interim statistical results meeting
Month 16: commence Delphi survey
Month 21: complete statistical analysis
Month 24: complete qualitative data collection & analysis; complete round 1 of Delphi survey
Month 24-30: complete qualitative study and Delphi survey, write up, dissemination

Anticipated impact & dissemination: inform evidence base to guide use of repeated intra-articular injections of corticosteroid. Establish priorities and feasibility of future primary research. Dissemination: written HTA report; peer-reviewed publications in journals (e.g. BMJ); NHS patient resources, Health Integration Teams; through RCGP, RSM, academic research networks and NIHR funded research centres.

4. Background and Rationale

Osteoarthritis is the most common musculoskeletal condition worldwide[1] and it is a global public health burden.[2] It is an irreversible and progressive disease, which leads to pain, morbidity, functional decline, and loss in quality of life. Osteoarthritis of the hip and knee 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 an increase in risk factors such as obesity, the prevalence of osteoarthritis is increasing. Global estimates show that 10% to 15% of adults 60 years and older have some degree of osteoarthritis.[5] It has been estimated that by 2050, 130 million will be affected by osteoarthritis globally and of these, 40 million will be severely disabled by the disease.[6] In the UK, data from Arthritis Research UK suggest that one third of people aged 45 years and over (representing 8.75 million people) are affected by osteoarthritis.[7]

The current common treatment regimens for osteoarthritis reduces pain and may improve function, but 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 osteoarthritis recommends treatment modalities such as biomechanical interventions, intra-articular corticosteroids, exercise (land-based and water-based), self-

management and education, strength training, and weight management.[1] In the UK, people with osteoarthritis are usually managed in primary care (General Practice). Management of osteoarthritis includes core treatment (education and advice, exercise, weight loss, and use of assistive devices) and may include physical therapy (physiotherapy, insoles, or braces) and pharmacotherapy (paracetamol and non-steroidal anti-inflammatory drugs as first line treatment for pain). A few patients proceed to secondary care management in which there are more invasive treatment options, which include joint replacement. The National Institute for Health and Care Excellence (NICE) Clinical Guideline for Osteoarthritis: care and management recommends the use of intra-articular corticosteroid injections as an adjunct to core treatments for the relief of moderate-to-severe, uncontrolled pain in people with osteoarthritis.[8] Evidence for this recommendation was based on limited data which indicated a short-term benefit of repeated intra-articular corticosteroids for pain relief in osteoarthritis of the knee.[9-12] The British National Formulary recommends repeat injections at intervals of 7-35 days and that no joint should be treated more than three times per year. In the USA, no greater than four injections a year in a given joint is recommended. Since the publication of the NICE guidance, further reports (individual studies as well as meta-analyses) on the benefits of intra-articular corticosteroid injections for osteoarthritis management have been published or presented.[13-17] The overall evidence from these further findings suggest a short-term benefit of intra-articular corticosteroids on pain relief and mild or no evidence of adverse effects with intra-articular corticosteroid therapy.

Given that the prevalence of osteoarthritis is expected to rise over the coming years and concerns that intra-articular corticosteroid injections will be used more frequently in patients, robust evidence on the long-term benefits and risks associated with recurrent use of intra-articular corticosteroid injections for osteoarthritis is urgently warranted. There is however limited and inconsistent evidence available. Results from small cohort observational studies comprising people with osteoarthritis with long-term follow-up suggest a link between intra-articular corticosteroids, particularly recurrent, and adverse joint outcomes such as joint degeneration or radiological OA progression and bone and cartilage damage. [18,19] These findings were supported by the findings of a recent randomised trial of 140 patients with symptomatic knee arthritis that found that intra-articular triamcinolone administered every 3 months over 2 years resulted in greater cartilage volume loss with no significant benefit on pain.[20] The authors concluded that their findings do not support the use of long-term repeated corticosteroid injections for the management of pain or structural progression in osteoarthritis, and in fact indicate that there may be more cartilage loss in people who receive steroids.[21] The results of that trial contrast with the findings of a single centre randomised controlled trial (RCT) that compared the long-term effects of intra-articular corticosteroids versus saline in 68 patients with symptomatic osteoarthritis of the knee, intra-articular triamcinolone administered every 3 months over 2 years resulted in significant improvement in pain and stiffness over the 2-year period.[22] No adverse local effects in the knee were reported. The authors concluded that repetitive intra-articular steroid injections appeared to be safe for osteoarthritis.

Evidence on the practice and patterns of use of intra-articular injections 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 intra-articular injections after treatment initiation in the UK and globally is very limited. In a recent review which aimed to examine the dosing regimen and frequency of corticosteroid injections for osteoarthritic knees, it was noted that the published medical literature concerning the frequency of

corticosteroid injection was non-existent and that all published information on this topic appeared to be based on professional opinion.[23] Analysis of 9 years of follow-up data from the US Osteoarthritis Initiative (OAI) comprising of patients with knee osteoarthritis, suggests that about 60 percent of participants who initiated corticosteroid injections had an average age of 69 years and were one-time users.[24] During the follow-up period, 24 percent continued treatment with corticosteroid injections whilst 17 percent switched treatment (to hyaluronic acid injections). The results suggested that the decision to continue or switch treatment was dependant on symptoms experienced after the initial injection. Limitations of the current evidence include use of observational designs, which are limited by reverse causation bias, with inadequate adjustment for residual confounding, methodological limitations of the trials which include small sample sizes, single-centre design, samples in trials limited to osteoarthritic knees, and the inconsistent results reported. Taking the overall evidence together suggests that the long-term clinically important benefits and risks associated with intra-articular steroid injections for osteoarthritis remain unclear. Data on the patterns of use of intra-articular injections after treatment initiation as well as factors influencing these patterns are also unavailable.

The data generated in this study will provide comprehensive and contemporary information on the pattern of use of intra-articular injections of joints for osteoarthritis in primary care. The safety of use and the treatment effect will be assessed as well as the effect of receiving the intervention on the timing of subsequent surgical interventions. Where the subsequent intervention is arthroplasty, the influence of intra-articular injection on the risk of adverse events following arthroplasty and patient reported pain and function will be assessed. Qualitative interviews will explore the experience and views of patients and clinicians on receiving/administering intra-articular injections. A Delphi consensus exercise will inform future research priorities and the feasibility of carrying out such research.

5. Evidence explaining why this research is needed now

This is a commissioned study by the HTA and as such has already been justified. HTA advice in such cases is to enter ‘not applicable’ in this section.
We can confirm however that since the commissioned call there have been no published systematic reviews, or RCTs that answer the commissioning brief.

6. Aims and Objectives

Aim 1: To establish the current practice of use of intra-articular corticosteroid injection for the treatment of joint pain due to osteoarthritis.
Aim 2: To establish the long-term effects of the use of recurrent intra-articular injections of corticosteroid.
Aim 3: To explore the views and experiences of patients and clinicians of the use of intra-articular injections of corticosteroid.
Aim 4: To assess priorities and associated feasibility considerations for future primary research.

Objectives: Following the NIHR HTA commissioning brief, we intend to use routinely collected observational data (Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES) and National Patient Reported Outcome Measures (PROMs) data) to achieve aim 1 and aim 2. The extent and depth of these routinely collected datasets allows

rapid and efficient assessment of interventions such as intra-articular injections in osteoarthritis in a generalisable sample of patients that is of sufficient size to achieve satisfactorily powered analyses. To address the issue of confounding, we will perform instrumental variable regression as our primary analysis. Propensity score matching and inverse probability weighting will be utilised as alternative complementary approaches for secondary analyses. Qualitative interviews and a Delphi survey will be conducted to further explore the experience and views of the use of intra-articular injections and the feasibility of future primary research, achieving aims 3 and 4.

7. Research Plan / Methods

Following the direction of the commissioned call, we will conduct research of routinely collected observational datasets (CPRD, HES and PROMs) to determine the use, safety and effect of intra-articular corticosteroid injections for osteoarthritis (WP 1). This will be supplemented by qualitative interviews to explore patient and clinician views on the use of these injections (WP 2) and a Delphi consensus survey of patients, clinicians, researchers and commissioners to identify priorities and associated feasibility considerations for future primary research (WP 3).

Health technologies being assessed:
This programme of research will assess intra-articular corticosteroid injections in patients with osteoarthritis compared to controls with a diagnosis of osteoarthritis who have not received an intra-articular corticosteroid injection.

WORK PACKAGE 1
Study design: Cohort study using routinely collected data

Data sources: The *Clinical Practice Research Datalink (CPRD)*[25] comprises the entire computerised medical records of a sample of patients attending general practitioners (GPs) in the UK. It contains information on over 11 million patients (around 7% of the population) registered at over 600 general practices in the UK that are representative of the population in terms of demographics such as age and sex. GPs in the UK play a key role in the delivery of healthcare by providing primary care and referral to specialist hospital services. Patients are registered with one practice that stores medical information from primary care and hospital attendances. The CPRD is administered by the Medicines and Healthcare products Regulatory Agency (MHRA). The CPRD records contain all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, prescription data, and hospital admissions. Data is stored using Read and Oxford Medical Information Systems (OXMIS) codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). Read codes are used as the standard clinical terminology system within UK primary care. Only practices that pass quality control are used as part of the CPRD database. Deleting or encoding personal and clinic identifiers ensures the confidentiality of information in the CPRD.

The *Hospital Episode Statistics (HES) database* holds information on all patients admitted to NHS hospitals in England, including diagnostic ICD codes providing information about a patient's illness or condition and OPCS4 procedural codes for surgery. It covers a smaller

geographical area than the CPRD and does not include privately-funded operations. HES provides information including detailed comorbidity information and deprivation indices, and about every NHS funded procedure (including length of stay). Additional records contain details of readmissions, reoperations, and revisions. Data for all-cause mortality are provided by the Office for National Statistics (ONS) and linked to the HES database.

Since April 2009, *Patient-Reported Outcome Measure (PROM)*[26] data has been collected on hip and knee replacements performed in NHS hospitals in England. Pre-operative and 6 month quality of life questionnaires (the EuroQol five domain (EQ5D)[27]) and joint-specific PROMs (the Oxford Hip Score (OHS)[28] and Oxford Knee Score (OKS)[29] are collected along with patient-reported measures of preoperative disability and postoperative satisfaction. Data are collected by the NHS trusts under whose care the procedure is performed, and co-ordinated by NHS Digital on behalf of the Department of Health.

CPRD data will be linked to the HES and PROMs databases (**CPRD-HES-PROMs**). CPRD already provide access to HES and PROMs data that is held under the CPRD Data Linkage Scheme. CPRD and HES linked data is available for around 50% of patients in the CPRD database. Previous research by the CPRD team has shown that linked practices/patients are representative of the CPRD GOLD population as a whole.

Population: The CPRD database will be screened to identify a first-ever clinical record of joint osteoarthritis identified using a Read code and occurring within the patients' up-to-standard registration period. The study population will only include incident patients (those with a first-ever record of osteoarthritis). Initial feasibility counts from CPRD suggest that between 2005-2017, the numbers of patients with joint specific OA given injections are: 25,818 (55%) knee, 9,649 (20.6%) hip, 5,302 (11.3%) hand, 3,008 (6.4%) shoulder, 2,130 (4.6%) ankle/foot, 689 (1.5%) wrist and 217 (0.5%) elbow. Feasibility counts provided by CPRD have demonstrated a wide spread of joints injected, limiting analysis to knee and hip osteoarthritis would capture 76% of the injections for osteoarthritis. We will provide descriptive data for IACI for all joints as described above. Data interrogation will be performed to establish whether we can reliably identify intra-articular injections performed for osteoarthritis or whether there may be overlap or confounding with other conditions and types of injection (e.g. soft tissue injections performed for trochanteric pain of the hip due to trochanteric bursitis or abductor tendon pathology). Where assumptions are made, these will be tested with sensitivity analyses to ensure robustness. Where we are confident that true IACI for osteoarthritis can be identified for a joint type, data on that joint will be included in the analyses of safety and outcomes.

Intervention: Intra-articular corticosteroid injection for osteoarthritis

Outcomes:
Current practice: joint site injected

Utilisation study:

- Population-level use: incidence and prevalence of use of injections, and secular trends of use over the CPRD overall population, practice level data will be explored to understand variations in treatment
- Patient-level utilisation: number of repeat injections over time, cumulative use (number of daily defined doses of steroid/s injected in total), and medication possession ratio

(number of daily defined doses of steroid injected over number of days from first to last injection)

- Safety: pain, bleeding, infection, diabetes decompensation, cardiovascular events
- Association with outcomes: drug utilisation (analgesics [paracetamol, topical & parenteral NSAIDs, steroid injections, opiates], oral corticosteroids), timing to intermediate surgical interventions (e.g. arthroscopy) and end-stage intervention (arthroplasty). For those that receive arthroplasty outcomes this will include: joint infection, further surgery to the same joint (e.g. debridement, manipulation under anaesthetic, revision), readmission due to thrombosis, myocardial infarction and stroke. Patient reported outcomes (PROMs) including Oxford Hip Score, Oxford Knee Score and EQ5D.

Feasibility: Measures of effect sizes for association with outcomes between patients that did compared to those that did not receive intra-articular injection of corticosteroid, proportion of primary care practitioners performing intra-articular injection of corticosteroid and practices in which intra-articular injection of corticosteroid are performed.

Confounders: We will conduct a review of the literature to identify all potentially relevant confounders for the outcomes of interest (safety (adverse events) and treatment outcomes (pain severity, future interventions, outcomes of arthroplasty)). Having collated a list of relevant confounders for each outcome, these will be reviewed by panels of experts within the field to ensure these are true confounders (not mediators), and that all relevant factors have been identified as a final comprehensive list. Potential relevant confounders identified at this stage include, but are not limited to, the following variables: geographical location by Strategic Health Authority, Index of Multiple Deprivation, Charlson comorbidity index, body mass index, age, gender, other types of arthritis, comorbidities, pre-existing medication prescriptions (anti-hypertensives, anticoagulants [warfarin, low-molecular-weight heparin, aspirin, clopidogrel, dipyridamole], diabetic medications, oral corticosteroids, antidepressants, bisphosphonates) and hypertension.

Statistical analysis

Current practice: Descriptive statistics (number (%)) will be used to describe the number of patients with osteoarthritis given intra-articular injections of corticosteroid and summarised across each of the different joint sites. We will look at trends in the rate of IACI use over time and look at whether there are inequalities according to patient sociodemographic groups, at the practice level and health region.

Safety and association with outcomes: The exposure of interest is whether or not a patient received an IACI. In an observational study design such as this, IACI is not randomly allocated therefore both known and unknown confounding factors must be considered in analyses. Unmeasured confounding may lead to a risk of biased effect estimates.

Primary analysis: Instrumental variables (IV) can be used, if fulfilling certain key assumptions, to address the issue of unmeasured confounding and produce unbiased estimates.[30] The instrument will be based on preference for IACI and calculated in a time dependent manner according to clinician performing IACI, date of IACI and calculating relative frequency of IACI over the previous 20 patients treated for OA (sensitivity analyses will be performed at different thresholds). If the relative frequency for a given clinician is above a specified threshold, we would define the clinician (at that point in time) as preferring IACI. The IV is then used in a 2-stage least squares linear regression. Treatment exposure is

the dependent variable in the first model containing the IV (clinician preference) and measured covariates. This first model provides the estimated probability of being exposed depending on IV status and measured confounders. These fitted values are then included along with measured confounders as independent variables into the second stage regression on the outcomes. The coefficient for the predicted probability of being treated with IACI (given the IV and measured covariates) is the result of interest. IV analyses are only valid if we have a good instrument and meet the core underlying assumptions: 1) The IV must be strongly associated with the exposure; 2) The IV must not have direct effects on the outcome except through its association with the exposure; 3) The IV is independent of confounders. Hence, we will perform secondary analyses to test our assumptions and see if consistent results are obtained.

Secondary analyses: Methods that we will use in the secondary analyses include: Propensity score (PS) matching, [31] where a logistic regression model is fitted with the outcome of IACI use (yes/no); and identified covariates listed are included as potential confounders. Matching of each patient not receiving IACI to a comparable IACI user using a 0.2 standard deviation calliper width[32] minimises confounding by indication, providing participants with balanced baseline characteristics in both groups and eliminating IACI users with no comparable non-user controls. [33] Greedy matching is used, where a random treated subject is selected and nearest neighbour (untreated subject) then selected for matching. Matched IACI users and non-users will be included in regression models, to determine the impact on safety and association with outcomes. As we will have a matched sample, this introduces a bias that must be accounted for in the analysis stage. Matched subjects will have correlation (greater similarity) in outcomes than two randomly selected subjects. This is because their baseline covariates are more similar, and baseline covariates are related to outcome. We must therefore account for the lack of independence in outcomes that has been induced by matching. Hence, to account for the matched nature of the sample, we will use a robust variance estimator that accounts for the clustering within matched sets.[34]

Inverse probability weights (IPW), this being the reciprocal of an individual's probability of receiving the intervention that they actually received. As with propensity scores, we use logistic regression to model the association of whether or not a person received IACI on the list of potential confounders. We then estimate each subject's probability of the treatment they actually received, and weight the analysis according to the inverse of these probabilities. Therefore, in weighted analysis, receipt of the intervention is no longer related to the confounders. Although PS and IPW analyses may seem similar, they can give very different results. [35] This is because PS matching focuses on the treated population, whereas IPW estimates the average effect of treatment in the entire study population (e.g. outcome if everyone got the intervention, compared with the outcome if no one got the intervention).

Immortal time bias is a common issue in observational studies, where the event of interest cannot occur for a certain time span.[36] In the case of this proposed study, immortal time bias would occur due to the definition of exposure, where in the time from diagnosis of incident osteoarthritis until receipt of intra-articular injection of corticosteroid those in the 'intra-articular injection of corticosteroid user group' cannot have the outcomes by design otherwise they would have been classified as non-users. To avoid this problem, we will use time varying exposures.

Missing data will be handled by using multiple imputation methods using the ICE (Imputation by Chained Equations) procedure.[37] The results of complete case analyses can be biased.[38] The cumulative effect of missing data in several variables often leads to exclusion of a substantial proportion of the original sample, causing a loss of precision and power. This bias can be overcome by using multiple imputation, which allows for the uncertainty about missing data by creating several plausible imputed datasets and appropriately combining their results. Standard errors are calculated using Rubins Rules. We include all predictor variables in the multiple imputation process, together with the outcome variable as this carries information about missing values of the predictors.

Consideration of competing risks is required, where death is an important competing risk that precludes development of outcomes. A standard Cox regression survival model treats the competing risk of death as a censored observation, but this assumes death is non-informative (e.g. that if they had not died, they would have the same chance of developing outcome as their peers). In order to account for the competing risk of death, we will use the method of Fine & Gray.[39] This allows us to model the risk of outcome (e.g. time to joint replacement) in those who are currently event free as well as those who have previously experienced a competing event (rather than only include those in the risk set that haven't died).

Sensitivity analyses: The limitation of the above methods is that only IV analyses have the potential to address unmeasured confounding and they are only valid if we have a good instrument and meet the core assumptions that underly the IV regression models: 1) The IV must be strongly associated with the exposure; 2) The IV must not have direct effects on the outcome except through its association with the exposure; 3) The IV is independent of confounders. Here the goal of sensitivity analysis is to quantify the degree to which the key assumption of no unmeasured confounders must be violated for the observed effect size to be reversed. A number of sensitivity analyses techniques have been developed to evaluate the impact of unmeasured confounding[37], such as the rule out approach or Rosenbaum Bounds, where we test how strong a single hypothetical unmeasured confounder would need to be to attenuate the observed association, and external adjustment for multiple unmeasured confounders using propensity score calibration (PSC), which can be applied when external information is available that does not contain outcome information.

Sample size: Initial feasibility counts from CPRD suggest that between 2005-2017, the numbers of patients with joint specific OA given injections are: 25,818 (55%) knee, 9,649 (20.6%) hip, 5,302 (11.3%) hand, 3,008 (6.4%) shoulder, 2,130 (4.6%) ankle/foot, 689 (1.5%) wrist and 217 (0.5%) elbow. For the most commonly injected joint (knee osteoarthritis), using a 2-sided log rank test for equality of survival curves, 90% power, 5% level of significance (alpha), where outcome is time to arthroplasty, with an anticipated arthroplasty rate of 7% over 4-years follow up[40] we can detect a hazard ratio of 0.85 (equivalent to a 7% arthroplasty rate in non intra-articular injection of corticosteroid users and 6% in intra-articular injection of corticosteroid users) with a total sample size of 24,613 (12,300 in each group). With an actual expected sample size of >100,000 knee osteoarthritis patients (where 25% are expected to have received an intra-articular injection of corticosteroid), we are adequately powered.

Ethical approval: CPRD obtains ethics approval to receive and supply patient data for public health research. This protocol will be reviewed and approved by the CPRD Independent Scientific Advisory Committee (ISAC) before the study commences.

WORK PACKAGE 2

Study design: Semi-structured in-depth interviews with patients who have received intra-articular injections of corticosteroid for osteoarthritis, those who have received recurrent injections, patients with osteoarthritis who have not received injections, clinicians who have experience of prescribing and administering intra-articular injections of corticosteroid and those who have not administered injections.

Population: Patients who have received intra-articular injections of corticosteroid for osteoarthritis and primary care clinicians with experience of administering intra-articular injections of corticosteroid to these patients.

Sampling and recruitment: Adults who have received intra-articular injections of corticosteroid for the treatment of osteoarthritis within a primary care setting, within the last 3 years, including those who have received surgical intervention will be identified through the Clinical Research Network (CRN) West of England research network, facilitated by the Bristol North Somerset & South Gloucestershire (BNSSG) CCG Research & Evidence Team (BNSSG R&ET), previously the BNSSG CCG Research and Evidence Team, using Read codes. Purposive maximum variation sampling will be used to stratify patients by age, employment, ethnic background, socioeconomic status, practice locale, affected joint and clinical setting.[41,42] Using a similar sampling strategy, patients who have the same conditions but have not received injections and those who have received recurrent injections will be identified. GPs serving diverse populations from across the South West of England will be identified through the CRN West of England. Those who have administered intra-articular injections of corticosteroid for osteoarthritis and those who have not (or only a small number of occasions) will be purposively sampled. Up to 40 patients and 30 GPs from across a range of GP practices in the South West region will be interviewed. It is estimated that these numbers will achieve data saturation, such that no new insights emerge by the time of completion.[43]

Methods: All interviews will be conducted face-to-face where possible or via telephone or Skype to increase opportunities for participation.

Interview topics with patients: Interviews with patients will explore their ideas of or experience of receiving intra-articular injections of corticosteroid for osteoarthritis, and the benefits and disadvantages of treatment, including impact on daily activities, and their motivations for choosing to undergo treatment or not, including to delay or prevent surgery, and their experience of accessing treatment. Topics will also include patient beliefs about the efficacy of intra-articular injections of corticosteroid and length of benefit, patient expectations and anxieties about treatment including perception of risks and patient knowledge about intra-articular injections of corticosteroid and information needs. Participants will also be invited to participate in the Delphi study where timelines allow for this.

Interview topics with clinicians: Interviews with clinicians will explore their views and where relevant experiences of prescribing/administering intra-articular injections of

corticosteroid, including their beliefs about the efficacy of intra-articular injections of corticosteroid for osteoarthritis, and their motivations for choosing to use them or not, including whether they are used to delay or prevent surgical intervention. Interviews will also explore factors affecting decision-making on use of intra-articular injections of corticosteroid including complications, comorbidities, and perceived risks of repeated use, and clinicians' awareness of and views on current guidelines and recommendations for the use of intra-articular injections of corticosteroid. We will also ask clinicians how they perceive that intra-articular injections of corticosteroid might best be incorporated into the treatment pathway. Participants will also be invited to participate in the Delphi study where timelines allow for this.

Analysis of qualitative interview data: Interviews will be audio-recorded and then transcribed, anonymised, and imported into QRS NVivo 11 data management software. Transcripts will be analysed using thematic analysis[44] comprising coding, independent double-coding and development of key themes. The analysis will focus on participant views and experiences of using intra-articular injections of corticosteroid for osteoarthritis and will be underpinned by health behaviour theories applicable to both patients and practitioners such as the Health Belief Model.[45] The analysis will also inform the development of an explanatory model and a narrative report to explain patient and clinician use of intra-articular injections of corticosteroid in the current management of osteoarthritis.[46]

Ethical approval: Ethical approval will be applied for from a Research Ethics Committee via the Health Research Authority prior to commencement of the study.

WORK PACKAGE 3

Aims: To gain expert consensus on the key questions for future research and any feasibility considerations with answering these research questions.

Study design: 3-round modified Delphi study

Population and sampling: The sample size for a Delphi study depends on group dynamics for obtaining consensus rather than statistical power. To ensure the four key stakeholder groups are represented equally, we will recruit 100 participants: 25 patients, 25 healthcare professionals involved in the treatment of patients with joint disease, will be recruited through the CRN West of England, and 25 academics and 25 commissioners will be recruited through academic networks and from CCGs via the BNSSG CCG Research & Evidence Team.

Methods:

<u>Round 1 questionnaire: Identifying questions</u>

Participants will be asked to identify up to 5 research questions and associated feasibility considerations in relation to intra-articular injections of corticosteroid in osteoarthritis. Responses will be collated and a list of candidate research questions developed. These will be supplemented by research questions identified from Work Packages 1 & 2 and through a workshop with our patient and public involvement (PPI) group. Comprehensive literature searches will ensure that only research questions with a lack of evidence or treatment uncertainty are included in Round 2. Research questions will be formulated into population, intervention, comparator, outcome (PICO) format and reviewed by our PPI group.

Round 2 questionnaire: Ranking
Participants will rate the importance of each research question from 1-9 (not important to very important). Free-text boxes will be provided to comment on the associated feasibility considerations. Research questions given an importance rating of 7–9 by ≥70% of participants will be carried forward to Round 3. To ensure that research questions considered exceptionally important by only one stakeholder group are not omitted, research questions rated as 7–9 by ≥90% of members of one panel, regardless of the ratings of the other panels will also be carried forward.

Round 3 questionnaire: Final consensus
Participants will be sent the retained research questions and the median group ratings from Round 2 to again rate the importance of each research question. Those questions given an importance rating of 7–9 by ≥70% of participants, or by ≥90% of members of one panel, will be included in the final research priority list. This list will provide recommendations on the key questions for future research and any feasibility considerations with answering these research questions.

Ethical approval: Ethical approval will be applied for from a Research Ethics Committee via the Health Research Authority prior to commencement of the study.

8. Dissemination, Outputs and anticipated Impact

A detailed manuscript and report will be provided to NIHR HTA for publication in the HTA Journal. We also plan to publish our research findings in high profile peer reviewed journals such as the BMJ, Lancet or JAMA. Wherever possible, we will publish our findings in open access journals, and have requested appropriate funding to cover these related fees for the predicted number of outputs.

Findings from the research will be presented at a variety of relevant conferences in order to ensure maximum dissemination of the findings. These will include the Royal College of General Practitioners Annual Conference, the Royal Society of Medicine minor surgery and joint injection courses, the British Society of Rheumatology, the European League against Rheumatism Conference, the British Orthopaedic Association, the British Association for Surgery of the Knee and the British Hip Society. BNSSG CCG Research & Evidence Team will lead our dissemination of results to local and national CCGs and they have an excellent track record in stakeholder engagement in this respect.

The study applicants between them have many national roles and collaborations providing excellent access and influence to disseminate the study findings nationally and internationally through the educational activities of societies such as the Royal College of General Practitioners and Royal Society of Medicine, academic research networks and funded research centres. The principal investigator is one of the founding members of the largest GP minor surgical skills course in the country and the course includes joint injections, the new findings would be disseminated through this course. The principal investigator is also currently defining the course content and learning resources for a musculoskeletal

update course for one of the largest GP education providers in the country. This route will also allow rapid dissemination of findings.

We will work with the 'Patient Experience Partnership in Research' (PEP-R) group[47] to develop accessible information which will be disseminated through press releases, web-based resources and other appropriate outlets.

We also engaged with the North Bristol NHS Trust's Communication & PPI Office and the University of Bristol's Centre of Public Engagement and Press Office as platforms for future dissemination to public and other audiences.

As identified in the commissioned call, the potential for future primary research in this area is important to consider and has already been identified as a priority by our PPI group. If the findings of the research indicate that future primary research is both feasible and needed, then we anticipate applying to NIHR for funding in the future in order to conduct this work.

9. Project / research timetable

A summary of the project work packages, package elements, start times and durations is included in the table below and represented in the Gantt chart figure attachment. These resources will be used to monitor the progress of the study and ensure that the project progresses as expected or plans are made to identify and address any areas that are not progressing as per the expected timelines at the 6 monthly reporting intervals required by NIHR.

Task	Start (month)	Duration (months)
Contract negotiations	-3	3
WP 1 (CPRD-HES-PROMS)	**1**	**30**
ISAC application, permissions and approvals	-2	4
Data extraction and linkage	3	2
Data management	4	2
Utilisation and safety analysis	5	6
Interim results meeting	9	1
Utilisation, safety and outcomes analysis	10	6
2nd interim results meeting	15	1
Final data analysis (outcomes)	16	6
Final results meeting	21	2
Study report and paper writing	23	6
Dissemination, submission and closure	27	4
WP 2 Qualitative interviews	**1**	**30**
Research document development with PPI	1	2
HRA and NHS REC approval process	2	3
Identify and recruit patients and clinicians	5	18
Interview patients and clinicians	6	18
Transcribe and analyse data	7	18
Study report and paper writing	25	6
Dissemination, submission and closure	26	5
WP 3 Delphi survey	**16**	**15**

Develop survey questions	16	2
HRA and NHS REC approval process	17	3
Participant recruitment and round 1 & analysis	20	4
Round 2 & analysis	24	2
Round 3 & analysis	26	2
Study report and paper writing	27	4
Dissemination, submission and closure	28	3

10. Project management

A Project Management Committee (PMC) will be constituted. This committee will be made up of all grant co-applicants, researchers, host representatives and sponsor representatives. The PPI co-ordinator is a member of the project team and will support our patient-partner co-applicant in the preparation for and during the meetings. The PMC will meet monthly for the period of the research and will be responsible for the day to day running of the research and communication between the work packages under the leadership of the principal and co-principal investigators. The progress of each of the work packages will be monitored and any issues encountered in each package discussed amongst the members of the PMC. Relevant data from each work package will be shared in order to help inform the conduct of the other work packages. At least three of the meetings will be arranged to coincide with or be conducted shortly after the interim results meetings.

A Project External Steering Committee (PESC) will be constituted. This will consist of three external members. It is anticipated that the committee would be constituted of a GP, a qualitative researcher and an epidemiologist, statistician or methodologist. The final make up of the committee will be at the discretion of the invited chair of the PESC. It is anticipated that the PESC would meet 3 times during the course of the research. Given the nature of the data being researched, it is not anticipated that a separate data monitoring committee would be required but again, this will be at the discretion of the PESC chair.

11. Ethics

Work package 1 of the proposed study will only use pseudonymised, retrospective, routinely collected data. The identified data sources CPRD and HES do not request ethics committee approval to access/extract their data. However, approval by internal independent data access committees is required, including the Independent Scientific Advisory Committee (ISAC) at MHRA for CPRD and linked HES data. Co-applicants on our research team have extensive experience of submitting and receiving approval for submissions to ISAC.

Work package 2 will involve qualitative research with NHS patients and staff and therefore we will apply for the required Health Research Authority and NHS Research Ethics Committee approval prior to commencing the research. Co-applicants have extensive experience of submitting successful ethics approval applications.

Work package 3 will involve NHS patients, and therefore Health Research Authority (HRA) approval will be obtained prior to commencing the research. Sponsorship and insurance will be obtained from the University of Bristol.

12. Patient and Public Involvement

Please describe how patients and the public have been involved in developing this proposal

This application was developed in collaboration with patient-partners. Meetings were carried out with our established, dedicated patient public involvement (The Patient Experience Partnership in Research Musculoskeletal: PEP-R MSK) which comprises members with musculoskeletal conditions and experience of relevant treatments such as joint injections and joint replacement. Through ongoing training and support from research staff and our dedicated patient involvement co-ordinator, group members are familiar with research design, conduct and the barriers to successful research. The group uses INVOLVE guidance to ensure that activity is appropriately organised and conducted. Meetings occurred in November 2017 with 8 members of the group. One of the members of the group is a co-applicant on the grant and will attend our monthly PMC meetings with the support of our PPI group coordinator.

When we met with the whole PEP-R group, there was interest that the proposed research was in response to a commissioned call from NIHR. They were pleased to hear that commissioned calls in research areas relevant to them were taking place and felt it was important that we were involved in research via this pathway. The group members felt that the call was timely and very relevant. Group members described different experiences of joint injections with some having had a number of injections and others not knowing that injections were an option for the treatment of osteoarthritis, demonstrating the variation in care offered to NHS patients. They were surprised to hear how little evidence there was in this area, particularly when repeated injections were used and therefore felt that this was an area of research priority. Those that had received injections commented that not all GPs performed joint injections and some only did injections to particular areas. In some cases, this had led to multiple appointments being required in order to receive injections. They felt it was important to establish where injections fitted into treatment pathways and said that they may have reconsidered having joint injections if they had been told this may delay a joint replacement. A minority recalled being told of possible adverse effects of injections and they felt that further good quality evidence was required in this area so that they could make fully informed choices.

Members of the group were very supportive of the proposed design and were pleased to hear that we would be analysing data that had already been collected, which they felt would be an efficient and valuable use of this data. They were particularly pleased to hear that we intended to incorporate qualitative interviews with patients to gather evidence on their views and experiences of injections and felt this was a vital component of the research. Likewise, they were very supportive of the prospect of future trials in this area and felt the use of a consensus survey was a very good way to establish how this research should be designed and carried out. They did comment that they felt that a health economics component would be vital in any future trial.

PEP-R MSK members offered very useful feedback on the plain English summary of the research. They felt it reflected the proposal well and used appropriate language. They particularly requested that the term “pain killers” was avoided as such medications alter pain

but do not “kill” it. Group members offered ongoing support and a willingness to be involved in the conduct of the research which will be vital to ensure that the project reflects the priorities of patients and is conducted to the best possible standards.

Please describe the ways in which patients and the public will be actively involved in the proposed research, including any training and support provided

One of the PEP-R group members group members is a co-applicant on the grant and will be one of the core members of the PMC and overall research team. The insight provided to date has already been invaluable and will continue to guide the development and conduct of the research, an essential element when conducting research with study designs such as we propose to keep the research questions and outputs focused on patient centric issues. The lived experience offered will be central to guiding the presentation and development of our research outputs as well as informing the focus and acceptability of future research studies in this area. Funding has been requested to support this role. The PEP-R MSK group as a whole meet five times a year and project updates will be provided to the group on five occasions throughout the period of research, allowing us to gain the insight and feedback of the wider group throughout the programme of work and incorporate this into the research and outputs. By utilising the group’s existing expertise and providing support and training, the research will benefit from their insights into what issues are important to patients, their own personal experiences and their experience from previous research projects.

Our dedicated PPI co-ordinator is an experienced and trained researcher with many years of experience supporting patient-partners in research. The support offered will include structured training sessions from the co-ordinator and other researchers, one-to-one or small group meetings and support in attending PMC meetings including with the material circulated prior to and after the meetings. The co-ordinator will act as a liaison between members of the research team and the patient-partners where this is preferred, or support them in direct two-way communication where that is preferred. Our unit and PEP-R MSK group already work closely with the ‘People in Health West of England’ consortium promoting and supporting service user involvement in research and patient-partners will continue to have access to events and the wider network.

References

1. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis. Osteoarthritis Cartilage. 2010 Apr;18(4):476–99.
2. Sun BH, Wu CW, Kalunian KC. New developments in osteoarthritis. Rheum Dis Clin North Am. 2007 Feb;33(1):135–48.
3. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014 Jul;73(7):1323–30.
4. Bitton R. The economic burden of osteoarthritis. Am J Manag Care. 2009 Sep 1;15(8 Suppl):S230–5.
5. World Health Organization. Department of Chronic Diseases and Health Promotion: Chronic rheumatic conditions. World Health Organisation. World Health Organization. Available from: http://www.who.int/chp/topics/rheumatic/en/
6. Kaplan W, Wirtz VJ, Mantel-Teeuwisse A, Stolk P, Duthey B, Laing R. Priority Medicines for Europe and the World Update Report, 2013. World Health Organization; 2013 Jul pp. 126–8. Available from: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1
7. Arthritis Research UK. Osteoarthritis in General Practice. 2013 Jul. Available from: https://www.arthritisresearchuk.org/arthritis-information/data-and-statistics/~/media/EFAEFCE432734F3AA5FB1C64329E02D1.ashx
8. National Institute for Health and Care Excellence (NICE). NICE Clinical guideline CG177 Osteoarthritis: Care and management in adults. National Institute for Health and Care Excellence; 2014. pp. 1–505. Available from: https://www.nice.org.uk/guidance/cg177/evidence/full-guideline-pdf-191761309
9. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006 Apr 19;21(2):CD005328.
10. Flanagan J, Casale FF, Thomas TL, Desai KB. Intra-articular injection for pain relief in patients awaiting hip replacement. Ann R Coll Surg Engl. 1988 May;70(3):156–7.
11. Qvistgaard E, Christensen R, Torp-Pedersen S, Bliddal H. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis Cartilage. 2006 Feb;14(2):163–70.
12. Meenagh GK, Patton J, Kynes C, Wright GD. A randomised controlled trial of intra-articular corticosteroid injection of the carpometacarpal joint of the thumb in osteoarthritis. Ann Rheum Dis. 2004 Oct;63(10):1260–3.
13. van Middelkoop M, Arden NK, Atchia I, Birrell F, Chao J, Rezende MU, et al. The OA Trial Bank: meta-analysis of individual patient data from knee and hip osteoarthritis trials show that patients with severe pain exhibit greater benefit from intra-articular glucocorticoids. Osteoarthritis Cartilage. 2016 Jul;24(7):1143–52.
14. Wang Q, Jiang X, Tian W. Does previous intra-articular steroid injection increase the risk of joint infection following total hip arthroplasty or total knee arthroplasty? A meta-analysis. Med Sci Monit. 2014 Oct 9;20:1878–83.
15. Conaghan PG, Cohen S, Jordan J, Berenbaum F, Lufkin J, Wilwerth C, et al. Sustained and profound analgesic benefits in people with osteoarthritis of the knee using FX006, an intra-articular extended-release formulation of triamcinolone acetonide: Results from a double-blind, randomized, parallel-group, dose-ranging study. Osteoarthritis Cartilage. 2016;24(S1):S49–S50.

16. Bodick N, Lufkin J, Willwerth C, Kumar A, Bolognese J, Schoonmaker C, et al. An intra-articular, extended-release formulation of triamcinolone acetonide prolongs and amplifies analgesic effect in patients with osteoarthritis of the knee: a randomized clinical trial. J Bone Joint Surg Am. 2015 Jun 3;97(11):877–88.

17. He W-W, Kuang M-J, Zhao J, Sun L, Lu B, Wang Y, et al. Efficacy and safety of intraarticular hyaluronic acid and corticosteroid for knee osteoarthritis: A meta-analysis. Int J Surg. 2017 Mar;39:95–103.

18. Wada J, Koshino T, Morii T, Sugimoto K. Natural course of osteoarthritis of the knee treated with or without intraarticular corticosteroid injections. Bull Hops Jt Dis. 1993;53(2):45–8.

19. Zeng C, Lane NE, Hunter DJ, Wei J, Choi HK, McAlindon TE, et al. Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2019 Jan 29. [Article in Press]

20. McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, Zhang M, et al. Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial. JAMA. 2017 May 16;317(19):1967–75.

21. Wise J. Steroid injections for knee osteoarthritis are not supported by study. BMJ. 2017 May 16;357:j2386.

22. Raynauld J-P, Buckland-Wright C, Ward R, Choquette D, Haraoui B, Martel-Pelletier J, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2003 Feb;48(2):370–7.

23. Douglas RJ. Corticosteroid injection into the osteoarthritic knee: drug selection, dose, and injection frequency. Int J Clin Pract. 2012 Jul;66(7):699–704.

24. Liu SH, Dubé CE, Driban JB, McAlindon TE, Eaton CB, Lapane KL. Patterns of intra-articular injection use after initiation of treatment in patients with knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis Cartilage. 2017;25:S435.

25. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Ther Adv Drug Saf. 2nd ed. 2012 Apr;3(2):89–99.

26. Dawson J, Doll H, Fitzpatrick R, Jenkinson C, Carr AJ. The routine use of patient reported outcome measures in healthcare settings. BMJ. 2010 Jan 1;340(jan18 1):c186–6.

27. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997 Nov;35(11):1095–108.

28. Dawson J, Fitzpatrick R, Carr A, Murray DW. Questionnaire on the perceptions of patients about total hip replacement. J Bone Joint Surg Br. 1996 Mar;78(2):185–90.

29. Dawson J, Fitzpatrick R, Murray DW, Carr A. Questionnaire on the perceptions of patients about total knee replacement. J Bone Joint Surg Br. 1998 Jan;80(1):63–9.

30. Brookhart MA, Wang PS, Solomon DH, Schneeweiss S. Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. Epidemiology. 2006 May;17(3):268–75.

31. Bachmann C, Abramovitch H, Barbu CG, Cavaco AM, Elorza RD, Haak R, et al. A European consensus on learning objectives for a core communication curriculum in health care professions. Patient Educ Couns. 2013 Oct;93(1):18–26.

32. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biom J. 2009 Feb;51(1):171–84.

33. Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol. 2006 Mar;98(3):253–9.

34. Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med. 2013 Jul 20;32(16):2837–49.

35. Kurth T, Walker AM, Glynn RJ, Chan KA, Gaziano JM, Berger K, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. Am J Epidemiol. 2006 Feb 1;163(3):262–70.

36. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010 Mar 12;340:b5087.

37. Royston P. Multiple imputation of missing values: Update of ice. SJ. 2005;5(4):527–36.

38. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009 Jun 29;338(jun29 1):b2393–3.

39. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc. 1999;94(446):496.

40. Leyland KM, Judge A, Javaid MK, Diez-Perez A, Carr A, Cooper C, et al. Obesity and the Relative Risk of Knee Replacement Surgery in Patients With Knee Osteoarthritis: A Prospective Cohort Study. Arthritis Rheumatol. 2nd ed. 2016 Apr;68(4):817–25.

41. Coyne IT. Sampling in qualitative research. Purposeful and theoretical sampling; merging or clear boundaries? J Adv Nurs. 1997 Sep;26(3):623–30.

42. Sandelowski M. Sample size in qualitative research. Res Nurs Health. 1995 Apr;18(2):179–83.

43. Guest G. How Many Interviews Are Enough?: An Experiment with Data Saturation and Variability. Field Methods. 2006 Feb 1;18(1):59–82.

44. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2):77–101.

45. Skinner CS, Tiro J, Champion VL. The health belief model. In: Glanz K, Rimer BK, Viswanath K, editors. Health behavior theory, research, and practice. 5 ed. San Francisco; 2015. pp. 75–94.

46. Bradbury-Jones C, Taylor J, Herber O. How theory is used and articulated in qualitative research: development of a new typology. Soc Sci Med. 2014 Nov;120:135–41.

47. Gooberman-Hill R, Burston A, Clark E, Johnson E, Nolan S, Wells V, et al. Involving patients in research: considering good practice. Musculoskelet Care. 2013 Dec;11(4):187–90.