ABSTRACT

Objective To evaluate the effectiveness of injection-based therapy in base of thumb osteoarthritis.

Design Systematic review and meta-analysis.

Data sources MEDLINE and EMBASE via OVID, CINAHL and SPORTDiscus via EBSCO were searched from inception to 22 May 2018.

Study selection Randomised controlled trials (RCTs) and non-RCTs of adults with base of thumb osteoarthritis investigating an injection-based intervention with any comparator/s.

Data extraction and analysis Data were extracted and checked for accuracy and completeness by pairs of reviewers. Primary outcomes were pain and function. Comparative treatment effects were analysed by random-effects model for short-term and medium-term follow-up.

Results In total, 9 RCTs involving 504 patients were identified for inclusion. All compared different injection-based therapies with each other, no studies compared an injection-based therapy with a non-injection-based intervention. Twenty injection-based intervention groups were present within these nine trials, consisting of hyaluronic acid (n=9), corticosteroid (n=7), saline placebo (n=3) and dextrose (n=1). Limited meta-analysis was possible due to the heterogeneity in the injections and outcomes used, as well as incomplete outcome data. Meta-analysis of two RCTs (92 patients) demonstrated reduced Visual Analogue Scale pain on activity with corticosteroid versus hyaluronic acid (mean difference (MD) −1.32, 95% CI −2.23 to −0.41) in the medium term, but no differences in other measures of pain or function in the short term and medium term. Overall, the available evidence does not suggest that any of the commonly used injection therapies are superior to placebo, one another or a non-injection-based comparator.

Conclusion Current evidence is equivocal regarding the use of injection therapy in base of thumb osteoarthritis, both in terms of which injection-based therapy is the most effective and in terms of whether any injection-based therapy is more effective than other non-injection-based interventions. Given limited understanding of both the short-term and long-term effects, there is a need for a large, methodologically robust RCT investigating the commonly used injection therapies and comparing them with other therapeutic options and placebo.

PROSPERO registration number CRD42018095384.

INTRODUCTION

Base of thumb osteoarthritis is a common condition that is frequently associated with significant levels of pain, dysfunction and disability. The key risk factors include increasing age and female gender. The majority of base of thumb pain is managed in primary care or at primary care interface musculoskeletal services by physiotherapists, occupational therapists and general practitioners. The aim of treatment is to improve pain and function, and usual care often encompasses the current guidance from the British Society of Surgery for the Hand advising avoidance of painful activities, analgesia, splintage and steroid injections, with surgery considered to be a ‘last resort’. Usual care is likely to be highly variable, while there is some evidence which suggests that a majority of patients respond to non-surgical interventions and avoid surgery.

There is a lack of high-quality evidence to guide the non-surgical management of base of thumb osteoarthritis, and the existing literature demonstrates no clear answer as regard the effectiveness of injection-based interventions such as corticosteroid.
injections have been more widely studied in treating shoulder pain in which a short-term benefit over placebo has been demonstrated, however concerns remain over their long-term clinical effects.

Given this lack of clarity, our aim was to perform a systematic review of the effectiveness of injection-based interventions compared with any comparator/s for base of thumb osteoarthritis in terms of patient-reported outcome measures and to assess the rates of adverse outcomes associated with these interventions.

METHODS
The systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, using methodology described in the Cochrane Handbook for Systematic Reviews of Interventions. The protocol was developed prospectively and peer reviewed locally before registration on the PROSPERO database (CRD42018095384).

Data sources and searches
A comprehensive search strategy was created in collaboration with a research librarian (NT) and was designed to capture all relevant articles pertaining to injection-based interventions for base of thumb osteoarthritis (see online supplementary material 1). The full search strategy is detailed on the PROSPERO website. The search strategy was applied to the following bibliographic databases from database inception until 22 May 2018: MEDLINE and EMBASE via OVID, CINAHL and SPORTDiscus via EBSCO from database inception until 22 May 2018.

Inclusion/exclusion criteria
The inclusion and exclusion criteria were defined prospectively during the protocol stage. Any prospective study relating to an injection-based intervention for base of thumb osteoarthritis (trapeziometacarpal) was included. Studies had to contain an injection-based intervention and a comparator/s (ie, both non-randomised controlled trials (non-RCT), and RCTs, including semi-randomised/quasi-randomised, cluster randomised trials and comparative case series). Studies were excluded if patients were under the age of 18 years and if treatment was for inflammatory arthritis such as rheumatoid. Review articles, studies not published as a full article (conference abstracts) and case studies were excluded.

Selection of studies
Duplicates were removed and relevant studies identified from the search were imported into Covidence for screening. Studies were independently screened by two authors (BJFD and MV-B). The references of all included studies and all relevant review articles on the topic were also reviewed to identify other potential studies for inclusion. This was followed by a full-text evaluation of the selected studies from the first selection step by these authors. Disagreement between the two reviewers was solved by consensus involving a third author (NR).

Data extraction
Two reviewers (MV-B and BJFD) independently extracted data. Data were extracted using a custom data extraction sheet in Covidence (http://www.covidence.org). The custom data extraction sheet was specifically designed to extract data relating to study design, details relating to the interventions undertaken and details regarding the other treatment undergone by trial participants alongside the described interventions. Any inconsistencies between the two reviewers’ forms were resolved by consensus discussion. A third review (NR) was available for any disagreement that could not be resolved by this initial discussion.

If data were not available from full-text articles or trial registrations, the authors were contacted to provide this information. If the authors were not contactable as regard additional data, then this aspect of the study was excluded from the data synthesis. If contactable authors did not respond to initial requests, they were sent two subsequent reminders over a minimum of 6 weeks. If there was still no response for the additional data, then this aspect of the study was excluded from the data synthesis.

Risk of bias assessment
Included studies were assessed for risk of bias by two independent raters (BJFD and MV-B) using the Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. This followed the description in the Cochrane Handbook for Systematic Review of Interventions, V.5.1 (Part 2: 8.5.1). Any disagreements between ratings were resolved by discussion between the raters. A third party (NR) was available in any case where disagreements persisted after discussion.

Outcomes
Patient-reported pain and function were the primary outcomes of interest, adverse events were also recorded. A priori we defined end points as short term (1 week up to but not including 3 months), medium term (3 months up to and including 6 months) and long term (above 6 months). Where outcome data were available for more than one time point in each time category (short, medium and long term) then the data for the longest time point was used.

Data analysis
Descriptive analysis was performed for all demographic, intervention and outcome data to facilitate narrative interpretation and comparison across studies. Details regarding concomitant treatments in the different study arms such as the use of analgesics, splintage and physiotherapy were also recorded. Due to limited data, a direct-comparison meta-analysis was only performed for corticosteroid versus hyaluronic acid for pain (ie, Visual Analogue Scale (VAS) rest and VAS activity) and function (ie, grip strength and tip pinch strength). This was the only area in which data were available for similar time.
points, outcomes and interventions across two or more studies. Mean difference was used for the meta-analysis of VAS pain and standardised mean difference was used for the meta-analysis of function (grip strength and tip pinch strength). Statistical heterogeneity was determined according to Cochrane interpretation (I² >75% considerable heterogeneity). Analysis was performed using RevMan using both random-effects and fixed-effects models.

Patient and public involvement
Patients have not been involved in this review.

RESULTS
Study selection
A total of 229 studies were identified by the search, after duplicates were removed. After screening by full-text, nine RCTs were identified as eligible for inclusion (figure 1). The number of studies identified and excluded at each stage is detailed in figure 1.

Study characteristics
Study characteristics of the included trials including the interventions and comparators are provided in table 1. Seven RCTs contained two injection therapy treatment groups, while two contained three injection therapy treatment groups. The most common comparison was steroid versus hyaluronic acid (four RCTs).12-15 Other trials compared placebo with hyaluronic acid,16 steroid versus hyaluronic acid versus placebo,17 steroid versus dextrose,18 steroid versus placebo19 and three different hyaluronic acid injection regimes.20 There was wide variation in terms of the number of injections, drugs and doses used, as well the mode of injection delivery (anatomical as opposed to guided by ultrasound or fluoroscopically). Only three RCTs performed injections under guidance, two of these used fluoroscopic guidance19 20 and one ultrasound.14 No RCTs compared injection with a non-injection compactor.

Table 2 details the inclusion and exclusion criteria, the basic demographics of the intervention and comparator
| Author                  | Year | Journal               | Setting                           | Type of study | Intervention detail                                                                 | Comparator 1 detail                                                                 | Comparator 2 detail |
|-------------------------|------|-----------------------|-----------------------------------|---------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------|
| Bahadir et al           | 2009 | Clin Rheumatol        | Hospital department, Turkey       | Parallel group RCT | Steroid-X1: one injection of trimamcinolone 20mg, anatomical                          | HA-X3: three injections of 5mg of sodium hyaluronate, anatomical (a week apart)     | N/A                 |
| Figen Ayhan and Ustün   | 2009 | Clin Rheumatol        | Rheumatology department, Turkey   | Parallel group RCT | Placebo (saline)-X1: one injection of 1 mL saline, anatomical                          | HA-X1: one injection of 8mg sodium hyaluronate, anatomical                         | N/A                 |
| Fuchs et al             | 2006 | Osteoarthritis and Cartilage | Hospital department, Germany      | Parallel group RCT | Steroid-X3: three injections of 10mg trimamcinolone, anatomical and 1 week apart      | HA-X3: three injections of 10mg hyaluronic acid, anatomical and 1 week apart       | N/A                 |
| Heyworth et al          | 2008 | Journal of Hand Surgery (American) | Orthopaedic hospital, USA         | Parallel group RCT | Steroid-X1 + placebo (saline)-X1: two injections, first saline 1 mL and then second 1 week later of 1 mL sodium betamethasone, anatomical | HA-X2: two injections, both 8mg sodium hyaluronate and 1 week apart, anatomical  | Placebo (saline)-X2: two injections, both 1 mL saline and 1 week apart, anatomical |
| Jahangiri et al         | 2014 | J Orthop Sci          | Medical department, Iran          | Parallel group RCT | Steroid-X1 + placebo (saline)-X2: 2 monthly injections of saline 1mL and then at 3 months injection of 40mg methylprednisolone and 2% lignocaine, anatomical | Hypertonic dextrose-X3: 0.5 mL of 20% dextrose mixed with 0.5 mL of 2% lignocaine every month for 3 months, anatomical | N/A                 |
| Meenagh et al           | 2004 | Ann Rheum Dis         | Hospital Rheumatology department, Northern Ireland | Parallel group RCT | Steroid-X1: 5mg of triamcinolone, guided fluoroscopically                             | Placebo (saline)-X1: 0.25 mL of 0.9% saline, guided fluoroscopically               | N/A                 |
| Monfort et al           | 2015 | Joint Bone Spine      | Hospital Rheumatology department, Spain | Parallel group RCT | Steroid-X3: 0.5 cm³ of betamethasone disodium phosphate 1.5mg and betamethasone acetate 1.5mg at weekly intervals for 3 weeks, ultrasound guided | HA-X3: 0.5 cm³ contained 5 mg of sodium hyaluronate at weekly intervals for 3 weeks, ultrasound guided | N/A                 |
| Roux et al              | 2007 | Joint Bone Spine      | Hospital Rheumatology department, France | Parallel group RCT | HA-X1: 1 mL containing 8mg of hyaluronic acid injected once, guided fluoroscopically | HA-X2: 1 mL containing 8mg of hyaluronic acid injected twice at weekly intervals, guided fluoroscopically | HA-X3: 1 mL containing 8mg of hyaluronic acid injected three times at weekly intervals, guided fluoroscopically |
| Stahl et al             | 2005 | J Clin Rheumatol      | Hand surgery unit, Israel         | Parallel group RCT | Steroid-X1: one injection of 40mg methylprednisolone, anatomical                      | HA-X1: 1 mL containing 15 mg of hyaluronic acid injected once, anatomical          | N/A                 |

N/A, not available; RCT, randomised controlled trial.
| Author           | Year | Inclusion criteria | Exclusion criteria                                                                 | Number of participants | Mean age of participants | Sex of participants | Data comments                                      |
|------------------|------|--------------------|-------------------------------------------------------------------------------------|------------------------|-------------------------|---------------------|---------------------------------------------------|
| Bahadir et al    | 2009 | Eaton-Littler grade 2 or 3 | Inflammatory arthritis, trauma, carpal tunnel, previous injection                    | 40                     | 61.9                    | 40 females          | Adequate data within original publication to enable potential meta-analysis. |
| Figen Ayhan and Ustün | 2009 | Bilateral symptoms with failed prior treatment, Eaton-Littler grade 1–4 | Injection within last 6 months, trauma, inflammatory arthritis, joint infection       | 66                     | 62.6                    | 66 females          | Incomplete outcome data and this was not provided by the authors on request. |
| Fuchs et al      | 2006 | Aged between 44 and 80 years with radiographic osteoarthritis symptomatic for at least 6 months | Alcohol/drug abuse, recent injection, inflammatory arthritis, uncontrolled diabetes, joint infection | 56                     | 60.3                    | 45 female, 11 males | Incomplete outcome data and this was not provided by the authors on request. |
| Heyworth et al   | 2008 | Symptomatic osteoarthritis without need for radiographic confirmation | More than two previous injections, pregnancy, previous surgery, trauma to joint, no benefit from previous steroid injection, inflammatory arthritis | 60                     | 63                      | 52 females, 8 males | Incomplete outcome data and this was not provided by the authors on request. |
| Jahangiri et al  | 2014 | Aged over 40 with symptoms for over 3 months and pain >30 mm VAS, radiographic grade 2 and above Eaton-Littler | Inflammatory arthritis, tendon pain, joint infection, use of splint or NSAIDs, pregnancy, injection within last 6 months | 60                     | 63.5                    | 44 females, 16 males | Incomplete outcome data and this was not provided by the authors on request. |
| Meenan et al     | 2004 | Symptomatic and satisfying ACR classification of hand osteoarthritis | Inflammatory arthritis, previous thumb trauma, previous injection to either thumb base | 40                     | 60                      | 36 females, 4 males | Incomplete outcome data and this was not provided by the authors on request. |
| Monfort et al    | 2015 | Symptomatic for at least 90 days, requiring analgesics, radiographic confirmation with at least grade 1 Kellgren-Lawrence | Pregnancy, severe renal/liver disease, injection within last 3 months, previous thumb surgery, previous physical therapy | 88                     | 38.5                    | Not stated          | Adequate data within original publication to enable potential meta-analysis. |
| Roux et al       | 2007 | Symptomatic with VAS <40 mm, refractory to other therapeutic interventions, radiographic confirmation with at least grade 1 Kellgren-Lawrence | Symptomatic osteoarthritis in other digits, blood coagulation disorder, hand trauma, hand infection, steroid injection within 6 months or any hyaluronic acid injection | 42                     | 65.6                    | 38 females, 4 males | Adequate data within original publication to enable potential meta-analysis. |
| Stähle et al     | 2005 | Symptomatic grade 2 according to Eaton-Littler classification | None                                                                                | 52                     | 62                      | 46 females, 6 males | Incomplete outcome data and this was kindly provided by the authors on request. |

ACR, American College of Rheumatology; NSAID, non-steroidal anti-inflammatory drug; VAS, Visual Analogue Scale.
groups as well as details relating to the outcome data. Inclusion and exclusion criteria were highly variable. All trials were solely related to adults with symptomatic base of thumb osteoarthritis, most specified a particular radiographic grading as an inclusion criterion, either the classification by Eaton and Littler or Kellgren and Lawrence were used. Two trials did not specify a particular grade of base of thumb osteoarthritis. One trial specified the need for bilateral symptoms as one side received steroid and the other placebo injection. Two trials were exclusively of females. The remaining trials included a minority of men, while one did not state the gender breakdown. The mean age of participants was close to 60 years, other than the study by Monfort et al, which had a mean age of 38.5 years. Only three trials contained adequate data within the published text for undertaking further analysis. We contacted the authors of the remaining six studies and one author responded to supply a complete data set.

Table 3 details the study outcomes, time points and a summary of results including adverse events. Only two of the nine trials clearly specified a primary outcome. The VAS for base of thumb pain was used by all trials, however it was used in several different formats such as the standard VAS (average of pain and activity), VAS (rest), VAS (activity), VAS (pressure) and VAS (average of pain, activity and pressure). The majority of trials final follow-up was at 6 months, the exceptions to this being the studies by Bahadir et al and Roux et al which followed participants until 12 and 3 months, respectively.

Table 4 describes the concomitant treatment undergone by the trial participants broken down into analgesia, splint use and other. Some trials made little mention of concomitant therapies, for example, Stahl et al made no mention of other treatments while Meenagh et al only mentioned that a splint was used for 48 hours after the injection. The approach to analgesics was highly variable. Meenagh et al did not mention analgesics Monfort et al and Roux et al allowed all analgesics while all the other trials prohibited the use of analgesics in a highly variable manner. The approach to splinting was also highly variable. Both Roux et al and Fuchs et al made no change to splint usage. While Jahangiri et al excluded patients who used splints and Bahadir et al prohibited the use of splints. Heyworth et al and Meenagh et al specified the use of a splint for a short period after injection therapy, but did not describe splint usage outside of this window. Monfort et al Stahl et al and Figen Ayhan and Ustün all made no mention of splint usage. Only two trials made any mention of hand therapy, Jahangiri et al instructed patients not to undergo any therapy, while Monfort et al excluded patients who had undergone hand therapy.

Adverse events
All trials reported that no adverse events had occurred as a result of any trial interventions, thus demonstrating the general safety of injection-based therapies. However, the absence of published study protocols and published details regarding what precisely constituted an ‘adverse event’ surveillance does make it difficult to be specific as to what this actually means.

Risk of bias within studies and across studies
Overall, the degree of bias was fairly heterogeneous across all bias domains. Only one trial was at high risk of bias in terms of sequence generation due to the use of a sequence generated by the patient’s hospital number. Blinding of participants was not possible in the trials by Bahadir et al and Roux et al due to the different number of injections received by both treatment groups, while the injecting clinician was not blinded in the trial by Heyworth et al. One study was at high risk of bias regarding incomplete outcome data due to a significantly greater loss to follow-up in the steroid injection group. The risk of bias summary is shown in figure 2 and the risk of bias graph is included as online supplementary file 2. Other sources of bias included the use of a single individual performing injections in a single centre, industry funding, the ‘random’ exclusion of a large group of patients, underpowering by not meeting study’s own stated number of patients, a lack of control group and the role of industry in providing sodium hyaluronate without charge.

Results of individual studies and synthesis of results
The results of the individual trials are summarised in table 3. Due to limited data, meta-analysis was only performed for the comparison of corticosteroid versus hyaluronic acid for pain (ie, VAS rest and VAS activity) and function (ie, grip strength and tip pinch strength) (figures 3–6).

Pain
Corticosteroid versus hyaluronic acid
Bahadir et al demonstrated that steroid was superior to hyaluronic acid in terms of pain (VAS (activity)) in the medium term (MD = −2.20, 95% CI −3.45 to −0.95) but not at long term. Fuchs et al showed a short term (2 and 3 weeks) superiority of steroid over hyaluronic acid in terms of pain (VAS). The studies by Heyworth et al, Monfort et al and Stahl et al showed no difference in pain in the short and medium term (figures 3 and 4).

Meta-analysis of the studies by Bahadir et al and Stahl et al showed a small reduction in pain (VAS (activity)) in medium term in those participants who received corticosteroid compared with control, however there was no difference in the short or long term (figure 3). Meta-analysis of the studies by Monfort et al and Stahl et al demonstrated no difference in pain (VAS (rest)) between corticosteroid and hyaluronic acid in the short and medium term (figure 4).

Corticosteroid versus placebo
The studies by Heyworth et al and Meenagh et al demonstrated no difference in pain (VAS) in the short and medium term, however no further analysis was possible due to the incomplete data provided.
Table 3  Details of study outcomes, time points and a summary of results

| Author          | Year | Outcomes (primary in italics if present) | Time points | Effect measures—mean difference (95% CI) in short term, medium term, long term | Summary of results and adverse events |
|-----------------|------|------------------------------------------|-------------|--------------------------------------------------------------------------------|---------------------------------------|
| Bahadir et al   | 2009 | VAS (activity), tip pinch strength, grip strength, Duruoz Hand Index | Baseline, 1 month, 3 months, 6 months, 12 months | VAS (activity) −1.60 (−3.21 to 0.01), −2.20 (−3.45 to −0.95), −1.10 (−2.37 to 0.17) Tip pinch strength 1.90 (0.60 to 3.20), 1.10 (−0.17 to 2.37), 1.10 (−0.11 to 2.31) Grip strength 8.60 (2.03 to 17.17), 6.40 (−0.05 to 12.85), 4.80 (−2.46 to 12.06) Duruoz Hand Index −10.20 (−17.24 to −3.16), −10.10 (−16.77 to −3.43), −3.80 (−11.57 to 3.97) | Greater statistically significant improvement in VAS with corticosteroid than with hyaluronic acid at 1 month and 6 months. No adverse events. |
| Figen Ayhan and Ustün | 2009 | VAS (average of rest/activity/pressure), tip pinch strength, tripod pinch strength, key pinch strength, Dreiser Index | Baseline, 6 weeks, 6 months | Not estimable from available data | No statistically significant difference in outcomes at any time point. No adverse events. |
| Fuchs et al     | 2006 | VAS pain, tip pinch strength, key pinch strength, range of movement | Baseline, 3 weeks, 14 weeks, 26 weeks | Not estimable from available data | Statistically significant superiority of corticosteroid over hyaluronic acid at 2 and 3 weeks time point in terms of pain relief. No causal adverse events. |
| Heyworth et al  | 2008 | VAS pain, tip pinch strength, grip strength, key pinch strength, DASH, range of motion (MCPJ) | Baseline, 2 weeks, 4 weeks, 12 weeks, 26 weeks | Not estimable from available data | No statistically significant difference between groups at most time points. No adverse events. |
| Jahangiri et al | 2014 | VAS (pressure), lateral pinch strength, VAS (activity), hand function (HAQ-DI) | Baseline, 1 month, 2 months, 6 months | VAS (pressure) data not provided for short term, 1.1 (0.2 to −2.0) in medium term VAS (activity) 1.0 (0.1 to 2.0), 1.1 (0.2 to 2.0) Lateral pinch strength 1.1 (−0.8 to 3.1), 0.8 (−1.3 to 2.9) HAQ-DI 1.0 (0.2 to 1.9), 1.0 (0.2 to 1.8) | Corticosteroid group had statistically significant reduction in VAS (pressure) at 1 month vs dextrose, while dextrose demonstrated statistically significant reduction in VAS (pressure) at 6 months vs corticosteroid. No adverse events. |
| Meenagh et al   | 2004 | VAS (pain), joint tenderness, patient global assessment, physician global assessment, joint stiffness | Baseline, 1 month, 3 months, 6 months | Joint tenderness −1.00 (−1.80 to −0.20), −2.00 (−3.92 to −0.08) Patient global assessment −2.00 (−3.92 to −0.08), −2.00 (−3.92 to −0.08) Physician global assessment −2.00 (−3.92 to −0.08), −1.00 (−1.27 to −0.73) Joint stiffness −1.00 (−1.27 to −0.73), −1.00 (−1.27 to −0.73) VAS (pain) not estimable from available data | No statistically significant difference between groups at all time points. No adverse events. |
| Monfort et al   | 2015 | VAS (rest), Dreiser Index, PCS-36, MCS-36 | Baseline, 1 week, 2 weeks, 1 month, 2 months, 6 months | VAS (rest) −0.56 (−1.58 to 0.46), 0.55 (−0.51 to 1.61) Dreiser Index 0.00 (−2.24 to 2.24), not estimable from available data at medium term PCS-36 0.00 (−2.24 to 2.24) at medium term MCS-36 0.00 (−2.24 to 2.24) at medium term | No statistically significant difference between groups at all time points in VAS and Dreiser Index. No adverse events. |
| Roux et al      | 2007 | VAS (rest), Dreiser Index | Baseline, 1 month, 3 months | HA1 vs HA2 VAS (rest) −1.90 (−21.48 to 17.68), 3.60 (−16.60 to 23.80) Dreiser Index −1.70 (−7.71 to 4.31), 0.00 (−2.24 to 2.24) HA1 vs HA3 VAS (rest) −0.06 (−0.84 to 0.73), 3.60 (−16.60 to 23.80) Dreiser Index −1.70 (−7.71 to 4.31), −1.70 (−7.71 to 4.31) HA2 vs HA3 VAS (rest) 0.53 (−0.29 to 1.34), 0.53 (−0.29 to 1.34) Dreiser Index −1.70 (−7.71 to 4.31), −1.70 (−7.71 to 4.31) | No statistically significant difference in outcomes between groups at all time points. No adverse events. |
| Stahl et al     | 2005 | Tip pinch strength, tripod pinch strength, key pinch strength, grip strength, VAS (rest), VAS (activity) | Baseline, 1 month, 3 months, 6 months | VAS (activity) 0.35 (−0.90 to 1.60), 0.30 (−1.64 to 1.04) Tip pinch strength 0.27 (−0.81 to 0.28), 0.15 (−1.09 to 1.59) Tripod pinch strength −0.77 (−1.43 to −0.11), −0.33 (−0.96 to 0.30) Key pinch strength −0.79 (−1.72 to 0.14), −0.45 (−1.34 to 0.44) Grip strength −0.33 (−0.96 to 0.30), −0.33 (−0.96 to 0.30) | No statistically significant difference in outcomes between groups at all time points. No adverse events. |

DASH, Disabilities of the Arm, Shoulder and Hand; HA1, one HA injection group; HA2, two HA injections group; HAQ-DI, Health Assessment Questionnaire - Disability Index; MCPJ, metacarpophalangeal joint; PCS, mental component summary of the SF-36; SF-36, physical component summary of the SF-36; SP-36, short form 36 health survey; VAS, Visual Analogue Scale.
### Table 4 Details of concomitant treatment alongside injection therapy

| Author          | Year | Analgesia                                                                 | Splintage                                                                 | Other                                                                 |
|-----------------|------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------|
| Bahadir et al   | 2009 | No concomitant analgesia allowed in all treatment groups                  | No splint used in all groups. No mention of how many had used splint regularly before study period. | Not mentioned.                                                       |
| Figen Ayhan and Ustün | 2009 | No analgesia allowed for 2 weeks before injection and not mentioned what was allowed after injection therapy | No mention of splint usage.                                               | No mention of other therapy after injection therapy.                 |
| Fuchs et al     | 2006 | Only paracetamol allowed and all other analgesics stopped in all groups   | No change in use of splintage and not recorded in terms of details.       | Not mentioned.                                                       |
| Heyworth et al  | 2008 | Two-week ‘wash-out’ period before injection during which no use of NSAIDs was allowed for all groups | Hand-based neoprene thumb spica splint used for minimum of 22 hours per day for the 2 weeks after injection therapy in all groups. | Spint was allowed as necessary and NSAIDs were allowed in all groups 2 weeks after the injection therapy. |
| Jahangiri et al | 2014 | Patients using NSAIDs excluded. Participants were instructed not to use analgesic medications. | Patients using splints excluded. Participants in the study were instructed not to use a splint. | All the patients were asked to return gradually to normal activities but to avoid pain-provoking physical stresses, especially within the first 48 hours after injection. Participants were instructed not to undergo physiotherapy. |
| Meenagh et al   | 2004 | Not mentioned                                                             | Splinted for 48 hours after injection therapy in all groups.              | Not mentioned.                                                       |
| Montfort et al  | 2015 | Medications were allowed and those used within 30 days before screening and throughout the study period, including paracetamol (maximum 3 g/day) as rescue medication, were recorded in a diary card | Not mentioned.                                                          | Patients excluded if physical therapy performed by a physiotherapist at home or in a specialised centre. |
| Roux et al      | 2007 | Treatment had not been modified for at least 3 months (analgesics/NSAIDs/osteoarthritis drugs). Patients were in failure of treatment and usual treatments (NSAIDs, analgesics) remained unchanged during the study period. | Treatment with splints had not been modified for at least 3 months. Splint treatment remained unchanged during the study period. | No other treatment was modified during study period. Therapy not mentioned specifically. |
| Stahl et al     | 2005 | Not mentioned                                                             | Not mentioned                                                             | Not mentioned.                                                       |

NSAID, non-steroidal anti-inflammatory drug.
Riley N, et al. BMJ Open 2019;9:e027507. doi:10.1136/bmjopen-2018-027507

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Figure 2 Risk of bias summary. Review the authors’ judgements about each risk of bias item for each included study.

Hyaluronic acid versus placebo
The studies by Heyworth et al. and Figen Ayhan et al. demonstrated no difference in pain in the short and medium term, again no further analysis was possible due to the incomplete data provided.

Corticosteroid versus dextrose
Jahangiri et al. found that the corticosteroid group had a reduction in VAS (rest) in the short term versus dextrose, however there was no difference in pain (VAS (activity)).

Jahangiri et al. also demonstrated a reduction in VAS (pressure) in the medium term in the dextrose group compared with the corticosteroid group, however there was no difference in pain (VAS (activity)) in the medium term.

Hyaluronic acid comparisons
Roux et al. demonstrated no difference in pain (VAS (rest)) in the short term with one versus two versus three hyaluronic acid injections in the short and medium term.

Function (tip pinch strength and grip strength)
Corticosteroid versus hyaluronic acid
The studies by Heyworth et al., Monfort et al. and Stahl et al. showed no difference in hand function in the short term and medium term. Bahadir et al. demonstrated that steroid was superior to hyaluronic acid in terms of function in the short and medium term (Duruoz Hand Index), but no differences in tip pinch strength and grip strength in the long term.

Meta-analysis of the results of the Stahl et al. and Bahadir et al. studies demonstrated no differences in tip pinch strength and grip strength in the short term and medium term (figures 5 and 6).

Corticosteroid versus placebo
The studies by Heyworth et al. and Meenagh et al. demonstrated no difference in function in the short and medium term, however no further analysis was possible due to the incomplete data provided.

Hyaluronic acid versus placebo
The studies by Heyworth et al. and Figen Ayhan et al. demonstrated no difference in function in the short and medium term, again no further analysis was possible due to the incomplete data provided.

Corticosteroid versus dextrose
Jahangiri et al. demonstrated no difference in function (Dreiser Index) in the short and medium term with one versus two versus three hyaluronic acid injections.

DISCUSSION
The key finding of this systematic review is that the current evidence is equivocal regarding the use of injection therapy in base of thumb osteoarthritis, both in terms of which injection-based therapy is the most effective and in terms of whether any injection-based therapy is more effective than other non-injection-based interventions. It is of interest that there is no prospective evidence in which an injection-based therapy is compared with a non-injection-based intervention.

The existing evidence base suggests that a majority of patients who present with painful base of thumb osteoarthritis avoid surgical intervention. It remains unclear as to which specific non-surgical interventions add value due to the significant methodological problems with the studies that have been carried out in this area. As a result, it is likely that the non-operative
The management of base of thumb osteoarthritis is highly variable, much as the surgical management appears to be. In the UK, corticosteroid injection is widely used, although data documenting the precise economic costs of this practice is lacking.

A previous robust systematic review by Kroon et al has reached similar conclusions to those of our study. However, by obtaining additional data from the authors we were able to undertake a meta-analysis demonstrating a reduced VAS pain on activity with corticosteroid versus hyaluronic acid (MD $-1.32$, 95% CI $-2.23$ to $-0.41$) in the medium term, this being a novel finding. In this context, it is particularly difficult to justify the use of the more expensive hyaluronic acid over corticosteroid in treating base of thumb osteoarthritis. There are some other key methodological differences between our study and the review by Kroon et al. We excluded studies which had not been published in full after peer review, while these were included by Kroon et al. We have also described the approach of trials to concomitant therapies in significantly greater detail as discussed below. Broadly we feel that our findings validate and add to this previous work by Kroon et al. Overall, the justification for future research in this area remains strong, as it is imperative to determine whether such widely used interventions provide any clinically meaningful advantages over placebo.

Our review has summarised the way in which trials have handled concomitant treatments in detail and we feel this is of key importance given the way in which patients with base of thumb osteoarthritis are managed in the real world. Several studies did not even record which concomitant treatments patients had undergone before or after study interventions, while concomitant treatments were frequently managed in a rather artificial non-pragmatic manner. This can be addressed by a more pragmatic trial design as described in the recently published HIT trial protocol that has addressed the problem of concomitant treatments in hip osteoarthritis by combining...
injection-based interventions with ‘best current treat-
ment’ and ensuring that all analgesic use is recorded;
in this way, the concomitant treatments become more
homogenous between patients and any differences can
be taken into account.26 Generally, patients in the real
world are not advised to stop taking other analgesics
before or after receiving an injection,27 however in several
of the included studies in this review this is precisely what
was done. A similar argument can be made about splint
usage, as generally most patients have received some
form of guidance about splint usage for symptom control
before undergoing any form of injection-based inter-
vention. Certainly, at a minimum the use of all concomitant
treatments should be recorded before and after trial
interventions have been administered.

Only two included studies used a specific symptom
threshold for inclusion, Jahangiri et al18 included those
with a VAS >30 mm while Roux et al20 excluded those
with a VAS >40 mm. The current Osteoarthritis Research
Society International (OARSI) guidelines advise having a
minimum cut-off for inclusion in terms of pain or func-
tion, obviously using pain or functional measures may
depend on the primary outcome measure.28 This factor
is another potential contributant to negative trial results
as by failing to have a minimum cut-off for trial inclusion,
trials are likely to have been including participants with
relatively minimal levels of symptoms which makes it less
likely that a clinically meaningful difference in outcomes
can be achieved.

| Study or Subgroup | Corticosteroid Mean | SD | Total | Hyaluronic acid Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|------------------|---------------------|----|-------|---------------------|----|-------|--------|----------------------------------|
| 1.2 short term   |                     |    |       |                     |    |       |        |                                  |
| Bahadir 2009     | 9.9                 | 2.1| 20    | 7.1                 | 2.1| 20    | 40.4%  | 0.69 [0.23, 1.54]                 |
| Stahl 2005       | 3.11                | 1.2| 26    | 3.38                | 1.2| 26    | 50.6%  | -0.63 [-1.20, -0.07]              |
| Subtotal (95% CI)| 46                  | 45 | 100%  | 45                  | 100% | 0.12  | 1.37, 1.61                      |
| Heterogeneity    | τ² (df = 1) = 1.06  |    |       | Ch² (df = 1) = 11.91 | 0.0006 | 92%  |
| Test for overall | effect: Z = 0.18 (P = 0.86) |    |       |                     |    |       |                                  |
| 1.4 medium term  |                     |    |       |                     |    |       |        |                                  |
| Bahadir 2009     | 8.6                 | 2  | 20    | 7.5                 | 2.1| 20    | 48.0%  | 0.53 [0.11, 1.16]                 |
| Stahl 2005       | 3.65                | 1.32| 27 | 3.98                | 0.99| 25    | 52.0%  | -0.26 [-0.92, 0.27]              |
| Subtotal (95% CI)| 47                  | 45 | 100%  | 45                  | 100% | 0.11  | -0.68, 0.89                     |
| Heterogeneity    | τ² (df = 1) = 0.23  |    |       | Ch² (df = 1) = 3.55 | 0.0008 | 72%  |
| Test for overall | effect: Z = 0.27 (P = 0.79) |    |       |                     |    |       |                                  |
| 1.5 long term    |                     |    |       |                     |    |       |        |                                  |
| Bahadir 2009     | 8.2                 | 1.9| 20    | 7.1                 | 2  | 20    | 100.0% | 0.55 [0.08, 1.19]                |
| Subtotal (95% CI)| 20                  | 20 | 100%  | 20                  | 100% | 0.55  | 0.08, 1.19                      |
| Heterogeneity    | Not applicable      |    |       |                     |    |       |                                  |
| Test for overall | effect: Z = 1.71 (P = 0.09) |    |       |                     |    |       |                                  |

Test for subgroup differences: Ch² = 0.65, df = 2 (P = 0.66), P = 0%
This review has highlighted several important aspects of trial methodology which must be considered carefully in the planning and design of future research. Future trials should clearly prespecify a primary outcome measure and ideally consider current guidelines relating to clinical trials in osteoarthritis. Trials should involve multiple centres and be adequately powered, the current evidence base consists of virtually exclusively small single-centre studies. It is also important to ensure that the current management of base of thumb osteoarthritis is assessed in some detail, as this is also an area in which little has been published. There may be considerable variations in practice in terms of which injection therapies are used and how the injection is delivered, and in terms of the threshold for injection. This review has highlighted how variable the approach of different studies has been to dealing with the issue of concomitant or previous treatments, this also presents a challenge to researchers in the future. As discussed above, it appears best to adopt a pragmatic approach based on an assessment of what is generally deemed to be standard best practice.

Limitations
The main limitations to this systematic review and meta-analysis are the limitations intrinsic to the included studies, which are detailed above. There are several fairly consistent methodological flaws present within the trials included in this review; the studies are all small single-centre studies which appear significantly underpowered, there is a consistent failure to clearly prespecify and state a primary outcome measure and the use of concomitant treatments has not been pragmatic. The meta-analysis has been significantly limited by a lack of adequate outcome data.

CONCLUSIONS
Current evidence is equivocal regarding the use of injection therapy in base of thumb osteoarthritis, both in terms of which injection-based therapy is the most effective and in terms of whether any injection-based therapy is more effective than other non-injection-based interventions. Given limited understanding of both the short-term and long-term effects, there is a need for large, methodologically robust multicentre RCTs investigating the commonly used injection therapies and comparison made with other therapeutic options and placebo.

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